Article

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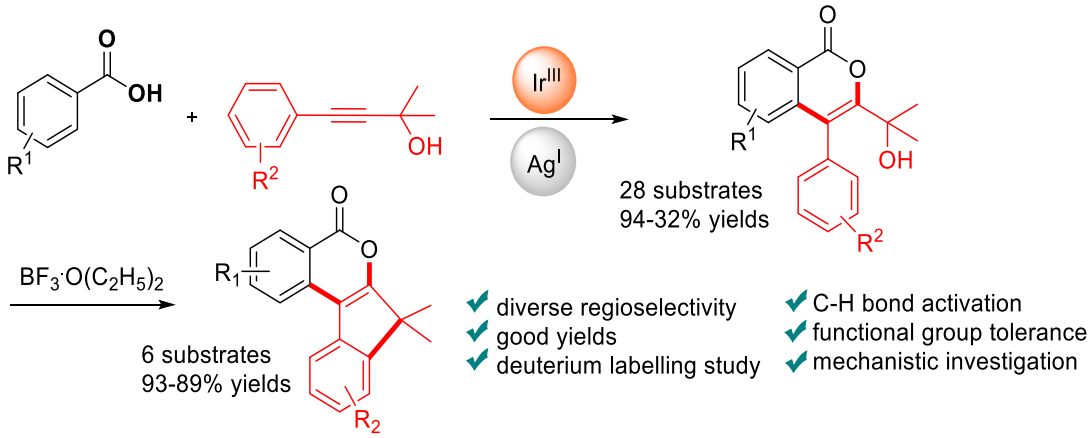


Abstract

An Ir(III)-catalyzed oxidative cyclization of benzoic acids with propargyl alcohols to give substituted isocoumarins in a highly regioselective manner is described. This protocol has broad substrate scope with high functional group tolerance. The observed isocoumarins were converted into biologically active tetracyclic indeno[2,1-*c*]isocoumarins by Lewis acid mediated cyclization. A possible reaction mechanism is proposed and strongly supported by the detailed mechanistic investigation and DFT.

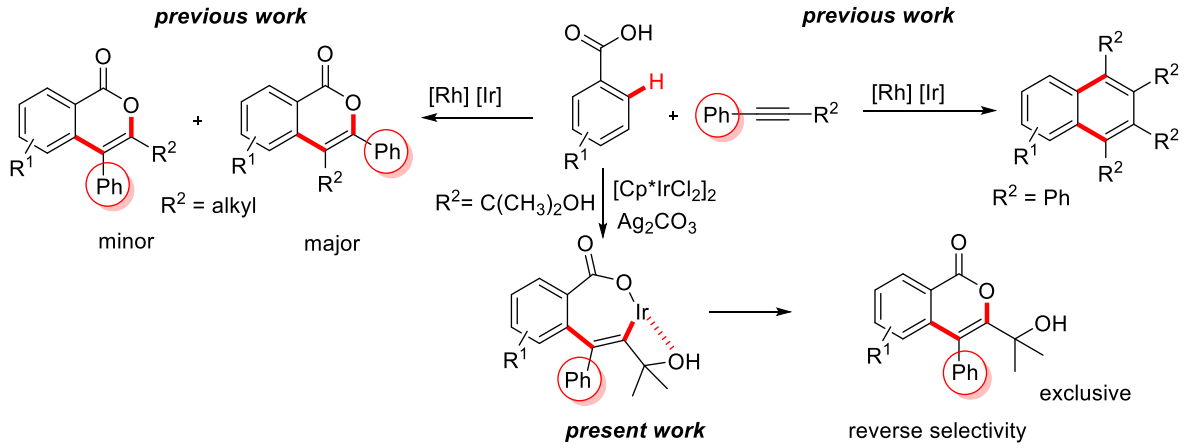
Introduction

Isocoumarins are privileged oxygen containing heterocyclic molecules and also the benzo derivative of α-pyranones. These are naturally occurring unsaturated lactones and its structural motifs are present in many natural products and biologically active molecules.[1] These molecules exhibit the wide range of biological activities as well as serve as a key intermediate for various synthetic transformations.[2] Considering all these importance, enormous effort has been devoted to synthesize isocoumarins.[3] In recent years, by using

