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# Cp*Co(III) catalyzed annulation of *N*-Cbz hydrazones for the redox-neutral synthesis of isoquinolines via C–H/N–N bond activation

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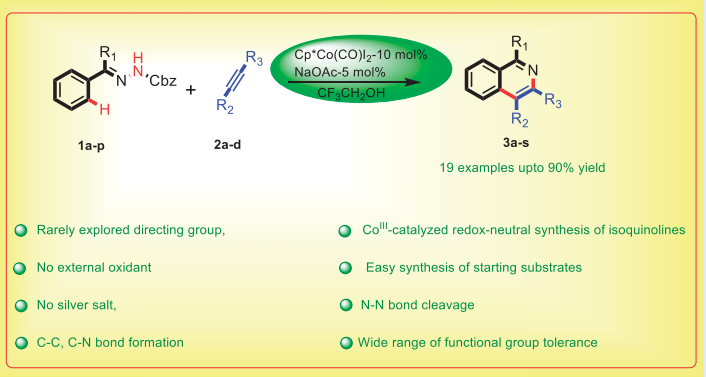
**ABSTRACT**

A new cascade oxidative cyclization reaction of *N*-Cbz hydrazones with internal alkynes has been explored for the preparation of isoquinoline derivatives using $Cp^*Co^{III}$-catalyst through C–H and N–N bond functionalization. *N*-Cbz hydrazones are rarely explored as directing group for redox-neutral [4 + 2] cyclization reaction through the cyclometallation and this catalyst system does not require any external oxidizing agent, as well as, silver or antimony salt. The current efficient approach has been utilized for the synthesis of different isoquinoline derivatives with good regioselectivity and yields.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
C–H/N–N bond activation; cobalt; *N*-Cbz hydrazone; silver salt-free

## Introduction

Transition metal-catalyzed C–H bond functionalization reactions showed a potential pathway for the transformation of various organic molecules.[1–5] The strategy of C–H bond activation has been widely used for the preparation of naturally occurring compounds, drug molecules, and intermediates of the biologically active compounds.[6] Also, C–H bond activation is an important tool in synthetic organic chemistry for the

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development of C=O, C–N, C–S, and C–C bonds considering the regioselective and green chemistry perspective.[7–9] Most of the C–H bond activation reactions involve the use of expensive metal catalysts. In the last few decades, first-row transition metals have become a prominent replacement to the expensive transition metals for C–H functionalization reactions due to their less toxicity, inexpensive nature and mode of coordination.[10,11] In this background, many research groups took efforts on the improvement of Cp*Co(CO)$I_2$ catalyzed C–H bond activation reactions.[12,13]

