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Metal-free coupling/isomerization reaction of isocyanide and cyclic 1,3-dione: a selective Csp^3-H functionalization strategy for C-C bond formation

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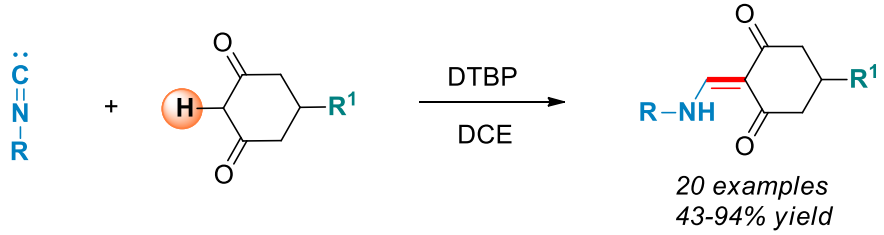
Abstract

A metal-free oxidative coupling/isomerization reaction of isocyanide and cyclic 1,3-dione has been disclosed. In the presence of di-*tert*-butylperoxide (DTBP), a series of isocyanides are subjected to reaction with subsituted 1,3-diones for direct synthesis of β-aminoenones. This strategy enables selective Csp^3-H functionalization with isocyanide, thus provides a new C-C bond formation from two basic chemicals.



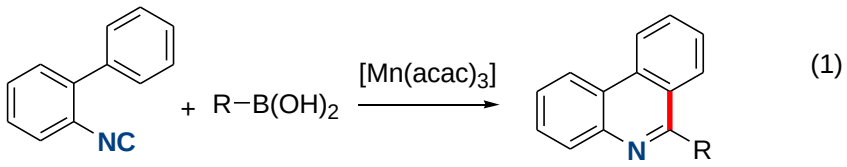
- **Metal-free oxidative coupling/isomerization strategy**
- **Selective Csp^3-H functionalization for C-C formation**

Keywords: Isocyanide, 1,3-dione, metal-free, C-H functionalization, coupling reaction

Introduction

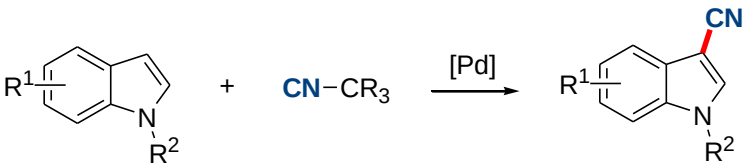
As an efficient strategy to generate molecular complexity, selective C-H functionalization has become one of the most challenging and highly valuable tools in organic synthesis.[1-3] As a consequence, many achievements have been made with respect to direct formation of C-C, C-O, and C-N bonds from unactivated carbon-hydrogen bonds including a number of elegant synthetic applications.[4] In this context, selective C-H functionalization including transition-metal-catalyzed C-H insertion by a metal-bound carbine or other intermediates has been extensively investigated.[5] Although these methods are powerful synthetic transformations, they require the use of expensive transition metals, and in many cases the corresponding ligands in the catalytic system. In addition, contamination of the final products caused by these metal residues also becomes a serious problem in the synthesis of pharmaceuticals and functional materials. Considering these issues, a metal-free approach towards selective C-H functionalization would obviate many of the aforementioned disadvantages. As a consequence, there is a continuous necessity for the chemists to develop straightforward and low-cost metal-free protocol with respect to green chemistry.

a) Mn-catalyzed Csp^2-H functionazation and cyclization



(1)

b) Pd-catalyzed Csp^2-H cyanation reaction with arene



(2)

Scheme 1. Representative Csp^2-H functionalization reaction with isocyanide.

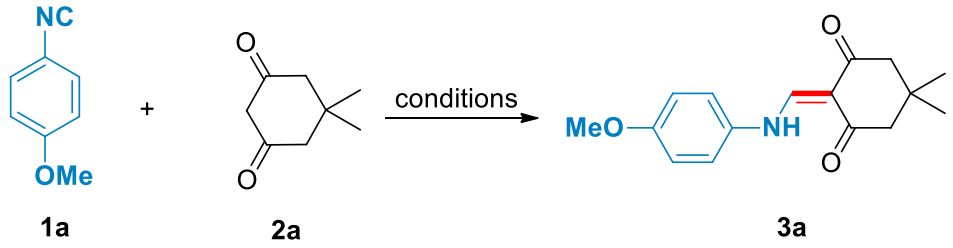
On the other hand, isocyanides are significant C1 synthons, thus being widely applied in the construction of carbon-carbon and carbon-heteroatom bonds.[6-10] Isocyanides have structurally unique divalent carbon, which makes them significant reaction components in various multicomponent reaction.[11] In this context, the classical four-component Ugi and three-component Passerini reaction have found applications in many fields such as asymmetric synthesis and total synthesis of natural products.[12-13] Furthermore, isocyanide-based insertion reactions[14-17] and related radical processes have also received considerable attention.[18-19] Recently, investigation on isocyanide-involving C-H functionalizations with tandem cyclization reactions had been employed in the construction of various hetero- and carbocyclic compounds (Scheme 1, eq 1).[20-22] Accordingly, reports on selective C-H functionalization for the cross-coupling reactions of isocyanides, without subsequent cyclization, were also disclosed (Scheme 1, eq 2).[23-24] A careful literature screening also revealed that most of the achievements were devoted towards Csp^2-H functionalization with isocyanide. In addition, some reported examples also had drawbacks such as the requirement of specific alignment, substrate structure, or special catalysts. As a consequence, successful examples with Csp^3-H functionalization with isocyanide was highly

desirable.[25] In the past several years, we have devoted our efforts to the exploration of isocyanide-based new transformations.[26-28] As a continuation, herein we report a metal-free Csp^3-H functionalization of isocyanide and cyclic 1,3-diones. To the best of our knowledge, no such examples have been reported.