metal catalysts, isocoumarins are prepared very efficiently. Generally, isocoumarins are prepared by the metal-catalyzed cyclization of *o*-haloaromatic esters or acid with π-components, carbonylative cyclization of *o*-halophenols with π-components and electrophilic cyclization of substituted alkynes.[3]

Transition-metal-catalyzed oxidative cyclization of substituted benzoic acids with alkynes *via* C-H bond activation is an efficient method for synthesizing isocoumarins in a highly atom-economical manner as compared with other metal-catalyzed reactions.[4] A few reports are available in the literature for synthesizing isocoumarins in the presence of Ru,[5b-c] Rh,[5d-i] Co[5j] and Ir[5k-l] complexes via C-H bond activation. In the known methodologies, Rh, Ir and Co metals provided regioisomeric mixtures of isocoumarin derivatives in the reaction of aromatic acids with unsymmetrical alkynes (Scheme 1). In the observed major product, the aryl substituted carbon of an alkyne prefers to stay at the C3 position. In the meantime, the ruthenium metal provides the cyclized product in a highly regioselective manner. Subsequently, the iridium metal also selectively provided naphthalene derivatives apart from isocoumarins.

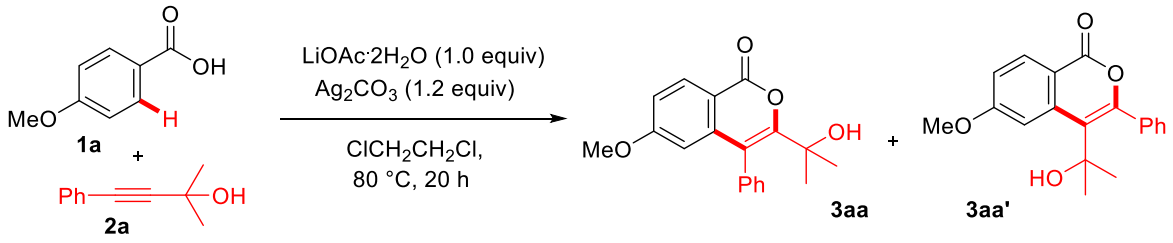
Scheme 1. Cyclization of Benzoic Acids with Alkynes



Herein, we report a diverse regioselective oxidative cyclization of benzoic acids with propargyl alcohols in the presence of metal catalysts such as Ru or Rh or Ir (Scheme 2). It is interesting to note that in the Ru and Ir metal catalysts; the phenyl group is attached at the C4 position and the alkyl group at the C3 position very selectively which is the diverse selectivity as compared with previous methods. However, in the rhodium-catalyzed reaction, mixture of regioisomeric products was observed. In the present cyclization reaction, the steric

as well as coordinating ability of tertiary hydroxyl group of propargyl alcohol plays a significant role for the high regioselectivity by coordinating with the Ir metal forming a seven-membered metalacycle intermediate. It is important to note that the other competitive reaction such as *ortho* allenylation followed by cyclization via β-hydroxyl elimination was not observed.[6]

Scheme 2. Metal-Catalyzed Oxidative Cyclization



[{Ru(CH$_3$CN)$_3$(*p*-cymene)}{SbF$_6$}$_2$] (10 mol %)	25%	-
[{Rh(CH$_3$CN)$_3$(Cp*)}{SbF$_6$}$_2$] (10 mol %)	76%	8%
[Cp*IrCl$_2$]$_2$ (3 mol %)	86%	-

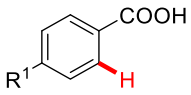
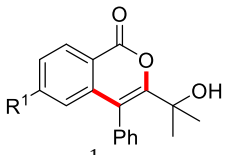
Results and Discussion

