JOC The Journal of Organic Chemistry

Article

Cobalt catalysed, hydroxyl assisted C-H bond functionalization: Access to diversely substituted polycyclic pyrans

Pratip Kumar Dutta, Mahesh Kumar Ravva, and Subhabrata Sen

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02446 • Publication Date (Web): 04 Jan 2019

Cobalt catalysed, hydroxyl assisted C-H bond functionalization: Access to diversely substituted polycyclic pyrans

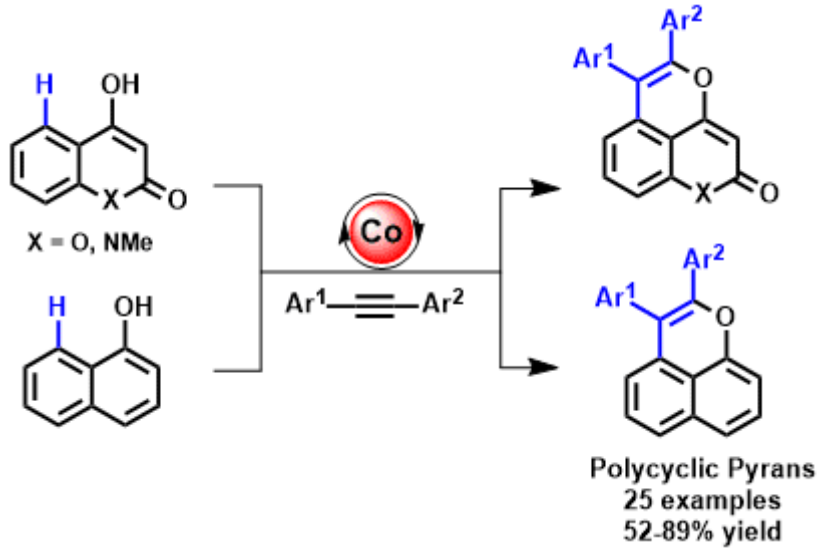
Pratip K. Dutta,[1] Mahesh Kumar Ravva,[2] Subhabrata Sen*,[1, 2]

1. Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Dadri, Chithera, Gautam Budh Nagar, Uttar Pradesh 201314, India
2. Department of Chemistry, SRM University-AP, Amaravati, Andhra Pradesh 522020, India

Abstract

Highly efficient oxidative annulation of alkynes furnished diversely substituted pyran[2, 3, 4-de]chromene-2-one derivatives and related polycycles in moderate to high yield. The reaction is catalysed by non-toxic, air stable and inexpensive Cp*Co(CO)I_2 catalyst. The hydroxyl moiety at the substrate acts as the directing group for the C-H bond activation.

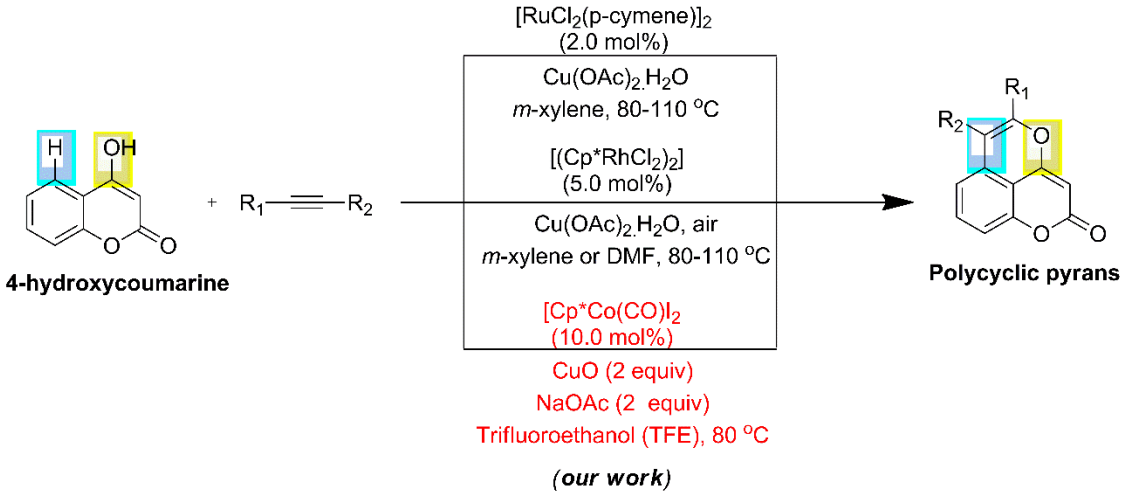
TOC Graphic



Introduction

Transition metal catalysed direct C-H functionalization has gained tremendous interest in recent times and thereby provided access to diversely substituted complex molecules through short, selective and step economical synthetic strategies.[1] During the early days of development of this methodology, Palladium and Rhodium catalysts were abundantly utilized, which gradually got replaced with ruthenium, iron and later by cobalt based catalysts.[2] In a bid to facilitate such transformations, diverse directing groups ranging from imidazoles, benzimidazoles, carboxylic acids, amides, indoles to pyridines and etc. were harnessed to activate the protons at their closest proximity.[3] Accordingly various organic scaffolds such as polyarenes, polycyclic isoquinolines, dihydroisoquinolines and many more were accessed.[4]

Interestingly substantial advancement in hydroxyl directed C-H bond functionalization happened with Palladium, Rhodium and Ruthenium catalysts.[5] While rather inexpensive, non-toxic and air stable cobalt complexes which have recently emanated as efficient catalysts for oxidative annulation of alkynes through C-H/N-H or C-H/C-O bond formation, have not been utilized for oxidative C-H bond activation harnessing all-pervasive hydroxyl moiety.[6] In our latest program involving catalytic C-H activation mediated reactions to access polycyclic pyrans we became curious in investigating the potential of site selective C-H bond transformation, directed by hydroxy functionality. To this extent we exploited 4-hydroxycoumarine derivatives **1a**-**e** as substrates. They were first used by Satoh in 2010 with symmetrical alkynes and then by Ackermann and co-workers in 2012 with unsymmetrical alkynes by utilizing Rh and Ru catalysts respectively (Scheme 1).[7] By virtue of their presence in bioactive building blocks and in optoelectronics, diversely substituted polycyclic pyrans have gained considerable importance among medicinal and material chemists.[8, 9] Hence we were interested to access these compounds *via* oxidative annulation of alkynes with $Cp^*Co(CO)I_2$ catalyst (Scheme 1).

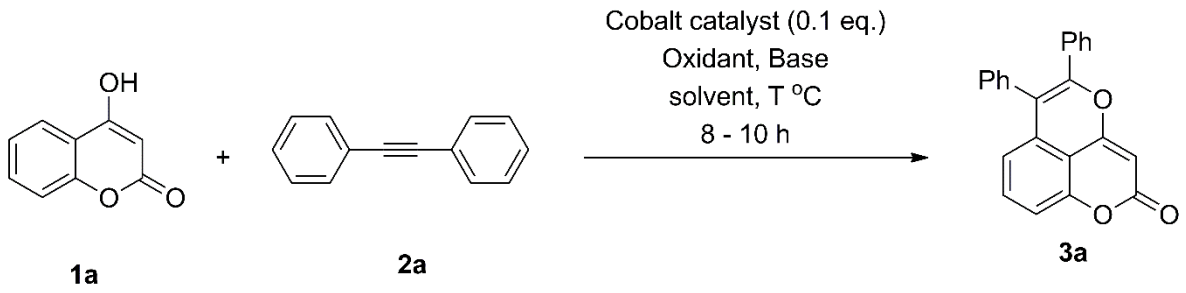


Scheme 1. Literature precedence and our work for metal catalysed, hydroxyl mediated C-H activation towards oxidative annulation of alkynes ($R_1 = R_2$)

