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ARTICLE

Ruthenium (II)-Catalyzed Synthesis of Indazolone-Fused Cinnolines via C-H Coupling with Diazo Compounds

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A robust, efficient and scalable method for the synthesis of 12*H*-indazolo[2,1-*a*]cinnolin-12-ones was developed. Significantly, a less developed cationic complex [Ru(*p*-cymene)$(MeCN)_3(SbF_6)_2$] was found effective for this transformation. In this reaction, a tandem pathway of C-H ruthenation, Ru(II)-carbene formation, migratory insertion and condensation was involved. The results of primary mechanistic study suggested that the C-H activation process might follow an electrophilic-type metalation/deprotonation mechanism.

Introduction

Cinnolines and heterocycle-fused cinnolines are highly valuable synthetic targets because of their widely presence in fluorescent chemicals, photoelectric materials and bioactive molecules.[1] For example, some representative molecules (Figure 1) exhibit good fluorescent properties,[2] anti-inflammatory,[3] antibacterial,[4] anticancer,[5] and immuno-regulatory activities.[6] As a consequence, various innovative methods have been developed for constructing the important scaffolds, mainly including Cu-catalyzed dehydrogenative cyclization[7] or tandem C-N bond formation,[8] Pd-catalyzed C-H arylation and subsequent C-N bond formation-deprotection process,[9] and Rh-catalyzed C-H activation/annulation with alkynes[10] or diazo[11] compounds. However, many of these procedures suffer from drawbacks such as tedious substrate preparation, harsh reaction conditions and longer reaction time.

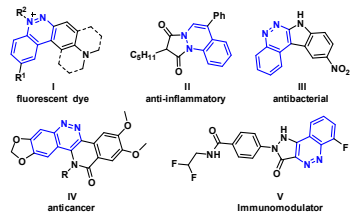

Figure 1. Representative functional molecules of heterocycle-fused cinnolines.

Especially, very limited methods are useful to furnish 1,2-fused cinnolines because the aromatic *N*-atoms cannot be functionalized directly.[10d-e, 11e] Therefore, an efficient and economical protocol to prepare novel 1,2-fused cinnolines under mild conditions is highly desirable.

In recent years, diazo compounds as carbene precursor have been incorporated into C-H functionalization initiated by Yu[12] in a new pattern involving C-H metalation, metal-carbene formation, and migratory insertion. Following this reaction model, numerous heterocycles have been constructed efficiently.[13] However, most of the reported works are limited to Rh(III),[14] Ir(III)[15] and Co(III)[16] catalytic systems. The cheap Cu(I) catalysts were also found to be effective for C-H coupling with diazo compounds. However, these reactions are limited to more acidic[17] C-H bonds. Consequently, the exploitation of alternative, especially cost-efficient catalytic systems is strongly desired.

On the other hand, rather inexpensive ruthenium complexes have been identified as promising alternatives for a broad range of site-selective C-H functionalizations.[18] Ru(II)-catalyzed carbenoid C-H insertion reactions were also broadly developed for both sp^3 and sp^2 C-H bond (Scheme 1a)[19], a concerted insertion or aromatic cyclopropanation-rearrangement reaction mechanism involved respectively. In sharp contrast, Ru(II)-catalyzed intermolecular coupling with diazo compounds via C-H activation (Scheme 1b) is far less developed and still a significant challenge. This is mainly because that the Ru(II)-carbene species of high reactivity is readily formed even in very mild condition[19b-e]. It is hard to limit its formation to the next step of C-H ruthenation. Actually, so far, only one example was reported by Li group very recently, wherein an elegant tandem cyclization was achieved between imidamides and diazo compounds by Ru(II)-catalyzed C-H activation[20]. To further explore new catalytic systems and other annulation forms of Ru-carbenes involved new reaction model as well as novel synthetic approach to 1,2-fused cinnolines, we herein present the first Ru(II)-catalyzed C-H alkylation/cyclization of 2-

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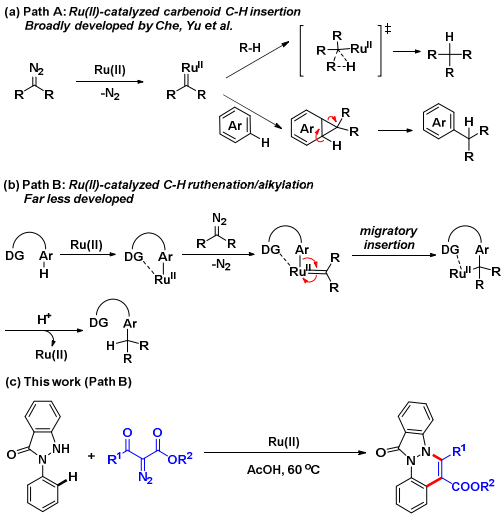
phenylindazo-lones and diazo compounds to furnish novel 12*H* indazolo[2,1-



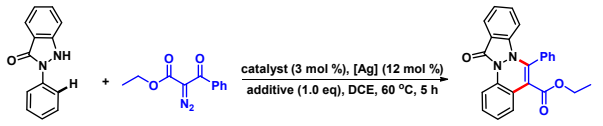
Scheme 1. C-H functionalization with Ru-carbenes.

a]cinnolin-12-ones (Scheme 1c). Notable features of this method include, a) secondary amine as directing group (amino groups have been regarded to be too strong to be involved in catalytic processes)[21], b) atom/step economy, c) broad substrate scope, d) mild reaction condition, e) good to excellent yield and f) water and air tolerance.

Results and discussion

We initiated our investigation by evaluating the the feasibility of the reaction between 2-phenylindazol-3-one (**1a**; Table 1) and ethyl 2-diazo-3-oxo-3-phenylpropanoate (**2a**). We started with Li's condition,[20] unfortunately, the reaction didn't occur (entry 1). To our delight, the desired product was isolated in low but encouraging 30% yield when using [Ru(*p*-cymene)Cl_2]$_2$/$AgSbF_6$ alone (entry 2). The bases (CsOAc or NaOAc) were found to have negative impact on the reaction (entries 3-4). Considering the acidification of the reaction medium could reduce the coordination ability of the amino directing group, hence facilitating the catalytic turnover,[21] we added HOAc into the reaction system to afford **3a** with an excellent yield of 95% (entry 5). The absence of $AgSbF_6$ or being replaced with AgOAc resulted in sharply reduced yield, whereas the addition of $AgNTf_2$ gave **3a** in 92% yield, indicating the cationic Ru(II) complex generated in situ was the active catalyst of this reaction (entries 6-8). [Ru(*p*-cymene)$(MeCN)_3(SbF_6)_2$] was hence synthesized[22] and examined to be also effective (entry 9). Furthermore, the impact of different solvents such as MeOH and THF was tested (76% and 72% respectively, entries 10-11). Yet it turned out that DCE was the most suitable. It is worth mentioning that the catalytic system was insensitive to H_2O (entry 12), showing its high reaction stability. Finally, the reaction was performed on a gram-scale (5 mmol) and **3a** was isolated in a maintained yield of 91% (entry 13).