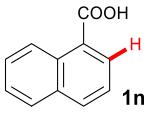
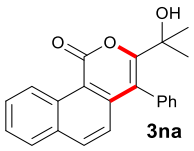
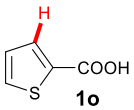
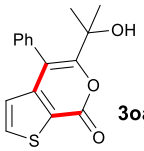
Treatment of 4-methoxybenzoic acid (**1a**) with propargyl alcohol **2a** in the presence of [Cp*IrCl$_2$]$_2$ (3 mol %), LiOAc·2H$_2$O (1.0 equiv) and Ag$_2$CO$_3$ (1.2 equiv) in ClCH$_2$CH$_2$Cl at 80 °C for 20 h gave isocoumarin derivative **3aa** in 86% isolated yield in a highly selective manner (Scheme 2). In the reaction, the other possible regioisomer **3aa'** was not observed. In product **3aa**, the alkyl substituted carbon of **2a** is attached at the C3 position and Ph group at the C4 position. Initially, the cyclization reaction of **1a** with **2a** was examined in the presence of [{Ru(CH$_3$CN)$_3$(*p*-cymene)}{SbF$_6$}$_2$] (10 mol %) in ClCH$_2$CH$_2$Cl at 100 °C for 24 h. In the reaction, product **3aa** was observed in 25% yield. The reaction was examined with various solvents and acetate sources. However, no improvement was observed in the yield (for detailed optimization studies, see Supporting Information (SI)). Meanwhile, the reaction was examined with various oxidants including Ag$_2$CO$_3$ along with LiOAc·2H$_2$O. The yield of product **3aa** was not increased. Next, the reaction was examined with other metal catalysts such as rhodium and iridium. The cyclization reaction of **1a** with **2a** in the presence of [{Rh(CH$_3$CN)$_3$(Cp*)}{SbF$_6$}$_2$] (10 mol %), LiOAc·2H$_2$O (1.0 equiv) and Ag$_2$CO$_3$ (1.2 equiv) in ClCH$_2$CH$_2$Cl at 100 °C for 24 h provided mixture of regioisomeric products **3aa** and **3aa'**

in 76% and 8% yields, respectively. It is very interesting to note that the same reaction was examined in the presence of $[Cp^*IrCl_2]_2$ (3 mol %). In the reaction, exclusively product **3aa** was observed in 86% yield. The reaction was examined without $LiOAc{\cdot}2H_2O$. In the reaction, product **3aa** was observed in 61% yield. Product **3aa** was not observed without Ag_2CO_3. Meanwhile, the product yield **3aa** was observed in 63% yield in the presence of 0.6 equiv of Ag_2CO_3. The optimization study clearly reveals that both Ag_2CO_3 and LiOAc are crucial for getting **3aa** in more yields and also $[Cp^*IrCl_2]_2$ is crucial for the high regioselectivity (see SI for the detailed optimization studies).

The scope of annulation reaction was examined with assorted substituted benzoic acids (Table 1). 4-Methyl benzoic acid (**1b**) or benzoic acid (**1c)** reacted with **2a** giving the expected products **3ba** and **3ca** in 89% and 88% yields, respectively (entries 1-2). Halogen I, Br, Cl, F substituent at the *para* position of benzoic acids **1d-g** effectively participated in the reaction, giving **3da-3ga** in 60%, 77%, 87% and 81% yields, respectively (entries 3-6). Electron-withdrawing 4-nitro and 4-cyano benzoic acids **1h-i** provided the expected products **3ha** and **3ia** in moderate 42% and 32% yields, respectively (entries 7 and 8). *ortho* Methyl and phenyl benzoic acids **1j-k** was also efficiently involved in the reaction, affording products **3ja** and **3ka** in 82% and 56%, respectively (entries 9 and 10). Interestingly, a free hydroxyl group substituted 3,5-dihydroxy benzoic acid **1l** as well as **1m** also efficiently participated in the reaction, yielding products **3la** and **3ma** in 53% and 75% yields, respectively. 1-Naphthoic acid (**1n)** reacted with **2a** giving **3na** in moderate 31% yield. Heterocyclic, thiophene 2-carboxylic acid **1o**, also efficiently participated in the reaction, giving product **3oa** in 40% yield.