Results and Discussion

We began our research by selecting 4-methoxyphenyl isocyanide **1a** and 5,5-dimethylcyclohexane-1,3-dione **2a** as model substrates. As shown in Table 1, heating the mixture of 1a, 2a and di-*tert*-butyl peroxide (DTBP) in DCE in the presence of catalytic copper (I) bromide essentially produced compound **3a** in 41 % yield (Table 1, entry 1). Then, several metal catalysts were used to enhance the yield of **3a** (Table 1, entries 2-5). To our surprise, 94 % of **3a** was isolated when the mixture of **1a** and **2a** was heated without the addition of any metal catalyst (Table 1, entry 6). Encouraged by this result, the effect of different experiment parameters such as solvents, peroxides, and temperature was subsequently carefully evaluated. The reaction optimization revealed that no formation of the desired compound was observed when reactions were conducted in THF or 1,4-dioxane (Table 1, entry 7 and entry 10). In addition, using MeCN, DCM, or DMF as solvents could not bring further improvement (Table 1, entries 8-11). Of the peroxides examined, dicumyl peroxide (DCP) showed some activity, whereas *tert*-butylhydroperoxide (TBHP) only led to negative result (Table 1, entries 12-13). Moreover, reaction temperature also played an important role for present oxidative coupling reaction. The reaction outcome exhibited that the yield of **3a** decreased dramatically when the reaction was conducted at 120 ^{o}C or 60 ^{o}C (Table 1, entries 14-15).

Table 1. Reaction optimization[a]