Table 1. Screening of reaction parameters.[a]



entry	catalyst	[Ag]	base	additive	yield(%)[b]
1	Cat 1[c]	$AgSbF_6$	CsOAc[d]	HOAc	NR
2	Cat 1	$AgSbF_6$	-	-	30
3	Cat 1	$AgSbF_6$	CsOAc	-	NR
4	Cat 1	$AgSbF_6$	NaOAc	-	NR
5	Cat 1	$AgSbF_6$	-	HOAc	95
6	Cat 1	-	-	HOAc	NR
7	Cat 1	AgOAc	-	HOAc	<5
8	Cat 1	$AgNTf_2$	-	HOAc	92
9	Cat 2[e]	-	-	HOAc	95
10[f]	Cat 2	-	-	HOAc	76
11[g]	Cat 2	-	-	HOAc	72
12[h]	Cat 2	-	-	HOAc	94
13[i]	Cat 2	-	-	HOAc	91

[a] Reactions were performed underan air atmosphere: 0.2 mmol of **1a**, 0.24 mmol of **2a**, 3 mol % of Ru catalyst, 0.024 mmol of [Ag], 0.2 mmol of base, 0.2 mmol of additive, 2 mL DCE, 60 °C, 5 h. [b] Yield of isolated product. [c] Cat 1 = [Ru(*p*-cymene)Cl_2]$_2$. [d] 50 mol % CsOAc. [e] Cat 2 = [Ru(*p*-cymene)$(MeCN)_3(SbF_6)_2$]. [f] In MeOH. [g] In THF. [h] 4 equivalents of H_2O was added. [i] Gram-scale.

We next examined the scope and limitation of this reaction upon the optimized conditions. As depicted in Scheme 2, a variety of 2-phenylindazol-3-one derivatives were synthesized and tested with **2a**. To our delight, the aryls bearing halogen (**3b**, **3d**-**g**) as well as electron-donating (**3c**, **3j**-**l**) groups were well tolerated, providing the desired products in high efficiency (85-95% yields). A relative low (36%) or moderate yield (61%) were obtained when electron-withdrawing CF_3 (**3h**) or ester group (**3i**) were introduced. What's more, the reaction was demonstrated to be insensitive to the *meta*- (**3k**) or *para*- (**3d**-**g**, **3j**) substituents on phenyl ring B (90-95% yields). However, the *ortho*- substituted product wasn't generated as expected probably because of the steric hindrance. Nevertheless, product **3t** was obtained in 81% yield when ethyl 2-diazo-3-oxobutanoate was used instead of **2a** (Scheme 3). In addition, the bromo- (**3f**), iodo- (**3g**) and ester- (**3i**) substituted products offered the opportunity for further transformation.[16c] Besides, disubstituted 2-phenylindazol-3-ones were also investigated to furnish corresponding products (**3k**-**l**) in excellent yields (91% and 93% respectively). Interestingly, the ^{1}H NMR spectroscopic analysis suggested that the reaction took place exclusively at the more sterically congested *ortho* site to afford **3l**, indicating there might be a secondary directing effect from the interaction between oxygen and Ru catalyst. The structure of the obtained products was confirmed by X-ray crystallographic analysis of **3f**.

Furthermore, we turned our attention to test different classes of diazo compounds. As illustrated in Scheme 3, the phenyl with different electronic properties were well

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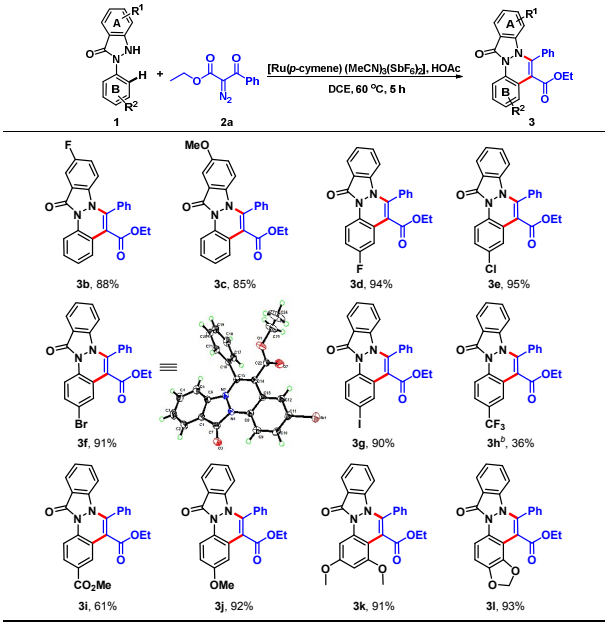
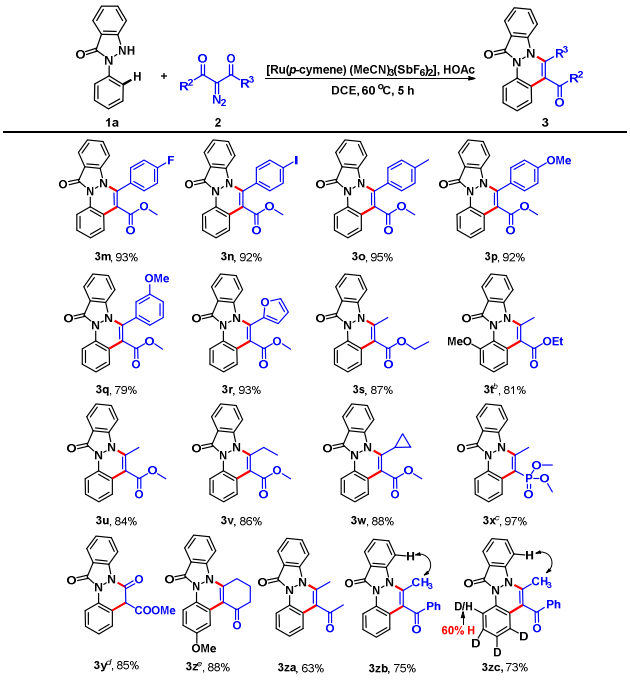
tolerated, providing the corresponding products **3m**-**p** (92-95%). Yet a slightly reduced yield (79%) was observed when the phenyl in the diazo possess a *meta*-methoxyl group (**3q**), possibly due to



Scheme 2. Substrate scope of 2-phenylindazol-3-ones. [a] Reaction conditions: 0.2 mmol of **1**, 0.24 mmol of **2a**, 3 mol % of [Ru(*p*-cymene)$(MeCN)_3(SbF_6)_2$], 0.2 mmol of HOAc, 2 mL of DCE, 60 °C. Isolated yields. [b] The reaction was performed under 80°C.



Scheme 3. Substrate scope of diazo components. [a] Reaction conditions: 0.2 mmol of **1a**, 0.24 mmol of **2**, 3 mol % of [Ru(*p*-cymene)$(MeCN)_3(SbF_6)_2$], 0.2 mmol of HOAc, 2 mL of DCE, 60 °C. Isolated yields. [b] 2-(2-Methoxyphenyl)-1,2-dihydro-3*H*-indazol-3-one was used instead of **1a**. [c] Dimethyl (1-diazo-2-oxopropyl)-phosphonate was used. [d] Dimethyl 2-diazomalonate was used. [e] 2-(4-Methoxyphenyl)-1,2-dihydro-3*H*-indazol-3-one was used.

the steric effects. Moreover, the furan-contained diazo was also compatible with our standard conditions to give the product in a high yield (**3r**, 93%). Pleasingly, the alkyl (methyl-, ethyl-, cyclopropyl-) α-diazoketoesters proceeded smoothly to give **3s**-**v** with satisfactory yields (84-88%). Of note, α-diazo of phosphonate and diester were also compatible and **3w**-**x** were produced in high efficiency (97% and 85% respectively). Moreover, diazo compounds derived from 1,3-diketone of cyclic and chain-like (symmetric or unsymmetric) were tested. The reaction underwent smoothly to deliver the corresponding products (3z-3zb) in good to high yields (63-88%) with excellent regioselectivity (3zb). When [D5]-1a was employed, the desired product 3zc was obtained in 73% yield. Meanwhile, 60% deuterium loss was observed, indicating that the C-H ruthenation process was reversible.[20] The structure of 3zb and 3zc was confirmed by NOESY analysis.

