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One-pot construction of diverse and functionalized isochromenoquinolinediones by Rh(III)-catalyzed annulation of unprotected arylamides with 3-diazoquinolinediones and their application for fluorescence sensor†

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A facile and efficient Rh(III)-catalyzed annulation of arylamides with 3-diazoquinolinediones for the construction of diverse and highly functionalized isochromenoquinolinediones is described. Furthermore, the methodology is applicable for delivering various relevant molecules such as pyridopyranoquinolindiones, thienopyranoquinolindiones, and indolopyranoquinolindione. The reaction proceeds via cascade C–H activation, carbene insertion, and intramolecular lactonization. The reaction exhibits high atom economy, good functional group tolerance, and high regioselectivity. The synthesized compound can also behave as a potent fluorescence sensor for Fe³⁺ ion.

Introduction

Molecules bearing isochromenones or quinolinones are widely found in bioactive natural products, synthetic molecules, and pharmaceuticals.^{1,2} They are also used as valuable building blocks for the synthesis of medicines and functional materials.^{3,4} Among them, isochromenones containing a six-membered lactone ring possess potent biological functions such as anticancer, antimicrobial, anti-inflammatory, anticoagulant, and anti-HIV activities (Fig. 1A).⁵ The nitrogen-containing heterocycles, quinolinones also have a broad range of biological properties including anticancer, antibiotic, antiviral, antibacterial, and antihypertensive activities (Fig. 1B).⁶

Owing to their importance and usefulness, various approaches for the synthesis of isochromenones or quinolinones have been developed. The typical methods for the preparation of isochromenones include nickel-catalyzed decarbonylative addition of anhydrides to alkynes,⁷ Rh(III)-catalyzed reaction of phosphonium ylides or benzamides with diazocarbonyl compounds,⁸ N-heterocyclic carbene/Lewis acid-catalyzed dimerization of 2-formylcinnamates,⁹ and Ru(II)-catalyzed electrooxidative [4 + 2] reaction of benzyl alcohols with alkynes.¹⁰ The representative strategies for the synthesis of

quinolinones include Rh-catalyzed C–H bond activation of anilines with CO and alkynes,¹¹ Rh-catalyzed decarbonylative coupling of isatins with alkynes,¹² Ru-catalyzed cyclization of anilides with propiolates or acrylates,¹³ Pd-catalyzed cascade reaction of anilines with acrylates,¹⁴ direct oxidation C–H amidation of amides.¹⁵ In addition, Rh(III)-catalyzed annulation of benzamides with diazo compounds for isoquinolinones was reported (Scheme 1a).¹⁶ Although a number of methods for the synthesis of isochromenones and quinolinones or isoquinolinones have been demonstrated, the direct construction of heterocycles bearing both isochromenones and quinolin-2-ones are only reported sporadically.¹⁷ Recently, the reported Pd(II)-catalyzed carbonylation of alkynes is one such example (Scheme 1b).¹⁷ However, there is no example for the direct construction of highly functionalized

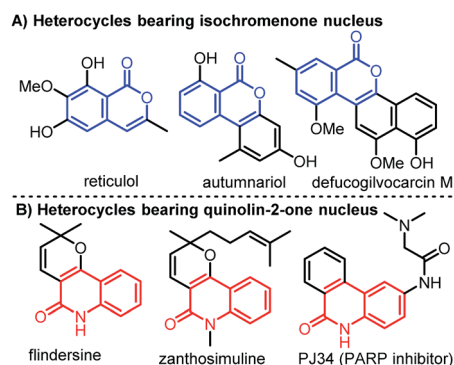
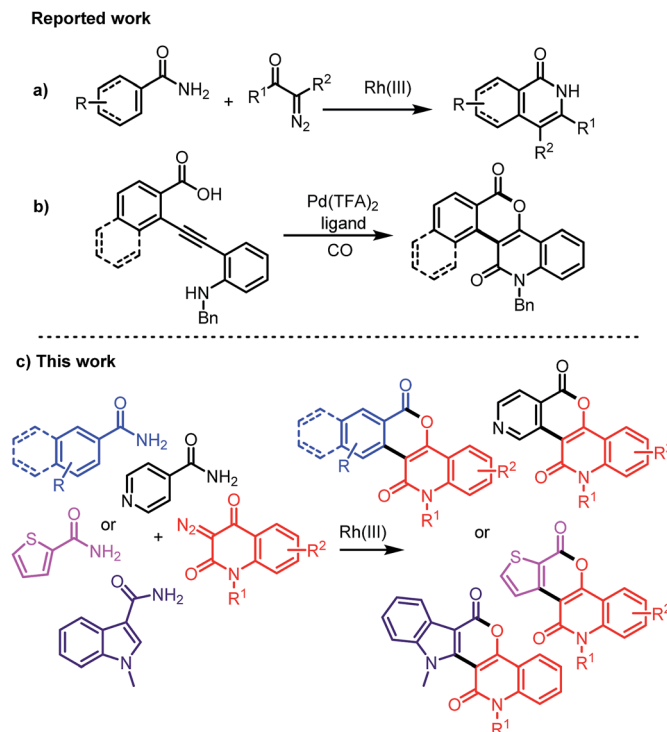


Fig. 1 Biologically active heterocycles bearing isochromenone or quinolinone moiety.

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Scheme 1 Representative strategies for the construction of isoquinolinones, isochromenoquinolinones, and their derivatives.

isochromenoquinolinediones by Rh(III)-catalyzed annulation of unprotected arylamides with 3-diazoquinolinediones.

As a part of our ongoing studies on the development of new synthetic methodologies for the construction of heterocycles utilizing diazo compounds,¹⁸ this paper describes an efficient Rh(III)-catalyzed annulation of unprotected arylamides, isonicotinamide, thiophene-2-carboxamide, and indole-3-carboxamide with various 3-diazoquinoline-2,4-diones for the construction of diverse and functionalized heterocycles bearing isochromenones and quinolinones (Scheme 1c).

Results and discussion

Our investigation commenced with the reaction of primary benzamide (**1a**) with 3-diazo-1-methylquinoline-2,4-dione (**2a**) in the presence of different catalysts, additives, and solvents (Table 1). The initial reaction with 2.5 mol% $[\text{RuCl}_2(p\text{-cymene})]_2$ and 20 mol% $\text{Cu}(\text{OAc})_2$ under reflux in 1,2-dichloroethane for 12 h provided the N–H insertion product **3a'** (48%), along with a trace amount of **3a** (entry 1). However, with 2.5 mol% of $[\text{RhCp}^*\text{Cl}_2]_2$ and 20 mol% $\text{Cu}(\text{OAc})_2$, **3a** was isolated in 64% yield as the sole product (entry 2). Importantly, $[\text{RhCp}^*\text{Cl}_2]_2$ showed superior catalytic activity than $[\text{RuCl}_2(p\text{-cymene})]_2$ for the synthesis of **3a**. To our delight, an increase in the amount of $\text{Cu}(\text{OAc})_2$ to 100 mol% improved the yield of **3a** to 72% (entry 3). Encouraged by this result, we screened other additives such as CsOAc , AgNO_3 , AgSbF_6 , Ag_2CO_3 , and AgOAc for this reaction, along with 2.5 mol% $[\text{RhCp}^*\text{Cl}_2]_2$ (entries 4–8). Among these, AgOAc was found to be the best additive for this transformation. Importantly, increasing the amount of AgOAc to 200 mol% not

only reduced the reaction time to 8 h, but also increased the yield of **3a** to 84% (entry 9). However, decreasing the loading of AgOAc to 20 mol% decreased the yield of **3a** to 52% (entry 10). In addition, decreasing the loading of $[\text{RhCp}^*\text{Cl}_2]_2$ to 1.0 mol% in the presence of 200 mol% AgOAc provided **3a** in 70% yield (entry 11). However, decreasing the reaction temperature to room temperature did not afford any product (entry 12). On the other hand, **3a** was not obtained in the absence of AgOAc or $[\text{RhCp}^*\text{Cl}_2]_2$ (entries 13–14). Further reactions using other nonpolar or polar solvents such as toluene, 2,2,2-trifluoroethanol (TFE), acetonitrile, and ethanol provided **3a** in lower yields (45–68%) (entries 15–18). The structure of **3a** was identified by the analysis of its spectral data. The ^1H NMR spectrum of **3a** revealed the characteristic *N*-methyl peak at δ 3.80 ppm and 8 aromatic proton peaks at δ 9.60, 8.40, 8.34, 7.86, 7.67, 7.89, 7.42, and 7.35 ppm. The ^{13}C NMR spectrum of **3a** exhibited peaks due to the carbonyl carbon of a conjugated lactone moiety at δ 160.7 ppm and a conjugated amide carbonyl carbon at δ 160.2 ppm. The structure of **3a** was further confirmed by single-crystal X-ray crystallographic analysis of the structurally related compound **3j** (Fig. 2).