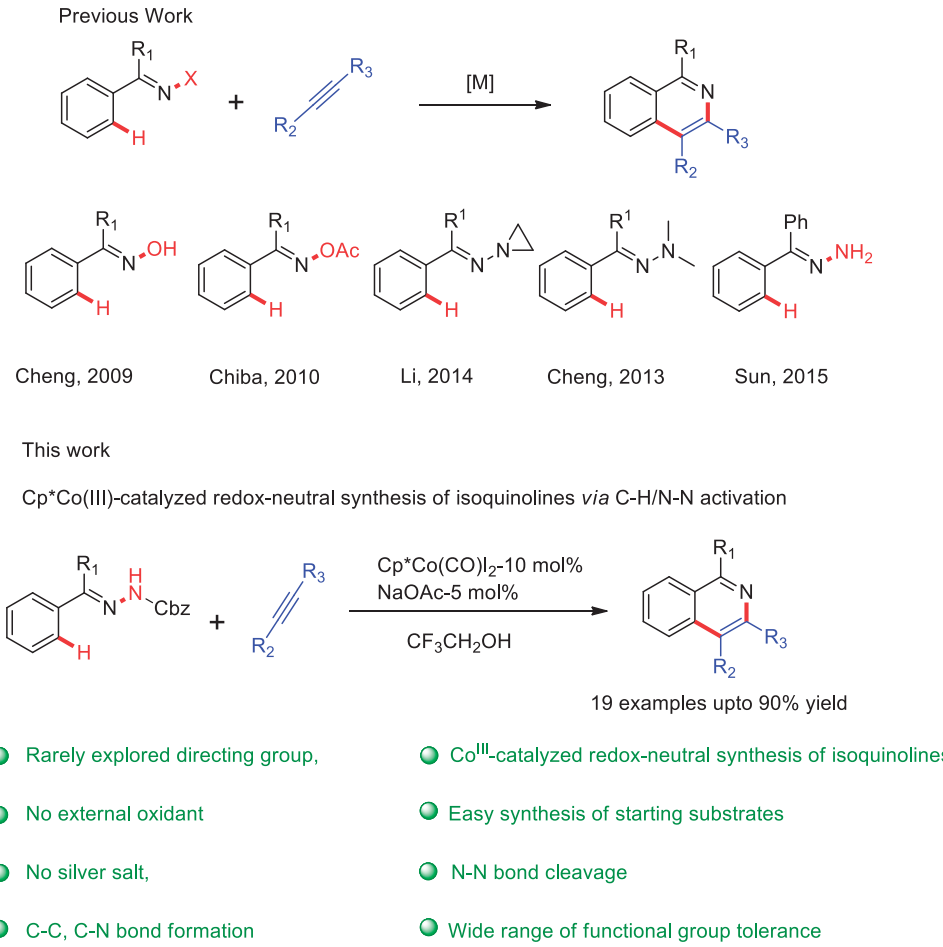
Isoquinoline derivatives are naturally occurring compounds which represent an essential class of heterocycles with a broad range of pharmacological activity.[14] Isoquinoline motifs can be used as ligands in various asymmetric catalysts and photochemical reactions.[15,16] They are also used in material sciences, dyes and paint industries.[17] Due to the importance of isoquinoline moieties, various name reactions such as Bischler–Napieralski,[18] Pomeranz–Fritsch,[19] and Pictet–Spengler[20] are reported for their synthesis. In the last few decades, C–H bond activation reactions have been recognized as a prominent route for the preparation of isoquinoline derivatives with promising yields.[21]

Transition metal-catalyzed divergent synthetic routes for the preparation of isoquinolines have been widely studied using various directing groups via N–O bond cleavage.[22–26] Also, N–N bond cleavage became a promising tool for the synthesis of isoquinolines using diverse directing groups assisted by transition metals (Scheme 1).[27–32] However, most of the above methods suffer from one or more drawbacks such as the use of external oxidants, expensive transition metal catalysts, and unavailability of starting material. Considering these limitations, cobalt, a relatively inexpensive catalyst has been employed for the preparation of isoquinolines through C–H/N–N bond activations.[33–35] In light of this, Zhu group demonstrated Co-catalyzed access to isoquinolines using bidentate directing group under air as an external oxidant.[36] Next, Lade and coworkers synthesized isoquinolines by annulation of arylhydrazones. This protocol having some lacunas like the use of silver salt and air as an external oxidant.[37] However, to the best of our knowledge *N*-Cbz hydrazone are rarely explored for the synthesis of isoquinolines. Also, considering above drawbacks for the synthesis of isoquinolines, there is need to develop its synthetic protocol using a relatively inexpensive Co catalyst which is efficient, free from the use of silver salt, as well as, external oxidant.

Recently our research group explored various directing groups to accelerate C–H bond activation at ortho position for the preparation of heterocycles and other biologically active scaffolds.[38–41] In view of this, herein, we decided to employ *N*-Cbz hydrazone, a rarely explored directing group for the cyclization reaction with alkynes using Cp*Co(III) as a catalyst via C–H/N–N bond activation for the preparation of isoquinolines. The proposed reaction methodology is elegant, relatively inexpensive and facile which works efficiently under external oxidant as well as silver salt-free conditions.