To demonstrate the synthetic utility of this method, we sought to introduce some typical substituents based on the C-Br bond of **3f**. As depicted in Scheme 4, the cyano- substituted **4** was obtained through Pd(0)-catalyzed cyanation in 95% yield. Besides, the hydrophobic phenyl and the hydrophilic morpholinyl group was introduced by Suzuki and Buchwald reaction respectively to provide **5** (91%) and **6** (60%).

To gain more mechanistic insight into this reaction, kinetic isotope effect experiment and competition experiment were carried out. As illustrated in Scheme 5, the kinetic isotope studies via intermolecular competition or parallel experiments revealed secondary KIE values (1.3 or 1.35), implying the C-H bond cleavage may not be involved in the rate-limiting step.[23] Moreover, the intermolecular competition experiment between equimolar amount of **1e** and **1j** delivered **3e** and **3j** in a ratio of 1:1.8, showing that electron-rich substrate is slightly more preferable in contrast to Li's reaction systems.[20] Overall, these studies suggested that C-H activation process might occur via an electrophilic-type metalation/deprotonation mechanism.

On the basis of the observed experimental results, a plausible mechanistic pathway of this reaction is proposed (Scheme 6). Initially, a five-membered cyclometalated Ru(II) complex **A** is generated by cationic Ru(II) complex-catalyzed electrophilic C-H metalation. Next, diazo compound **2a** coordinates to interme-
diate **A** and a ruthenium carbene species **B** is formed after the release of N_2. The subsequent migration insertion of **B** provides

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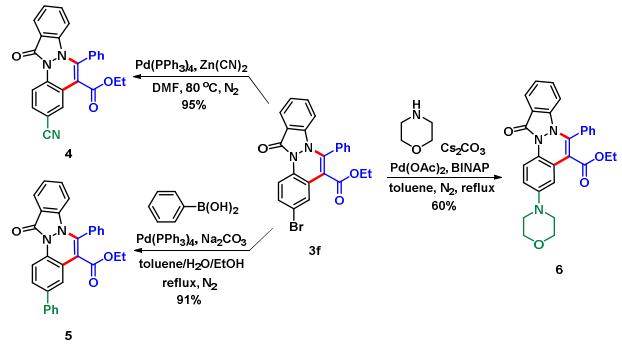
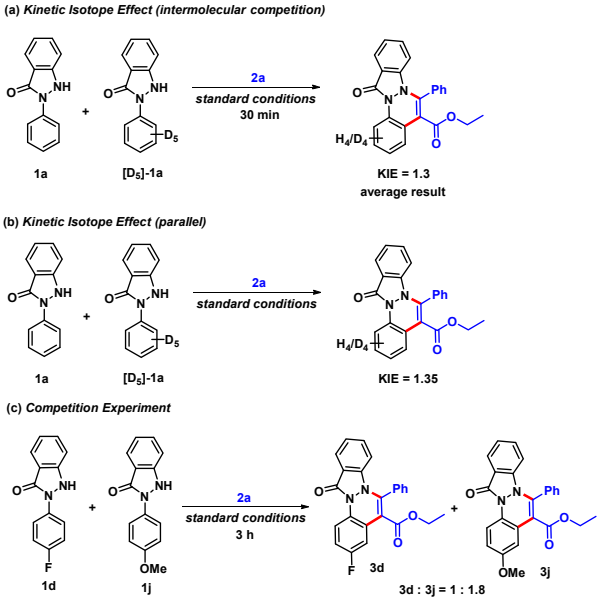
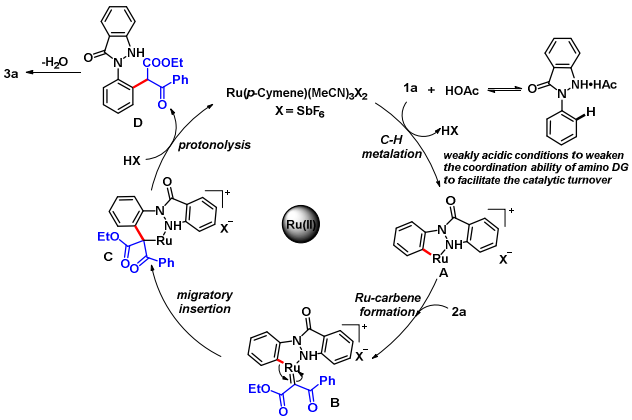


Scheme 4. Transformation of cinnoline product **3f**.



Scheme 5. Primary mechanistic study.



Scheme 6. Proposed mechanism.

a six-membered ruthenacyclic intermediate **C**, which could undergo protonolysis to afford intermediate **D** and regenerate Ru(II) catalyst simultaneously. Finally, the intramolecular dehydration of **D** gives the title product **3a**. It is notable that the adding of equivalent AcOH can promote the reaction significantly. The function may come from keeping a weak acidic condition to weaken the coordination ability of secondary amine to facilitate the catalytic turnover.[14j,21] Besides, some other beneficial effects such as accelerating the protonolysis[14j] and activating the carbonyl group of intermediate **D** to promote the intramolecular cyclization may also involved.[14m,16a]

Conclusions

In summary, we have developed a robust, efficient and scalable method for the synthesis of 12*H*-indazolo[2,1-*a*]cinnolin-12-ones via cationic ruthenium (II)-catalyzed C-H activation/ cyclization between readily available 2-phenylindazol-3-ones and diazo compounds. The results of primary mechanistic study suggested that the C-H activation process might follow an electrophilic-type metalation/deprotonation mechanism. This method features secondary amine as directing group, atom/step economy, broad substrate scope, mild reaction condition, good to excellent yield and water and air tolerance. The biological study of these novel 12*H*-indazolo[2,1-*a*]cinnolin-12-ones is ongoing in our laboratory and will be published in due course.

Experimental section

General Information.

All commercially available organic compounds were purchased from Sigma-Aldrich and adamas-beta in China. Unless otherwise noted, all commercial reagents and solvents were used without additional purification. NMR spectra were recorded on Bruker AM-400, Bruker AM-500 and Bruker AM-600 instruments. Chemical shifts are reported in δ (ppm) referenced to TMS as an internal standard for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR. High-resolution mass spectra were obtained on a Finnigan MAT-95 mass spectrometer. The substrates **1** were prepared according to literature methods.[24] The diazo compounds were prepared according to literature methods.[25]

General Procedure for Synthesis and the Characterization of 3a-3zb.

To the solution of 1 (0.2 mmol, 1 equiv) and 2 (0.24 mmol, 1.2 equiv) in 2.0 mL DCE was added 3 mol % (5 mg, 0.03 equiv) [Ru(*p*-cymene) $(MeCN)_3(SbF_6)_2$] and 0.2 mmol (12 mg, 1 equiv) HOAc in a 10 mL test tube. The reaction was stirred at 60 °C for 5 hours. The solvent was removed and the residue was purified by silica gel chromatography using PE/EA to afford the desired compounds.

