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PAPER

N-Heterocyclic carbene-catalyzed cascade annulation reaction of *o*-vinylarylaldehydes with nitrosoarenes: one-step assembly of functionalized 2,3-benzoxazin-4-ones†

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The NHC-catalyzed reactions of *ortho* electron-deficient vinyl substituted arylaldehydes with nitrosoarenes were studied. The reactions produced multifunctional 2,3-benzoxazin-4-ones in good to excellent yields *via* a cascade aza-benzoin reaction between aldehyde and nitroso groups followed by an intramolecular oxo-Michael addition. The resulting 1-acetate substituted 2,3-benzoxazinones were transformed into a new type of β-hydroxycarboxylate derivatives or 3-oxo-1-isobenzofuranacetates, respectively, under different reductive conditions. This work not only provides a simple and efficient method for the construction of multifunctional 2,3-benzoxazin-4-ones of potential pharmacological interest, but also expands the application of NHC-catalyzed cascade reactions in the formation of carbon–heteroatom and heteroatom–heteroatom bonds.

Introduction

Since the discovery of umpolung reactivity of carbonyls triggered by *N*-heterocyclic carbenes (NHC), NHC-catalyzed carbon–carbon bond forming reactions have become a very intense area of organic chemistry.[1] In recent years, the cascade processes promoted by *N*-heterocyclic carbenes have received great attentions due to the rapid generation of complexity of products.[2] Most of the NHC-catalyzed cascade reactions are initiated by the interaction of umpolung carbonyls with carbon electrophiles to form carbon–carbon bonds and to produce cyclic compounds. For example, in the presence of NHC catalysts, the cascade reactions of aldehydes with (1,2-phenylene)bis(2-propenones),[3a] (2-formylphenyl)acrylates with imines,[3b] phthalaldehydes with 1,4-diarylbutene-1,4-diones,[3c] imines,[3d] or *o*-vinylarylaldehydes,[3e,f] and the dimerization of *o*-vinylarylaldehydes[3e,f] or phthalaldehydes,[3g] afford various indene, indanone or spiro-indene derivatives. While the NHC-catalyzed cascade [4 + 2] cycloaddition of α,β-unsaturated acid fluorides with silyl dienol ethers forms 1,3-cyclohexadienes,[4] the reactions of 2-propargyloxy-1-arylaldehydes with aldehydes produce chroman-4-one or benzofuran-3-one derivatives under different conditions.[5] The NHC-catalyzed cascade reactions of formylcyclopropane 1,1-diesters with indole-2-carbaldehydes or salicylaldehydes leads to pyrrolo[1,2-*a*]indoles or coumarin.[6] Although various cascade reactions promoted by *N*-heterocyclic carbenes have been reported, the NHC-catalyzed cascade carbon–heteroatom and heteroatom–heteroatom bonds formations are still largely unexplored.

Only a few examples of NHC-catalyzed reactions of carbonyl compounds with nitrosoarenes have been documented in literature, which constitute an efficient method for the formation of carbon–nitrogen bonds.[7–9] Under the catalysis of NHC, the reaction of aldehydes with nitrosoarenes has led to direct amidation of aldehydes to provide *N*-arylhydroxamic acids,[7] while in the reactions of α,β-unsaturated aldehydes with nitroso compounds, isoxazolidin-5-ones intermediates or products were formed, and could further convert into isoxazol-5-ones, β-amino acid esters or benzo[*b*][1,4]oxazepin-2-ones.[8] The NHC-catalyzed reaction between ketenes and nitrosoarenes has been reported to proceed *via* a formal [2 + 2] cycloaddition to form oxazetidinones.[9] We envisioned that, if an aldehyde is linked with a Michael acceptor, the reaction between the aldehyde and a nitroso compound would probably proceed *via* cascade carbon–nitrogen and carbon–oxygen bond formation to produce highly functionalized 2,3-benzoxazine derivatives, which represent a bioactive scaffold.[10] We report herein the study on the reactions of *ortho* electron-deficient vinyl substituted arylaldehydes with nitrosoarenes.

Results and discussion

We began our study with the examination of the reaction between *o*-formylcinnamate **1a** and nitrosobenzene **2a**

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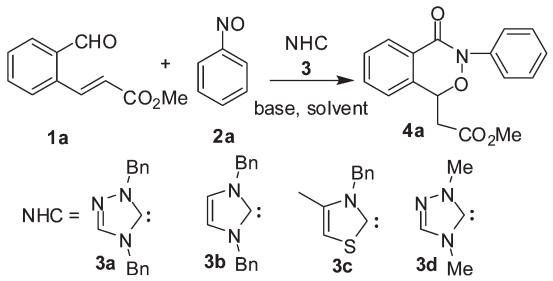
†Electronic supplementary information (ESI) available: The copies of ^{1}H NMR and ^{13}C NMR spectra of products **4**, **6**, **10** and **11** are available. CCDC 862111. For ESI and crystallographic data in CIF or other electronic format see 10.1039/c2ob25137j