With the optimized conditions in hand, we further explored the generality of the reactions by employing diversely substituted 3-diazoquinoline-2,4-diones **2b–2o** (Table 2). The reactions of **1a** with *N*-substituted 3-diazoquinoline-2,4-diones **2b–2h** bearing *N*-chloropropyl, *N*-but-3-en-1-yl, *N*-benzyl, *N*-allyl, *N*-prenyl, *N*-cinnamyl, and *N*-*trans,trans*-farnesyl groups were successfully carried out to produce the desired products **3b–3h** in 62–82% yields. In addition, reactions of other 3-diazoquinolindiones **2i–2o** bearing various substituents on the



Table 1 Optimization of the reaction conditions^a


Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Temp.	Time	Yield ^b (%)	
						3a	3a'
1	[RhCl ₂ (<i>p</i> -cym)] ₂ (2.5)	Cu(OAc) ₂ (20)	DCE	Reflux	12	Trace	48
2	[RhCp*Cl ₂] ₂ (2.5)	Cu(OAc) ₂ (20)	DCE	Reflux	12	64	0
3	[RhCp*Cl ₂] ₂ (2.5)	Cu(OAc) ₂ (100)	DCE	Reflux	12	72	0
4	[RhCp*Cl ₂] ₂ (2.5)	CsOAc (100)	DCE	Reflux	12	67	0
5	[RhCp*Cl ₂] ₂ (2.5)	AgNO ₃ (100)	DCE	Reflux	12	68	0
6	[RhCp*Cl ₂] ₂ (2.5)	AgSbF ₆ (100)	DCE	Reflux	12	74	0
7	[RhCp*Cl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	DCE	Reflux	12	76	0
8	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (100)	DCE	Reflux	12	80	0
9	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (200)	DCE	Reflux	8	84	0
10	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (20)	DCE	Reflux	12	52	0
11	[RhCp*Cl ₂] ₂ (1.0)	AgOAc (200)	DCE	Reflux	12	70	0
12	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (200)	DCE	rt	12	0	0
13	[RhCp*Cl ₂] ₂ (2.5)	—	DCE	Reflux	12	0	0
14	—	AgOAc (20)	DCE	Reflux	12	0	0
15	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (20)	Toluene	100 °C	12	68	0
16	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (20)	TFE	Reflux	12	65	0
17	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (20)	CH ₃ CN	Reflux	12	45	0
18	[RhCp*Cl ₂] ₂ (2.5)	AgOAc (20)	EtOH	Reflux	12	58	0

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol) in solvent (5 mL) under N₂. ^b Isolated yields after column chromatography.

benzene ring were successful. Treatment of **1a** with 3-diazo-*N*-methylquinolindione compounds **2i–2k** bearing electron-donating groups such as 6-Me, 6-*i*-Pr, and 7-OMe provided the desired products **3i–3k** in 74%, 81%, and 68% yields, whereas that with diazo compounds **2l–2o** bearing electron-withdrawing groups such as 5-Cl, 6-Cl, 6-Br, and 7-Cl afforded the corresponding products **3l–3o** in 79–85% yields.

To demonstrate the versatility of this protocol, further reactions of various benzamides **1b–1m** with 3-diazo-*N*-methylquinoline-2,4-dione (**2a**) were investigated (Table 3). Treatment of **2a** with benzamides **1b–1d** bearing electron-donating groups such as 4-Me, 4-OMe, and 4-Ph on the

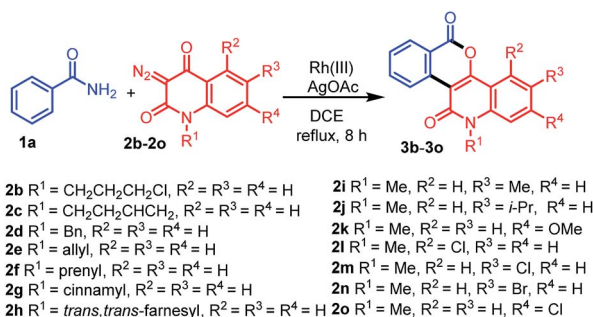
benzene ring provided **4a–4c** in 75%, 72%, and 78% yields, respectively, whereas the reactions with benzamides **1e–1i** bearing electron-withdrawing groups such as 4-Cl, 4-Br, 4-COMe, 4-CO₂Me and 4-CN afforded **4d–4h** in 62–86% yields. However, the reaction of **1j** bearing a strong electron-withdrawing –NO₂ group at 4-position of the benzene ring did not afford the expected product **4i**. On the other hand, the reactions of *ortho*-substituted benzamides **1k** and **1l** with **2a** afforded the desired products **4j** and **4k** in 76% and 74% yields, respectively. In addition, when 3,4-dichlorobenzamide (**1m**) bearing two electron-withdrawing groups on the benzene ring was allowed to react with **2a**, the desired product **4l** was produced in 84% yield. In this case, other possible regioisomers were not observed.

After demonstrating the generality and versatility of this methodology, we investigated the possibility of using other arylamides **1n–1p** bearing polyaromatic and heteroatomic rings with diazo compounds (Scheme 2). For example, the reaction of 2-naphthamide (**1n**) with **2a** or **2d** provided **5** and **6** in 76% and 71% yields, respectively, while that of isonicotinamide (**1o**) bearing a *N*-heteroaromatic ring with **2a** or **2l** afforded the desired products **7** and **8** in 48% and 58% yields, respectively. On the other hand, treatment of thiophene-2-carboxamide (**1p**) bearing an *S*-heteroaromatic ring with **2a** or **2j** led to the formation of the expected products **9** and **10** in 62% and 63% yields, respectively.



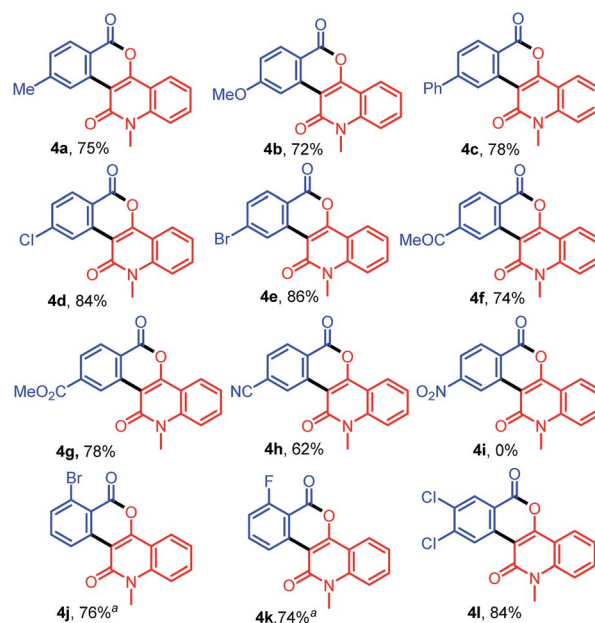
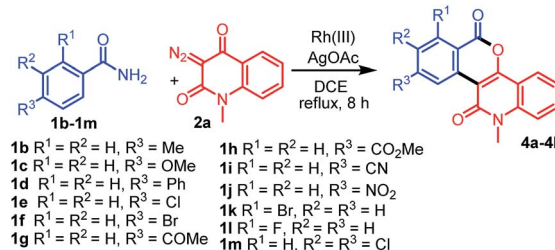
Fig. 2 X-ray structure of compound **3j** (CCDC 1878962).



Table 2 Synthesis of diverse fused isochromenoquinolinediones **3b–3o** by the reaction of **1a** with **2b–2o**

As an application of this protocol, diversely oriented polycyclic heterocycle **11** was next prepared in 62% yield employing 1-methyl-1*H*-indole-3-carboxamide (**1q**) with diazo compound **2a** under standard reaction conditions (Scheme 3).