*Ethyl 12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3a**).* Following the general procedure, **3a** was obtained as a yellow solid (72.6 mg, 95% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.05 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.35 (td, *J* = 7.2, 1.2 Hz, 1H), 7.21 (td, *J* = 7.2, 1.2 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.16 – 7.12 (m, 1H), 5.61 (d, *J* = 8.4 Hz, 1H), 3.94 (q, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 157.3, 138.9, 136.3, 133.9, 131.6, 131.2, 130.5, 129.9, 129.1, 128.4, 125.9, 123.8, 123.5,

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122.4, 120.0, 116.6, 116.1, 112.9, 110.4, 61.0, 13.5. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{19}N_2O_3]^+$ 383.1390, found 383.1382.

*Ethyl 10-fluoro-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3b**).* Following the general procedure, **3b** was obtained as a yellow solid (70.4 mg, 88% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.53 (m, 3H), 7.42 (m, 2H), 7.39 – 7.33 (m, 1H), 7.23 (td, *J* = 7.8, 1.2 Hz, 1H), 6.90 (td, *J* = 9.0, 3.0 Hz, 1H), 5.56 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.94 (q, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3, 158.2 (d, *J* = 242.9 Hz), 156.5, 138.8, 133.6, 132.8, 131.4, 130.7, 129.9, 129.3, 128.4, 126.2, 123.9, 120.2, 120.0 (d, *J* = 2.3 Hz), 117.4 (d, *J* = 9.0 Hz), 116.3, 114.7 (d, *J* = 7.8 Hz), 110.4, 108.3 (d, *J* = 23.9 Hz), 61.0, 13.5. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{18}FN_2O_3]^+$ 401.1296, found 401.1294.

*Ethyl 10-methoxy-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3c**).* Following the general procedure, **3c** was obtained as a yellow solid (70.1 mg, 85% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.54 (m, 3H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 9.6, 3.0 Hz, 1H), 5.50 (d, *J* = 9.6 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 157.1, 155.7, 139.4, 133.6, 131.8, 131.3, 130.5, 129.9, 129.2, 128.2, 125.9, 123.8, 122.3, 120.3, 117.3, 116.3, 114.4, 109.3, 102.8, 60.9, 55.8, 13.5. HRMS (ESI) calcd for $[M+H]^+$ $[C_{25}H_{21}N_2O_4]^+$ 413.1496, found 413.1501.

*Ethyl 3-fluoro-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3d**).* Following the general procedure, **3d** was obtained as a yellow solid (75.3 mg, 94% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.03 (dd, *J* = 9.0, 5.4 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 9.6, 3.0 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.01 (ddd, *J* = 9.0, 7.8, 2.4 Hz, 1H), 5.58 (d, *J* = 9.0 Hz, 1H), 3.92 (q, *J* = 7.2 Hz, 2H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 160.1 (d, *J* = 243.6 Hz), 157.1, 140.7, 136.1, 131.4, 131.3, 130.7, 130.0 (d, *J* = 2.1 Hz), 129.7, 129.2, 123.5, 122.9, 122.4 (d, *J* = 9.2 Hz), 117.7 (d, *J* = 8.1 Hz), 116.7, 114.4 (d, *J* = 22.5 Hz), 113.1, 111.1 (d, *J* = 26.1 Hz), 109.0, 61.1, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{18}FN_2O_3]^+$ 401.1296, found 401.1297.

*Ethyl 3-chloro-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3e**).* Following the general procedure, **3e** was obtained as a yellow solid (79.2 mg, 95% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.54 (m, 3H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.27 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.18 (m, 1H), 7.17 – 7.13 (m, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 157.2, 140.4, 136.3, 132.3, 131.4, 131.4, 131.2, 130.7, 129.7, 129.2, 127.9, 123.7, 123.5, 122.8, 121.9, 117.2, 116.5, 113.0, 108.9, 61.1, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{18}ClN_2O_3]^+$ 417.1000, found 417.0095.

*Ethyl 3-bromo-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3f**).* Following the general procedure, **3f** was obtained as a yellow solid (83.9 mg, 91% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.94 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.43 (m, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.18 – 7.14 (m, 1H), 5.59 (d, *J* = 8.4 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 157.3, 140.4, 136.3, 132.9, 131.5, 131.4, 130.9, 130.7, 129.8, 129.2, 126.6, 123.6, 122.8, 122.1, 119.0, 117.5, 116.6, 113.1, 108.9, 61.1, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{18}BrN_2O_3]^+$ 461.0495, found 461.0493.

*Ethyl 3-iodo-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3g**).* Following the general procedure, **3g** was obtained as a yellow solid (91.5 mg, 90% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.18 (m, 1H), 7.17 – 7.13 (m, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 157.3, 140.2, 136.9, 136.3, 133.5, 132.3, 131.5, 131.4, 130.7, 129.8, 129.2, 123.6, 122.8, 122.2, 117.6, 116.5, 113.0, 108.7, 89.9, 61.1, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{18}IN_2O_3]^+$ 509.0357, found 509.0360.

*Ethyl 12-oxo-6-phenyl-3-(trifluoromethyl)-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3h**).* Following the general procedure, **3h** was obtained as a yellow solid (32.0 mg, 36% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.84 (s, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54 – 7.58 (m, 3H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.25 – 7.15 (m, 2H), 5.59 (d, *J* = 8.5 Hz, 1H), 3.95 (q, *J* = 7.0 Hz, 2H), 0.83 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 157.6, 140.9, 136.5, 136.4, 131.9, 131.3, 130.8, 129.7, 129.3, 127.7 (d, *J* = 32.8 Hz), 125.2 (d, *J* = 3.5 Hz), 123.7, 123.6 (q, *J* = 270.3 Hz), 123.0, 121.0 (d, *J* = 3.8 Hz), 120.8, 116.3, 116.0, 113.1, 108.8, 61.2, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{25}H_{18}F_3N_2O_3]^+$ 451.1264, found 451.1271.

*5-Ethyl 3-methyl 12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-3,5-dicarboxylate (**3i**).* Following the general procedure, **3i** was obtained as a yellow solid (53.7 mg, 61% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 8.8 Hz, 1H), 8.17 (s, 1H), 8.01 (m, 2H), 7.66 – 7.59 (m, 1H), 7.55 (t, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.23 – 7.14 (m, 2H), 5.59 (d, *J* = 7.6 Hz, 1H), 3.98 (q, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.0, 157.6, 139.7, 137.3, 136.6, 131.8, 131.3, 130.7, 130.0, 129.8, 129.2, 127.2, 125.1, 123.7, 122.7, 120.2, 116.2, 115.6, 113.0, 109.6, 61.2, 52.2, 13.5. HRMS (ESI) calcd for $[M+H]^+$ $[C_{26}H_{21}N_2O_5]^+$ 441.1445, found 441.1451.

*Ethyl 3-methoxy-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3j**).* Following the general procedure, **3j** was obtained as a yellow solid (75.9 mg, 92% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.88 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.59 (d, *J* = 9.0 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 157.3, 156.7, 139.6, 136.0, 131.7, 130.9, 130.5, 129.9, 129.1, 127.5, 123.4, 122.6, 121.5, 117.5, 116.9, 113.0, 112.9, 109.9, 109.6, 61.0, 55.5, 13.5. HRMS (ESI) calcd for $[M+H]^+$ $[C_{25}H_{21}N_2O_4]^+$ 413.1496, found 413.1499.