Results and Discussion

We began our endeavour by exploring the most suitable procedure for this transformation. Accordingly 4-hydroxycoumarine (**1a**) and diphenyl acetylene (**2a**) were reacted in presence of 10 mol% of the dimeric cobalt catalyst $[Cp^*CoI_2]_2$ with 1.5 equiv of silver acetate (AgOAc) as the oxidant and 2 equiv of sodium acetate as the base (Table 1, entry 1). Unless otherwise mentioned trifluoroethanol (TFE) was used as the solvent. This initial effort afforded the desired product **3a** in only 10% yield. Increasing the ratio of AgOAc and the catalyst to 2 equiv and 20 mol% respectively or changing the oxidant to silver carbonate (Ag_2CO_3) could not improve the yield (Table 1, entry 2 and 3). Increasing the temperature only marginally improved the yield (Table 1, entry 4 and 5). Interestingly in our next effort, replacing the dimeric catalyst with $Cp^*Co(CO)I_2$ improved the yield nearly fourfold (Table 1, entry 6). However altering the oxidants (Ag_2CO_3, silver hexafluoroantimonate [$AgSbF_6$] and silver trifluoroborane [$AgBF_4$]) or the bases (lithium acetate and sodium carbonate) could not improve the yield (Table 1, entry 7 $\rightarrow$ 11). To our utmost pleasure using copper (II) oxide as the oxidant could ultimately improve the yield to nearly 70% (Table 1, entry 12). Reducing the stoichiometric ratio of CuO to 1.5 equiv (Table 1, entry 13) or utilizing other bases such as lithium acetate (LiOAc), sodium carbonate (Na_2CO_3) or sodium phosphate (Na_3PO_4) (Table 1, entry 14-16) proved detrimental for the reaction, as they lead to reduction of yield. Other copper based oxidants such as copper (II) acetate dihydrate ($Cu(OAc)_2.2H_2O$) or copper (II) bromide were much less competent than copeer (II) oxide (Table 1, entry 17 and 18), under same reaction condition. Reaction in other solvents such as *m*-xylene or dichloroethane (DCE) were much less efficient that TFE (Table entry 19 and 20). Reactions without the oxidant or without the catalyst could not afford any product (Table 1, entry 21-22). This further highlighted their importance in our reaction condition. Finally the reaction at room temperature only rendered 6% product (Table 1, entry 23). Hence the optimized procedure for this oxidative annulation involved 10 mol% of $Cp^*Co(CO)I_2$ as catalyst with one equiv of **1a** and 0.8 equiv of **2a** in presence of CuO (2 equiv) and NaOAc (2 equiv) in TFE at 80 °C.

Table 1. Reaction optimization for hydroxyl mediated oxidative annulation[a]



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

Entry	Catalyst (mol%)	Oxidant (eq.)	Base (eq.)	Temp (°C)	Yield (%)
1.	$[Cp^*CoI_2]_2$ (10)	AgOAc (1.5)	NaOAc (2.0)	60	10
2.	″	AgOAc (2.0)	″	″	10
3.	$[Cp^*CoI_2]_2$ (20)	Ag_2CO_3 (2.0)	″	″	<10
4.	$[Cp^*CoI_2]_2$ (20)	AgOAc (2.0)	″	80	23
5.	″	″	″	100	20
6.	$Cp^*Co(CO)I_2$ (10)	″	″	80	38
7.	″	Ag_2CO_3 (2.0)	″	″	33
8.	″	AgOAc (2.0)	LiOAc (2.0)	″	27
9.	″	″	Na_2CO_3 (2.0)	″	20
10.	″	$AgSbF_6$ (2.0)	NaOAc (2.0)	″	34
11.	″	$AgBF_4$ (2.0)	″	″	n.d.
12.	″	**CuO (2.0)**	″	″	**73**
13.	″	CuO (1.5)	″	″	48
14.	″	CuO (2.0)	LiOAc (2.0)	″	33
15.	″	″	Na_2CO_3 (2.0)	″	26
16.	″	″	Na_2PO_4 (2.0)	″	21
17.	″	$Cu(OAc)_2.\ 2H_2O$ (2.0)	NaOAc (2.0)	″	24
18	″	$CuBr_2$ (2.0)	″	″	n.d
19.	″	CuO (2.0)	″	″	56[b]

20.	″	″	″	″	63[c]
21.	″	-	″	″	<5
22.	-	CuO (2.0)	″	″	-
23.	″	″	″	rt	6

[a] Reaction condition: **1a** (0.6 mmol), **2a** (0.5 mmol), oxidant (1.5-2 mmol), base (2 equiv), solvent (5 mL); isolated yields. [b] m-Xylene as a solvent, [c] Dichloroethane as a solvent

With the reaction condition optimized, next we investigated the generic viability of our strategy in the reaction of diversely substituted alkynes **2a** - **j** with 4-hydroxycoumarine derivatives **1a** - **e**, 1-napthol **4** and 4-hydroxy-1-methylquinoline-2-one **5** (Figure 1). The cobalt catalyst was exceptionally effective in the oxidative annulation of **1a** with variety of substituted diaryl, dialkyl and aryl alkyl acetylenes **2a**-**2j** (encrusted with both electron donating and electron withdrawing functionalities at the aromatic ring *viz*. *p*-fluoro, *m*-fluoro, *o*-fluoro and *m*-chloro, *m*-cyano) to furnish compounds **3b** $\rightarrow$ **3e** and **3p** in good to excellent yield (67-89%). The catalyst was remarkably tolerant towards 1,2-di(thiophen-2-yl)ethyne **2i** to generate the desired product **3t** in 69% yield. The catalyst system was equally efficient towards substituted 4-hydroxycoumarines **1b** - **e** (7-methyl, 6-fluoro, 7-bromo and 7-methoxy-4-hydroxycoumarines respectively) to generate the desired products **3f** $\rightarrow$ **3o**, **3q**, **3s and 3u.** in 52-84% yield. Our system was not restricted to 4-hydroxycoumarine derivatives only. This extremely facile oxidative annulation when extended to 1-naphthol and 4-hydroxy-1-methylquinoline-2-one provided the desired products **6a**, **b** and **7a** in 65-85% yield (Figure 1).

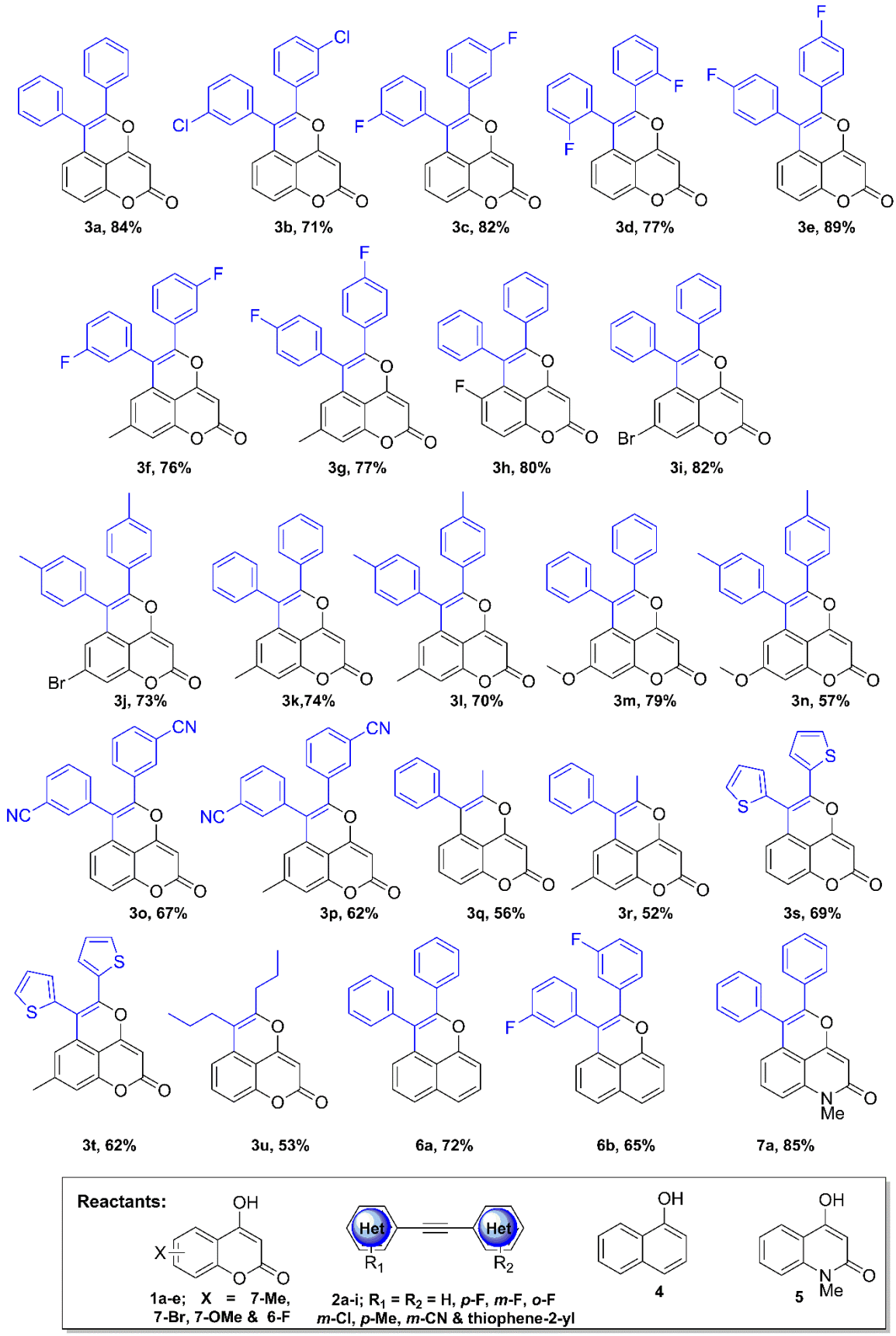


Figure 1. Cobalt catalysed annulation with 4-hydroxycoumarine, 1-Naphthol and 4-hydroxy-1-methylquinoline-2-one

By their ubiquitous presence in bioactive molecules polycyclic pyran systems have gained enormous importance among medicinal chemists. It is always an advantage if a synthetic route is efficient enough to provide molecules in larger scale. Hence, to explore the efficiency of our catalytic system towards scale-up reactions we reacted a gram of 4-hydroxycoumarine with diphenyl acetylene (1 equiv) under the optimized reaction condition. To our utmost satisfaction it generated 537 mg of **3a** in 53% (Figure 2).