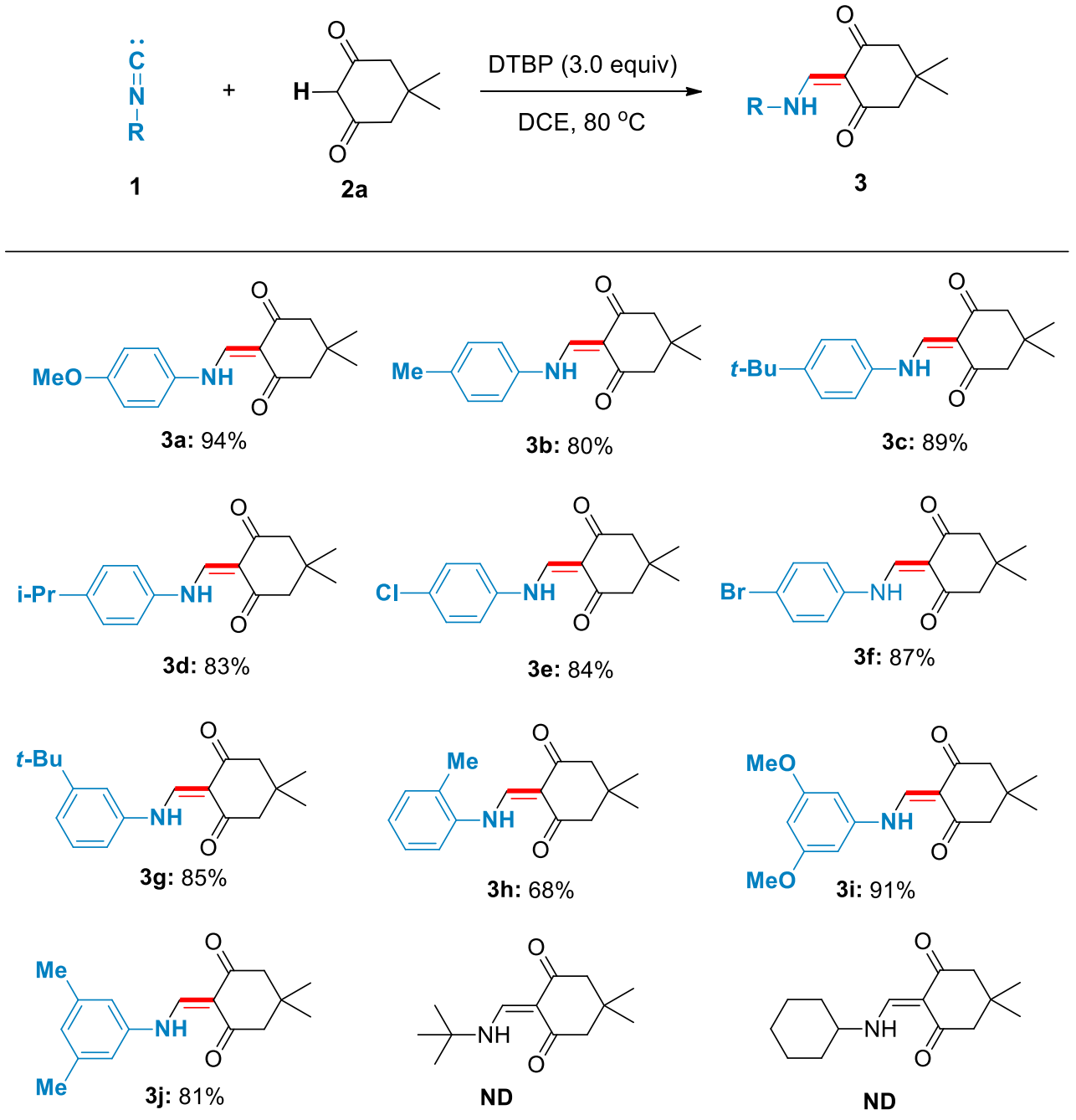
1a **2a** **3a**

Entry	Catalyst	Solvent	Peroxide	Temp (°C)	Yield (%)[b]
1	CuBr	DCE	DTBP	80	41
2	$Cu(OAc)_2$	DCE	DTBP	80	53
3	$FeCl_3$	DCE	DTBP	80	46
4	$FeCp_2$	DCE	DTBP	80	63
5	$FeCl_2$	DCE	DTBP	80	36
6	-	DCE	DTBP	80	94
7	-	THF	DTBP	80	0
8	-	MeCN	DTBP	80	21
9	-	DCM	DTBP	80	85
10	-	1,4-dioxane	DTBP	80	0
11	-	DMF	DTBP	80	trace
12	-	DCE	DCP	80	35
13	-	DCE	TBHP	80	0
14	-	DCE	DCE	100	82
15	-	DCE	DCE	120	trace
16	-	DCE	DCE	60	trace

[a] Unless otherwise noted, all reactions were carried out with 4-methoxyphenyl isocyanide **1a** (0.5 mmol), 1,3-dione **2a** (1.0 mmol), peroxide (3 equiv.), solvent (5 mL), 80 °C, 12 hours in sealed tube. [b] Isolated yields.

With the optimized condition in hand, we sought to investigate the feasibility of different isocyanides. As shown in Scheme 2, a series of substituted aromatic isocyanides **1** having electron-donating and -withdrawing groups including methoxy, alkyl, and halide groups at the para-, meta- and ortho- position of the aromatic ring were firstly used to react with substrate **2a**. Pleasingly, these reactions proceeded smoothly to produce the desired compounds **3a**-**3h** and all new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (see

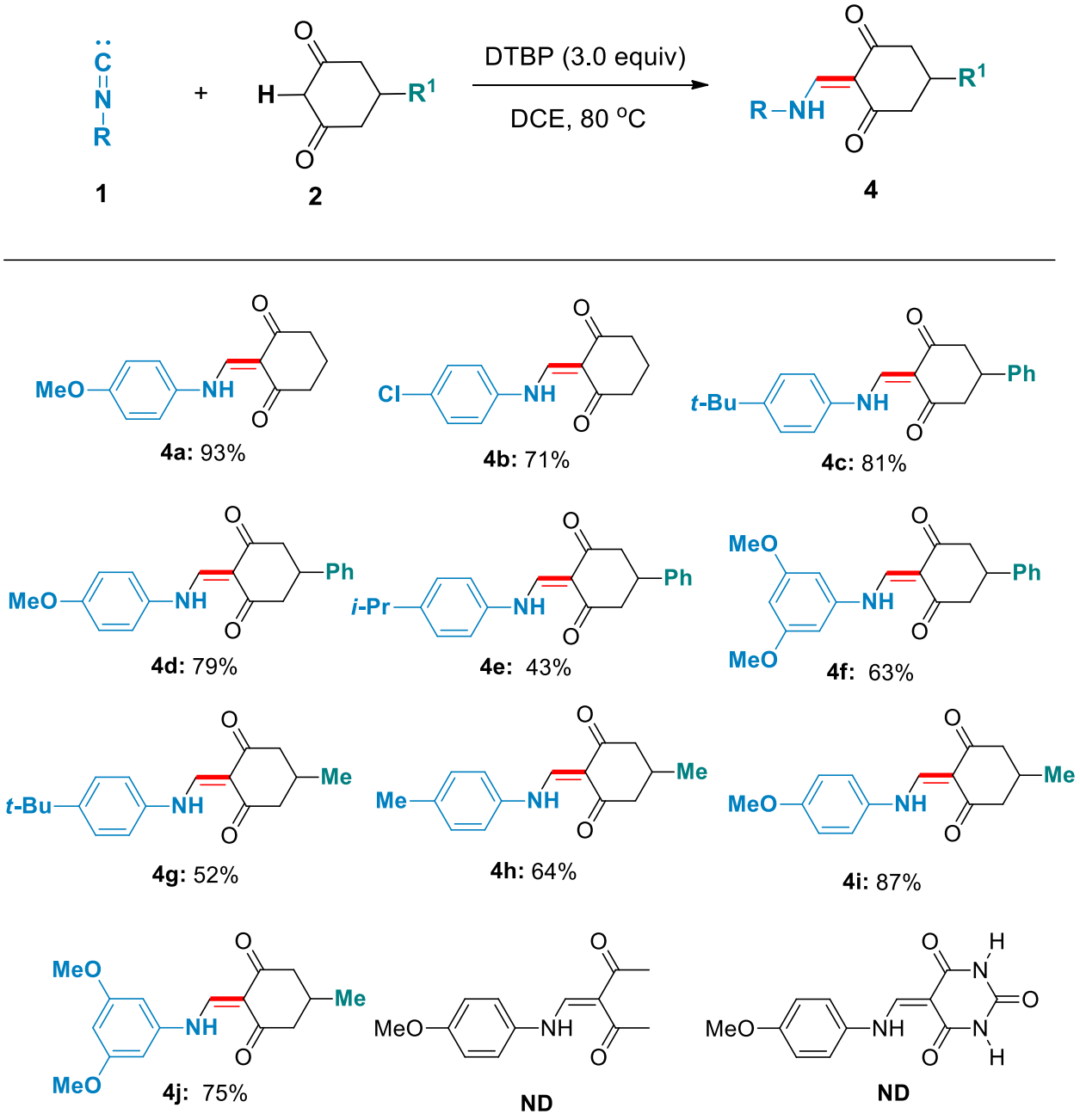
the Supporting Information for the details). Moreover, disubstituted aromatic isocyanides **1i** and **1j** also worked well to deliver the corresponding products **3i** and **3l**. Next, we investigated the scope of substrates by the optimal reaction conditions. Unfortunately, aliphatic isocyanides such as *tert*-butyl and cyclohexyl isocyanides faild to experience the corresponding oxidative coupling reactions.