Table 1 Optimization of reaction conditions



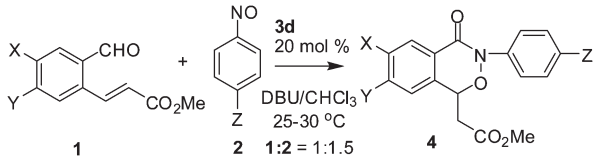
Entry	Reaction conditions[a] 3	mol% of 3	Base	Sol.	T (°C)	T (h)	Yield of 4a (%)
1	**3a**	20	DBU	$CHCl_3$	25–30	18	60
2	**3b**	20	DBU	$CHCl_3$	25–30	18	38
3	**3c**	20	DBU	$CHCl_3$	25–30	18	14
4	**3d**	20	DBU	$CHCl_3$	25–30	9	71
5	**3d**	10	DBU	$CHCl_3$	25–30	16	46
6	**3d**	20	DBU	$CHCl_3$	0	17	36
7	**3d**	20	DBU	$CHCl_3$	Reflux	9	53
8	**3d**	20	DBU	THF	25–30	10	60
9	**3d**	20	DBU	CH_3CN	25–30	12	64
10	**3d**	20	DBU	Benzene	25–30	12	44
11	**3d**	20	DBU	Dioxane	25–30	12	51
12	**3d**	20	DBU	DCE[b]	25–30	12	58
13	**3d**	20	*t*-BuOK	$CHCl_3$	25–30	10	17
14	**3d**	20	NaH	$CHCl_3$	25–30	10	14
15	**3d**	20	Et_3N	$CHCl_3$	25–30	10	11

[a] **1a** : **2a** = 1 : 1.5. [b] DCE = $ClCH_2CH_2Cl$.

employing a catalytic amount of different *N*-heterocyclic carbene catalysts **3**. The *N*-heterocyclic carbenes **3** were generated from deprotonation of azolium salts by DBU. At 25–30 °C and in chloroform, the reaction of *o*-formylcinnamate **1a** with nitrosobenzene **2a** (**1a** : **2a** = 1 : 1.5) in the presence of 20 mol% of *N*, *N*-dibenzyl-1,2,4-triazole, -imidazole, or -thiazole carbene produced 2-(4-oxo-3-phenyl-2,3-benzoxazin-1-yl)acetate **4a** in 60%, 38%, or 14% yield, respectively (Table 1, entries 1–3. X-ray crystal structure of **4a** was shown in ESI†).[11] The yield of **4a** was improved to 71% yield, when *N*,*N*-dibenzyltriazole carbene **3a** was replaced by *N*,*N*-dimethyltriazole carbene **3d** (Table 1, entry 4). Decreasing of catalyst loading of **3d** to 10 mol% led to the formation of **4a** in lower yield (46%) (Table 1, entry 5). Under the catalysis of dimethyltriazole carbene **3d** (20 mol%), the reaction conditions were further optimized by varying temperature, solvents and bases that were used to generate carbene catalyst. Unfortunately, however, the use of other solvents including THF, acetonitrile, benzene, 1,4-dioxane and 1,1,2-trichloroethane, or other bases like *t*-BuOK, NaH and Et_3N, or at higher and lower temperature, all diminished the yield of product (Table 1, entries 6–15).

Under the optimized conditions, we tested the reaction scope by using a variety of substituted *o*-formylcinnamates **1** and nitrosoarenes **2**. As shown in Table 2, the substituents on formylcinnamates **1** have influence on the reaction efficiency. For example, 2-formylcinnamate **1a**, 4,5-dimethyl-2-formylcinnamate **1b**, 4,5-dibromo-2-formylcinnamate **1d** and 4-nitro-2-formylcinnamate **1e** reacted efficiently with nitrosobenzene **2a** to

Table 2 The reaction of *o*-formylcinnamates **1** and nitrosoarenes **2** under optimized conditions



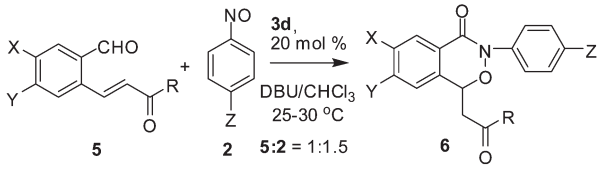
Entry	1	X, Y	2	Z	T (h)	Yield of 4 (%)
1	**1a**	H, H	**2a**	H	10	**4a**: 71
2	**1b**	Me, Me	**2a**	H	15	**4b**: 63
3	**1c**	OMe, OMe	**2a**	H	—	**4c**: —
4	**1d**	Br, Br	**2a**	H	3	**4d**: 80
5	**1e**	NO_2, H	**2a**	H	2	**4e**: 77
6	**1a**	H, H	**2b**	Me	12	**4f**: 76
7	**1a**	H, H	**2c**	OMe	18	**4g**: 78
8	**1a**	H, H	**2d**	Cl	10	**4h**: 69
9	**1a**	H, H	**2f**	NO_2	—	**4i**: —