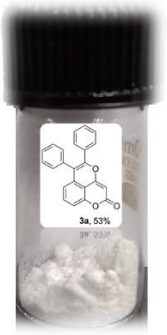
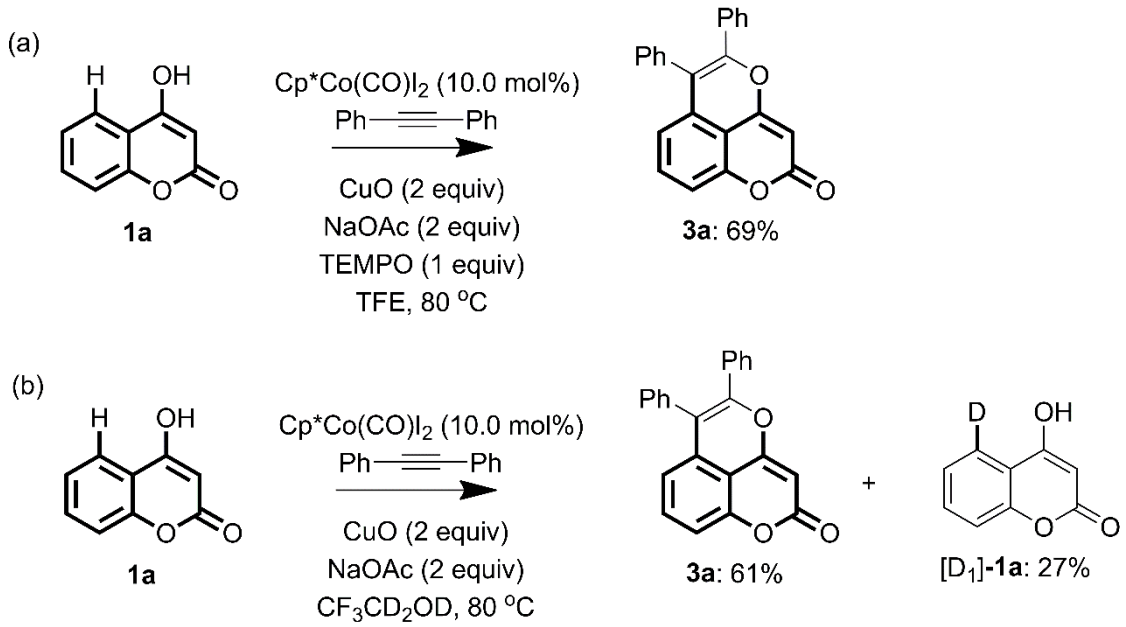


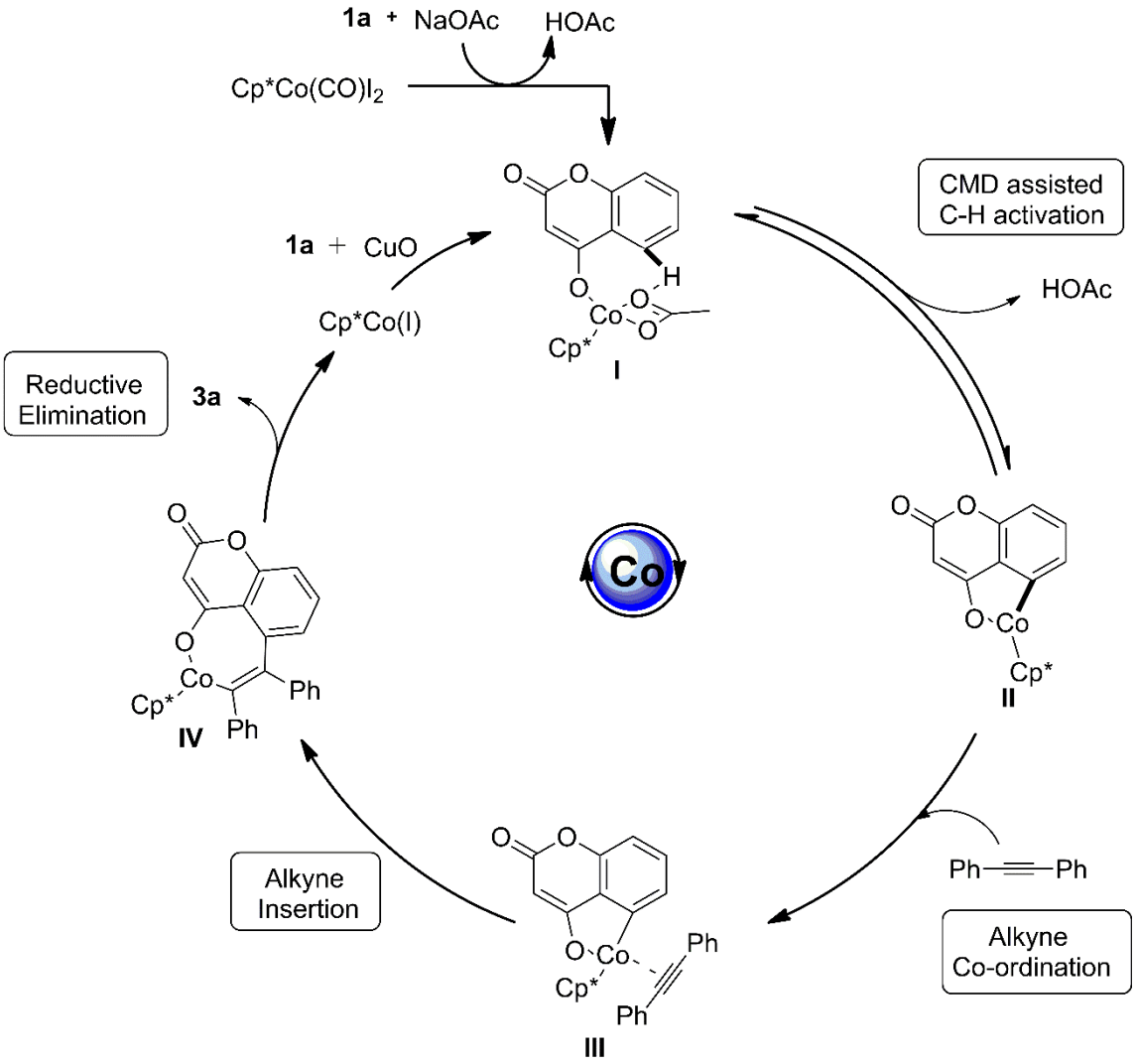
Figure 2. Scale-up reaction of compound **3a**

To gain further insights into the reaction mechanism of the Cp*Co(CO)I_2 catalyst system, control experiments were performed under various condition. When 1 equiv of TEMPO (2, 2, 6, 6-tetramethylpiperidine-N-oxyl, an archetypal radical initiator) was added to a reaction of **1a** with **2a** under standard reaction condition, no TEMPO adduct was formed, instead the desired compound **3a** was formed in 69% yield (Scheme 2a). This suggested that our Cp*Co(CO)I_2 catalyzed C-H activation is not a radical mediated pathway. Next, the catalytic C-H bond exchange in the presence of D_2O with excess of **1a** ensued in substantial D/H exchange at the *peri*-position of the recovered starting material [D_1]-**1a** (Scheme 2b), thereby providing proof for a cobalt mediated reversible C-H bond formation step (refer *1*H-NMR of **[D_1]-1a** in *SI*).



Scheme 2. Control experiments to understand the reaction mechanism of Cp*Co(CO)I_2 catalysed C-H activation

Based on the control experiments a catalytic cycle was proposed (Scheme 3) which involved formation of organocobalt intermediate II *via* hydroxy assisted C-H activation followed by insertion of the cobalt catalyst (Scheme 3). Alkyne coordination (III) and subsequent insertion facilitates the formation of cobalta-cycle IV which provides the desired product **3a** *via* reductive elimination. Re-oxidation further generates the active catalyst (Scheme 3).