Scheme 2. Substrate scope for with respect to isocyanide. [a] Reaction condition **A**: isocyanide **1** (0.5 mmol), 1,3-dione **2a** (1.0 mmol), DTBP (3 equiv.), DCE (5 mL), 80 °C, 12 hours in sealed tube. [b] Isolated yields.

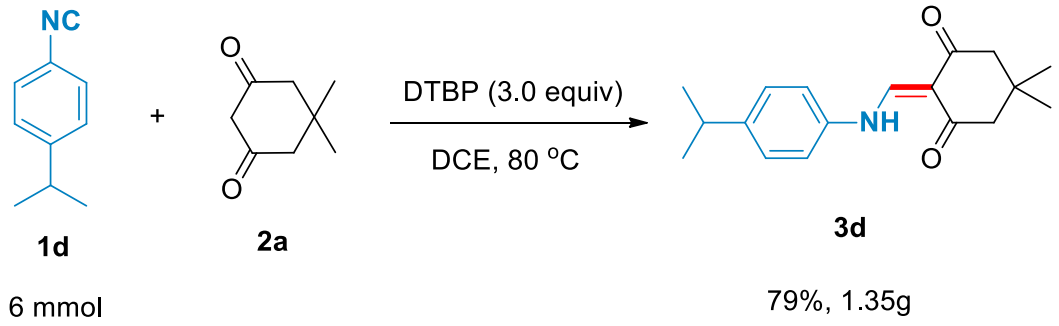
After a broad scope of isocyanide was established, we turned our attention to the feasibility of different 1,3-diones **2**. As shown in Scheme 3, several substituted cyclic 1,3-diones **2** were used to react with isocyanide substrates. To our delight, these reactions worked well to produce the desired compounds **4a**-**4j**. Next,

reactions with linear 1,3-dione **2e** and cyclic **2f** were also carried out, whereas no desired compounds were detected in such cases.



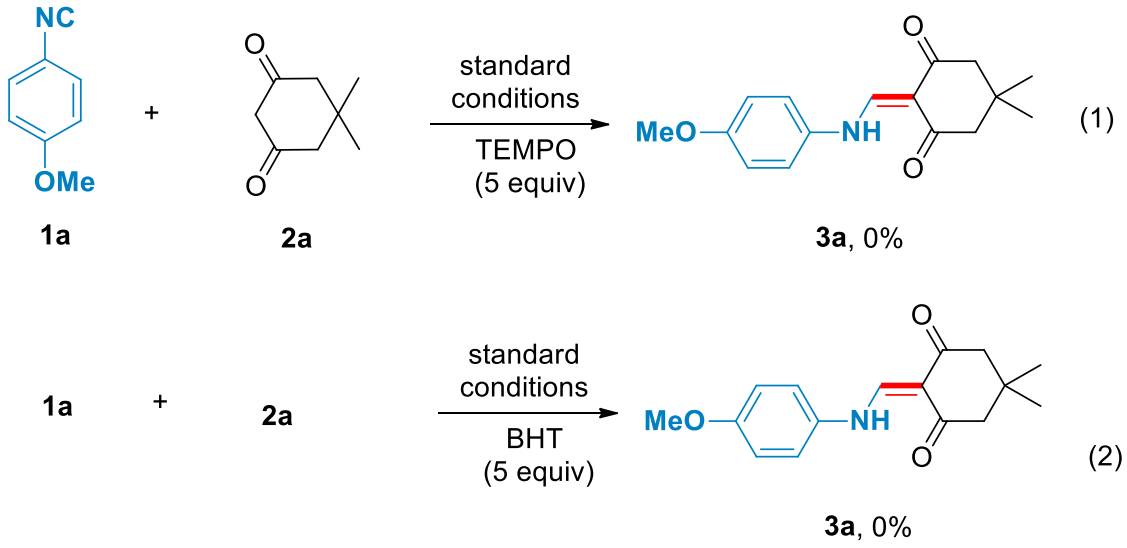
Scheme 3. Substrate scope with respect to cyclic 1,3-dione. [a] Reaction condition **A**. [b] Isolated yields.

Next, the scalability of this reaction was verified by using 6 mmol **1d** with **2a** under the optimal reaction conditions. Pleasingly, the desired compound **3d** was isolated in 79 % yields (Scheme 4), which suggested that present oxidative coupling reaction was an economic and practical process.