produce corresponding products **4** in 63–80%, whereas the more electron-rich 4,5-dimethoxy-2-formylcinnamate **1c** was inert in this reaction (Table 2, entries 1–5). On the other hand, the reactions of 2-formylcinnamate **1a** with nitrosobenzenes **2** that are substituted by methyl, methoxy and chlorine groups all produced 2,3-benzoxazin-4-ones **4** in good yields (Table 2, entries 6–8). However, no expected product was obtained from the reaction of 2-formylcinnamate **1a** with 1-nitro-4-nitrosobenzene **2f**. The inertness of 4,5-dimethoxy-2-formylcinnamate **1c** in the reaction with nitrosobenzene **2a** was most probably due to the electron-donating effect of methoxy groups that deactivates the aldehyde towards nucleophilic carbene. In contrast, the inactivity of 2-formylcinnamate **1a** toward 1-nitro-4-nitrosobenzene **2f** in the presence of triazole carbene and DBU was most likely attributable to the instability of 1-nitro-4-nitrosobenzene under reaction conditions.

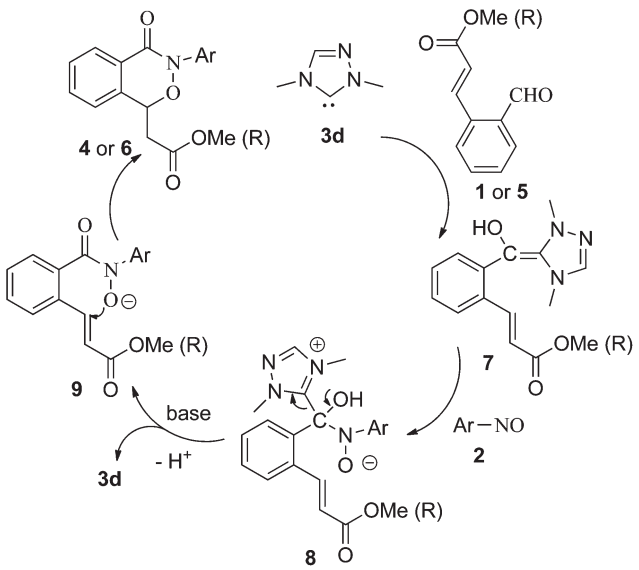
The generality of the cascade annulation reaction was further expanded to the reactions of nitrosoarenes with *o*-formylchalcones and their analogues (Table 3). It was found that the NHC-catalyzed reactions of *o*-(3-aryl (or alkyl)-3-oxo-1-propenyl)benzaldehydes **5a–5h** and 3-(3-oxo-3-phenylprop-1-enyl)-2-naphthaldehyde **5i** with nitrosoarenes **2** were more efficient than those of *o*-formylcinnamates **1** with **2**. As indicated in Table 3, the reaction showed good tolerance to the substituents of both aldehydes **5** and nitrosoarenes **2**. For example, when *o*-formylchalcone **5a** reacted with nitrosobenzene, and methyl, methoxy, chlorine substituted nitrosobenzenes **2a–2d**, all reactions produced 1-(2-oxo-2-phenylethyl)-2,3-benzoxazin-4-ones **6a–6d** in good yields. On the other hand, various benzaldehydes bearing an *ortho* vinyl ketone moiety and 2-naphthaldehyde **5** reacted efficiently with nitrosobenzene **2a** to afford 2,3-benzoxazin-4-ones **6e–6l** in good to excellent yields (Table 3). The higher reactivity of *o*-formylchalcones **5** than *o*-formylcinnamates **1** in the reaction with nitrosobenzenes **2** is best explained by the stronger electron-withdrawing effect of ketone carbonyl than ester carbonyl, which facilitates the intramolecular nucleophilic addition during the formation of oxazinone rings.

Mechanistically, we proposed that the reaction would commence with the addition of NHC to aldehydes of

Table 3 The reaction of 2-(3-oxo-1-propenyl)benzaldehydes **5** and nitrosoarenes **2** under optimized conditions



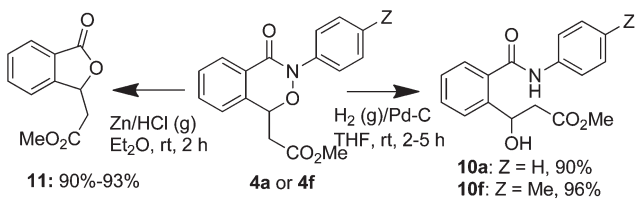
Entry	5	X, Y	R	2	Z	*T* (h)	Yield of 6 (%)
1	**5a**	H, H	Ph	**2a**	H	4	**6a**: 81
2	**5a**	H, H	Ph	**2b**	Me	4	**6b**: 83
3	**5a**	H, H	Ph	**2c**	OMe	5	**6c**: 86
4	**5a**	H, H	Ph	**2d**	Cl	5	**6d**: 78
5	**5b**	Me, Me	Ph	**2a**	H	11	**6e**: 79
6	**5c**	Br, Br	Ph	**2a**	H	2	**6f**: 92
7	**5d**	H, H	Me	**2d**	H	5	**6g**: 88
8	**5e**	H, H	$PhCH_2CH_2$	**2f**	H	8	**6h**: 84
9	**5f**	H, H	*p*-MeOPh	**2a**	H	11	**6i**: 77
10	**5g**	H, H	*p*-BrPh	**2a**	H	4	**6j**: 82
11	**5h**	H, H	*p*-NO_2Ph	**2a**	H	2	**6k**: 88
12	**5i**	$(CH{=}CH)_2$	Ph	**2b**	Me	6	**6l**: 85



Scheme 1 Proposed mechanism.

o-formylcinnamates **1** or *o*-formylchalcones **5** to form the Breslow intermediates **7**. Nucleophilic addition of the resulting enols **7** to the nitroso group of **2** followed by elimination of carbene moiety forms *N*-hydroxybenzamide anions **9**. Intramolecular oxo-Michael addition of oxygen anions to α,β-unsaturated esters or ketones of **9** affords 2,3-benzoxazin-4-ones **4** or **6** (Scheme 1).