Scheme 3. Proposed mechanism for the hydroxyl assisted oxidative annulation

Ab initio studies are conducted to verify the putative proposal (Figure 3). All geometry optimizations and vibrational frequencies of reactants and products were carried out in the gas phase using B3LYP method. The standard 6-31G(d,p) basis set for all nonmetals and LANL2DZ basis set for Co were used (referred as BS1 in the manuscript). Vibrational frequency analyses were performed to confirm that each local minimum has no imaginary frequency. All calculations were carried out using Gaussian 16 software.[10] The corresponding change in molecular energies between the conversion of intermediate **III** to **IV** and from **IV** to product **3a** was estimated to be 12.22 kcal/mol and -15.73 kcal/mol, with product **3a** at a lower energy (Figure 3). This suggests that **3a** is energetically more stable than **IV**, which facilitates the formation of the product.

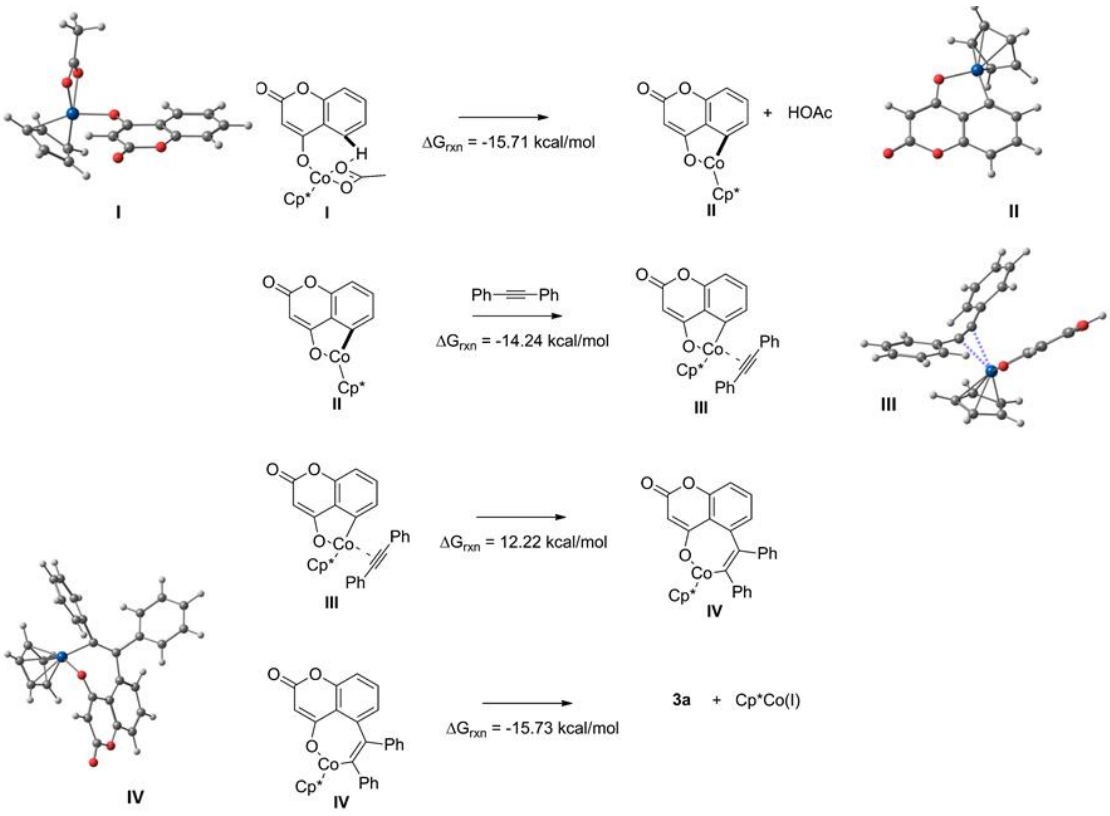


Figure 3. Calculated reaction free energies of each reaction (in kcal/mol) with optimized geometries of various Co (III) complexes of reaction intermediates as obtained using B3LYP/BS1 level of theory. Blue, red, black and grey colour represent the cobalt, oxygen, carbon and hydrogen atoms, respectively.

Hence to conclude, we have reported the first cobalt catalysed oxidative annulation of alkynes with 4-hydroxycoumarines, 1-naphthol and 4-hydroxy-1-methylquinoline-2-one. To the best of our knowledge this is perhaps the first cobalt catalysed hydroxyl directed C-H activation, which provided pyrano chromenones and related polycyclic derivatives in good yield. Control experiments provided mechanistic insight for the transformation. *Ab initio* experiment provided further support to the putative mechanism.

Experimental

General. All reactions were carried out under N_2 atmosphere as specified. Reaction was monitored by thin layer chromatography (TLC, Silica gel 60 F_{254}), using UV light to visualize the course of the reaction. **1a**-**f**, **2a**-**g**, **4** and **5** were procured from multiple commercial vendors. ^{1}H NMR and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal standard at ambient temperature unless otherwise indicated with Bruker 400 MHz and 500 MHz instruments at 400 MHz or 500 MHz for ^{1}H NMR and 100 MHz or 125 MHz for ^{13}C NMR spectroscopy. Splitting patterns are designated as singlet

(s), broad singlet (br, s), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Mass spectrometry analysis was done with a 6540 UHD Accurate-Mass QTOF LC-MS system (Agilent Technologies) equipped with an Agilent 1290 LC system obtained by the Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Uttar Pradesh 201314, India. HPLC experiments were carried out in Agilent Eclipse Plus C18 column.

General procedure for oxidative annulation

An oven dried screw capped pressure tube, equipped with magnetic stir bar, was charged with 4-hydroxycoumarine (100 mg, 0.6 mmole), diphenyl acetylene (87 mg, 0.5 mmol), Cp*Co(CO)I_2 (29 mg, 0.06 mmol), CuO (98 mg, 1.2 mmol) and NaOAc (110 mg, 1.2 mmol) in 2,2,2-trifluoroethanol (3 ml) and allowed to stir at 80°C under air for 12 hours. The crude reaction mixture was then filtered through a plug of celite and washed with EtOAc. The solvent was removed under reduced pressure and purified by column chromatography using the indicated eluent.

5,6-diphenyl-2H-pyrano[2,3,4-de]chromen-2-one (3a): EtOAc/*n*-hexane (12:88); white crystalline solid (175 mg, 84% yield), m. p. 225-226°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (t, *J* = 10 Hz, 1H), 7.40 (m, 1H), 7.39-7.38 (m, 2H), 7.27 (m, 1H), 7.26-7.25 (m, 1H), 7.23 (m, 2H), 7.22 (m, 2H), 7.21 (m, 1H), 7.20-7.19 (m, 1H), 6.76 (d, *J* = 5 Hz, 1H), 5.81 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 163.4, 163.1, 153.7, 150.0, 134.0, 133.7, 132.5, 131.7, 130.8, 129.4, 129.3, 129.2, 128.4, 128.1, 118.3, 117.3, 117.3, 115.2, 109.9, 100.0, 89.6. HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{15}O_3$ $[M+H]^+$: 339.1016, found: 339.1014.

5,6-bis(3-chlorophenyl)-2H-pyrano[2,3,4-de]chromen-2-one (3b): EtOAc/*n*-hexane (10:90); white crystalline solid (177.5 mg, 71% yield), m. p. 250-251°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 1H), 7.42-7.39 (m, 1H), 7.38-7.35 (m, 1H), 7.34-7.33 (m, 1H), 7.29-7.27 (m, 1H), 7.25-7.22 (m ,2H), 7.17-7.14 (m, 1H), 7.12-7.10 (m, 1H), 7.07-7.04 (m, 1H), 6.72 (d, *J* = 10 Hz, 1H), 5.83 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 162.8, 162.7, 153.6, 148.7, 134.1, 130.8, 130.7, 129.8, 129.5, 129.1, 129.0, 127.4, 118.3, 116.9, 115.9, 109.9, 90.2. HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{13}Cl_2O_3$ $[M+H]^+$: 407.0236, found: 407.0241.