*Ethyl 2,4-dimethoxy-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3k**).* Following the general procedure, **3k** was obtained as a yellow solid (80.5 mg, 91% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.4 Hz, 1H), 7.94 (m, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.15 – 7.08 (m, 2H), 6.35

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(d, *J* = 2.4 Hz, 1H), 5.72 – 5.63 (m, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 160.9, 157.5, 155.0, 136.8, 136.4, 134.7, 131.3, 131.1, 130.4, 130.3, 128.7, 123.4, 121.9, 116.2, 112.8, 109.9, 103.2, 97.1, 93.8, 60.9, 56.1, 55.8, 13.9. HRMS (ESI) calcd for $[M+H]^+$ $[C_{26}H_{23}N_2O_5]^+$ 443.1601, found 443.1598.

*Ethyl 13-oxo-7-phenyl-13H-[1,3]dioxolo[4,5-f]indazolo[2,1-a]cinnoline-6-carboxylate (**3l**)*. Following the general procedure, **3l** was obtained as a yellow solid (79.2 mg, 93% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.45 (m, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.14 – 7.09 (m, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 5.99 (s, 2H), 5.61 (d, *J* = 8.4 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3, 157.0, 145.5, 141.6, 137.9, 136.6, 131.2, 130.7, 130.5, 130.3, 129.0, 128.1, 123.5, 122.5, 116.7, 112.8, 110.0, 107.1, 105.2, 101.7, 61.36, 13.68. HRMS (ESI) calcd for $[M+H]^+$ $[C_{25}H_{19}N_2O_5]^+$ 427.1288, found 427.1287.

*Methyl 6-(4-fluorophenyl)-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3m**)*. Following the general procedure, **3m** was obtained as a yellow solid (71.8 mg, 93% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04 (d, *J* = 7.8 Hz, 1H), 8.03 (m, 1H), 7.49 – 7.40 (m, 3H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.28 (m, 1H), 7.25 – 7.18 (m, 4H), 5.91 – 5.51 (m, 1H), 3.53 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 163.8 (d, *J* = 250.7 Hz), 157.3, 138.2, 136.2, 133.9, 132.0 (d, *J* = 8.4 Hz), 131.4, 128.6, 127.4 (d, *J* = 3.5 Hz), 125.9, 123.8 (d, *J* = 35.1 Hz), 122.7, 119.8, 116.7, 116.6, 116.4, 116.1, 112.7, 110.8, 51.9. HRMS (ESI) calcd for $[M+H]^+$ $[C_{23}H_{16}FN_2O_3]^+$ 387.1139, found 387.1146.

*Methyl 6-(4-iodophenyl)-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3n**)*. Following the general procedure, **3n** was obtained as a yellow solid (90.9 mg, 92% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.01 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.75 (d, *J* = 7.8 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 157.3, 138.4, 138.2, 136.3, 134.0, 131.5, 131.4, 130.9, 128.7, 125.9, 124.0, 123.8, 122.7, 119.8, 116.7, 116.1, 112.8, 110.7, 96.9, 52.0. HRMS (ESI) calcd for $[M+H]^+$ $[C_{23}H_{16}IN_2O_3]^+$ 495.0200, found 495.0208.

*Methyl 12-oxo-6-(p-tolyl)-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3o**)*. Following the general procedure, **3o** was obtained as a yellow solid (72.6 mg, 95% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.05 (d, *J* = 7.8 Hz, 1H), 8.05 – 7.92 (m, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.22 – 7.12 (m, 3H), 5.76 – 5.61 (m, 1H), 3.49 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 157.3, 140.8, 139.2, 136.3, 133.9, 131.2, 129.8, 129.6, 128.4, 128.3, 125.8, 123.8, 123.5, 122.4, 120.0, 116.5, 116.1, 113.1, 110.3, 51.8, 21.6. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{19}N_2O_3]^+$ 383.1390, found 383.1393.

*Methyl 6-(4-methoxyphenyl)-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3p**)*. Following the general procedure, **3p** was obtained as a yellow solid (73.4 mg, 92% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.04 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.02 – 7.94 (m, 1H), 7.41 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.23 – 7.15 (m, 3H), 7.07 – 7.01 (m, 2H), 5.91 – 5.60 (m, 1H), 3.92 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 161.1, 157.4, 138.9, 136.3, 133.9, 131.2, 131.2, 128.3, 125.8, 123.7, 123.5, 123.3, 122.4, 120.1, 116.5, 116.1, 114.5, 113.1, 110.5, 55.4, 51.9. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{19}N_2O_4]^+$ 399.1339, found 399.1337.

*Methyl 6-(3-methoxyphenyl)-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3q**)*. Following the general procedure, **3q** was obtained as a yellow solid (62.8 mg, 79% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.05 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.06 – 7.95 (m, 1H), 7.47 – 7.41 (m, 2H), 7.37 – 7.33 (m, 1H), 7.24 – 7.16 (m, 3H), 7.12 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.98 – 6.91 (m, 1H), 5.76 – 5.68 (m, 1H), 3.81 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 160.1, 157.3, 138.8, 136.3, 133.9, 132.5, 131.3, 130.3, 128.5, 125.9, 123.8, 123.5, 122.5, 122.0, 119.9, 116.6, 116.5, 116.2, 114.7, 113.1, 110.2, 55.5, 51.9. HRMS (ESI) calcd for $[M+H]^+$ $[C_{24}H_{19}N_2O_4]^+$ 399.1339, found 399.1341.

*Methyl 6-(furan-2-yl)-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3r**)*. Following the general procedure, **3r** was obtained as a yellow solid (66.5 mg, 93% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.19 (td, *J* = 7.8, 1.2 Hz, 1H), 6.74 (d, *J* = 3.0 Hz, 1H), 6.63 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 3.63 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 157.6, 144.3, 144.2, 142.7, 136.3, 134.7, 132.0, 131.8, 129.3, 129.1, 125.9, 124.5, 123.6, 122.7, 119.4, 116.4, 116.1, 114.5, 113.4, 112.0, 111.5, 52.3. HRMS (ESI) calcd for $[M+H]^+$ $[C_{21}H_{15}N_2O_4]^+$ 359.1026, found 359.1031.

*Ethyl 6-methyl-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3s**)*. Following the general procedure, **3s** was obtained as a yellow solid (55.5 mg, 87% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.63 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.26 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.21 – 7.17 (m, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.68 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 157.0, 138.1, 136.9, 133.3, 131.9, 127.8, 125.8, 124.1, 123.6, 122.9, 120.3, 117.3, 116.2, 113.7, 109.6, 61.5, 18.4, 14.3. HRMS (ESI) calcd for $[M+H]^+$ $[C_{19}H_{17}N_2O_3]^+$ 321.1234, found 321.1228.