The chemoselectivity of the reactions of different benzamides with diazo compound **2a** was investigated under standard conditions (Scheme 4). Treatment of two different benzamides **1a** (0.5 mmol) and **1c** (0.5 mmol) with diazo compound **2a** (0.5 mmol) for 8 h afforded the products **3a** and **4b** in 40% and 28% yields, respectively (Scheme 4, eqn (1)). On the other hand, the reaction of benzamides **1a** (0.5 mmol) and **1f** (0.5 mmol) afforded **3a** and **4e** in 37% and 42% yields,

Table 3 Synthesis of diverse isochromenoquinolinediones **4a–4l** by the reaction of **1b–1m** with **2a**

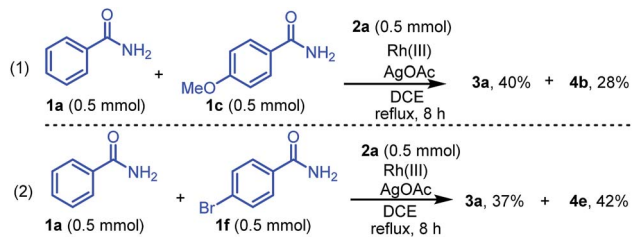
^a Reaction time = 18 h.

respectively (Scheme 4, eqn (2)). These results indicated that benzamide **1f** bearing the electron-withdrawing group on the benzene ring is more chemoselective than the unsubstituted

**Scheme 2** Construction of diverse fused heterocycles **5–10** bearing polyaromatic and heteroaromatics by the reaction of **1n–1p** with **2a**, **2d**, **2l**, or **2j**.



Scheme 3 Construction of polycyclic heterocycle **11** by the reaction of **1q** with **2a**.



Scheme 4 Chemoselectivity of different benzamides **1a**, **1c**, or **1f** with diazo compound **2a**.

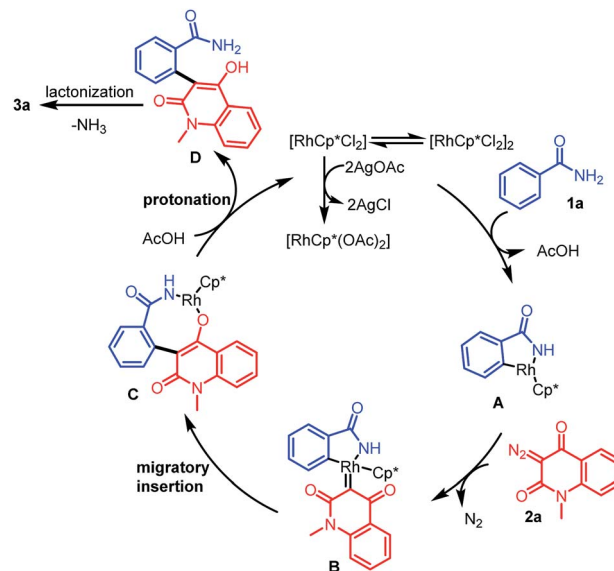
benzamide **1a** and the benzamide **1c** bearing electron-donating groups.

To elucidate the reaction mechanism, some deuterium labelling experiments were performed (Scheme 5). The H/D exchange experiment was first carried out with 2.5 mol% Rh(III) and AgOAc (2 equivalents) of **1a** (Scheme 5a). A significant deuterium exchange (65%) was observed at each of the two *ortho* positions of the benzamide to afford the product **1a'**.^{19a} This result suggested that the rhodation–proto(deuterio)derhodation process is reversible at the *ortho* positions. A kinetic isotope effect (KIE) experiment was next carried out (Scheme 5b).^{19b} A significant primary KIE value ($K_H/K_D = 3.5$) was observed *via* ¹H NMR analysis, which indicated that C–H bond cleavage occurs during the rate-determining step.

On the basis of the control experiments and available literature,²⁰ a plausible mechanism for the formation of **3a** is depicted in Scheme 6. Initially, an active catalyst $[\text{RhCp}^*(\text{OAc})_2]$ is generated through anion exchange from $[\text{RhCp}^*\text{Cl}_2]_2$ and AgOAc. A coordination reaction between the activated catalyst



Scheme 5 Deuterium labelling experiments.



Scheme 6 Reaction mechanism for the formation of **3a**.

and **1a** gives rhodacyclic intermediate **A** *via* a concerted metalation/deprotonation pathway. Then, diazo compound **2a** reacts with intermediate **A** to form carbene intermediate **B** through the release of nitrogen. Subsequently, the migratory insertion of the carbene group into the Rh–C bond delivers the eight membered rhodacycle intermediate **C** that is protonated



Fig. 3 (a) Fluorescence responses of different compounds (10 μM , $\lambda_{\text{ex}} = 350 \text{ nm}$). (b) Fluorescence responses of **4a** in the presence of various metal cations (10 μM , $\lambda_{\text{ex}} = 350 \text{ nm}$).





Fig. 4 (a) Fluorescence spectra of **4a** in the presence of different concentrations of aqueous Fe^{3+} (100 to 900 μM). (b) Plot of quenching efficiency versus the concentration of Fe^{3+} ions.

by AcOH to yield the intermediate **D**, with regeneration of Rh(III) catalyst for the next catalytic cycle. Finally, rapid lactonization of **D** furnishes **3a**.²¹

The synthesized compounds were evaluated as fluorescent sensor for sensing Fe^{3+} ions. Currently, the use of fluorescent molecular probes emitting in the visible region has become quite significant and have attracted considerable attention in academic and industrial research.²² Initially, the compound **4a** (10 μM) was optimized in seven different solvents: 1,4-dioxane, dimethyl sulfoxide (DMSO), 1,2-dichloroethane (DCE), acetonitrile (ACN), dichloromethane (DCM), tetrahydrofuran (THF) and ethanol (EtOH) (Fig. S1†). Among these solvents, the compound **4a** in 1,4-dioxane emitted the highest fluorescence maximum at 395 nm wavelength with intensity 3725 a.u. upon excitation at 350 nm. Hence, we examined the fluorescent properties of some of the synthesized compounds, viz. **3a**, **3g**, **3j**, **3l**, **4a**, **4c**, **4d**, **5**, **7**, and **10** in 1,4-dioxane.

Interestingly, compound **4a** emitted the highest fluorescence intensity amongst all the compounds examined (Fig. 3a). Therefore, the fluorescence response of 10 μM **4a** was recorded against various metal ions in water (Fig. 3b). Indeed, as indicated in Fig. 3b, among the different metal ions, the compound **4a** selectively sensed Fe^{3+} . Following this, the fluorescence response of **4a** (excitation at 350 nm) was examined against various concentrations of Fe^{3+} (100 to 900 μM) in water (Fig. 4a). The fluorescent intensity of compound **4a** was quenched linearly by increasing Fe^{3+} concentration with a correlation coefficient (R^2) of 0.9961 (Fig. 4b). Hence, the

compound **4a** can be utilized as a potent fluorescence sensor for Fe^{3+} ions.

Conclusions

In conclusion, we have developed an efficient protocol for the Rh(III)-catalyzed direct annulation of unprotected arylamides, isonicotinamide, thiophene-2-carboxamide, and indole-3-carboxamide with various 3-diazoquinoline-2,4-diones to synthesize various isochromenoquinolinediones, pyridopyranoquinolinediones, thienopyranoquinolinediones, and indolopyranoquinolinedione that can be widely used as a significant building block for the synthesis of bioactive natural products and pharmaceuticals. This protocol provides a rapid access to fused analogs of isochromenones as a one-pot procedure, and has several advantages such as high atom economy, high regioselectivity, and good tolerance of various functional groups with good yields. In addition, the synthesized compounds showed potent turn-off fluorescence sensing for Fe^{3+} ion.

Experimental

General information

All the reactions were carried out under nitrogen atmosphere in a 25 mL two-necked round-bottom flask with magnetic stirring. Merck silica gel plates (Art. 5554) precoated with a fluorescent indicator were used for analytical TLC analysis. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined using micro-cover glasses on a Fisher-Johns apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on Varian VNS (600 MHz and 150 MHz, respectively) spectrometers in CDCl_3 . Chemical shifts for protons were reported as parts per million in δ scale using solvent residual peak (CHCl_3 : 7.24 ppm) as internal standard. Chemical shifts of ^{13}C NMR spectra were reported in ppm from the central peak of CDCl_3 (77.00 ppm) on the δ scale. Fourier transform infrared (FT-IR) spectra were recorded on a PerkinElmer FT-IR spectrometer Spectrum Two™. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-700 spectrometer at the Korea Basic Science Institute.

General procedure for the synthesis of isochromenoquinolinone, pyridopyranoquinolinone, thienopyranoquinolinone, and indolopyranoquinolinone derivatives (3–11)

In an oven dried two-necked flask, a mixture of benzamide **1** (0.5 mmol) and 3-diazo-*N*-substituted quinoline-2,4-dione **2** (0.5 mmol) were dissolved in DCE (5 mL). This was then followed by addition of $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%), and AgOAc (2.0 equiv.) under nitrogen atmosphere. The reaction mixture was stirred under reflux condition, and the progress of the reaction was followed by TLC analysis. After completion, the reaction mixture was cooled to room temperature. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography (Hex : EtOAc = 1 : 5) to obtain the desired products **3–11**.