The resulting 2,3-benzoxazin-4-ones are useful in organic synthesis. To demonstrate their synthetic utility, we conducted their reductive transformation. Under the catalysis of Pd–C in THF, hydrogenation of **4a** and **4f** produced 3-(*N*-arylcarbamoyl)-phenyl-3-hydroxypropanoates **10a** and **10f** in 90% and 96% yields. Instead of Pd-catalyzed hydrogenation, the reduction of 2,3-benzoxazin-4-ones **4** using Zn/HCl in ethyl ether afforded directly 3-oxo-1-isobenzofuranacetate **11** in 90–93% yields (Scheme 2).



Scheme 2 Reductive transformations of 2,3-benzoxazinones **4**.

Conclusions

In summary, we have shown that the NHC-catalyzed reactions of *o*-formylcinnamates, *o*-formylchalcones and their analogues with nitrosoarenes proceeded *via* a cascade aza-benzoin and oxo-Michael addition to produce multifunctional 2,3-benzoxazinones in good to excellent yields. The reductive transformations of the acetate substituted 2,3-benzoxazinones **4** under different conditions led to the formation of a new type of β-hydroxycarboxylate derivatives and 3-oxo-1-isobenzofuranacetates, respectively. This work not only provides a simple and efficient method for the construction of 2,3-benzoxazinones that represent a bioactive scaffold,[10] but also expands the application of NHC-catalyzed cascade reactions in the carbon–heteroatom and heteroatom–heteroatom bond formation.

Experimental section

1. General procedure for the reaction of *o*-formylcinnamates 1, *o*-formylchalcones and their analogues 5 with nitrosoarenes 2

Under nitrogen atmosphere and at 25–30 °C, a mixture of *N*,*N*-dimethyl-1,2,4-triazolium salt (0.2 mmol) and DBU (0.3 mmol) in dry chloroform (10 mL) was stirred for 10 min, and then a solution of *o*-formylcinnamates **1**[12] (1 mmol), or *o*-(3-oxo-1-propenyl)benzaldehydes **5**[13] (1 mmol), and nitrosoarenes **2**[14] (1.5 mmol) in chloroform (10 mL) was added. The reaction

mixture was stirred at 25–30 °C until the aldehydes **1** or **5** were consumed. The solvent was removed under vacuum and the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (6 : 1) to afford 2,3-benzoxazin-4-ones **4** or **6**, respectively.

Methyl 2-(4-oxo-3-phenyl-3,4-benzoxazin-1-yl)acetate 4a. White solid, 71%, mp 66–67 °C; IR ν (cm^{-1}) 1741, 1660; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.7 Hz, 1H), 7.77 (d, J = 7.7 Hz, 2H), 7.57 (td, J = 7.5, 1.3 Hz, 1H), 7.51 (t, J = 7.0 Hz, 1H), 7.40 (t, J = 8.4 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 5.81 (dd, J = 8.9, 4.7 Hz, 1H), 3.69 (s, 3H), 3.12 (dd, J = 16.2, 8.9 Hz, 1H), 2.99 (dd, J = 16.2, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.1, 161.6, 139.5, 138.8, 133.0, 128.7, 128.6, 128.5, 126.8, 125.7, 122.8, 120.3, 77.3, 52.1, 37.2; MS (EI): 91 (100), 297 (M^+, 47%); Anal. Calcd for $C_{17}H_{15}NO_4$: C 68.68; H 5.09; N 4.71; Found: C 68.68, H 5.12, N 4.65.

Methyl 2-(6,7-dimethyl-4-oxo-3-phenyl-3,4-benzoxazin-1-yl)-acetate 4b. White solid, 63%, mp 88–89 °C; IR ν (cm^{-1}) 1737, 1662; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (s, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 6.95 (s, 1H), 5.72 (dd, J = 9.0, 4.6 Hz, 1H), 3.68 (s, 3H), 3.07 (dd, J = 16.2, 9.0 Hz, 1H), 2.94 (dd, J = 16.2, 4.6 Hz, 1H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.2, 162.0, 142.6, 139.7, 137.4, 136.5, 129.3, 128.6, 125.4, 124.2, 123.9, 120.2, 77.2, 52.1, 37.4, 20.3, 19.6; HRMS (ESI): $[M + H]^+$ calcd for $C_{19}H_{20}NO_4$: 326.1392; found: 326.1419.