*Ethyl 1-methoxy-6-methyl-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3t**)*. Following the general procedure, **3t** was obtained as a yellow solid (56.7 mg, 81% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.60 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.24 (dd, *J* = 16.2, 8.4 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.87 (dd, *J* = 7.8, 0.6 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 2.50 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 157.7, 151.2, 144.1, 141.3, 131.2, 128.1, 126.9, 124.7, 123.7, 120.5, 119.5, 116.0, 115.5, 112.5, 110.3, 61.3, 56.3, 17.6, 14.2. HRMS (ESI) calcd for $[M+H]^+$ $[C_{20}H_{19}N_2O_4]^+$ 351.1339, found 351.1346.

*Methyl 6-methyl-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3u**)*. Following the general procedure, **3u** was obtained as a yellow solid (51.5 mg, 84% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.62 (m, 2H), 7.36 – 7.32 (m, 1H), 7.32 – 7.28 (m, 1H), 7.23 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.20 – 7.16 (m, 1H), 3.94 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 157.0, 138.6, 136.9, 133.3, 131.9, 127.8, 125.8, 124.1, 123.7, 122.9, 120.2, 117.4, 116.2, 113.7, 109.3, 52.3, 18.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{18}H_{15}N_2O_3]^+$ 307.1077, found 307.1073.

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*Methyl 6-ethyl-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3v**)*. Following the general procedure, **3v** was obtained as a yellow solid (54.9 mg, 86% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.22 – 7.16 (m, 2H), 3.94 (s, 3H), 2.99 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 157.1, 143.2, 136.3, 133.3, 132.3, 127.8, 125.9, 124.2, 123.6, 122.9, 120.4, 117.3, 116.3, 113.1, 108.7, 52.3, 23.4, 13.3. HRMS (ESI) calcd for $[M+H]^+$ $[C_{19}H_{17}N_2O_3]^+$ 321.1234, found 321.1231.

*Methyl 6-cyclopropyl-12-oxo-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3w**)*. Following the general procedure, **3w** was obtained as a yellow solid (58.2 mg, 88% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 2.24 – 2.10 (m, 1H), 1.20 – 1.11 (m, 2H), 0.77 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 157.1, 141.3, 136.5, 133.5, 131.4, 128.2, 125.8, 123.7, 123.2, 122.5, 119.9, 116.6, 116.1, 114.2, 111.6, 52.3, 13.7, 10.2. HRMS (ESI) calcd for $[M+H]^+$ $[C_{20}H_{17}N_2O_3]^+$ 333.1234, found 333.1233.

*Dimethyl (6-methyl-12-oxo-12H-indazolo[2,1-a]cinnolin-5-yl)phosphonate (**3x**)*. Following the general procedure, **3x** was obtained as a yellow solid (69.3 mg, 97% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.65 (td, *J* = 7.8, 1.2 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.29 (td, *J* = 7.8, 1.2 Hz, 1H), 7.20 (td, *J* = 7.8, 1.2 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.11 (d, *J* = 2.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 149.9 (d, *J* = 24.7 Hz), 137.5, 133.4 (d, *J* = 11.1 Hz), 132.1, 127.4, 125.9, 125.4, 124.1, 123.7, 121.3 (d, *J* = 8.8 Hz), 118.5, 115.8, 115.1, 99.2 (d, *J* = 200.5 Hz), 52.3 (d, *J* = 16.8 Hz), 18.6. HRMS (ESI) calcd for $[M+H]^+$ $[C_{18}H_{18}N_2O_4P]^+$ 357.0999, found 357.1002.

*Methyl 6,12-dioxo-5,6-dihydro-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**3y**)*. Following the general procedure, **3y** was obtained as a yellow solid (52.6 mg, 85% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.83 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.71 (m, 1H), 7.52 – 7.45 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.29 (td, *J* = 7.8, 0.6 Hz, 1H), 4.88 (s, 1H), 3.71 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 158.5, 157.8, 138.1, 134.6, 132.1, 129.7, 128.4, 126.3, 126.1, 123.9, 119.6, 119.0, 117.7, 116.8, 115.7, 53.6, 53.0. HRMS (ESI) calcd for $[M+H]^+$ $[C_{17}H_{13}N_2O_4]^+$ 309.0870, found 309.0874.

*3-Methoxy-7,8-dihydro-14H-benzo[c]indazolo[1,2-a]cinnoline-5,14(6H)-dione (**3z**)*. Following the general procedure, **3z** was obtained as a yellow solid (58.4 mg, 88% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (d, *J* = 9.0 Hz, 1H), 8.38 (d, *J* = 3.0 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.84 (s, 3H), 3.23 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 2.30 – 2.21 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.4, 157.2, 156.2, 151.1, 136.2, 131.8, 126.6, 124.2, 124.1, 121.0, 119.0, 117.0, 114.4, 113.2, 111.1, 109.1, 55.5, 37.9, 28.3, 21.0. HRMS (ESI) calcd for $[M+H]^+$ $[C_{20}H_{17}N_2O_3]^+$ 333.1234, found 333.1238.

*5-Acetyl-6-methyl-12H-indazolo[2,1-a]cinnolin-12-one (**3za**)*. Following the general procedure, **3za** was obtained as a yellow solid (36.7 mg, 63% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.31 – 7.35 (m, 2H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.0 Hz, 1H), 2.55 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 157.1, 137.3, 135.5, 133.7, 132.0, 128.0, 125.9, 124.2, 123.2, 122.9, 120.5, 117.9, 117.3, 116.5, 113.7, 31.8, 17.8. HRMS (ESI) calcd for $[M+H]^+$ $[C_{18}H_{15}N_2O_2]^+$ 291.1128, found 291.1126.

*5-benzoyl-6-methyl-12H-indazolo[2,1-a]cinnolin-12-one (**3zb**)*. Following the general procedure, **3zb** was obtained as a yellow solid (52.6 mg, 75% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.68 – 7.58 (m, 3H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.35 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H), 7.26 – 7.30 (m, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 157.2, 137.2, 136.9, 135.3, 134.2, 133.1, 132.0, 129.8, 129.0, 127.9, 125.8, 124.2, 123.9, 122.7, 121.5, 116.9, 116.5, 114.8, 113.4, 18.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{23}H_{17}N_2O_2]^+$ 353.1285, found 353.1291.

*5-benzoyl-6-methyl-12H-indazolo[2,1-a]cinnolin-12-one-2,3,4-d_3 (**3zc**)*. Following the general procedure, **3zc** was obtained as a yellow solid (51.8 mg, 73% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 0.6H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 7.67 – 7.57 (m, 3H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 157.2, 137.2, 136.8, 135.3, 134.2, 133.0, 131.9, 129.8, 129.0, 124.1, 122.7, 121.4, 116.9, 116.3, 114.8, 113.4, 18.4.HRMS (ESI) calcd for $[M+H]^+$ $[C_{23}H_{14}D_3N_2O_2]^+$ 356.1473, found 356.1461. HRMS (ESI) calcd for $[M+H]^+$ $[C_{23}H_{13}D_4N_2O_2]^+$ 357.1536, found 357.1522.

Procedure for the Synthesis and the Characterization of 4.

Compound **3f** (46.1 mg, 0.1 mmol, 1 equiv) was combined with $Zn(CN)_2$ (7.1 mg, 0.06 mmol, 0.6 equiv) and $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol, 0.04 equiv) and was dissolved in 1.0 mL DMF. The reaction was stirred at 100 °C under N_2 and monitored by TLC. After completion, water was added and the reaction mixture was extracted with EtOAc. The organic phase was washed by brine, then dried by anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel using petroleum ether/EtOAc as the eluent to afford compound **4**.