***N*-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)benzamide (3a').** Yield: 48% (70 mg); white solid; mp: 190–192 °C. IR (ATR): 3299, 1757, 1643, 1617, 1597, 1464, 1374, 1360, 1087 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 13.11 (1H, s), 9.56 (1H, s), 8.17 (1H, d, *J* = 7.8 Hz), 7.97 (2H, t, *J* = 7.8 Hz), 7.59–7.54 (2H, m), 7.51 (2H, t, *J* = 7.2 Hz), 7.33–7.28 (2H, m), 3.75 (3H, s). ¹³C NMR (150 MHz, CDCl₃): δ 166.7, 159.8, 149.0, 136.6, 132.8, 132.2, 130.5, 128.9, 127.6, 124.8, 122.6, 117.3, 113.7, 109.2, 29.99. HRMS *m/z* (*M*⁺): calcd for C₁₇H₁₄N₂O₃: 294.1004; found: 294.1007.

12-Methyl-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3a). Yield: 84% (116 mg); white solid; mp: 286–288 °C. IR (ATR): 2923, 1754, 1625, 1503, 1466, 1340, 1254, 1234, 1202, 1025, 972, 802 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.6 (1H, d, *J* = 8.4 Hz), 8.40 (1H, d, *J* = 8.4 Hz), 8.34 (1H, d, *J* = 7.8 Hz), 7.86 (1H, t, *J* = 8.4 Hz), 7.67 (1H, t, *J* = 8.4 Hz), 7.59 (1H, t, *J* = 7.8 Hz), 7.42 (1H, d, *J* = 9 Hz), 7.35 (1H, t, *J* = 7.8 Hz), 3.80 (3H, s). ¹³C NMR (150 MHz, CDCl₃): δ 160.6, 160.1, 154.6, 139.0, 135.6, 134.7, 132.6, 129.9, 128.8, 127.2, 124.1, 122.7, 120.6, 114.2, 113.6, 105.0, 29.8. HRMS *m/z* (*M*⁺): calcd for C₁₇H₁₁NO₃: 277.0739; found: 277.0738.

12-(3-Chloropropyl)-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3b). Yield: 82% (138 mg); white solid; mp: 200–202 °C. IR (ATR): 3166, 2923, 2857, 1792, 1654, 1602, 1526, 1428, 1390, 1285, 1239, 1193, 1121, 994, 859 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.55 (1H, d, *J* = 8.4 Hz), 8.39 (1H, dd, *J* = 8.4, 1.8 Hz), 8.34 (1H, dd, *J* = 8.4, 1.8 Hz), 7.85 (1H, t, *J* = 7.2 Hz), 7.68 (1H, *J* = 8.4 Hz), 7.59 (1H, t, *J* = 7.8 Hz), 7.50 (1H, d, *J* = 9.0 Hz), 7.35 (1H, t, *J* = 7.2 Hz), 4.53 (2H, t, *J* = 7.2 Hz), 3.74 (2H, t, *J* = 6 Hz), 2.29–2.25 (2H, m). ¹³C NMR (150 MHz, CDCl₃): δ 160.5, 160.0, 154.7, 138.1, 135.6, 134.5, 132.8, 129.9, 128.9, 127.1, 124.4, 122.8, 120.6, 113.9, 113.8, 104.8, 42.7, 40.7, 30.3. HRMS *m/z* (*M*⁺): calcd for C₁₉H₁₄ClNO₃: 339.0662; found: 339.0660.

12-(But-3-en-1-yl)-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3c). Yield: 68% (95 mg); white solid; mp: 180–182 °C. IR (ATR): 2995, 2917, 1824, 1769, 1539, 1597, 1479, 1375, 1254, 1097, 1023, 908, 856 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.52 (1H, d, *J* = 7.8 Hz), 8.34 (1H, d, *J* = 7.2 Hz), 8.26 (1H, d, *J* = 8.4 Hz), 7.82–7.80 (1H, m), 7.62–7.60 (1H, m), 7.56–7.54 (1H, m), 7.35 (1H, d, *J* = 8.4 Hz), 7.28 (1H, t, *J* = 8.4 Hz), 5.94–5.80 (1H, m), 5.16–5.13 (1H, m), 5.09 (1H, d, *J* = 9.6 Hz), 4.37 (2H, t, *J* = 7.8 Hz), 2.52–2.49 (2H, m). ¹³C NMR (150 MHz, CDCl₃): δ 160.1, 159.9, 154.4, 138.0, 135.5, 134.5, 134.1, 132.4, 129.7, 128.7, 127.0, 124.2, 122.5, 120.4, 117.4, 114.0, 113.6, 104.7, 42.0, 31.7. HRMS *m/z* (*M*⁺): calcd for C₂₀H₁₅NO₃: 317.1052; found: 317.1054.

12-Benzyl-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3d). Yield: 76% (134 mg); white solid; mp: 198–200 °C. IR (ATR): 2880, 1785, 1661, 1599, 1514, 1490, 1395, 1352, 1258, 1172, 1037, 841 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.61 (1H, d, *J* = 9.0 Hz), 8.40 (1H, d, *J* = 8.4 Hz), 8.33 (1H, d, *J* = 7.8 Hz), 7.85 (1H, t, *J* = 7.8 Hz), 7.60 (1H, d, *J* = 7.8 Hz), 7.52 (1H, t, *J* = 7.8 Hz), 7.32–7.28 (4H, m), 7.24–7.22 (3H, m), 5.63 (2H, s). ¹³C NMR (150 MHz, CDCl₃): δ 160.7, 160.0, 154.8, 138.4, 136.0, 135.6, 134.6, 132.5, 129.8, 128.9, 128.8, 127.4, 127.2, 126.4, 124.0, 122.8, 120.5, 115.0, 113.7, 104.8, 46.2. HRMS *m/z* (*M*⁺): calcd for C₂₃H₁₅NO₃: 353.1052; found: 353.1049.

12-Allyl-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3e). Yield: 64% (96 mg); white solid; mp: 165–167 °C. IR (ATR): 2988, 2894, 2014, 1917, 1766, 1469, 1382, 1244, 1101, 1054, 845 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.54 (1H, d, *J* = 8.4 Hz), 8.36–8.35 (1H, m), 8.29 (1H, dd, *J* = 8.4, 1.2 Hz), 7.83–7.80 (1H, m), 7.60–7.55 (2H, m), 7.34–7.28 (2H, m), 6.01–5.95 (1H, m), 5.24–5.22 (1H, m), 5.13–5.10 (1H, m), 5.00–4.99 (2H, m). ¹³C NMR (150 MHz, CDCl₃): δ 160.2, 160.0, 154.7, 138.3, 135.5, 134.5, 132.4, 131.5, 129.8, 128.7, 127.1, 124.0, 122.7, 120.5, 117.3, 114.7, 113.6, 104.7, 44.9. HRMS *m/z* (*M*⁺): calcd for C₁₉H₁₃NO₃: 303.0895; found: 303.0894.

12-(3-Methylbut-2-en-1-yl)-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3f). Yield: 81% (134 mg); white solid; mp: 195–197 °C. IR (ATR): 2881, 1753, 1661, 1590, 1497, 1391, 1257, 1166, 1134, 1031, 947, 897 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.59 (1H, d, *J* = 8.4 Hz), 8.37 (1H, dd, *J* = 9.6, 1.2 Hz), 8.30 (1H, dd, *J* = 7.8, 1.2 Hz), 7.85–7.82 (1H, m), 7.62–7.59 (1H, m), 7.58–7.56 (1H, m), 7.34–7.29 (2H, m), 5.16–5.14 (1H, m), 4.99 (2H, d, *J* = 4.8 Hz), 1.91 (3H, s), 1.72 (3H, s). ¹³C NMR (150 MHz, CDCl₃): δ 160.3, 160.1, 154.6, 138.4, 136.4, 135.5, 134.7, 132.4, 129.8, 128.7, 127.2, 124.1, 122.5, 120.5, 119.1, 114.6, 113.7, 104.9, 41.2, 25.6, 18.4. HRMS *m/z* (*M*⁺): calcd for C₂₁H₁₇NO₃: 331.1208; found: 331.1210.