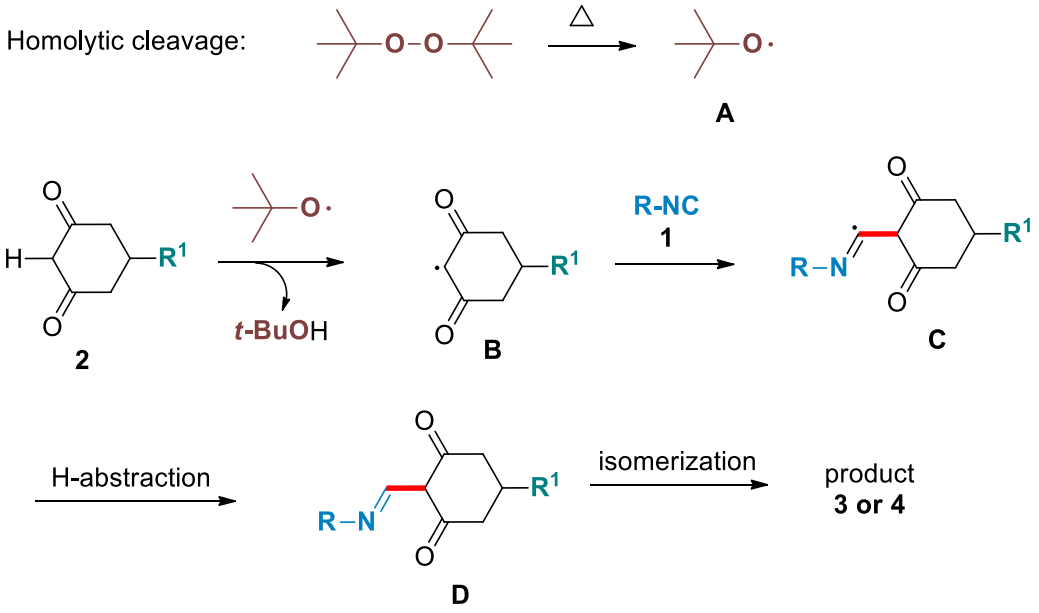
Scheme 4. Gram-scale coupling reaction.

To have more insight into present oxidative coupling reaction, two preliminary mechanistic experiments were conducted. As shown in Scheme 5, the coupling reaction of **1a** and **2a** was completely inhibited when excessive radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), or BHT (2,6-di-*tert*-butyl-4-methylphenol) were added into the reaction (Scheme 5, eq 1 and eq 2). These results indicated that this oxidative coupling reaction involved a radical pathway.



Scheme 5. Preliminary mechanistic studies.

Based on previous reports and the aforementioned experimental results, a plausible mechanism is depicted in Scheme 6 to explain the present oxidative coupling reaction. The beginning of this reaction involves the formation of alkoxyl radical **A** through homolysis of the peroxide. The reaction between the alkoxyl radical **A** and **2** generate a new radical B and the removal of tert-butyl alcohol as byproduct. Then, isocyanide **1** as a good radical acceptor can react with **B** to produce **C**. Further H-abstraction and isomerization essentially leads to the product **3** or **4**.



Scheme 6. Possible mechanism.

Conclusions

In conclusion, we have developed an efficient metal-free oxidative coupling/isomerization reaction of isocyanides and cyclic 1,3-diones. The present selective Csp^3-H functionalization strategy allows for the formation of new C-C bond from two basic chemicals. Thus, this strategy represents a straightforward and eco-friendly protocol and most of the drawbacks of traditional methods can be avoided. Also, a reasonable mechanistic proposal is advanced. As a consequence, this method has potential to be further applied. Further study on the application of present method is currently underway in our laboratory

Experimental Section

General. The NMR spectra were recorded on Bruker AC-500 spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) with $CDCl_3$ as the solvent and TMS as internal reference. ^{1}H NMR spectral data were reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constant (Hz). ^{13}C NMR spectral data were reported in terms of the chemical shift. The following abbreviations were used to indicate multiplicities: s singlet; d doublet; t triplet; q quartet; m multiplet. Low-resolution mass spectra were obtained on a Shimadzu LCMS-2010EV spectrometer in ESI mode and reported as *m/z*. High-resolution mass spectra (HRMS) were recorded on a Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS instrument. Melting points were obtained on a X-4 digital melting point apparatus without correction. Purification of products was accomplished by column chromatography packed with silica gel. Unless otherwise stated, all reagents were commercially purchased and used without further purification.

General Procedure. Under air atmosphere, a sealable reaction tube with a Teflon-coated screw cap equipped with a magnetic stir bar was charged with isocyanide **1** (0.5 mmol), 1,3-dione **2** (1.0 mmol) and DTBP (3.0

equiv.) in DCE (5.0 mL) at room temperature. The rubber septum was then replaced by a Teflon-coated screw cap, and the reaction vessel placed in an oil bath at 80 °C for 12 h. After the reaction was completed, it was cooled to room temperature and monitored by TLC. The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford product **3**-**4.**

2-(((4-Methoxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3a). 128.4 mg, 94 % yield, white solid: mp 155-156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.78 (d, *J* 13.5 Hz, 1H), 8.38 (d, *J* 14.0 Hz, 1H), 7.07 (d, *J* 9.0 Hz, 2H), 6.80 (d, *J* 9.0 Hz, 2H), 3.68 (s, 3H), 2.32 (s, 2H), 2.28 (s, 2H), 0.97 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.4, *196*.0, 158.1, 150.4, 131.6, 119.5, 115.0, 108.4, 55.5, 51.4, 51.1, 31.1, 28.5. HRMS (ESI): calcd. for C16H20NO3 $[M+H]^+$ 274.1443, Found: 274.1453.