Methyl 2-(6,7-dibromo-4-oxo-3-phenyl-3,4-benzoxazin-1-yl)-acetate 4d. White solid, 80%, mp 128–129 °C; IR ν (cm^{-1}) 1722, 1667; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.40 (s, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.52 (s, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 5.72 (dd, J = 8.4, 5.1 Hz, 1H), 3.70 (s, 3H), 3.10 (dd, J = 16.4, 8.5 Hz, 1H), 2.97 (dd, J = 16.4, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.5, 159.8, 139.0, 138.9, 133.6, 130.1, 128.8, 128.5, 127.9, 126.2, 125.5, 120.4, 76.5, 52.3, 36.9; MS (EI): 91 (100), 452 (M^+, 7%)/454 (M+2, 16%); Anal. Calcd for $C_{17}H_{13}Br_2NO_4$: C 44.87; H 2.88; N 3.08; Found: C 44.55, H 2.82, N2.93.

Methyl 2-(6-nitro-4-oxo-3-phenyl-3,4-benzoxazin-1-yl)acetate 4e. White solid, 77%, mp 156–157 °C; IR ν (cm^{-1}) 1743, 1665; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.03 (d, J = 2.3 Hz, 1H), 8.42 (dd, J = 8.4, 2.4 Hz, 1H), 7.76 (dd, J = 8.8, 1.0 Hz, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.45 (t, J = 8.5 Hz, 2H), 7.26 (t, J = 7.7 Hz, 1H), 5.88 (dd, J = 8.2, 5.3 Hz, 1H), 3.71 (s, 3H), 3.17 (dd, J = 16.5, 8.2 Hz, 1H), 3.05 (dd, J = 16.5, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.5, 159.5, 148.4, 144.8, 138.8, 128.9, 128.7, 127.3, 126.4, 124.8, 123.8, 120.3, 77.0, 52.4, 36.8; MS (EI): 91 (100), 342 (M^+, 16%); Anal. Calcd for $C_{17}H_{14}N_2O_6$: C 59.65; H 4.12; N 8.18; Found: C 59.64, H 4.37, N 8.45.

Methyl 2-(4-oxo-3-(*p*-tolyl)-3,4-benzoxazin-1-yl)acetate 4f. White solid, 76%, mp 96–97 °C; IR ν (cm^{-1}) 1738, 1657; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.56 (td, J = 7.5, 1.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.2 Hz, 3H), 5.78 (dd, J = 8.8, 4.7 Hz, 1H), 3.70 (s, 3H), 3.12 (dd, J = 16.2, 8.9 Hz, 1H), 2.99 (dd, J = 16.2, 4.7 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.1, 161.5, 138.8, 136.9, 135.7, 132.9, 129.2, 128.7, 128.4, 126.8, 122.8, 120.8, 77.2, 52.1, 37.2, 21.0; MS (EI): 105 (100), 311 (M^+, 26%); Anal. Calcd for $C_{18}H_{17}NO_4$: C 69.44; H 5.50; N 4.50; Found: C 69.26, H 5.41, N 4.40.

Methyl 2-(3-(*p*-methoxyphenyl)-4-oxo-3,4-benzoxazin-1-yl) acetate 4g. White solid, 78%, mp 88–89 °C; IR ν (cm^{-1}) 1739, 1662; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 9.1 Hz, 2H), 7.56 (td, J = 7.4, 1.2 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 9.1 Hz, 2H), 5.78 (dd, J = 8.9, 4.6 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.14 (dd, J = 16.2, 9.0 Hz, 1H), 2.98 (dd, J = 16.2, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.1, 161.6, 157.8, 138.7, 132.8, 132.3, 128.6, 128.3, 126.6, 123.5, 122.8, 113.9, 77.2, 55.5, 52.2, 37.3; MS (EI): 121 (100), 327 (M^+, 18%); Anal. Calcd for $C_{18}H_{17}NO_5$: C 66.05; H 5.23; N 4.28; Found: C 65.8, H 5.01, N 4.27.

Methyl 2-(3-(*p*-chlorophenyl)-4-oxo-3,4-benzoxazin-1-yl)-acetate 4h. White solid, 69%, mp 114–115 °C; IR ν (cm^{-1}) 1737, 1657; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 9.0 Hz, 2H), 7.58 (td, J = 7.5, 1.3 Hz, 1H), 7.51 (t, J = 6.9 Hz, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.21 (d, J = 7.5, 1H), 5.80 (dd, J = 9.0, 4.6 Hz, 1H), 3.71 (s, 3H), 3.09 (dd, J = 16.3, 9.1 Hz, 1H), 2.98 (dd, J = 16.3, 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 161.6, 138.7, 138.1, 133.2, 130.7, 128.8, 128.7, 128.5, 126.5, 122.8, 121.1, 77.4, 52.1, 37.0; MS (EI): 125 (100), 331 (M^+, 81%); Anal. Calcd for $C_{17}H_{14}ClNO_4$: C 61.55; H 4.25; N 4.22; Found: C 61.45, H 4.32, N 3.97.