12-Cinnamyl-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3g). Yield: 62% (117 mg); white solid; mp: 226–228 °C. IR (ATR): 2926, 1799, 1675, 1579, 1492, 1442, 1323, 1238, 1193, 1017, 962, 898 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.62 (1H, d, *J* = 2.4 Hz), 8.41 (1H, d, *J* = 7.8 Hz), 8.37 (1H, d, *J* = 8.4 Hz), 7.89–7.86 (1H, m), 7.66–7.63 (1H, m), 7.61 (1H, t, *J* = 8.4 Hz), 7.48 (1H, d, *J* = 8.4 Hz), 7.35 (1H, t, *J* = 7.8 Hz), 7.31 (2H, d, *J* = 8.4 Hz), 7.26–7.24 (2H, m), 7.19 (1H, t, *J* = 7.2 Hz), 6.59 (1H, d, *J* = 16 Hz), 6.37–6.32 (1H, m), 5.20 (2H, d, *J* = 5.4 Hz). ¹³C NMR (150 MHz, CDCl₃): δ 160.4, 160.1, 154.9, 138.4, 136.1, 135.6, 134.7, 132.8, 132.6, 129.9, 128.9, 128.5, 127.9, 127.2, 126.4, 124.2, 123.0, 122.8, 120.6, 114.7, 113.8, 104.9, 44.6. HRMS *m/z* (*M*⁺): calcd for C₂₅H₁₇NO₃: 379.1208; found: 379.1211.

12-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3h). Yield: 72% (168 mg); white solid; mp: 85–87 °C. IR (ATR): 2880, 1771, 1658, 1599, 1515, 1394, 1357, 1354, 1131, 1170, 1070, 1035, 966, 831 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.61 (1H, d, *J* = 7.8 Hz), 8.39 (1H, d, *J* = 1.8 Hz), 8.38 (1H, d, *J* = 1.8 Hz), 7.86–7.83 (1H, m), 7.63–7.57 (2H, m), 7.34–7.30 (2H, m), 5.17 (1H, t, *J* = 6 Hz), 5.02–4.97 (4H, m), 2.09–2.01 (4H, m), 1.95–1.91 (5H, m), 1.87–1.85 (2H, m), 1.61 (3H, s), 1.51 (6H, d, *J* = 3.6 Hz). ¹³C NMR (150 MHz, CDCl₃): δ 160.3, 160.2, 154.6, 139.8, 138.4, 135.5, 135.4, 134.7, 132.4, 131.3, 129.8, 128.7, 127.2, 124.2, 124.1, 123.5, 122.6, 120.6, 119.1, 114.7, 113.7, 104.9, 41.2, 39.6, 39.4, 26.7, 26.2, 25.6, 17.6, 16.8, 16.01. HRMS *m/z* (*M*⁺): calcd for C₃₁H₃₃NO₃: 467.2460; found: 467.2458.

3,12-Dimethyl-6*H*-isochromeno[4,3-*c*]quinoline-6,11(12*H*)-dione (3i). Yield: 74% (107 mg); white solid; mp: 246–248 °C. IR (ATR): 2924, 1757, 1624, 1573, 1503, 1473, 1413, 1300, 1265, 1234, 1105, 1055, 975 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 9.46 (1H, d, *J* = 8.4 Hz), 8.29 (1H, d, *J* = 7.2 Hz), 7.78 (1H, t, *J* = 7.8 Hz), 7.78 (1H, t, *J* = 7.8 Hz), 7.53 (1H, t, *J* = 6.6 Hz), 7.26–7.24



(1H, m), 7.10 (1H, d, $J = 9.0$ Hz), 3.63 (3H, s), 3.340 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): 160.1, 160.0, 154.1, 136.7, 135.3, 134.6, 133.7, 132.4, 129.6, 128.5, 127.0, 123.2, 120.3, 113.9, 113.0, 104.5, 29.6, 20.7. HRMS m/z (M^+): calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_3$: 291.0895; found: 291.0893.

3-Isopropyl-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (3j). Yield: 81% (129 mg); white solid; mp: 228–230 °C. IR (ATR): 2978, 1902, 1772, 1692, 1539, 1405, 1379, 1292, 1154, 1024, 978, 817 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.57 (1H, dd, $J = 8.4, 1.2$ Hz), 8.37 (1H, dd, $J = 7.8, 1.2$ Hz), 8.12 (1H, d, $J = 1.8$ Hz), 7.84–7.81 (1H, m), 7.57–7.55 (1H, m), 7.53 (1H, dd, $J = 8.4, 2.4$ Hz), 7.31 (1H, d, $J = 9.0$ Hz), 3.75 (3H, s), 3.07–3.01 (1H, m), 1.31 (6H, d, $J = 6.6$ Hz). ^{13}C NMR (150 MHz, CDCl_3): δ 160.5, 160.3, 154.6, 143.5, 137.3, 135.5, 134.8, 131.4, 129.8, 128.6, 127.1, 121.1, 120.4, 114.3, 113.4, 104.7, 33.6, 29.7, 24.0. HRMS m/z (M^+): calcd for $\text{C}_{20}\text{H}_{17}\text{NO}_3$: 319.1208; found: 319.1201.

2-Methoxy-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (3k). Yield: 68% (100 mg); white solid; mp: 252–254 °C. IR (ATR): 2880, 1839, 1657, 1600, 1493, 1393, 1352, 1256, 1180, 1127, 1034, 911, 814 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.48 (1H, d, $J = 8.4$ Hz), 8.34 (1H, dd, $J = 7.8, 1.2$ Hz), 8.17 (1H, d, $J = 9.0$ Hz), 7.83–7.80 (1H, m), 7.54–7.52 (1H, m), 6.87 (1H, dd, $J = 9.0, 2.4$ Hz), 6.74 (1H, d, $J = 2.4$ Hz), 3.90 (3H, s), 3.71 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 163.3, 161.0, 160.3, 154.8, 140.8, 135.5, 135.0, 129.7, 128.1, 126.7, 125.7, 120.0, 110.3, 107.3, 102.5, 98.5, 55.67, 29.72. HRMS m/z (M^+): calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_4$: 307.0845; found: 307.0843.

4-Chloro-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (3l). Yield: 84% (130 mg); white solid; mp: 260–262 °C. IR (ATR): 2881, 2025, 1656, 1529, 1445, 1400, 1312, 1235, 1140, 1032, 911 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.55 (1H, d, $J = 8.4$ Hz), 8.37 (1H, dd, $J = 7.8, 1.2$ Hz), 7.85–7.82 (1H, m), 7.61–7.59 (1H, m), 7.46 (1H, t, $J = 8.4$ Hz), 7.34–7.31 (2H, m), 3.77 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.0, 159.3, 154.4, 141.0, 135.0, 134.3, 132.5, 131.5, 129.5, 129.1, 127.4, 126.8, 120.4, 113.2, 111.4, 105.8, 30.8. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{ClNO}_3$: 311.0349; found: 311.0398.

3-Chloro-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (3m). Yield: 85% (132 mg); white solid; mp: 250–252 °C. IR (ATR): 2881, 2025, 1656, 1529, 1445, 1400, 1312, 1235, 1140, 1032, 911 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.40 (1H, dd, $J = 8.4, 1.2$ Hz), 8.36 (1H, dd, $J = 7.8, 1.2$ Hz), 8.21 (1H, d, $J = 2.4$ Hz), 7.84–7.81 (1H, m), 7.60–7.57 (1H, m), 7.55 (1H, dd, $J = 9.4, 2.4$ Hz), 7.30 (1H, d, $J = 8.4$ Hz), 3.73 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.1, 159.6, 153.3, 137.3, 135.6, 134.6, 132.5, 129.9, 129.2, 128.6, 127.2, 123.3, 120.6, 115.7, 114.5, 105.6, 29.9. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{ClNO}_3$: 311.0349; found: 311.0347.

3-Bromo-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (3n). Yield: 83% (146 mg); white solid; mp: 278–280 °C. IR (ATR): 2933, 1739, 1543, 1470, 1329, 1238, 1151, 1105, 1024, 970 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.51 (1H, d, $J = 4.2$ Hz), 8.39–8.36 (2H, m), 7.85 (1H, t, $J = 3.6$ Hz), 7.71–7.69 (1H, m), 7.60 (1H, t, $J = 4.2$ Hz), 7.25 (1H, t, $J = 4.2$ Hz), 3.74 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.2, 159.6, 153.3, 137.7, 135.7, 135.3, 134.2, 130.0, 129.2, 127.2, 126.3, 120.6, 115.9, 114.9, 105.6, 29.9. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{BrNO}_3$: 354.9844; found: 354.9846.