5,5-Dimethyl-2-((*p*-tolylamino)methylene)cyclohexane-1,3-dione (3b). 102.9 mg, 80 % yield, white solid: mp 141-142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.76 (d, *J* 13.5 Hz, 1H), 8.47 (dd, *J* 13.5, 1.5 Hz, 1H), 7.09 (d, *J* 8.0 Hz, 2H), 7.04 (d, *J* 7.0 Hz, 2H), 2.34 (s, 2H), 2.30 (s, 2H), 2.24 (s, 3H), 0.99 (d, *J* 1.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.6, 196.1, 150.3, 136.3, 135.9, 130.4, 118.0, 108.5, 51.5, 51.2, 31.1, 28.5, 20.9. HRMS (ESI): calcd. for C16H20NO2 $[M+H]^+$ 258.1494, Found: 258.1490.

2-(((4-(*tert*-Butyl)phenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3c). 133.1 mg, 89 % yield, white solid: mp 174-175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.80 (d, *J* 14.0 Hz, 1H), 8.51 (d, *J* 13.5 Hz, 1H), 7.32 (d, *J* 8.5 Hz, 2H), 7.10 (d, *J* 9.0 Hz, 2H), 2.36 (s, 2H), 2.32 (s, 2H), 1.23 (s, 9H), 1.00 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.3, 195.7, 150.0, 149.3, 135.6, 126.4, 117.5, 108.3, 51.2, 50.9, 34.2, 30.9, 30.8, 28.2. HRMS (ESI): calcd. for C19H26NO2 $[M+H]^+$ 300.1964, Found: 300.1969.

2-(((4-Isopropylphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3d). 118.3 mg, 83 % yield, white solid: mp 103-104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.81 (d, *J* 13.0 Hz, 1H), 8.52 (d, *J* 13.5 Hz, 1H), 7.18 (d, *J* 8.5 Hz, 2H), 7.11 (d, *J* 8.5 Hz, 2H), 2.86-2.81 (m, 1H), 2.37 (s, 2H), 2.33 (s, 2H), 1.18 (s, 3H), 1.17 (d, *J* 7.0 Hz, 6H), 1.01 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.7, 196.2, 150.4, 147.4, 136.2, 127.8, 118.1, 108.6, 51.5, 51.2, 33.6, 31.1, 28.5, 23.9. HRMS (ESI): calcd. for C18H24NO2 $[M+H]^+$ 286.1807, Found: 286.1806.

2-(((4-Chlorophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3e). 116.4 mg, 84 % yield, white solid: mp 170-171 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.81 (d, *J* 13.0 Hz, 1H), 8.49 (d, *J* 13.5 Hz, 1H), 7.33 (d, *J* 9.0 Hz, 2H), 7.16 (d, *J* 9.0 Hz, 2H), 2.41 (s, 2H), 2.37 (s, 2H), 1.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.1, 196.2, 150.2, 137.1, 131.8, 130.0, 119.3, 109.1, 51.6, 51.3, 31.1, 28.5. HRMS (ESI): calcd. for C15H17BrNO2 $[M+H]^+$ 322.0443, Found: 322.0438.

2-(((4-Bromophenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3f). 139.7 mg, 87 % yield, white solid: mp 174-175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.79 (d, *J* 13.0 Hz, 1H), 8.49 (d, *J* 13.5 Hz, 1H), 7.48 (d, *J* 9.0 Hz, 2H), 7.10 (d, *J* 8.5 Hz, 2H), 2.41 (s, 2H), 2.37 (s, 2H), 1.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.2, 196.2, 150.0, 137.6, 133.0, 119.6, 119.4, 109.1, 51.6, 51.3, 31.1, 28.5. HRMS (ESI): calcd. for C15H17BrNO2 $[M+H]^+$ 322.0443, Found: 322.0438.

2-(((3-(*tert*-Butyl)phenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3g). 127.2 mg, 85 % yield, white solid: mp 175-176 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.89 (d, *J* 13.5 Hz, 1H), 8.60 (d, *J* 13.5 Hz, 1H), 7.32 (t, *J* 7.5 Hz, 1H), 7.26-7.24 (m, 1H), 7.20 (t, *J* 2.0 Hz, 1H), 7.09-7.07 (m, 1H), 2.44 (s, 2H), 2.40 (s, 2H), 1.31 (s, 9H), 1.08 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.9, 196.4, 153.6, 150.6, 138.2, 129.6, 123.7, 115.7, 115.0, 108.7, 51.7, 51.3, 34.9, 31.2, 31.1, 28.6. HRMS (ESI): calcd. for C19H26NO2 $[M+H]^+$ 300.1964, Found: 300.1970.

5,5-Dimethyl-2-((*o*-tolylamino)methylene)cyclohexane-1,3-dione (3h). 87.4 mg, 68 % yield, white solid: mp 101-102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 13.07 (d, *J* 12.5 Hz, 1H), 8.61 (d, *J* 13.5 Hz, 1H), 7.35 (d, *J* 8 Hz, 1H), 7.27-7.21 (m, 2H), 7.14-7.11 (m, 1H), 2.45 (s, 2H), 2.40 (s, 2H), 2.39 (s, 3H), 1.07 (s, 6H). ^{13}C NMR (125

MHz, $CDCl_3$): δ (ppm) 199.9, 196.3, 150.6, 137.1, 131.4, 128.2, 127.6, 126.4, 116.1, 109.1, 51.6, 51.3, 31.2, 28.6, 17.5. HRMS (ESI): calcd. for C16H20NO2 $[M+H]^+$ 258.1494, Found: 258.1487.