1-(2-Oxo-2-phenylethyl)-3-phenyl-3,4-benzoxazin-4-one 6a. White solid, 81%, mp 105–106 °C; IR ν (cm^{-1}) 1683, 1667, 1651; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (d, J = 7.5 Hz, 1H), 7.91 (dd, J = 7.2, 1.2 Hz, 2H), 7.75 (d, J = 7.8, 2H), 7.56 (tt, J = 7.6, 1.8 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.33 (t, J = 8.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.10 (dd, J = 7.4, 5.1 Hz, 1H), 3.89 (dd, J = 17.4, 7.5 Hz, 1H), 3.51 (dd, J = 17.4, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.0, 161.8, 139.7, 139.5, 136.4, 133.7, 133.0, 128.7, 128.6, 128.5, 128.4, 128.2, 126.8, 125.5, 123.1, 120.0, 76.7, 40.9; HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{18}NO_3$: 344.1287; found: 344.1289.

1-(2-Oxo-2-phenylethyl)-3-(*p*-tolyl)-3,4-benzoxazin-4-one 6b. White solid, 84%, mp 89–90 °C; IR ν (cm^{-1}) 1687, 1658; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 7.3 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.55 (td, J = 7.6, 1.3 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 6.09 (dd, J = 7.3, 5.2 Hz, 1H), 3.88 (dd, J = 17.2, 7.4 Hz, 1H), 3.51 (dd, J = 17.4, 5.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.0, 161.7, 139.7, 137.0, 136.5, 135.5, 133.7, 132.8, 129.2, 128.7, 128.5, 128.3, 128.2, 126.9, 123.1, 120.5, 77.2, 41.0, 20.9; MS (EI): 105 (100), 357 (M^+, 20%); Anal. Calcd for $C_{23}H_{19}NO_3$: C 77.29; H 5.36; N 3.92; Found: C 77.14, H 5.56, N 3.51.

1-(2-Oxo-2-phenylethyl)-3-(*p*-methoxyphenyl)-3,4-benzoxazin-4-one 6c. White solid, 86%, mp 112–113 °C; IR ν (cm^{-1}) 1693, 1655; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 7.2 Hz, 2H), 7.61 (d, J = 9.1 Hz, 2H), 7.53–7.60 (m, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 9.1 Hz, 2H), 6.08 (dd, J = 7.4, 5.0 Hz, 1H), 3.89 (dd, J = 17.4, 7.5 Hz, 1H), 3.78 (s, 3H), 3.52 (dd, J = 17.4, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.0, 161.7, 157.6, 139.6, 136.5, 133.7, 132.8, 132.5, 128.8, 128.5, 128.3, 128.2, 126.8, 123.1, 123.0, 113.9, 77.3, 55.4, 40.9; MS (EI): 121 (100), 373 (M^+, 37%); Anal. Calcd for $C_{23}H_{19}NO_4$: C 73.98; H 5.13; N 3.75; Found: C 73.63, H 5.01, N 3.69.

1-(2-Oxo-2-phenylethyl)-3-(*p*-chlorophenyl)-3,4-benzoxazin-4-one 6d. White solid, 78%, mp 99–100 °C; IR ν (cm^{-1}) 1679, 1663; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 9.2 Hz, 2H), 7.56–7.61 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.45(t, J = 7.6 Hz, 2H), 7.27 (d, J = 9.6 Hz, 2H), 7.29 (d, J = 6.8 Hz, 1H), 6.09 (dd, J = 7.9, 4.6 Hz, 1H), 3.87 (dd, J = 17.4, 8.0 Hz, 1H), 3.47 (dd, J = 17.4, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.8, 161.7, 139.6, 138.1, 136.4, 133.8, 133.1, 130.4, 128.8, 128.6, 128.5, 128.2, 126.6, 123.7, 120.9, 77.0, 40.7; MS (EI): 105 (100), 377 (M^+, 37%); Anal. Calcd for $C_{22}H_{16}ClNO_3$: C 69.94; H 4.27; N 3.71; Found: C 69.88, H 4.43, N 3.55.

6,7-Dimethyl-1-(2-oxo-2-phenylethyl)-3-phenyl-3,4-benzoxazin-4-one 6e. White solid, 79%, mp 123–124 °C; IR ν (cm^{-1}) 1696, 1661; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96 (s, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.73 (d, J = 7.8, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 6.03 (dd, J = 7.6, 4.8 Hz, 1H), 3.86 (dd, J = 17.3, 7.7 Hz, 1H), 3.45 (dd, J = 17.3, 4.8 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.2, 162.2, 142.5, 139.8, 137.4, 137.2, 136.6, 133.6, 129.2, 128.7, 128.6, 128.2, 125.2, 124.4, 124.2, 120.0, 77.3, 41.1, 20.2, 19.5; MS (EI): 105 (100), 371 (M^+, 9%), Anal. Calcd for $C_{24}H_{21}NO_3$: C 77.61; H 5.70; N 3.77; Found: C 77.58, H 5.76, N 3.67.