2-Chloro-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (3o). Yield: 79% (122 mg); white solid; mp: 268–270 °C. IR (ATR): 2878, 2120, 1702, 1652, 1510, 1434, 1348, 1321, 1212, 1121, 1037, 966, 827 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.52 (1H, dd, $J = 8.4, 1.2$ Hz), 8.38 (1H, dd, $J = 7.8, 1.2$ Hz), 8.23 (1H, d, $J = 8.4$ Hz), 7.87–7.84 (1H, m), 7.61–7.58 (1H, m), 7.39 (1H, d, $J = 1.2$ Hz), 7.30 (1H, dd, $J = 8.4, 1.2$ Hz), 3.76 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.5, 159.8, 154.2, 139.6, 138.9, 135.7, 134.4, 130.0, 129.0, 127.1, 125.4, 123.3, 120.5, 114.3, 112.1, 105.0, 29.9. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{ClNO}_3$: 311.0349; found: 311.0349.

9,12-Dimethyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4a). Yield: 75% (109 mg); white solid; mp: 271–273 °C. IR (ATR): 2921, 2855, 1800, 1724, 1640, 1372, 1238, 1191, 1029, 907, 836 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.37 (1H, s), 8.29 (1H, dd, $J = 7.8, 1.2$ Hz), 8.26 (1H, d, $J = 7.8$ Hz), 7.65–7.62 (1H, m), 7.38 (2H, d, $J = 9.0$ Hz), 7.33–7.30 (1H, m), 3.77 (3H, s), 2.53 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.7, 160.1, 154.7, 146.9, 138.8, 134.6, 132.4, 130.0, 129.9, 127.2, 124.1, 122.7, 118.1, 114.1, 113.6, 104.9, 29.7, 22.6. HRMS m/z (M^+): calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_3$: 291.0895; found: 291.0898.

9-Methoxy-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4b). Yield: 72% (110 mg); white solid; mp: 273–275 °C. IR (ATR): 2922, 2853, 1925, 1799, 1729, 1640, 1562, 1466, 1382, 1245, 1044, 975, 880 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.14 (1H, d, $J = 2.4$ Hz), 8.32 (1H, dd, $J = 8.4, 1.8$ Hz), 8.27 (1H, d, $J = 9.0$ Hz), 7.67–7.64 (1H, m), 7.40 (1H, d, $J = 7.8$ Hz), 7.33 (1H, t, $J = 7.8$ Hz), 7.09 (1H, dd, $J = 9.0$ Hz), 3.99 (3H, s), 3.78 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 165.4, 160.8, 159.8, 155.3, 138.9, 137.1, 132.6, 131.8, 124.2, 122.8, 117.7, 114.2, 113.7, 113.4, 109.0, 104.8, 55.8, 29.7. HRMS m/z (M^+): calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_4$: 307.0845; found: 307.0842.

2-Methyl-9-phenyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4c). Yield: 78% (137 mg); white solid; mp: 263–265 °C. IR (ATR): 3062, 1757, 1656, 1599, 1386, 1253, 1180, 1030, 1018, 846 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.89 (1H, d, $J = 1.8$ Hz), 8.42 (1H, d, $J = 8.4$ Hz), 8.33 (1H, dd, $J = 8.4, 1.2$ Hz), 7.82 (1H, dd, $J = 8.4, 1.2$ Hz), 7.77–7.75 (2H, m), 7.67–7.64 (1H, m), 7.50–7.47 (2H, m), 7.43–7.40 (2H, m), 7.34 (1H, t, $J = 7.2$ Hz), 3.80 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.7, 160.1, 154.9, 148.1, 139.6, 139.0, 135.1, 132.6, 130.4, 129.0, 128.7, 127.7, 127.5, 125.5, 124.1, 122.8, 119.1, 114.2, 113.6, 104.0, 29.8. HRMS m/z (M^+): calcd for $\text{C}_{23}\text{H}_{15}\text{NO}_3$: 353.1052; found: 353.1055.

9-Chloro-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4d). Yield: 84% (130 mg); white solid; mp: 284–286 °C. IR (ATR): 3106, 2881, 2017, 1658, 1539, 1459, 1352, 1226, 1165, 1073, 1037, 909, 878 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.67 (1H, d, $J = 1.8$ Hz), 8.34–8.31 (2H, m), 7.72–7.69 (1H, m), 7.55 (1H, dd, $J = 8.4, 2.4$ Hz), 7.44 (1H, d, $J = 8.4$ Hz), 7.38–7.35 (1H, m), 3.81 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.4, 159.5, 155.4, 142.8, 139.2, 136.0, 133.1, 131.3, 129.3, 127.0, 124.2, 122.9, 118.8, 114.3, 113.3, 104.0, 29.8. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{ClNO}_3$: 311.0349; found: 311.0347.

9-Bromo-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4e). Yield: 86% (152 mg); white solid; mp: 276–278 °C. IR (ATR): 2926, 1737, 1638, 1577, 1553, 1379, 1309, 1466, 1238, 1115,



1038, 910 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.84 (1H, d, $J = 2.4$ Hz), 8.33 (1H, dd, $J = 8.4, 1.2$ Hz), 8.22 (1H, d, $J = 8.4$ Hz), 7.72–7.68 (2H, m), 7.43 (1H, d, $J = 8.4$ Hz), 7.38–7.35 (1H, m), 3.80 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.3, 159.6, 155.3, 139.2, 135.9, 133.0, 132.2, 131.7, 131.2, 130.0, 124.2, 122.9, 119.2, 114.3, 113.3, 103.9, 29.8. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{BrNO}_3$: 354.9844; found: 354.9846.

9-Acetyl-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4f). Yield: 74% (118 mg); white solid; mp: 290–292 °C. IR (ATR): 3118, 2923, 1761, 1743, 1732, 1642, 1584, 1560, 1417, 1382, 1252, 1121, 1058 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 10.24 (1H, s), 8.46 (1H, d, $J = 8.4$ Hz), 8.34 (1H, d, $J = 8.4$ Hz), 8.14 (1H, dd, $J = 8.4, 1.8$ Hz), 7.71 (1H, t, $J = 7.2$ Hz), 7.46 (1H, d, $J = 2.4$ Hz), 7.39 (1H, t, $J = 7.2$ Hz), 3.83 (3H, s), 2.78 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 197.9, 160.5, 159.4, 155.9, 142.7, 139.1, 135.2, 133.0, 130.2, 127.8, 127.3, 124.2, 123.3, 123.0, 114.4, 113.3, 104.4, 29.8, 27.1. HRMS m/z (M^+): calcd for $\text{C}_{19}\text{H}_{13}\text{NO}_4$: 319.0845; found: 319.0844.

Methyl 12-methyl-6,11-dioxo-11,12-dihydro-6H-isochromeno[4,3-c]quinoline-9-carboxylate (4g). Yield: 78% (130 mg); white solid; mp: 290–292 °C. IR (ATR): 3136, 2953, 1785, 1720, 1623, 1592, 1465, 1385, 1236, 1146, 1059 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 10.25 (1H, s), 8.46 (1H, d, $J = 7.8$ Hz), 8.34 (1H, d, $J = 7.8$ Hz), 8.22 (1H, d, $J = 8.4$ Hz), 7.70 (1H, t, $J = 9.0$ Hz), 7.45 (1H, d, $J = 8.4$ Hz), 7.38 (1H, t, $J = 7.8$ Hz), 4.00 (3H, s), 3.83 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 166.1, 160.4, 159.5, 155.0, 139.1, 136.3, 134.8, 133.0, 130.0, 129.2, 128.4, 124.1, 123.4, 122.9, 114.3, 113.4, 104.5, 52.8, 29.8. HRMS m/z (M^+): calcd for $\text{C}_{19}\text{H}_{13}\text{NO}_5$: 335.0794; found: 335.0797.

12-Methyl-6,11-dioxo-11,12-dihydro-6H-isochromeno[4,3-c]quinoline-9-carbonitrile (4h). Yield: 62% (93 mg); white solid; mp: 295–297 °C. IR (ATR): 3482, 3110, 2237, 1747, 1635, 1618, 1586, 1556, 1501, 1479, 1403, 1305, 1259, 1138, 1033 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 10.03 (1H, s), 8.47 (1H, d, $J = 8.4$ Hz), 8.33 (1H, d, $J = 7.8$ Hz), 7.81 (1H, d, $J = 8.4$ Hz), 7.74 (1H, t, $J = 7.8$ Hz), 7.47 (1H, d, $J = 8.4$ Hz), 7.39 (1H, t, $J = 7.8$ Hz), 3.82 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.1, 158.7, 155.6, 139.4, 135.4, 133.5, 131.5, 131.0, 130.5, 124.2, 123.1, 119.1, 117.7, 114.5, 113.1, 110.1, 103.5, 29.9. HRMS m/z (M^+): calcd for $\text{C}_{18}\text{H}_{10}\text{N}_2\text{O}_3$: 302.0691; found: 302.0689.