2-(((3,5-Dimethoxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3i). 137.9 mg, 91 % yield, white solid: mp 118-119 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 13.00 (d, *J* 14.0 Hz, 1H), 8.55 (d, *J* 14.5 Hz, 1H), 7.29 (d, *J* 9.5 Hz, 1H), 6.51-6.49 (m, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 2.43 (s, 2H), 2.38 (s, 2H), 1.07 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.3, 196.4, 159.0, 150.8, 148.8, 121.4, 116.5, 108.7, 104.8, 99.3, 56.0, 55.6, 51.6, 51.3, 31.2, 28.6. HRMS (ESI): calcd. for C17H22NO4 $[M+H]^+$ 304.1549, Found: 304.1556.

2-(((3,5-Dimethylphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione (3j). 109.8 mg, 81 % yield, white solid: mp 144-145 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.76 (d, *J* 13.0 Hz, 1H), 8.58 (d, *J* 13.5 Hz, 1H), 6.87 (s, 3H), 2.44 (s, 2H), 2.40 (s, 2H), 2.32 (d, *J* 0.5 Hz, 6H), 1.08 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.8, 196.5, 150.5, 139.9, 138.2, 128.3, 115.9, 108.7, 51.6, 51.3, 31.2, 28.6, 21.3. HRMS (ESI): calcd. for C17H22NO2 $[M+H]^+$ 272.1651, Found: 272.1661.

2-(((4-Methoxyphenyl)amino)methylene)cyclohexane-1,3-dione (4a). 114.0 mg, 93 % yield, white solid: mp 173-174 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.86 (d, *J* 13.5 Hz, 1H), 8.43 (d, *J* 14.0 Hz, 1H), 7.08 (d, *J* 9.0 Hz, 2H), 6.82 (d, *J* 9.0 Hz, 2H), 3.71 (s, 3H), 3.69-3.67 (m, 1H), 2.48 (t, *J* 6.5 Hz, 2H), 2.42 (t, *J* 6.5 Hz, 2H), 1.94-1.89(m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.2, 196.7, 158.2, 151.0, 131.6, 119.6, 115.1, 109.6, 55.5, 37.8, 37.5, 19.7. HRMS (ESI): calcd. for C13H13ClNO2 $[M+H]^+$ 250.0635, Found: 250.0630.

2-(((4-Chlorophenyl)amino)methylene)cyclohexane-1,3-dione (4b). 86.2 mg, 71 % yield, white solid: mp 154-155 oC. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.89 (d, *J* 13.2 Hz, 1H), 8.55 (d, *J* 13.6 Hz, 1H), 7.37-7.35 (m, 2H), 7.20-7.17 (m, 2H), 2.57 (t, *J* 6.1 Hz, 2H), 2.52 (t, *J* 6.1 Hz, 2H), 2.04-1.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.7, 196.8, 150.8, 137.0, 131.9, 130.0, 119.3, 110.2, 37.9, 37.5, 19.6. HRMS (ESI): calcd. for C13H13ClNO2 $[M+H]^+$ 250.0635, Found: 250.0630.

2-(((4-(*tert*-Butyl)phenyl)amino)methylene)-5-phenylcyclohexane-1,3-dione (4c). 59.2 mg, 41 % yield, white solid: mp 164-165 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.99 (d, *J* 13.2 Hz, 1H), 8.68 (d, *J* 13.5 Hz, 1H), 7.44 (d, *J* 8.7 Hz, 2H), 7.38-7.35 (m, 2H), 7.29-7.25 (m, 3H), 7.22 (d, *J* 8.7 Hz, 2H), 3.46-3.39 (m, 1H), 2.87-2.82 (m, 3H), 2.79-2.72 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.0, 195.4, 150.8, 149.8, 142.6, 135.5, 128.6, 126.7, 126.6, 126.4, 117.7, 109.0, 45.0, 44.6, 37.2, 34.4, 31.0. HRMS (ESI): calcd. for C23H26NO2 [M+H]+ 348.1964, Found: 348.1957.

2-(((4-Methoxyphenyl)amino)methylene)-5-phenylcyclohexane-1,3-dione (4d). 126.9 mg, 79 % yield, oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.98 (d, *J* 10.0 Hz, 1H), 8.56 (d, *J* 15.0 Hz, 1H), 7.35-7.32 (m, 2H), 7.25-7.22 (m, 3H), 7.18 (d, *J* 10.0 Hz, 2H), 6.91 (d, *J* 10.0 Hz, 2H), 3.79 (s, 3H), 3.39-3.36 (m, 1H), 2.83-2.78 (m, 3H), 2.73-2.67 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.0, 195.6, 158.4, 151.1, 142.8, 131.5, 128.8, 126.9, 126.6, 119.7, 115.1, 108.9, 55.6, 45.1, 44.8, 37.4. HRMS (ESI): calcd. for C20H20NO3 $[M+H]^+$ 322.1443, Found: 322.1440.