6,7-Dibromo-1-(2-oxo-2-phenylethyl)-3-phenyl-3,4-benzoxazin-4-one 6f. White solid, 92%, mp 144–145 °C; IR ν (cm^{-1}) 1677, 1661; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42 (s, 1H), 7.92 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H), 7.61 (s, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 8.5 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 6.03 (t, J = 6.4 Hz, 1H), 3.86 (dd, J = 17.6, 7.0 Hz, 1H), 3.51 (dd, J = 17.6, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.3, 160.0, 139.9, 139.1, 136.2, 133.9, 133.5, 130.0, 128.8, 128.8, 128.2, 127.4, 126.0, 125.3, 120.1, 76.1, 40.7; MS (EI): 105 (100), 499 (M^+, 5%)/501 (11%); Anal. Calcd for $C_{22}H_{15}Br_2NO_3$: C 52.72; H 3.02; N 2.79; Found: C 52.73, H 2.88, N 2.65.

1-(2-Oxopropyl)-3-phenyl-3,4-benzoxazin-4-one 6g. White solid, 88%, mp 82–83 °C; IR ν (cm^{-1}) 1724, 1656; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (dd, J = 7.7, 1.0 Hz, 1H), 7.78 (dd, J = 8.8, 1.1 Hz, 2H), 7.55 (td, J = 7.5, 1.3 Hz, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 8.5 Hz, 2H), 7.18–7.22 (m, 2H), 5.87 (dd, J = 8.0, 4.7 Hz, 1H), 3.29 (dd, J = 17.4, 8.1 Hz, 1H), 3.01 (dd, J = 17.5, 4.7 Hz, 1H), 2,15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.3, 161.7, 139.6, 139.4, 132.9, 128.7, 128.5, 128.4, 126.8, 125.6, 122.9, 120.0, 76.4, 45.5, 30.9; MS (EI): 91 (100), 281 (M^+, 51%); Anal. Calcd for $C_{17}H_{15}NO_3$: C 72.58; H 5.37; N 4.98; Found: C 72.57, H 5.42, N 4.78.

1-(2-Oxo-4-phenylbutyl)-3-phenyl-3,4-benzoxazin-4-one 6h. White solid, 83%, mp 77–78 °C; IR ν (cm^{-1}) 1716, 1653; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.18 (dd, J = 7.4, 1.2 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.53 (td, J = 7.4, 1.4 Hz, 1H), 7.48 (td, J = 7.6, 1.2 Hz, 1H), 7.39 (t, J = 8.5 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 8.6 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 7.1 Hz, 2H), 5.87 (dd, J = 8.0, 4.4 Hz, 1H), 3.25 (dd, J = 17.2, 8.0 Hz, 1H), 2.91 (dd, J = 17.2, 4.4 Hz, 1H), 2.83–2.88 (m, 2H), 2.66–2.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.7, 161.6, 140.4, 139.6, 139.4, 132.9, 128.7, 128.5, 128.4, 128.3, 126.7, 126.2, 125.6, 122.9, 120.0, 76.5, 45.3, 44.9, 29.4; MS (EI): 91 (100), 371 (M^+, 88%), Anal. Calcd for $C_{24}H_{21}NO_3$: C 77.61; H 5.70; N 3.77; Found: C 77.68, H 5.42, N 3.46.

1-(2-(4-Methoxyphenyl)-2-oxoethyl)-3-phenyl-3,4-benzoxazin-4-one 6i. White solid, 61%, mp 126–127 °C; IR ν (cm^{-1}) 1680, 1652; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.9 Hz, 2H), 7.75 (d, J = 8.0, 2H), 7.55 (td, J = 7.4, 1.2 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.09 (dd, J = 7.3, 5.2 Hz, 1H), 3.85 (s, 3H), 3.84 (dd, J = 17.0, 7.1 Hz, 1H), 3.44 (dd, J = 17.1, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.4, 164.0, 161.8, 140.0, 139.6, 132.9, 130.6, 129.6, 128.6, 128.5, 128.3, 126.9, 125.4, 123.2, 120.0, 113.9, 77.2, 55.5, 40.5; MS (EI): 135 (100), 373 (M^+, 11%); Anal. Calcd for $C_{22}H_{17}NO_3$: C 73.98; H 5.13; N 3.75; Found: C 73.87, H 5.25, N 3.37.

1-(2-(4-Bromophenyl)-2-oxoethyl)-3-phenyl-3,4-benzoxazin-4-one 6j. White solid, 77%, mp 116–117 °C; IR ν (cm^{-1}) 1678, 1662; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (dd, J = 7.5, 1.1 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 8.6 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.07 (dd, J = 7.6, 4.8 Hz, 1H), 3.86 (dd, J = 17.3, 7.8 Hz, 1H), 3.43 (dd, J = 17.3, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.1, 161.7, 139.50, 139.46, 135.2, 132.1, 129.7, 129.0, 128.6, 128.5, 126.8, 125.5, 123.1, 120.0, 77.2, 40.8; MS (ESI): 422 $[M + H]^+$; Anal. Calcd for $C_{22}H_{16}BrNO_3$: C 62.57; H 3.82; N 3.32; Found: C 62.41, H 3.84, N 3.10.