5,6-bis(3-fluorophenyl)-2H-pyrano[2,3,4-de]chromen-2-one (3c): EtOAc/*n*-hexane (7:93); white crystalline solid (188 mg, 82% yield), m. p. 188-189°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 1H), 7.43-7.39 (m, 1H), 7.24-7.22 (m, 1H), 7.21-7.18 (m, 1H), 7.14-7.10 (m, 1H), 7.03-7.02 (m, 2H), 7.01-6.98 (m, 2H), 6.97-6.94 (m, 1H), 6.74 (d, *J* = 5 Hz, 1H), 5.82 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ

163.25 (d, $^1J_{C\text{-}F}$ = 247 Hz) 162.26 (d, $^1J_{C\text{-}F}$ = 245 Hz) , 162.8, 162.7, 153.7, 148.7, 135.5 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 134.1, 131.15 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 130.8, 129.9 (d, $^3J_{C\text{-}F}$ = 9 Hz), 126.6 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 124.9 (d, $^4J_{C\text{-}F}$ = 4

Hz), 118.3, 117.75 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 116.9, 116.8 (d, $^{2}J_{C\text{-}F}$ = 20 Hz), 116.2, 115.9 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz), 115.8, 109.9, 90.1. . HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{13}F_2O_3$ $[M+H]^+$: 375.0827, found: 375.0823

5,6-bis(2-fluorophenyl)-2H-pyrano[2,3,4-de]chromen-2-one (3d): EtOAc/*n*-hexane (7:93); white crystalline solid (177 mg, 77% yield), m. p. 195-196°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 10 Hz, 1H), 7.34-7.29 (m, 2H), 7.28-7.26 (m, 1H), 7.24-7.22 (m, 1H), 7.15-7.12 (m, 1H), 7.09-7.08 (m, 1H), 7.07-7.04 (m, 1H), 7.01-6.97 (m, 1H), 6.70-6.68 (m, 1H), 5.78 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 162.8, 162.4 (d, $^{1}J_{C\text{-}F}$ = 207.5 Hz), 159.9 (d, $^{1}J_{C\text{-}F}$ = 251 Hz), 153.7, 147.2, 134.1, 132.3 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 132.1 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 131.2 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz), 130.9, 130.8, 130.2, 124.6 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 124.1 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 117.9, 116.1 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 115.9 (d, $^{2}J_{C\text{-}F}$ = 19 Hz), 114.9, 110.1, 90.3. HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{13}F_2O_3$ $[M+H]^+$: 375.0827, found: 375.0830.

5,6-bis(4-fluorophenyl)-2H-pyrano[2,3,4-de]chromen-2-one (3e): EtOAc/*n*-hexane (10:90); white crystalline solid (204 mg, 89% yield), m. p. 196-197°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 10 Hz, 1H), 7.25-7.18 (m, 5H), 7.12 (t, *J* = 8 Hz, 2H), 6.94 (t, *J* = 8 Hz, 2H), 6.72 (d, *J* = 8 Hz, 1H), 5.81 (s, 1H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 163.98, 162.97 (d, $^{1}J_{C\text{-}F}$ = 250 Hz) 162.7, 162.6 (d, $^{1}J_{C\text{-}F}$ = 247 Hz), 153.6, 149.25, 137.6, 134.0, 132.8, 132.5 (d, $^{3}J_{C\text{-}F}$ =8 Hz), 131.3, 131.1 (d, $^{3}J_{C\text{-}F}$ =9 Hz), 129.4 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 128.4 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 124.20, 122.88, 119.4 (d, $^{2}J_{C\text{-}F}$ = 19 Hz), 118.0, 117.03, 116.3 (d, $^{2}J_{C\text{-}F}$ = 15Hz), 115.5, 115.4, 115.3 (d, $^{3}J_{C\text{-}F}$ = 10 Hz), 109.8, 90.47, 89.8. HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{13}F_2O_3$ $[M+H]^+$: 375.0827, found: 375.0825.

5,6-bis(3-fluorophenyl)-8-methyl-2H-pyrano[2,3,4-de]chromen-2-one (3f): EtOAc/*n*-hexane (10:90); yellow crystalline solid (167 mg, 76% yield), m. p. 178-179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 1H), 7.22-7.17 (m 1H), 7.15-7.10 (m, 1H), 7.05 (s, 1H), 7.02-7.01 (m ,1H), 7.00-6.99 (m, 2H), 6.97-6.93 (m, 2H),6.52 (s, 1H), 5.76 (m, 1H), 2.36 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 163.2 (d, $^{1}J_{C\text{-}F}$ = 247 Hz), 163.2 (d, $^{4}J_{C\text{-}F}$ = 245 Hz), 163.03, 162.9, 153.8, 148.7, 145.7, 135.6, 134.2, 131.0 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 130.4, 129.7 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 126.5 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 124.8 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 119.0, 117.7 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 116.6 (d, $^{2}J_{C\text{-}F}$ = 20 Hz), 116.1, 115.9 (d, $^{4}J_{C\text{-}F}$ = 5 Hz), 115.6, 107.6, 89.0, 22.4. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{15}F_2O_3$ $[M+H]^+$: 389.0984, found: 389.0969.

(4-fluorophenyl)-8-methyl-2H-pyrano[2,3,4-de]chromen-2-one (3g): : EtOAc/*n*-hexane (10:90); yellow crystalline solid (169 mg, 77% yield), m. p. 183-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.23 (m, 1H), 7.22-7.21 (m, 1H), 7.20-7.19 (m, 1H), 7.18-7.16 (m, 1H), 7.14-7.10 (m, 2H), 7.03 (s, 1H), 6.95-6.90 (m, 2H), 6.50 (s, 1H), 5.73 (m, 1H), 2.35 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 163.07, 162.7 (d, $^{1}J_{C\text{-}F}$ = 284 Hz), 153.8, 149.3, 145.6, 132.5 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 131.1 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 131.0, 129.5, 118.8, 116.5 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 115.8, 115.3 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 107.6, 88.8, 22.4. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{15}F_2O_3$ $[M+H]^+$: 389.0984, found: 389.0990.

7-fluoro-5,6-diphenyl-2H-pyrano[2,3,4-de]chromen-2-one (3h): EtOAc/*n*-hexane (10:90); yellow crystalline solid (157 mg, 80% yield), m. p. 185-186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 2H), 7.30 (m, 1H), 7.29-7.27 (m, 1H), 7.24-7.22 (m, 3H), 7.21-7.20 (m, 3H), 7.19-7.18 (m, 2H), 5.82 (s, 1H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 162.5, 152.6 (d, $^{1}J_{C-F}$ = 250 Hz), 151.1, 149.8 (d, $^{4}J_{C-F}$ = 3 Hz), 134.8 (d, $^{4}J_{C-F}$ = 3 Hz), 132.2, 130.5 (d, $^{4}J_{C-F}$ = 3 Hz), 129.4, 129.3, 128.3, 127.9 (d, $^{4}J_{C-F}$ = 3 Hz), 122.4 (d, $^{2}J_{C-F}$ = 26 Hz), 117.7 (d, $^{3}J_{C-F}$ = 10 Hz), 116.6 (d, $^{3}J_{C-F}$ = 7 Hz), 113.6 (d, $^{4}J_{C-F}$ = 3 Hz), 110.7 (d, $^{4}J_{C-F}$ = 4 Hz), 90.2. HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{14}FO_3$ $[M+H]^+$: 357.0921, found: 357.0932.

8-bromo-5,6-diphenyl-2H-pyrano[2,3,4-de]chromen-2-one (3i): EtOAc/*n*-hexane (10:90); yellow crystalline solid (159 mg, 82 % yield), m. p. 192-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.42 (m, 1H), 7.41-7.40 (m, 1H), 7.37 (d, *J* = 4 Hz, 1H), 7.30-7.27 (m, 1H), 7.24 (s, 1H), 7.23 (brs, 2H), 7.21 (brs, 1H), 7.21-7.20 (m, 1H), 7.19 (m, 1H), 7.87 (d, *J* = 4 Hz, 1H), 5.81 (s, 1H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 162.8, 162.1, 153.8, 151.0, 132.9, 132.1, 130.7, 129.6, 129.4, 129.1, 128.6, 128.5, 128.1, 121.3, 118.3, 116.3, 108.7, 89.7. HRMS (ESI-TOF+) m/z calcd. for $C_{23}H_{14}BrO_3$ $[M+H]^+$: 417.0121 and 419.0103, found : 417.0111 and 419.0117.

8-bromo-5,6-di-p-tolyl-2H-pyrano[2,3,4-de]chromen-2-one (3j): EtOAc/*n*-hexane (3:97); yellow crystalline solid (134 mg, 73 % yield), m. p. 222-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4 Hz, 1H), 7.22 (d, *J* = 8 Hz, 2H), 7.14 (d, *J* = 8 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 7.02 (d, *J* = 8 Hz, 2H), 6.86 (s, 1H), 5.79 (s, 1H), 2.41 (s, 3H), 2.30 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 162.9, 162.3, 153.8, 151.0, 139.8, 138.4, 133.3, 130.4, 130.1, 130.0, 129.3, 128.9, 128.8, 128.4, 121.2, 118.0, 115.7, 108.6, 89.4, 21.4, 21.4. HRMS (ESI-TOF+) m/z calcd. for $C_{25}H_{18}BrO_3$ $[M+H]^+$: 445.0434 and 447.0417, found : 445.0423 and 447.0426.