7-Bromo-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4j). Yield: 76% (134 mg); white solid; mp: 276–278 °C. IR (ATR): 3124, 1733, 1650, 1629, 1524, 1463, 1282, 1239, 1100, 1020, 912 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.74 (1H, dd, $J = 8.4, 1.2$ Hz), 8.33 (1H, dd, $J = 8.4, 1.2$ Hz), 7.89 (1H, t, $J = 7.8, 0.6$ Hz), 7.71–7.68 (1H, m), 7.62 (1H, t, $J = 8.4$ Hz), 7.42 (1H, d, $J = 8.4$ Hz), 7.37 (1H, t, $J = 7.2$ Hz), 3.80 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.3, 156.7, 154.9, 139.1, 137.8, 135.7, 135.2, 133.0, 126.4, 125.0, 124.2, 122.8, 118.9, 114.2, 113.1, 104.2, 29.9. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{BrNO}_3$: 354.9844; found: 354.9846.

7-Fluoro-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4k). Yield: 74% (109 mg); white solid; mp: 276–278 °C. IR (ATR): 3391, 3186, 1980, 1747, 1640, 1564, 1474, 1366, 1258, 1114, 1026 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.74 (1H, dd, $J = 8.4, 1.2$ Hz), 8.33 (1H, dd, $J = 8.4, 1.2$ Hz), 7.89 (1H, t, $J = 7.8, 0.6$ Hz), 7.71–7.68 (1H, m), 7.62 (1H, t, $J = 8.4$ Hz), 7.42 (1H, d, $J = 8.4$ Hz), 7.37 (1H, t, $J = 7.2$ Hz), 3.80 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 163.9,

162.1, 160.3, 155.3 (d, $J = 21$ Hz), 139.1, 136.9 (d, $J = 42$ Hz), 136.8, 133.2, (d, $J = 249$ Hz), 132.9, 124.2, 122.7 (d, $J = 6$ Hz), 116.2 (d, $J = 21$ Hz), 114.2, 113.1, 109.4, 104.0, 29.8. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_{10}\text{FNO}_3$: 295.0645; found: 295.0645.

8,9-Dichloro-12-methyl-6H-isochromeno[4,3-c]quinoline-6,11(12H)-dione (4l). Yield: 84% (144 mg); white solid; mp: 277–279 °C. IR (ATR): 2848, 1853, 1677, 1490, 1433, 1330, 1285, 1192, 1145, 1069, 984, 814 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.75 (1H, s), 8.40 (1H, s), 8.28 (1H, dd, $J = 7.8, 1.2$ Hz), 7.71–7.68 (1H, m), 7.42 (1H, d, $J = 8.4$ Hz), 7.36 (1H, t, $J = 7.2$ Hz), 3.78 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.1, 158.4, 155.3, 141.0, 139.2, 133.8, 133.3, 133.2, 131.1, 129.1, 124.2, 123.0, 120.0, 114.4, 113.2, 103.5, 29.8. HRMS m/z (M^+): calcd for $\text{C}_{17}\text{H}_9\text{Cl}_2\text{NO}_3$: 344.9959; found: 344.9962.

14-Methyl-6H-benzo[6,7]isochromeno[4,3-c]quinoline-6,13(14H)-dione (5). Yield: 76% (124 mg); white solid; mp: 265–267 °C. IR (ATR): 2874, 1840, 1641, 1616, 1452, 1393, 1227, 1180, 1052, 952 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 9.99 (1H, s), 8.92 (1H, s), 8.28 (1H, dd, $J = 7.8, 1.8$ Hz), 8.01 (1H, d, $J = 8.4$ Hz), 7.96 (1H, d, $J = 8.4$ Hz), 7.64–7.59 (2H, m), 7.55 (1H, t, $J = 7.2$ Hz), 7.35 (1H, d, $J = 8.4$ Hz), 7.30 (1H, t, $J = 7.2$ Hz), 3.77 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 160.7, 160.4, 153.5, 138.7, 136.8, 132.3, 132.5, 131.9, 129.5, 129.3, 129.1, 128.5, 127.4, 127.0, 123.9, 122.6, 118.5, 114.1, 113.6, 105.0, 29.7. HRMS m/z (M^+): calcd for $\text{C}_{21}\text{H}_{13}\text{NO}_3$: 327.0895; found: 327.0897.

14-Benzyl-6H-benzo[6,7]isochromeno[4,3-c]quinoline-6,13(14H)-dione (6). Yield: 71% (143 mg); white solid; mp: 116–118 °C. IR (ATR): 2880, 1839, 1657, 1600, 1493, 1352, 1256, 1127, 1070, 963 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 10.04 (1H, s), 8.95 (1H, s), 8.29 (1H, d, $J = 7.2$ Hz), 7.98–7.94 (2H, m), 7.59 (1H, d, $J = 7.2$ Hz), 7.52 (1H, t, $J = 6.6$ Hz), 7.46 (1H, t, $J = 7.8$ Hz), 7.20–7.24 (4H, m), 7.19–7.17 (3H, m), 5.62 (2H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 161.0, 160.5, 154.0, 138.4, 136.9, 136.3, 132.4, 132.3, 132.1, 129.6, 129.3, 129.2, 129.0, 128.5, 127.5, 127.4, 127.3, 126.4, 124.1, 122.9, 118.5, 115.0, 114.0, 105.1, 46.4. HRMS m/z (M^+): calcd for $\text{C}_{27}\text{H}_{17}\text{NO}_3$: 403.1208; found: 403.1206.

6-Methyl-5H-pyrido[3',4':4,5]pyrano[3,2-c]quinoline-5,12(6H)-dione (7). Yield: 48% (66 mg); brown solid; mp: 270–272 °C. IR (ATR): 2917, 1746, 1639, 1462, 1352, 1254, 1104, 1044, 973, 843 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 10.84 (1H, s), 8.90 (1H, d, $J = 1.2$ Hz), 8.27 (1H, d, $J = 7.8$ Hz), 8.13 (1H, d, $J = 3.6$ Hz), 7.70–7.68 (1H, m), 7.42 (1H, d, $J = 9.0$ Hz), 7.35 (1H, t, $J = 7.8$ Hz), 3.80 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 159.8, 158.5, 155.6, 149.2, 147.9, 139.5, 133.5, 126.8, 124.1, 123.1, 121.7, 114.5, 113.1, 103.2, 29.9. HRMS m/z (M^+): calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_3$: 278.0691; found: 278.0694.

8-Chloro-6-methyl-5H-pyrido[3',4':4,5]pyrano[3,2-c]quinoline-5,12(6H)-dione (8). Yield: 58% (90 mg); brown solid; mp: 289–291 °C. IR (ATR): 3080, 1765, 1599, 1540, 1486, 1445, 1397, 1251, 1125, 940 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 10.81 (1H, s), 8.90 (1H, d, $J = 2.7$ Hz), 8.14 (1H, d, $J = 2.4$ Hz), 7.52 (1H, t, $J = 4.2$ Hz), 7.37–7.35 (2H, m), 3.80 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 159.2, 157.8, 155.2, 150.1, 148.9, 141.4, 132.6, 132.3, 128.5, 127.1, 126.0, 120.8, 113.5, 111.0, 104.3, 30.8. HRMS m/z (M^+): calcd for $\text{C}_{16}\text{H}_9\text{ClN}_2\text{O}_3$: 312.0302; found: 312.0289.

5-Methyl-4H-thieno[3',2':4,5]pyrano[3,2-c]quinoline-4,11(5H)-dione (9). Yield: 62% (87 mg); brown solid; mp: 266–268 °C. IR



(ATR): 2924, 2857, 1789, 1657, 1602, 1525, 1428, 1389, 1384, 1339, 1120, 1093, 988 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 8.52 (1H, d, J = 4.8 Hz), 8.32 (1H, d, J = 8.4 Hz), 7.96 (1H, d, J = 4.8 Hz), 7.66 (1H, t, J = 7.8 Hz), 7.42 (1H, d, J = 8.4 Hz), 7.35 (1H, t, J = 7.8 Hz), 3.79 (3H, m). ^{13}C NMR (150 MHz, CDCl_3): δ 159.6, 156.1, 155.8, 144.4, 138.9, 137.4, 132.5, 127.2, 124.1, 123.6, 123.0, 114.5, 113.7, 105.8, 29.7. HRMS m/z (M^+): calcd for $\text{C}_{15}\text{H}_9\text{NO}_3\text{S}$: 283.0303; found: 283.0300.