## Results and discussion

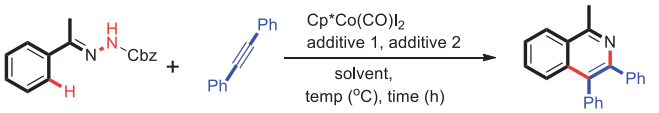
Optimization of reaction conditions has been carried out employing 0.5 mmol of *N*-Cbz hydrazone (*E*)-benzyl 2-(1-phenylethylidene)hydrazine carboxylate and




**Scheme 1.** Transition metal catalyzed annulation reaction for the synthesis of isoquinoline.

diphenylacetylene as model substrates using 2 mL of trifluroethanol as a solvent (Table 1). Initially, the reaction was performed using model substrates in presence of $Cp^*Co(CO)I_2$ as a catalyst and NaOAc and $AgSbF_6$ as additives for 16 h at 100 °C, which could produce isoquinoline **3a** with a satisfactory yield of 71% (Table 1, entry 1). With these satisfactory results, we then screened different acetate sources such as KOAc, CsOAc, $Zn(OAc)_2$, AgOAc and $Cu(OAc)_2$ for the model reaction to check their effect on the yield of isoquinoline product, however, they are found to be less effective for the given transformation (Table 1, entries 2–6). Next, we have tested the solvent effect on the model reaction. Using 1,2-DCE as a solvent instead of TFE for the model reaction results in a lower product yield (Table 1, entry 7). On the other hand, MeOH and *t*-AmOH as a solvent found to be less effective for the proposed conversion (Table 1, entries 8 and 9). When the reaction was carried out in the absence of NaOAc, sudden decrease in the yield of product was observed. This is possibly due to the requirement of acetate ligand for the removal of hydrogen at the ortho position of the directing group (Table 1, entry 10). Considering the environmental impact of silver and antimony salt, we next, checked its necessity for our protocol. Surprisingly, no effect on