5,6-di-p-tolyl-2H-pyrano[2,3,4-de]chromen-2-one (3k): EtOAc/*n*-hexane (10:90); yellow crystalline solid (148 mg, 74% yield), m. p. 213-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.40 (m, 1H), 7.39-7.38 (m, 2H), 7.25-7.24 (m, 3H), 7.23-7.22 (m, 2H), 7.21-7.18 (m, 2H), 7.02 (s, 1H), 6.55 (s, 1H), 2.34 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 163.4, 163.4, 153.8, 150.0, 145.5, 133.7, 132.6, 131.3, 130.8, 130.8, 129.25, 129.14, 129.09, 128.25, 127.97, 118.98, 117.23, 115.55, 107.66, 88.5, 22.4. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{17}O_3$ $[M+H]^+$: 353.1172, found: 353.1168.

8-methyl-5,6-di-p-tolyl-2H-pyrano[2,3,4-de]chromen-2-one (3l): EtOAc/*n*-hexane (10:90); yellow crystalline solid (150 mg, 70% yield), m. p. 224-225 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.02 (s, 1H), 7.00 (d, (d, *J* = 4 Hz, 1H), 6.55 (s, 1H), 5.71 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 163.5, 163.4, 153.8, 150.0, 145.4, 139.4, 137.9, 131.7, 130.8, 130.6, 129.9, 129.8, 128.9, 128.7, 118.9, 116.6, 115.3, 107.6, 88.3. HRMS (ESI-TOF+) m/z calcd. for $C_{26}H_{21}O_3$ $[M+H]^+$: 381.1485, found: 381.1473.

8-methoxy-5,6-diphenyl-2H-pyrano[2,3,4-de]chromen-2-one (3m): EtOAc/*n*-hexane (10:90); green crystalline solid (151 mg, 79 %% yield), m. p. 226-227 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.42 (m, 1H), 7.41-7.40 (m, 2H), 7.32-7.30 (m, 1H), 7.30-7.28 (m, 3H), 7.26-7.22 (m, 3H), 7.67 (s, 1H), 7.34 (m, 1H), 5.70 (s, 1H), 3.81 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 164.6, 163.5, 163.4, 155.7, 15.3, 133.6, 132.7, 132.5, 130.7, 129.3, 129.2, 129.1, 128.3, 128.0, 117.1, 105.8, 103.8, 99.7, 86.8, 55.8. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{17}O_4$ $[M+H]^+$: 369.1121, found: 369.1128.

8-methoxy-5,6-di-p-tolyl-2H-pyrano[2,3,4-de]chromen-2-one (3n): EtOAc/*n*-hexane (10:90); pale yellow crystalline solid (117 mg, 57% yield), m. p. 231-232 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8 Hz, 2H), 7.17-7.14 (m, 2H), 7.08 (d, *J* = 8 Hz, 2H), 7.01(d, *J* = 8 Hz, 2H), 6.07 (s, 1H), 6.29 (s, 1H), 5.64 (s, 1H), 3.77 (s, 3H), 2.38 (s, 3H), 2.29 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 164.6, 163.5, 155.7, 150.33, 139.5, 138.00, 133.15, 130.65, 130.51, 129.9, 129.7, 129.0, 128.7, 116.5, 105.6, 103.8, 99.6, 86.5, 55.8, 21.4. HRMS (ESI-TOF+) m/z calcd. for $C_{26}H_{21}O_4$ $[M+H]^+$: 397.1434, found: 397.1441

3,3'-(2-oxo-2H-pyrano[2,3,4-de]chromene-5,6-diyl)dibenzonitrile (3o): EtOAc/*n*-hexane (40:60); pale yellow crystalline solid (160 mg, 67 % yield), m. p. 235-236 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8 Hz, 1H), 7.63-7.59 (m, 2H), 7.58-7.54 (m, 2H), 7.52-7.49 (m, 2H), 7.42-7.36 (m, 2H), 7.28 (d, J = 8 Hz. 1H), 7.64 (d, *J* = 8 Hz, 1H), 5.86 (s,1H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 162.2, 162.1, 153.7, 148.2, 134.0, 133.1, 132.6, 132.5, 130.5, 129.8, 129.4, 118.1, 117.8, 117.7, 116.8, 116.5, 114.0, 113.1,109.8, 90.8. HRMS (ESI-TOF+) m/z calcd. for $C_{25}H_{14}N_2O_3$ $[M+H]^+$: 389.0921, found: 389.0935.

3,3'-(8-methyl-2-oxo-2H-pyrano[2,3,4-de]chromene-5,6-diyl)dibenzonitrile (3p): EtOAc/*n*-hexane (30:70); brown crystalline solid (141 mg, 62 % yield), m. p. 227-229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8 Hz, 1H), 7.62-7.58 (m, 2H), 7.53 (s, 1H), 7.51-7.48 (m, 2H), 7.41-7.35 (m, 2H), 7.09 (s, 1H), 6.41 (s, 1H), 5.79 (s, 1H), 2.38 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 162.5, 148.3, 146.0, 135.3, 134.6, 134.1, 133.3, 133.1, 132.6, 130.5, 129.3, 118.9, 117.9, 117.7, 116.9, 114.0, 113.0, 107.6, 89.7, 22.4. HRMS (ESI-TOF+) m/z calcd. for $C_{26}H_{16}N_2O_3$ $[M+H]^+$: 403.1077, found: 403.1093.

6-methyl-5-phenylbenzo[de]chromen-2(4H)-one (3q): EtOAc/*n*-hexane (10:90); off white crystalline solid (95 mg, 56 % yield), m. p. 142-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 1H), 7.54 (brs, 1H), 7.53 (brs, 1H), 7.50-7.48 (m, 2H), 7.26 (s, 1H), 7.25-7.22 (m, 1H), 7.17 (d, *J* = 8 Hz, 1H), 5.71 (s, 1H), 2.19 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 153.7, 134.0, 132.8, 131.6, 129.8, 129.3, 128.5, 116.2, 150.1, 109.8, 89.2, 13.6. HRMS (ESI-TOF+) m/z calcd. for $C_{18}H_{14}O_3$ $[M+H]^+$: 277.0859, found: 277.0865.

6,8-dimethyl-5-phenyl-2H-pyrano[2,3,4-de]chromen-2-one (3r): EtOAc/*n*-hexane (10:90); white crystalline solid (85 mg, 52 % yield), m. p. 138-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.53 (m, 1H), 7.52-7.50 (m, 2H), 7.49-7.48 (m, 1H), 7.47 (m, 1H), 7.30 (s, 1H), 6.97 (s, 1H), 5.63 (s, 1H), 2.50 (s, 3H),

2.17 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 163.5, 163.4, 153.8, 150.1, 145.5, 132.9, 131.2, 129.7, 129.3, 128.5, 117.2, 115.4, 109.8, 107.7, 88.1, 22.5, 13.6. HRMS (ESI-TOF+) m/z calcd. for $C_{19}H_{16}O_3$ $[M+H]^+$: 291.1016, found: 291.1023.

5,6-di(thiophen-2-yl)-2H-pyrano[2,3,4-de]chromen-2-one (3s): EtOAc/*n*-hexane (10:90); pale yellow solid (149 mg, 69% yield), m. p. 142-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 4 Hz, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.36 (d, *J* = 4 Hz, 1H), 7.26 (bs, 1H), 7.25 (s, 1H), 7.17 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 4 Hz, 1H), 6.99 (t, *J* = 4 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 5.86 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 162.7, 162.4, 153.3, 146.8, 134.1, 133.2, 132.3, 130.4, 130.1, 129.4, 128.9, 128.4, 127.1, 118.1, 115.0, 109.1, 107.9, 90.1. HRMS (ESI-TOF+) m/z calcd. for $C_{19}H_{11}O_3S_2$ $[M+H]^+$: 351.0144, found: 351.0139.

8-methyl-5,6-di(thiophen-2-yl)-2H-pyrano[2,3,4-de]chromen-2-one (3t): EtOAc/*n*-hexane (10:90); yellow crystalline solid (136 mg, 75 % yield), m. p. 137-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (m, 1H), 7.35-7.33, 7.27-7.26 (m, 1H), 7.25-7.23 (m, 1H), 7.09-7.08 (m, 1H), 6.99 (brs, 1H), 6.98-6.97 (m, 1H), 6.50 (s, 1H), 5.79 (s, 1H), 2.36 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 163.1, 162.5, 153.5, 146.8, 145.7, 134.2, 133.3, 131.9, 130.4, 130.0, 129.3, 128.9, 128.4, 127.0, 118.9, 115.4, 106.9, 89.0, 22.4. HRMS (ESI-TOF+) m/z calcd. for $C_{20}H_{13}O_3S_2$ $[M+H]^+$: 365.0301, found: 365.0314.