8-Isopropyl-5-methyl-4H-thieno[3',2':4,5]pyrano[3,2-c]quinoline-4,11(5H)-dione (10). Yield: 63% (102 mg); white solid; mp: 255–257 °C. IR (ATR): 2961, 1730, 1643, 1582, 1422, 1375, 1244, 1037, 960 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 8.53 (1H, d, J = 5.4 Hz), 8.15 (1H, d, J = 1.8 Hz), 7.96 (1H, d, J = 5.4 Hz), 7.55 (1H, dd, J = 8.4, 1.8 Hz), 7.35 (1H, d, J = 8.4 Hz), 3.77 (3H, m), 3.08–3.01 (1H, m), 1.32 (6H, d, J = 7.2 Hz). ^{13}C NMR (150 MHz, CDCl_3): δ 159.5, 156.3, 155.9, 144.6, 143.8, 137.3, 131.4, 127.2, 123.6, 121.2, 114.5, 113.6, 105.7, 33.7, 29.7, 24.0. HRMS m/z (M^+): calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_3\text{S}$: 325.0773; found: 325.0771.

2,13-Dimethyl-2,13-dihydroindolo[2',3':4,5]pyrano[3,2-c]quinoline-1,8-dione (11). Yield: 62% (102 mg); white solid; mp: 296–298 °C. IR (ATR): 2951, 1728, 1644, 1611, 1588, 1557, 1522, 1498, 1458, 1386, 1307, 1276, 1130, 1012 cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 8.44 (1H, d, J = 8.4 Hz), 8.31 (1H, d, J = 7.8 Hz), 7.67 (1H, t, J = 7.2 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.46 (1H, t, J = 7.2 Hz), 7.42–7.38 (2H, m), 7.36 (1H, t, J = 7.8 Hz), 4.34 (3H, s), 3.84 (3H, s). ^{13}C NMR (150 MHz, CDCl_3): δ 159.0, 157.2, 157.0, 142.5, 141.0, 139.2, 132.7, 125.3, 124.9, 124.2, 123.2, 122.9, 121.2, 114.4, 114.21, 110.6, 103.0, 102.3, 36.4, 30.0. HRMS m/z (M^+): calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3$: 330.1004; found: 330.1005.

Fluorescence sensing of compound 4a on Fe^{3+} . 0.50 mL of compound 4a (10 μM) in 1,4-dioxane was taken in a 4 mL quartz cuvette as a fluorescent probe and was titrated with 0.50 mL of various metal ions (100 μM) in water for selectivity studies. Further, the fluorescence sensitivity of compound 4a (10 μM) was studied towards different concentrations of Fe^{3+} in water. All the fluorescence (Hitachi-7000 F) measurements were carried out after 5 min of incubation at room temperature at 350 nm (excitation wavelength) with 5 nm of slit width, 250 V of photomultiplier tube voltage and a scan speed of 240 nm min^{-1} .

Conflicts of interest

There are no conflicts to declare.

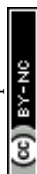
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Notes and references

- (a) X. Luo, X. Lin, L. Salendra, X. Pang, Y. Dai, B. Yang, J. Liu, J. Wang, X. Zhou and Y. Liu, *Mar. Drugs*, 2017, **15**, 204; (b)

- A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers and M. R. Prinsep, *Nat. Prod. Rep.*, 2019, **36**, 122–173; (c) T. El-Elmat, H. A. Raja, M. Figueroa, J. O. Falkinham III and N. H. Oberlies, *Phytochemistry*, 2014, **104**, 114–120.
- (a) T. Shiro, T. Fukaya and M. Tobe, *Eur. J. Med. Chem.*, 2015, **97**, 397–408; (b) I. Jarak, M. Kralj, L. Suman, G. Pavlovic, J. Dogan, I. Piantanida, M. Zinic, K. Pavelic and G. Karminski-Zamola, *J. Med. Chem.*, 2005, **48**, 2346–2360.
- (a) Y. Ikuma, H. Hochigai, H. Kimura, N. Nunami, T. Kobayashi, K. Uchiyama, Y. Furuta, M. Sakai, M. Horiguchi, Y. Masui, K. Okazaki, Y. Sato and H. Nakahira, *Bioorg. Med. Chem.*, 2012, **20**, 5864–5883; (b) P. Pahari, M. K. Kharel, M. D. Shepherd, S. G. van Lanen and J. Rohr, *Angew. Chem.*, 2012, **124**, 1242–1246; *Angew. Chem., Int. Ed.*, 2012, **51**, 1216–1220.
- (a) B. D. Patel and M. D. Ghate, *J. Med. Chem.*, 2014, **74**, 574–605; (b) E. J. Jung, B. H. Park and Y. R. Lee, *Green Chem.*, 2010, **12**, 2003–2011.
- (a) D.-S. Lim, Y.-S. Kwak, J.-H. Kim, S.-H. Ko, W.-H. Yoon and C. H. Kim, *Chemotherapy*, 2003, **49**, 146–153; (b) A. Matsumoto and P. C. Hanawalt, *Cancer Res.*, 2000, **60**, 3921–3936; (c) T. Kawano, N. Agata, S. Kharbanda, D. Avigan and D. Kufe, *Cancer Chemother. Pharmacol.*, 2007, **59**, 329–335.
- (a) V. Duraipandian and S. Ignacimuthu, *J. Ethnopharmacol.*, 2009, **123**, 494–498; (b) I. S. Chen, S. J. Wu and I. L. Tsai, *J. Nat. Prod.*, 1994, **57**, 1206–1211; (c) S. H. Huang, M. Xiong, X. P. Chen, Z. Y. Xiao, Y. F. Zhao and Z. Y. Huang, *Oncol. Rep.*, 2008, **20**, 567–572.
- Y. Kajita, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2008, **130**, 17226–17227.
- (a) Y. Li, Q. Wang, X. Yang, F. Xie and X. Li, *Org. Lett.*, 2017, **19**, 3410–3413; (b) R. Chen and S. Cui, *Org. Lett.*, 2017, **19**, 4002–4005.
- H.-Y. Dang, Z.-T. Wang and Y. Cheng, *Org. Lett.*, 2014, **16**, 5520–5523.
- M.-J. Luo, M. Hu, R.-J. Song, D.-L. He and J.-H. Li, *Chem. Commun.*, 2019, **55**, 1124–1127.
- X. Li, X. Li and N. Jiao, *J. Am. Chem. Soc.*, 2015, **137**, 9246–9249.
- R. Zeng and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 1408–1411.
- R. Manikandan and M. Jeganmohan, *Org. Lett.*, 2014, **16**, 3571.
- J. Wu, S. Xiang, J. Zeng, M. Leow and X.-W. Liu, *Org. Lett.*, 2015, **17**, 222–225.
- Y. Moon, E. Jang, S. Choi and S. Hong, *Org. Lett.*, 2018, **20**, 240–243.
- Y. Wu, P. Sun, K. Zhang, T. Yang, H. Yao and A. Lin, *J. Org. Chem.*, 2016, **81**, 2166–2173.
- D. Ding, G. Zhu and X. Jiang, *Angew. Chem.*, 2018, **130**, 9166–9170; *Angew. Chem., Int. Ed.*, 2018, **57**, 9028–9032.
- (a) G. E. Park, S. M. B. Maezono, J. H. Ha, J.-J. Shim, S. H. Kim and Y. R. Lee, *Adv. Synth. Catal.*, 2018, **360**, 4523–4532; (b) R. S. Thombal, S.-T. Kim, M.-H. Baik and Y. R. Lee, *Chem. Commun.*, 2019, **55**, 2940–2943; (c) R. P. Pandit and Y. R. Lee, *Adv. Synth. Catal.*, 2015, **357**, 2657–2664; (d)



- R. P. Pandit, S. H. Kim and Y. R. Lee, *Adv. Synth. Catal.*, 2016, **358**, 3586–3599.
- 19 (a) J. A. Brown, S. Irvine, A. R. Kennedy, W. J. Kerr, S. Andersson and G. N. Nilsson, *Chem. Commun.*, 2008, 1115–1117; (b) E. M. Simmons and J. F. Hartwig, *Angew. Chem.*, 2012, **124**, 3120–3126; *Angew. Chem., Int. Ed.*, 2012, **51**, 3066–3072.
- 20 H. Wang and F. Glorius, *Angew. Chem.*, 2012, **124**, 7430–7434; *Angew. Chem., Int. Ed.*, 2012, **51**, 7318–7322.
- 21 L. Pan, J. Dong, D. Xie, Y. Li and Q. Liu, *Adv. Synth. Catal.*, 2018, **360**, 958–964.
- 22 (a) B. N. G. Giepmans, S. R. Adams, M. H. Ellisman and R. Y. Tsien, *Science*, 2006, **312**, 217–224; (b) A. Baker, *Environ. Sci. Technol.*, 2001, **35**, 948–953.