**Table 1.** Optimization of Co(III)-catalyzed cyclization of *N*-Cbz hydrazones.[a]




1a 2a 3a

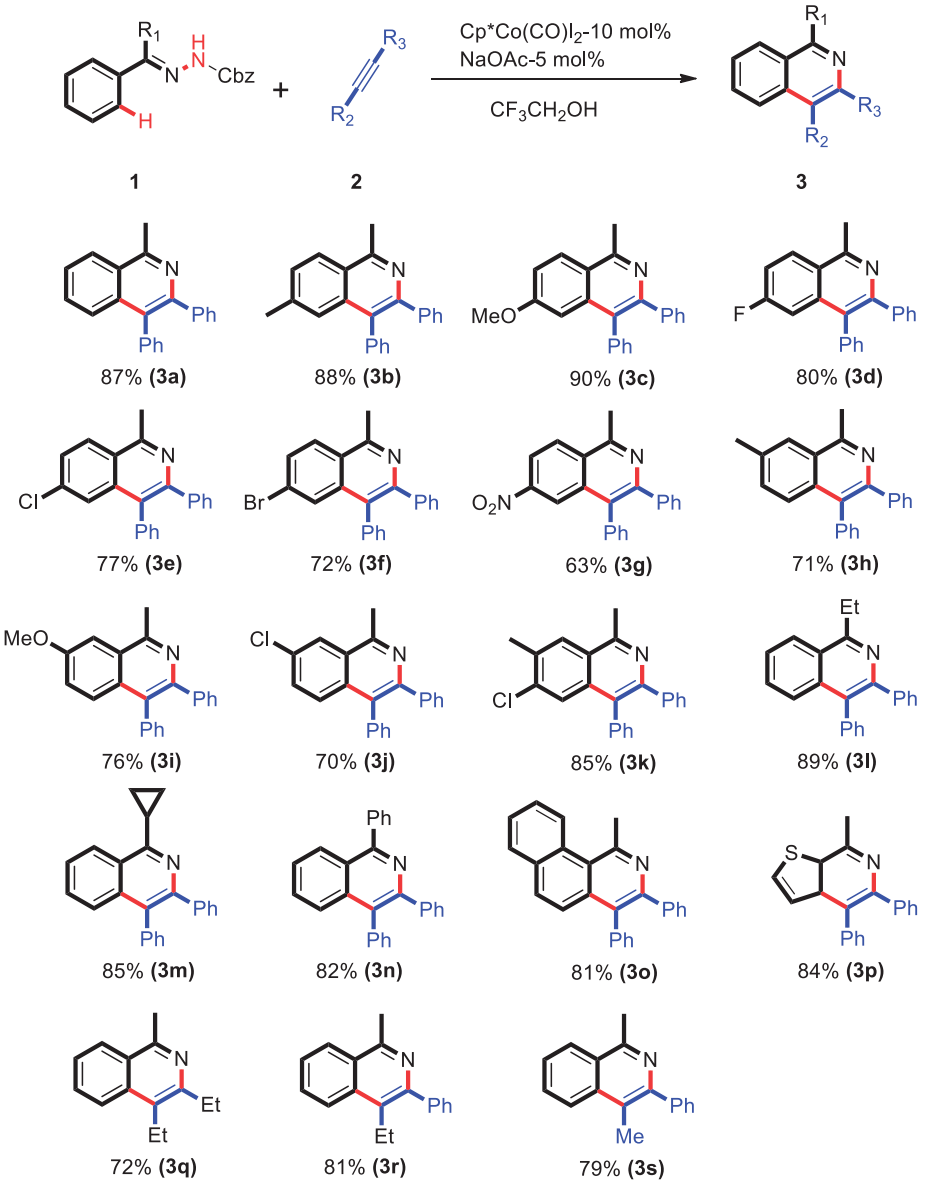
| entry | Additive 1 | Additive 2 | solvent | temp (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | NaOAc | $AgSbF_6$ | TFE | 100 | 71 |
| 2 | KOAc | $AgSbF_6$ | TFE | 100 | 52 |
| 3 | CsOAc | $AgSbF_6$ | TFE | 100 | 46 |
| 4 | $Zn(OAc)_2$ | $AgSbF_6$ | TFE | 100 | 35 |
| 5 | AgOAc | $AgSbF_6$ | TFE | 100 | 42 |
| 6 | $Cu(OAc)_2$ | $AgSbF_6$ | TFE | 100 | 48 |
| 7 | NaOAc | $AgSbF_6$ | 1,2-DCE | 100 | 58 |
| 8 | NaOAc | $AgSbF_6$ | MeOH | 100 | 14 |
| 9 | NaOAc | $AgSbF_6$ | $^t$AmOH | 100 | 26 |
| 10 | – | $AgSbF_6$ | TFE | 100 | 15 |
| 11 | NaOAc | – | TFE | 100 | 69 |
| 12 | NaOAc | – | TFE | 110 | 87 |
| 13 | NaOAc | – | TFE | 120 | 88 |
| 14[c] | NaOAc | – | TFE | 110 | 87 |
| 15[d] | NaOAc | – | TFE | 110 | 75 |
| 16[e] | NaOAc | – | TFE | 110 | 45 |
| 17[f] | NaOAc | – | TFE | 110 | 88 |

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $Cp^*Co(CO)I_2$ (10 mol%), NaOAc (5 mol%), $AgSbF_6$ (20 mol%) in TFE (2 mL) for 16 h. [b]GC yield, [c]reaction performed for 18 h, [d]reaction performed for 14 h, [e]5 mol% [$Cp^*Co(CO)I_2$] was used and [f]15 mol% [$Cp^*Co(CO)I_2$] catalyst was used.

the yield of the final product was observed when the reaction was carried out in the absence of silver hexafluoroantimonate salt. (Table 1 entry 11).

Next, the effect of temperature on the model reaction was studied. When the temperature of the reaction was increased to 110 °C, a substantial effect on the yield of product was observed. Further, with the increase of temperature up to 120 °C, no significant change in the yields of the titled product was observed (Table 1, entry 12 and 13). Furthermore, reaction time increased to 18 h, which does not change the yield of the titled product (Table 1, entry 14). On the other hand, low product yield was obtained on decreasing time to 14 h (Table 1, entry 15). Further, we also studied the optimum catalyst loading for the model reaction which suggests that 10 mol% catalysts are optimum for the proposed transformation (Table 1, entries 16 and 17).