*Ethyl 3-cyano-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**4**)*. Compound **4** was obtained as a yellow solid (38.6 mg, 95% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.4 Hz, 1H), 8.00 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.59 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.25 – 7.16 (m, 2H), 5.59 (d, *J* = 8.4 Hz, 1H), 3.94 (q, *J* = 7.2 Hz, 2H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 157.7, 141.4, 137.2, 136.7, 132.2, 132.1, 131.1, 130.9, 129.6, 129.3, 127.4, 123.9, 123.2, 121.3, 118.4, 116.2, 116.1, 113.1, 109.3, 108.1, 61.3, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{25}H_{18}N_3O_3]^+$ 408.1343, found 408.1350.

Procedure for the Synthesis and the Characterization of 5.

Compound **3f** (46.1 mg, 0.1 mmol, 1 equiv) was combined with phenylboronic acid (15.9 mg, 0.13 mmol, 1.3 equiv), Na_2CO_3 (77.4 mg, 0.73 mmol, 7.3 equiv), $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol, 0.04

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equiv). The mixture was dissolved in 2.2 mL solvent (toluene/H_2O/EtOH=5/5/1). The reaction was refluxed under N_2 and monitored overnight. After completion, the mixture was cooled to room temperature. Water was added and the reaction mixture was extracted with EtOAc. The organic phase was washed by brine, then dried by anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel using petroleum ether/EtOAc as the eluent to afford compound **5**.

*Ethyl 12-oxo-3,6-diphenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**5**)*. Compound **5** was obtained as a yellow solid (41.5 mg, 91% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.64 – 7.60 (m, 3H), 7.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.48 – 7.42 (m, 4H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.14 (m, 2H), 5.62 (d, *J* = 8.4 Hz, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 157.2, 140.1, 139.2, 138.7, 136.3, 133.1, 131.6, 131.3, 130.6, 129.9, 129.2, 128.8, 127.5, 126.9, 126.9, 123.6, 122.6, 122.4, 120.4, 116.5, 116.5, 113.0, 110.2, 61.1, 13.5. HRMS (ESI) calcd for $[M+H]^+$ $[C_{30}H_{23}N_2O_3]^+$ 459.1703, found 459.1711.

Procedure for the Synthesis and the Characterization of 6.

Compound **3f** (46.1 mg, 0.1 mmol, 1 equiv) was combined with morpholine (10.5 mg, 0.12 mmol, 1.2 equiv), Cs_2CO_3 (65.2 mg, 0.2 mmol, 2 equiv), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol, 0.04 equiv) and BINAP (2.5 mg, 0.004 mmol, 0.04 equiv). The mixture was dissolved in 2.0 mL toluene. The reaction was refluxed under N_2 overnight. After completion, the mixture was cooled to room temperature. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel using petroleum ether/EtOAc as the eluent to afford compound **6**.

*Ethyl 3-morpholino-12-oxo-6-phenyl-12H-indazolo[2,1-a]cinnoline-5-carboxylate (**6**)*. Compound **6** was obtained as a yellow solid (28.0 mg, 60% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96 (d, *J* = 9.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 7.12 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 6.89 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 3.91 (q, *J* = 7.2 Hz, 2H), 3.89 – 3.84 (m, 4H), 3.26 – 3.12 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 156.6, 149.1, 139.4, 136.0, 131.9, 130.8, 130.5, 129.9, 129.1, 126.8, 123.4, 122.5, 120.9, 117.2, 116.9, 114.9, 113.0, 110.8, 110.0, 66.8, 60.9, 49.2, 13.4. HRMS (ESI) calcd for $[M+H]^+$ $[C_{28}H_{26}N_3O_4]^+$ 468.1918, found 468.1920.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) B. Parrino, A. Carbone, M. Muscarella, V. Spano, A. Montalbano, P. Barraja, A. Salvador, D. Vedaldi, G. Cirrincione, P. Diana, *J. Med. Chem.* 2014, **57**, 9495; (b) H. Yang, F. N. Murigi, Z. Wang, J. Li, H. Jin, Z. Tu, *Bioorg. Med. Chem. Lett.* 2015, **25**, 919; (c) J.-C. Chen, H.-C. Wu, C.-J. Chiang, L.-C. Peng, T. Chen, L. Xing and S.-W. Liu, *Polymer* 2011, **52**, 6011; (d) A. Rajapakse, K. S. Gates, *J. Org. Chem.* 2012, **77**, 3531.
2 Y. Shen, Z. Shang, Y. Yang, S. Zhu, X. Qian, P. Shi, J. Zheng, Y. Yang, *J. Org. Chem.* 2015, **80**, 5906.
3 W. Lewgowd, A. Stanczak, *Arch. Pharm. Chem. Life Sci.* 2007, **340**, 65.
4 P. Barraja, P. Diana, A. Lauria, A. Passannanti, A. M. Almerico, C. Minnei, S. Longu, D. Cogiu, C. Musiu, P. La Colla, *Bioorg. Med. Chem.* 1999, **7**, 1591.
5 A. L. Ruchelman, S. K. Singh, A. Ray, X. Wu, J. M. Yang, N. Zhou, A. Liu, L. F. Liu, E. J. LaVoie, *Bioorg. Med. Chem.* 2004, **12**, 795.
6 I. R. Mathews, PCT Int. Appl. WO 2004081011, 2004.
7 (a) G. Zhang, J. Miao, Y. Zhao, H. Ge, *Angew. Chem. Int. Ed.* 2012, **51**, 8318; (b) C. Lan, Z. Tian, X. Liang, M. Gao, W. Liu, Y. An, W. Fu, G. Jiao, J. Xiao, B. Xu, *Adv. Synth. Catal.* 2017, **359**, 3735.
8 C. J. Ball, J. Gilmore, M. C. Willis, *Angew. Chem. Int. Ed.* 2012, **51**, 5718.
9 (a) Z. Fan, K. Wu, L. Xing, Q. Yao, A. Zhang, *Chem. Commun.* 2014, **50**, 1682; (b) B. V. S. Reddy, C. R. Reddy, M. R. Reddy, S. Yarlagadda, B. Sridhar, *Org. Lett.* 2015, **17**, 3730.
10 (a) K. Muralirajan, C.-H. Cheng, *Chem. Eur. J.* 2013, **19**, 6198; (b) D. Zhao, Q. Wu, X. Huang, F. Song, T. Lv, J. You, *Chem. Eur. J.* 2013, **19**, 6239; (c) L. Xing, Z. Fan, C. Hou, G. Yong, A. Zhang, *Adv. Synth. Cat.* 2014, **356**, 972; (d) S. Rajkumar, S. A. Savarimuthu, R. S. Kumaran, C. M. Nagaraja, T. Gandhi, *Chem. Commun.* 2016, **52**, 2509; (e) S. Mayakrishnan, Y. Arun, C. Balachandran, N. Emi, D. Muralidharan, P.-T. Perumal, *Org. Biomol. Chem.* 2016, **14**, 1958.
11 (a) J.-Y. Son, S. Kim, W.-H. Jeon, P.-H. Lee, *Org. Lett.* 2015, **17**, 2518; (b) S. Sharma, S.-H. Han, S. Han, W. Ji, J. Oh, S.-Y. Lee, J.-S. Oh, Y.-H. Jung, I.-S. Kim, *Org. Lett.* 2015, **17**, 2852; (c) P. Sun, Y. Wu, Y. Huang, X. Wu, J. Xu, H. Yao, A. Lin, *Org. Chem. Front.* 2016, **3**, 91; (d) C. Song, C. Yang, F. Zhang, J. Wang, J. Zhu, *Org. Lett.* 2016, **18**, 4510; (e) P. Li, X. Xu, J. Chen, H. Yao, A. Lin, *Org. Chem. Front.* 2018, **5**, 1777.
12 W.-W. Chan, S.-F. Lo, Z. Zhou, W.-Y. Yu, *J. Am. Chem. Soc.* 2012, **134**, 13565.
13 Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* 2017, **117**, 13810.
14 (a) T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.* 2013, **135**, 5364; (b) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* 2013, **135**, 12204; (c) S. Cui, Y. Zhang, D. Wang, Q. Wu, *Chem. Sci.* 2013, **4**, 3912; (d) B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* 2014, **53**, 7896; (e) S. J. Yu, S. Liu, Y. Lan, B. S. Wan, X. W. Li, *J. Am. Chem. Soc.* 2015, **137**, 1623; (f) L. Shi, K. Yu, B. Wang, *Chem. Commun.* 2015, **51**, 17277; (g) B. Zhou, Z. Chen, Y. Yang, W. Ai, H. Tang, Y. Wu, W. Zhu, Y. Li, *Angew. Chem. Int. Ed.* 2015, **54**, 12121; (h) Y. Cheng, C. Bolm, *Angew. Chem. Int. Ed.* 2015, **54**, 12349; (i) J. Shi, J. Zhou, Y. Yan, J. Jia, X. Liu, H. Song, H. E. Xu, W. Yi, *Chem. Commun.* 2015, **51**, 668; (j) P. Bai, X.-F. Huang, G.-D. Xu, Z.-Z. Huang, *Org. Lett.* 2016, **18**, 3058; (k) X. Chen, X. Hu, S. Bai, Y. Deng, H. Jiang, W. Zeng, *Org. Lett.* 2016, **18**, 192; (l) P. Sun, S. Gao, C. Yang, S. Guo, A. Lin, H. Yao, *Org. Lett*. 2016, **18**, 6464; (m) J.-Q. Wu, Z. Yang, S.-S. Zhang, C.-Y. Jiang, Q. Li, Z.-S. Huang, H. Wang, *ACS Catal.* 2015, **5**, 6453; (n) K. Yan, B. Li, B. Wang, *Adv. Synth. Catal.* 2018, **360**, 2113; (o) X. Chen, G. Zheng, G. Song, X. Li, *Adv. Synth. Catal.* 2018, 360, 2836;