1-(2-(4-Nitrophenyl)-2-oxoethyl)-3-phenyl-3,4-benzoxazin-4-one 6k. White solid, 87%, mp 98–99 °C; IR ν (cm^{-1}) 1697, 1667; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 6.1 Hz, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.2, 2H), 7.59 (td, J = 7.5, 1.2 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.27–7.34 (m, 3H), 7.13 (t, J = 7.4 Hz, 1H), 6.08 (dd, J = 8.0, 4.6 Hz, 1H), 3.96 (dd, J = 17.3, 8.0 Hz, 1H), 3.47 (dd, J = 17.3, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.8, 161.7, 150.6, 140.8, 139.5, 139.1, 133.1, 129.2, 128.8, 128.7,

128.6, 126.8, 125.6, 123.9, 123.1, 119.9, 77.3, 41.3; HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{16}N_2O_5$: 389.1059; found: 389.1169.

1-(2-Oxo-2-phenylethyl)-3-phenyl-3,4-naphthoxazin-4-one 6l. White solid, 85%, mp 152–153 °C; IR ν (cm^{-1}) 1675, 1658; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.78 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 7.3 Hz, 2H), 7.87 (d, J = 8.0, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.70 (s, 1H), 7.55–7.63 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 8.4 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 6.26 (dd, J = 7.0, 5.3 Hz, 1H), 3.94 (dd, J = 17.4, 7.4 Hz, 1H), 3.66 (dd, J = 17.4, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.0, 162.0, 139.5, 136.5, 135.7, 135.0, 133.7, 132.5, 130.1, 129.5, 128.8, 128.6, 128.2, 127.8, 127.0, 125.5, 124.7, 122.0, 120.1, 77.4, 41.1; HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{19}NO_3$: 394.1443; found: 394.1448.

2. Pd-catalyzed hydrogenation of 2-(3-aryl-4-oxo-3,4-dihydro-3,4-benzoxazin-1-yl)acetates 4a and 4f

At ambient temperature, 2,3-benzoxazinone **4a** or **4f** (0.5 mmol) was mixed with Pd–C (8 mg, 10% w/w) in THF. The air in flask was sucked by an oil pump and hydrogen gas was then bubbled into the solution of reactant **4**. The reaction mixture was stirred at room temperature for 2–5 h. After removal of THF under vacuum, the residue was dissolved in dichloromethane and washed with saturated NaCl aqueous solution. The organic layer was dried and evaporated, and the product 3-(*N*-arylcarbamoyl) phenyl-3-hydroxypropanoate **10a** or **10f**, was isolated by chromatography on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (4 : 1).

Methyl 3-hydroxy-3-(2-(phenylcarbamoyl)phenyl)propanoate 10a. White solid, 90%, mp 55–57 °C; IR ν (cm^{-1}) 3473, 3417, 1727, 1637; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (s, 1H), 7.62 (t, J = 8.3 Hz, 3H), 7.55 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.36–7.41 (m, 3H), 7.17 (t, J = 7.4 Hz, 1H), 5.37 (t, J = 6.7 Hz, 1H), 4.30 (s, 1H), 3.68 (s, 3H), 2.95 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 168.3, 140.6, 138.0, 135.3, 131.0, 129.0, 128.1, 127.3, 124.7, 120.5, 68.3, 51.9, 41.4; HRMS (ESI): $[M + Na]^+$ calcd for $C_{17}H_{17}NO_4Na$: 322.1055; found: 322.1049.

Methyl 3-hydroxy-3-(2-(*p*-tolylcarbamoyl)phenyl)propanoate 10f. White solid, 96%, mp 47–48 °C; IR ν (cm^{-1}) 3434, 3315, 1727, 1646; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.47–7.55 (m, 4H), 7.38 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 5.35 (t, J = 6.7 Hz, 1H), 4.40 (s, 1H), 3.67 (s, 3H), 2.93 (d, J = 6.8 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8, 167.9, 140.6, 135.6, 135.2, 134.6, 131.1, 129.6, 128.2, 127.8, 127.4, 120.4, 68.5, 51.9, 41.2, 20.9; HRMS (ESI): $[M + Na]^+$ calcd for $C_{18}H_{19}NO_4Na$: 336.1212; found: 336.1220.

3. Reduction of 2-(3-aryl-4-oxo-3,4-dihydro-3,4-benzoxazin-1-yl)-acetates 4a and 4f using Zn/HCl

At ambient temperature, 2,3-benzoxazinones **4** (0.5 mmol) were mixed with Zn powder (10 mmol) in ethyl ether (10 mL) and then HCl gas was bubbled into the solution of reactants 4 with stirring for 2 h. After removal of solvent, the residue was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous solution was extracted with ethyl acetate (50 × 3 mL), and the combined extraction was dried and evaporated. The residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (5 : 1) to give product **11** in 90–93% yields.

Methyl 2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate 11.[15] White solid, 90% from 4a and 93% from 4f, mp 64–65 °C (bp^{15} 175 °C/0.3 mmHg). IR ν (cm^{-1}) 1753, 1736; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 5.82 (t, J = 6.6 Hz, 1H), 3.70 (s, 3H), 2.78–2.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.8, 169.7, 148.7, 134.3, 129.6, 125.94, 125.85, 122.1, 77.1, 52.2, 39.4; HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_{11}O_4$: 207.0657; found: 207.0663.

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