5,6-dipropylbenzo[de]chromen-2(4H)-one (3u): EtOAc/*n*-hexane (10:90); off white crystalline solid (87 mg, 53 % yield), m. p. 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.58-6.57 (brs, 1H), 5.48 (s, 1H), 3.88 (s, 3H), 2.48 (t, *J* = 8 Hz, 2H), 2.43 (t, *J* = 8 Hz, 2H), 1.73-1.65 (m, 2H), 1.55 (sextet, *J* = 8 Hz), 1.03-0.99 (m, 6H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 164.7, 163.7, 163.6, 156.0, 153.5, 131.8, 112.4, 104.0, 103.4, 98.6, 85.9, 55.8, 32.5, 28.4, 22.1, 21.1, 14.2, 13.8. HRMS (ESI-TOF+) m/z calcd. for $C_{17}H_{20}O_3$ $[M+H]^+$: 285.1485, found: 285.1493.

2,3-diphenylbenzo[de]chromene (6a): Petroleum ether (100%), yellow crystalline solid (159 mg, 72 % yield), m. p. 118-120°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.38 (brs, 1H), 7.36-7.34 (m, 1H), 7.33 (brs, 1H), 7.32-7.31 (m, 1H), 7.30-7.28 (m, 1H), 7.28-7.27 (m, 1H), 7.23-7.21 (m, 2H), 7.20-7.18 (m, 1H), 7.17-7.14 (m, 1H), 6.89 (d, *J* = 8 Hz, 1H), 6.47 (d, *J* = 8 Hz, 1H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 152.7, 149.5, 135.6, 134.8, 134.2, 132.0, 131.0, 129.1, 128.9, 128.4, 127.7, 127.5, 127.4, 123.7, 122.9, 119.2, 117.6, 115.7, 107.0. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{17}O$ $[M+H]^+$: 321.1274, found: 321.1269.

2,3-bis(3-fluorophenyl)benzo[de]chromene (6b): Petroleum ether (100%), yellow crystalline solid (160 mg, 65 % yield), m. p. 177-178°C . ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 10 Hz, 1H), 7.34-7.32 (m, 1H), 7.31 (brs, 1H), 7.30-7.29 (m, 1H), 7.28-7.27 (m, 1H), 7.26-7.23 (m, 1H), 7.19-7.15 (m, 1H), 7.06-7.05 (m, 1H), 7.04-7.01 (m, 2H), 6.96 (t, *J* = 10 Hz, 1H), 6.84-6.82 (m, 1H), 6.37 9d, *J* = 10 Hz, 1H). ^{13}C{1H}

NMR (125 MHz, CDCl3) δ 160.0 (d, $^{1}J_{C\text{-}F}$ = 249 Hz), 155.67 (d, $^{3}J_{C\text{-}F}$ = 12.5 Hz), 155.02, 152.7, 152.1, 147.04, 134.9, 132.6 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 131.2 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz), 131.2, 131.1. 130.0 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 127.6 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 124.4 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 124.3, 123.8 (d, $^{4}J_{C\text{-}F}$ = 4 Hz), 123.0, 119.7, 115.9, 115.7 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz), 115.3, 107.4. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{15}F_2O$ $[M+H]^+$: 357.0185, found: 357.0179.

1-methyl-5,6-diphenylpyrano[2,3,4-de]quinolin-2(1H)-one (7a): EtOAc/*n*-hexane (15:85); off white crystalline solid (170 mg, 85 % yield), m. p. 260-261°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8 Hz, 1H), 7.43-7.44 (m, 1H), 7.42-7.40 (m, 1H), 7.39-7.38 (m, 1H), 7.37-7.36 (m, 1H), 7.28 (brs, 1H), 7.27 (brs, 1H), 7.25-7.24 (m, 1H), 7.24-7.22 (m, 1H), 7.23-7.22 (m, 1H), 7.22-7.21 (m, 1H), 7.09 (d, *J* = 8 Hz, 1H), 6.60 (d, *J* = 8 Hz, 1H), 6.17 (s, 1H), 3.64 (s, 3H). ^{13}C{1H} NMR (100 MHz, CDCl3) δ 159.7, 140.1, 134.5, 132.6, 131.0, 129.1, 129.0, 128.0, 127.9, 116.7, 115.6, 111.9, 96.7, 29.3. HRMS (ESI-TOF+) m/z calcd. for $C_{24}H_{18}NO_2$ $[M+H]^+$: 352.1332, found: 352.1340.

Scale up synthesis:

An oven dried two necked round bottom flask, equipped with magnetic stir bar, was charged with 4-hydroxycoumarine (1 g, 6.17 mmole), diphenyl acetylene (870 mg, 4.9 mmol), Cp*(CO)CoI_2 (290 mg, 0.61 mmol), CuO (980 mg, 12.32 mmol) and NaOAc (1.1 g, 13.41 mmol) in 2,2,2-trifluoroethanol (20 ml) and allowed to stir at 80°C under air for 24 hours. The crude reaction mixture was then filtered through a plug of celite and washed with EtOAc. The solvent was removed under reduced pressure and purified by column chromatography using EtOAc/*n*-hexane (7:93) to afford 537 mg (53% yield) of 3a.

Deuterium scrambling experiment with D_2O-[D_1]-1a

An oven dried screw capped pressure tube, equipped with magnetic stir bar, was charged with 4-hydroxycoumarine (50 mg, 0.3 mmole), Cp*Co(CO)I_2 (14.5 mg, 0.03 mmole), CuO (49 mg, 0.6 mmole) and NaOAc (5 mg, 0.06 mmole) in CF_3CD_2OD (1 ml) and allowed to stir at 80°C under air for 24 hours. The crude reaction mixture was then filtered through a plug of celite and washed with EtOAc. The solvent was removed under reduced pressure and purified by column chromatography on silica gel using EtOAc/n-Hexane (30:70) to yield the white powdered starting material [D_1]-1a. The deuterium incorporation was found to be 80% from NMR spectroscopy.

White powdered solid**.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (brs, 1H), 7.67-7.63 (m, 1H), 7.39-7.34 (m, 2H), 5.60 (s, 1H).

Acknowledgment

We thank Shiv Nadar University for the financial support. MKR thanks SRM Supercomputer Center, SRM Institute of Science and Technology for providing the computational facility.

Supporting Information

Computational data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Reference

1. (a) Hickman, A. J.; Sanford, M. S. High-valent organometallic copper and palladium in catalysis. *Nature* **2012**, *484*, 177–185. (b) Yeung, C. S.; Dong, V. M. Catalytic dehydrogenative cross-coupling: forming carbon-carbon bonds by oxidizing two carbon− hydrogen bonds. *Chem. Rev.* **2011**, *111*, 1215–1292. (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C-H bond functionalisation. *Chem. Soc. Rev*. **2011**, *40*, 1885–1898. (d) Daugulis, O. Palladium and Copper Catalysis in Regioselective, Intermolecular Coupling of C-H and C-Hal Bonds. *Top. Curr. Chem*. **2010**, *292*, 57–84. (e) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. Mechanisms of C-H bond activation: rich synergy between computation and experiment. *Dalton Trans*. **2009**, 5820–5831. (f) Ackermann, L.; Vicente, R; Kapdi, A. Transition-metal-catalyzed direct arylation of (hetero) arenes by C-H bond cleavage. *Angew. Chem., Int. Ed*. **2009**, *48*, 9792–9826. (g) Hartwig, J. F.; Larsen, M. A. Undirected, homogeneous C-H bond functionalization: challenges and opportunities. *ACS Cent. Sci*. **2016**, *2*, 281-292.
2. (a) Lyons, T. W.; Sanford, M. S. Palladium-catalyzed ligand-directed C-H functionalization reactions. *Chem Rev*. **2010**, *110*, 1147-1169. (b) Crabtree, R. H.; Lei, A. Introduction: C-H activation. *Chem. Rev*. **2017**, *117*, 8481-8482. (c) Wencel-Delord, J.; Droege, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C-H bond activation. *Chem. Soc. Rev*. **2011**, *40*, 4740-4761. (d) Shang, R.; Ilies, L; Nakamura, E. Iron-Catalyzed C-H Bond Activation. *Chem. Rev*. **2017**, *117*, 9086-9139. (e) Arockiam, P. B.; Bruneau, C; Dixneuf, P. H. Ruthenium (II)-catalyzed C-H bond activation and functionalization. *Chem. Rev*. **2012**, *112*, 5879-5918. (f) Nareddy, P.; Jordan, F.; Szostak, M. Recent Developments in Ruthenium-Catalyzed C-H Arylation: Array of Mechanistic Manifolds. *ACS Catal*. **2017**, *7*, 5721-5745. (g) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C-H Activation. *ACS Catal*. **2016**, *6*, 498-525. (h) Prakash, S.; Kuppuswamy, R.; Cheng, C-H. Cobalt-Catalyzed Annulation Reactions *via* C-H Bond Activation. *Chem. Cat. Chem*. **2017**, *10*, 683-710. (i) Ujwaldev, S. M.; Harry, N. A.; Divakar, M. A.; Anilkumar, G. Cobalt-catalyzed C-H activation: recent progress in heterocyclic chemistry. *Catal. Sci. Technol*., **2018**, 10.1039/C8CY01418C.