View Article Online
DOI: 10.1039/C8OB02071J

(p) A. Biswas, R. Samanta, *Eur. J. Org. Chem.* 2018, 1426; (q) M. Wang, L. Kong, Q. Wu, X. Li, *Org. Lett*. 2018, **20**, 4597.

15 (a) R. S. Phatake, P. Patel, C. V. Ramana, *Org. Lett*. 2016, **18**, 292; (b) S.-S. Li, Y.-Q. Xia, F.-Z. Hu, C.-F. Liu, F. Su, L. Dong, *Chem. Asian. J*. 2016, **11**, 3165; (c) P. Patel, G. Borah, *Chem. Commun*. 2017, **53**, 443; (d) K. Yan, B. Li, B. Wang, *Adv. Synth. Catal.* 2018, **360**, 2272; (e) U. Karmakar, D. Das, R. Samanta, *Eur. J. Org. Chem.* 2017, 2780.

16 (a) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed*. 2015, **54**, 4508; (b) J.-H. Kim, S. Greβies, F. Glorius, *Angew. Chem. Int. Ed*. 2016, **55**, 5577; (c) J. Li, M. Tang, L. Zang, X. Zhang, Z. Zhang, L. Ackermann, *Org. Lett*. 2016, **18**, 2742; (d) X. Hu, X. Chen, Y. Shao, H. Xie, Y. Deng, Z. Ke, H. Jiang, W. Zeng, *ACS Catal*. 2018, **8**, 1308; (e) S.-Y. Yan, P.-X. Ling, B.-F. Shi, *Adv. Synth. Catal.* 2017, **359**, 2912.

17 (a) S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed*. 2015, *54*, 4669-4672; (b) A. Biswas, U. Karmakar, A. Pal, R. Samanta, *Chem. Eur. J*. 2016, *22*, 13826-13830.

18 (a) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev*. 2012, **112**, 5879; (b) L. Ackermann, *Acc. Chem. Res*. 2014, **47**, 281. (c) R. Manikandan, P. Madasamy, M. Jeganmohan, *ACS Catal*. 2016, **6**, 230; (d) S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett*. 2002, **4**, 1783; (e) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* 1993, **366**, 529; (f) C. Shan, X. Luo, X. Qi, S. Liu, Y. Li, Y. Lan, Organometallics 2016, **35**, 1440; (g) C. Shan, L. Zhu, L.-B. Qu, R. Bai, Y. Lan, Chem. Soc. Rev. 2018, **47**, DOI: 10.1039/c8cs00036k.

19 (a) M. K.-W. Choi, W.-Y. Yu, C.-M. Che, *Org. Lett*. 2005, **7**, 1081; (b) Vanessa K.-Y. Lo, Z. Guo, M. K.-W. Choi, W.-Y. Yu, J.-S. Huang, C.-M. Che, *J. Am. Chem. Soc*. 2012, **134**, 7588; (c) W.-W. Chan, S.-H. Yeung, Z.-Y. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett*. 2010, **12**, 604; (d) W.-W. Chan, T.-L. Kwong, W.-Y. Yu, *Org. Biomol. Chem*. 2012, **10**, 3749; (e) K. Yamamoto, Z. Qureshi, J. Tsoung, G. Pisella, M. Lautens, *Org. Lett*. 2016, **18**, 4954; (f) N. Liu, Q.-P. Tian, Q. Yang, S.-D. Yang, *Synlett* 2016, **27**, 2621.

20 Y. Li, Z. Qi, H. Wang, X. Yang, X. Li, *Angew. Chem. Int. Ed*. 2016, **55**, 11877.

21 (a) S. De Sarkar, W. Liu, S.-I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* 2014, **356**, 1461; (b) C. Suzuki, K. Hirano, T. Satoh, M. Miura, *Org. Lett*. 2013, **15**, 3990.

22 Y. Zhao, Z. He, S. Li, J. Tang, G. Gao, J. Lan, J. You, *Chem. Commun*. 2016, **52**, 4613.

23 E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* 2012, **51**, 3066.

24 (a) H. A. Ardakani, R. K. Smalley, *Tetrahedron Letters* 1979, **49**, 4765. (b) A. Y. Shaw, Y.-Ru. Chen, C.-H. Tsai, *Synthetic Commun.* 2009, **39**, 2647. (c) Z. Wang, Z. Yin, F. Zhu, Y. Li, X.-F. Wu, *ChemCatChem* 2017, **9**, 3637.

25 (a) J. Kim, Y. J. Seo, S. Kang, J. Han, H. K. Lee, *Chem. Commun.* 2014, **50**, 13706. (b) P. Meffre, S. Hermann, P. Durand, G. Reginato, A. Riu, *Tetrahedron* 2002, **58**, 5159.