Table 1. Scope of Aromatic Acids 1b-o[a]

Entry	**1**	product **3**	yield (%)[b]
			
1	**1b**: R^1 = Me	**3ba**: R^1 = Me	89
2	**1c**: R^1 = H	**3ca**: R^1 = H	88
3	**1d**: R^1 = I	**3da**: R^1 = I	60
4	**1e**: R^1 = Br	**3ea**: R^1 = Br	77
5	**1f**: R^1 = Cl	**3fa**: R^1 = Cl	87
6	**1g**: R^1 = F	**3ga**: R^1 = F	81
7	**1h**: R^1 = NO_2	**3ha**: R^1 = NO_2	42

8	**1i**: R^1 = CN	**3ia**: R^1 = CN	32
9	**1j**: R^1 = Me	**3ja**: R^1 = Me	82
10	**1k**: R^1 = Ph	**3ka**: R^1 = Ph	56
11	**1l**: R^1 = OH	**3la**: R^1 = OH	53
12	**1m**: R^1 = OMe	**3ma**: R^1 = OMe	75
13	 **1n**	 **3na**	31
14	 **1o**	 **3oa**	40

[a]All reactions were carried out using **1b-o** (0.057 gm, 0.37 mmol), **2a** (0.050 gm, 0.3 mmol), $[Cp^*IrCl_2]_2$ (0.007 gm, 0.009 mmol), $LiOAc{\cdot}2H_2O$ (0.032 gm, 0.3 mmol) and Ag_2CO_3 (0.103 gm, 0.37 mmol) in $ClCH_2CH_2Cl$ (2.0 mL) under N_2 at 80 °C for 20 h. [b]Isolated yield.

Interestingly, *meta* Cl **1p** and Br **1q** substituted benzoic acids reacted with **2a** providing single regioisomeric products **3pa** and **3qa** in 50% and 63% yields, respectively (Scheme 3). However, 3-methoxy benzoic acid **1r** provided mixture of regioisomeric products **3ra** and **3ra'** in 82% combined yields in a 1:1 ratio. 3,4-Dimethoxy benzoic acid **1s** reacted with **2a** giving cyclized product **3sa** in 92% in a highly selective manner. However, piperonylic acid (**1t**) afforded regioisomeric products **3ta** and **3ta'** in combined 73% yields in 3:1 ratio. At present, the exact rationale behind the observation of difference in the regioselectivity of benzoic acids **1p-t** is unclear. It is believed that the steric hindrance could play an important role for the high regioselectivity.