3. (a) Song, G.; Wang, F.; Li, X. C-C, C-O and C-N bond formation via rhodium (iii)-catalyzed oxidative C-H activation. *Chem. Soc. Rev*. **2012**, *41*, 3651–3678 and the references there is in. (b) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. Highly diastereoselective synthesis of tetrahydropyridines by a C-H activation–cyclization–reduction cascade. *J. Am. Chem. Soc*. **2012**, *134*, 4064–4067. (c) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. Nickel-catalyzed chelation-assisted transformations involving ortho C-H bond activation: regioselective oxidative cycloaddition of aromatic amides to alkynes. *J. Am. Chem. Soc*. **2011**, *133*, 14952–14955. (d) Shi,Z.; Ding, S.; Cui, Y.; Jiao, N. A Palladium-Catalyzed Oxidative Cycloaromatization of Biaryls with Alkynes Using Molecular Oxygen as the Oxidant. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895–7898. (e) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. Fluorescent Naphthyl-and Anthrylazoles from the Catalytic Coupling of Phenylazoles with Internal Alkynes through the Cleavage of Multiple C-H Bonds. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019– 4022. (f) Ueura, K.; Satoh, T.; Miura, M. An efficient waste-free oxidative coupling via regioselective C− H bond cleavage: Rh/Cu-catalyzed reaction of benzoic acids with alkynes and acrylates under air. *Org. Lett*. **2007**, *9*, 1407–1409.

4. (a) Colby, D. A.; Bergman, R. G.; Ellman, R. A. Rhodium-catalyzed C-C bond formation via heteroatom-directed C− H bond activation. *Chem. Rev*. **2010**, *110*, 624-655. (b) Kakiuchi, F.; Kochi, T. Transition-Metal-Catalyzed Carbon-Carbon Bond Formation via Carbon-Hydrogen Bond Cleavage. *Synthesis* **2008**, 19, 3013-3039. (c) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. C–H bond functionalizations with palladium (II): intramolecular oxidative annulations of arenes. *Tetrahedron* **2008**, *64*, 5987-6001. (d) Park, Y. J.; Park, J.-W.; Jun, C.-H. Metal− organic cooperative catalysis in C− H and C−C bond activation and its concurrent recovery. *Acc. Chem. Res*. **2008**, *41*, 222-234. (e) Herrerias, C. I. Yao, X.; Li, Z.; Li, C.-J. Reactions of C-H bonds in water. *Chem. Rev*. **2007**, *107*, 2546-2562. (f) Jia, C.; Kitamura, T.; Fujiwara, Y. Catalytic functionalization of arenes and alkanes via C− H bond activation. *Acc. Chem. Res*. **2001**, *34*, 633-639. (g) Dyker, G. Transition metal catalyzed coupling reactions under C− H activation *Angew. Chem*. **1999**, *111*, 1808-1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698-1712. (h) Shilov, A. E.; Shul'pin, G. B. Activation of C− H bonds by metal complexes. *Chem. Rev*. **1997**, *97*, 2879-2932.

5. (a) Yan, K.; Li, B.; Wang, B. Hydroxyl-Directed Rhodium-Catalyzed C-H bond activation and cyclization Leading to Naphthol[1, 8-*bc*]pyran Derivatives and its Analogues. *Adv, Synth. Catal*. **2018**, *360*, 2113-2118. (b) Wang, X.; Lu, Y.; Dai, H-X.; Yu, J.-Q. Pd (II)-Catalyzed Hydroxyl-Directed C− H Activation/C− O Cyclization: Expedient Construction of Dihydrobenzofurans. *J. Am. Chem. Soc*. **2010**, *132*, 12203-12205. (c) a) Mochida, S.; Shimizu, M.; Hirano, K. Satoh, T.;

Miura, M. Synthesis of Naphtho[1,8-bc]pyran Derivatives and Related Compounds through Hydroxy Group Directed C-H Bond Cleavage under Rhodium Catalysis. *Chem. Asian J*. **2010**, *5*, 847−851; (d) Wang, F.; Song, G.; Du, Z.; Li, X. Oxidative Coupling of NH Isoquinolones with Olefins Catalyzed by Rh (III). *J. Org. Chem*. **2011**, *76*, 2926- 2932; (e) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. Synthesis of isochromene and related derivatives by rhodium-catalyzed oxidative coupling of benzyl and allyl alcohols with alkynes. *J. Org. Chem.* **2011**, *76*, 9548−9551; (f) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. Rhodium (III)-catalyzed dearomatizing (3+ 2) annulation of 2-alkenylphenols and alkynes. *J. Am. Chem. Soc*. **2014**, *136*, 7607-7610; (g) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulias, M. Straightforward Assembly of Benzoxepines by Means of a Rhodium(III)-Catalyzed C–H Functionalization of o-Vinylphenols. *J. Am. Chem. Soc*. **2013**, *136*, 834-837.

6. (a) Chirila, P. G.; Whiteoak, C. J. Recent advances using [Cp*Co(CO)I_2] catalysts as a powerful tool for C–H functionalisation. *Dalton Trans*., **2017**, *46*, 9721-9739. (b) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C-H Activation. *ACS Catal*., **2016**, *6*, 498-525 and the references there in. (c) Yoshida, M.; Kawai, K.; Tanaka, R.; Yoshino, T.; Matsunaga, S. Cp*Co^{III}-catalyzed directed C-H trifluoromethylthiolation of 2-phenylpyridines and 6-arylurines. *Chem. Commun*. **2017**, *53*, 5974-5977. (d) Sakata, K.; Eda, M.; Kitaoka, Y.; Yoshino, T.; Matsunaga, S. Cp*Co^{III}-Catalyzed C-H Alkenylation/ Annulation Reactions of Indoles with Alkynes: A DFT Study. *J. Org. Chem*. **2017**, *82*, 7379-7387. (e) Fukugawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. Cobalt (III)/ Chiral Carboxylic Acid-Catalyzed Enantioselective C(sp^3)-H Amidation of Thioamides. *Angew. Chem. Int. Ed*. **2018**, just accepted. (f) Sen, M.; Mandal, R.; Das, A.; Kalsi, D.; Sundararaju, B. Cp*Co^{III}-Catalyzed Bis-isoquinolone Synthesis by C-H Annulation of Arylamide with 1, 3-Diyne. **2017**, *23*, 17454-17457. (g) Mandal, R.; Sundararaju, B. Cp*Co(III)-Catalyzed Annulation of Carboxylic Acids with Alkynes. *Orglett*. **2017**, *19*, 2544-2547.
7. (a) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. Hydroxyl-directed ruthenium-catalyzed C–H bond functionalization: versatile access to fluorescent pyrans. *Org. Lett*. **2012**, *14*, 3416-3419. (b) Mochida, S.; Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. Synthesis of Naphtho[1,8-bc]pyran Derivatives and Related Compounds through Hydroxy Group Directed C-H Bond Cleavage under Rhodium Catalysis. *Chem. Asian. J.* **2010**, *5*, 847-851.
8. (a) Shin, D.-Y.; Kim, S. N.; Chae, J.-H.; Hyun, S.-S.; Seo, S.-Y.; Lee, Y.-S.; Lee, K.-O.; Kim, S.-H.; Lee, Y.-S.; Jeong, J. M.; Choi, N.-S.; Suh, Y.-G. Syntheses and anti-MRSA activities of the C3 analogs of mansonone F, a potent anti-bacterial sesquiterpenoid: insights into its structural requirements for anti-MRSA activity. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 4519–4523. (b) Liang,

Y.; Xie, X.; Chen, L.; Yan, S.; Ye, X.; Anjum, K.; Huang, H.; Lian, X.; Zhang, Z. Bioactive Polycyclic Quinones from Marine Streptomyces sp. 182SMLY Mar. Drugs 2016, 14, 10-19.

9. (a) Christensen, J. B.; Johannsen, I.; Bechgaard, K. Synthesis and properties of substituted 1, 6-dioxapyrene donors. *J. Org. Chem*. **1991**, ***56***, 7055–7058. (b) Tyson, D. S.; Fabrizio, E. F.; Panzner, M. J.; Kinder, J. D.; Buisson, J.-P.; Christensen, J. B.; Meador, M. A. Synthesis, characterization, and optical properties of a cyano-functionalized 2, 3, 7, 8-tetraaryl-1, 6-dioxapyrene. J. *Photochem. Photobiol*. *A* **2005**, *172*, 97–107.
10. Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.