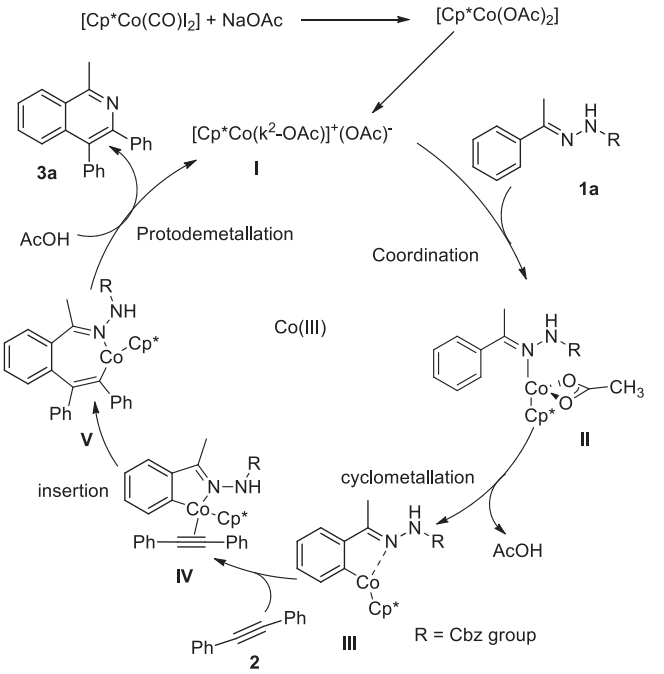
Employing the above-optimized reaction conditions, we further investigated the versatility of the proposed protocol for different substituted *N*-Cbz hydrazones (Scheme 2). For this, we employed various *N*-Cbz hydrazones containing electron-donating, as well as, electron-withdrawing groups such as methyl, methoxy, fluoro, chloro, bromo, and nitro for annulation with internal alkynes to give respective isoquinoline products with promising yields (87–78%). *N*-Cbz hydrazone with no substituent gave a prominent yield of titled product (**3a**). The incorporation of methyl and methoxy group at the para position of the phenyl ring of *N*-Cbz hydrazone slightly increased the yields of **3b** and **3c** by 88 and 90%, respectively. Next, the introduction of electron-deficient functional groups like fluoro, chloro, bromo and nitro at the para position of *N*-Cbz hydrazone affected the reaction providing **3d–g** product yields in 80, 77, 72, and 63%, respectively. When the functional group is present at different positions of the *N*-Cbz hydrazone, it




[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Cp*Co(CO)$I_2$ (10 mol %), NaOAc (5 mol %) in TFE (2 mL) at 110 °C for 16 h.

**Scheme 2.** The scope of substituted *N*-Cbz hydrazones and Alkynes. Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Cp*Co(CO)$I_2$ (10 mol%), NaOAc (5 mol%) in TFE (2 mL) at 110 °C for 16 h.

shows the marginal effect of the yields of the desired product. The reaction of methyl substituent at meta position of *N*-Cbz hydrazone with diphenyl acetylene generated corresponding isoquinoline product in 71% yield (**3h**). Methoxy and chloro group present at the meta position of *N*-Cbz hydrazone lead to a slight decrease in yields of corresponding products (**3i** and **3j**). Next, we moved to annulation of disubstituted *N*-Cbz




**Scheme 3.** Plausible reaction mechanism.

hydrazones with diphenyl acetylene to give desired product **3k** in 85% yield. Pleasantly, *N*-Cbz hydrazone derived from different ketones such as propiophenone (**1l**), cyclopropyl phenyl ketone (**1m**), benzophenone (**1n**) and acetylnaphthalene(**1o**), also produced desired isoquinoline products **3l–o** with 89, 85, 82, and 81% product yields, respectively.

Gratifyingly, *N*-Cbz hydrazone derived from heterocyclic ketone also reacts efficiently with diphenyl acetylene to afford the desired product (**3p**) with satisfactory yield. After the scope of *N*-Cbz hydrazones had been examined, we next turned our attention to explore the scope of alkyne for the preparation of isoquinoline derivatives. Symmetrical aliphatic alkyne i.e. 3-hexyne reacts with *N*-Cbz hydrazone (**1a**) affording good yields of the isoquinoline product (**3q**). Similarly, the reaction of unsymmetrical alkyne (i.e., but-1-yn-1-ylbenzene and prop-1-yn-1-ylbenzene) with *N*-Cbz hydrazone (**1a**) generated corresponding products **3r** and **3s** with 81 and 79% yields, respectively.