2-(((4-Isopropylphenyl)amino)methylene)-5-phenylcyclohexane-1,3-dione (4e). 63.5 mg, 43 % yield, white solid: mp 128-129 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.98 (d, *J* 13.7 Hz, 1H), 8.67 (d, *J* 13.8 Hz, 1H), 7.36 (t, *J* 7.6 Hz, 2H), 7.29-7.26 (m, 5H), 7.22 (d, *J* 8.6 Hz, 2H), 3.46-3.39 (m, 1H), 2.96-2.90 (m, 1H), 2.87-2.82 (m, 3H), 2.79-2.72 (m, 1H), 1.27 (d, *J* 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.0, 195.5, 150.8, 147.6, 142.6, 135.9, 128.7, 127.8, 126.8, 126.5, 118.1, 109.0, 45.0, 44.7, 37.3, 33.5, 23.7. HRMS (ESI): calcd. for C22H24NO2 $[M+H]^+$ 334.1807, Found: 334.1812.

2-(((3,5-Dimethoxyphenyl)amino)methylene)-5-phenylcyclohexane-1,3-dione (4f). 99.5 mg, 63 % yield, yellow solid: mp 153-154 °C. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.85 (d, *J* 13.2 Hz, 1H), 8.59 (d, *J* 13.5 Hz, 1H), 7.33 (t, *J* 7.5 Hz, 2H), 7.25-7.22 (m, 3H), 6.38 (d, *J* 2.1 Hz, 2H), 6.31 (t, *J* 2.0 Hz, 1H), 3.77 (s, 6H), 3.41-3.34 (m, 1H), 2.83-2.78 (m, 3H), 2.74-2.67 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.2, 195.5, 161.7, 150.6,

142.5, 139.7, 128.6, 126.8, 126.4, 109.1, 98.5, 96.5, 55.4, 45.0, 44.7, 37.1. HRMS (ESI): calcd. for C21H22NO4 [M+H]+ 352.1549, Found: 352.1545.

2-(((4-(*tert*-Butyl)phenyl)amino)methylene)-5-methylcyclohexane-1,3-dione (4g). 68.4 mg, 52 % yield, white solid: mp 148-149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.90 (d, *J* 13.5 Hz, 1H), 8.59 (d, *J* 13.7 Hz, 1H), 7.41-7.38 (m, 2H), 7.19-7.16 (m, 2H), 2.62-2.57 (m, 2H), 2.31-2.17 (m, 3H), 1.30 (s, 9H), 1.08 (d, *J* 5.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.0, 196.5, 150.7, 149.8, 135.7, 126.8, 117.8, 109.1, 46.0, 45.7, 34.5, 31.2, 26.9, 21.1. HRMS (ESI): calcd. for C18H24NO2 $[M+H]^+$ 286.1807, Found: 286.1805.

5-Methyl-2-((*p*-tolylamino)methylene)cyclohexane-1,3-dione (4h). 35.2 mg, 34 % yield, white solid: mp 121-122 °C. 1H NMR (500 MHz, CDC_{l3}): δ (ppm) 12.87 (d, *J* 13.0 Hz, 1H), 8.56-8.53 (m, 1H), 7.17 (d, *J* 7.8 Hz, 2H), 7.11 (d, *J* 7.3 Hz, 2H), 2.59-2.55 (m, 2H), 2.31 (s, 3H), 2.28-2.18 (m, 3H), 1.06 (d, *J* 4.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.9, 196.4, 150.7, 136.4, 135.8, 130.3, 118.0, 109.0, 45.9, 45.6, 26.9, 21.1, 20.8. HRMS (ESI): calcd. for C15H18NO2 $[M+H]^+$ 244.1338, Found: 244.1340.

2-(((4-Methoxyphenyl)amino)methylene)-5-methylcyclohexane-1,3-dione (4i). 112.7 mg, 87 % yield, oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.90 (d, *J* 15.0 Hz, 1H), 8.47 (d, *J* 15.0 Hz, 1H), 7.14 (d, *J* 10.0 Hz, 2H), 6.87 (d, *J* 10.0 Hz, 2H), 3.76 (s, 3H), 2.57-2.53 (m, 2H), 2.26-2.15 (m, 3H), 1.04 (d, *J* 5.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.8, 196.4, 158.3, 150.9, 131.6, 119.6, 115.1, 109.0, 55.6, 45.9, 45.7, 27.0, 21.2. HRMS (ESI): calcd. for C15H18NO3 $[M+H]^+$ 260.1287, Found: 260.1291.

2-(((3,5-Dimethoxyphenyl)amino)methylene)-5-methylcyclohexane-1,3-dione (4j). 59.3 mg, 45 % yield, yellow solid: mp 142-143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 12.74 (d, *J* 13.2 Hz, 1H), 8.5 (d, *J* 13.1 Hz, 1H), 6.29 (s, 2H), 6.23 (s, 2H), 3.72 (s, 6H), 2.55-2.51 (m, 2H), 2.24-2.11 (m, 3H), 1.02 (d, *J* 3.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 199.9, 196.2, 161.6, 150.3, 139.8, 109.1, 98.3, 96.3, 55.3, 45.8, 45.5, 26.6, 20.9. HRMS (ESI): calcd. for C16H20NO4 $[M+H]^+$ 290.1392, Found: 290.1385.

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Supplementary Material

The experimental procedures and IR, ^{1}H NMR and ^{13}C NMR spectra associated with this article are available as supplementary data.

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