The plausible reaction mechanism for the proposed transformation is shown in Scheme 3. In the first step, $Cp^*Co^{III}$ forms complex **I** in presence of NaOAc. Complex **I** then coordinates with *N*-Cbz hydrazone **1a** to give intermediate **II**. Next, intermediate **II** undergoes concerted cyclometallation-deprotonation with the release of HOAc to form five-membered cobaltocycle intermediate **III**. In a further step, intermediate **III** coordinates with alkyne **2** to form intermediate **IV** followed by insertion of alkyne to form the seven-membered intermediate **V**. Finally, isoquinoline **3a** releases from the catalytic cycle in presence of HOAc to regenerate active catalytic species **I** for the further cycle.

## Conclusion

In conclusion, we develop the Cp*$Co^{III}$-catalyzed dehydrative cyclization of *N*-Cbz hydrazones with alkynes through the C–H and N–N bond activation. This protocol is the redox neutral type and no external oxidant as well as silver salt required for the preparation of isoquinoline derivatives. Utilizing this facile and efficient methodology for the various substituted and disubstituted *N*-Cbz hydrazones (nitro, fluoro, chloro, bromo, and methoxy groups) to form multi-substituted isoquinoline derivatives. This pathway is useful for the reaction of different alkynes with *N*-Cbz hydrazones to afford corresponding isoquinoline derivatives in good to excellent yields.

## Experimental procedure

### *Materials and methods*

All chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC) with a flame ionization detector (FID) with a capillary column (30 m × 0.25 mm × 0.25 µm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. GC-MS (Rtx-17, 30 m × 25 mm ID, film thickness (df = 0.25 µm) (column flow 2 mL $min^{-1}$, 80 to 240 °C at 10 °C $min^{-1}$ rise) was used for the mass analysis of the products. Products were purified by column chromatography on 100–200 mesh silica gel. The $^{1}H$ NMR spectra were recorded on 400 and 500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. The $^{13}C$ NMR spectra were recorded at 100 and 125 MHz and chemical shifts were reported in parts per million ($\delta$) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (*J*) values were reported in hertz (Hz). The splitting patterns of the proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) in $^{1}H$ NMR spectroscopic analysis. The products were confirmed by GCMS, $^{1}H$ and $^{13}C$ NMR spectroscopy analysis.

### *General experimental procedure for the preparation of isoquinoline derivative*

A dry reaction tube with a magnetic stirrer was charged with *N*-Cbz hydrazone **1** (0.5 mmol), alkyne **2** (0.6 mmol), NaOAc (5 mol%), and [Cp*Co(CO)$I_2$] (10 mol%). Then the tube was evacuated and nitrogen was purged three to four times in the reaction tube. Next, TFE (2 mL) was added to the tube with the help of a syringe. The reaction mixture was stirred at 110 °C for 16 h. After the completion of the reaction, the reaction mixture was allowed to cool at room temperature followed by extraction with 25 mL of ethyl acetate; the organic layer was washed with brine solution, dried over anhydrous $Na_2SO_4$ and filtered. Finally, the solvent was removed under vacuum on a rotary evaporator. The resulting mixture was purified by silica gel column chromatography using pet ether/ethyl acetate as eluent to get the pure final product **3** in good yield.

### *1-Methyl-3,4-diphenylisoquinoline (3a)*

Pale yellow solid; mp 154–156 °C; Yield 87%; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20–8.18 (m, 1H), 7.64 (d, $J = 4.6$ Hz, 1H), 7.59–7.56 (m, 2H), 7.36–7.32 (m, 5H), 7.24–7.16 (m, 5H), 3.07 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 156.74, 148.45, 140.03, 136.61, 135.04, 130.43, 129.29, 128.92, 128.21, 127.20, 126.61, 126.13, 126.03, 125.94, 125.53, 125.22, 125.19, 124.54, 21.72; GCMS (EI 70 eV) *m*/*z* (% rel. inten.) 295 (M+, 51), 294, 252, 146, 139.

Supplementary data (copies of $^{1}$H and $^{13}$C NMR spectra of all the synthesized compounds) associated with this article can be found through the "Supplementary Content" section of this article's webpage.

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