Scheme 3. Scope of Unsymmetrical Benzoic Acids

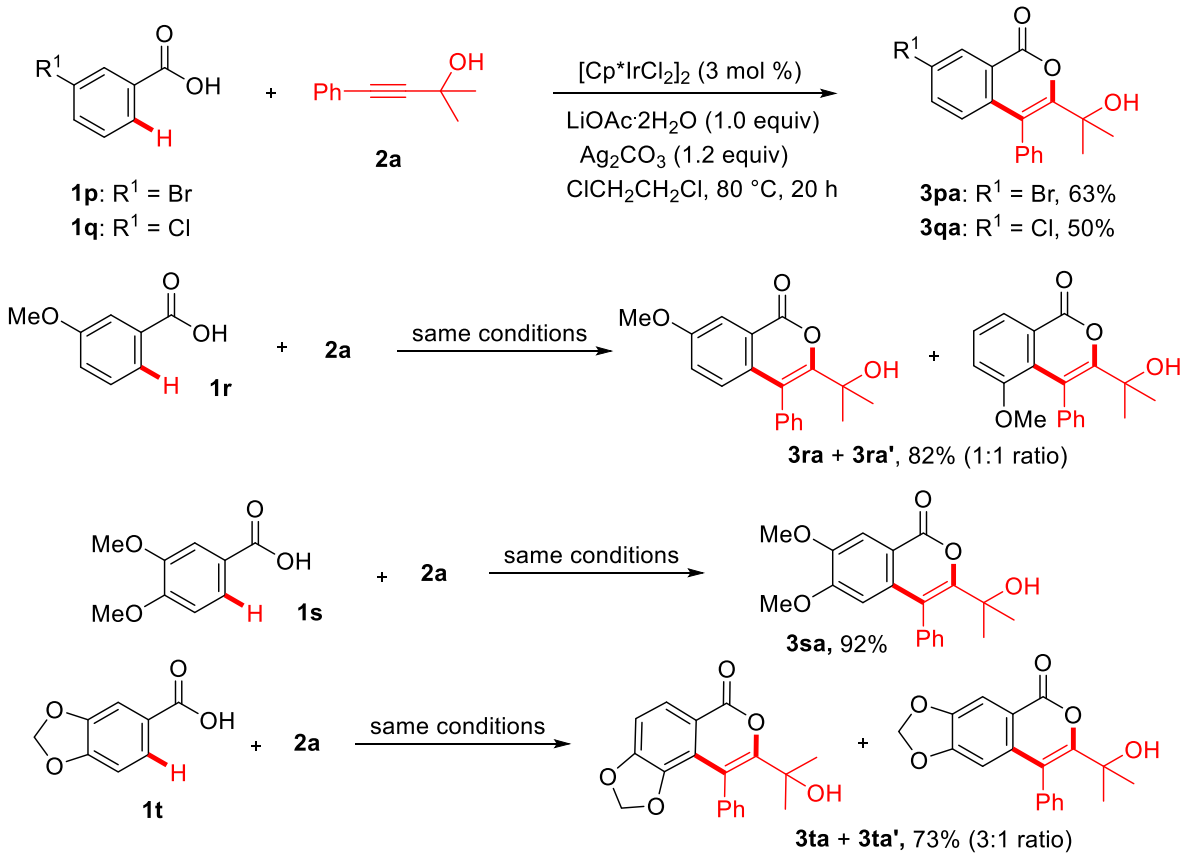
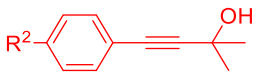
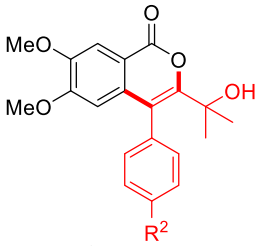
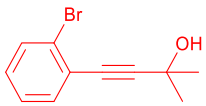
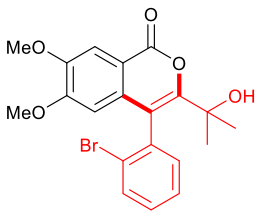
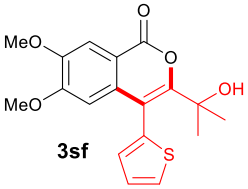
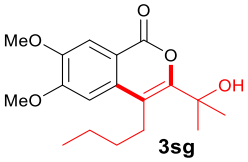
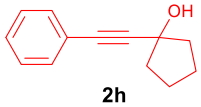
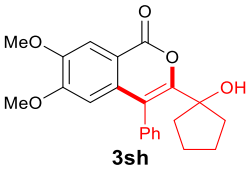
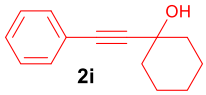
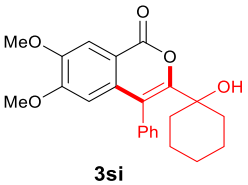


Table 2. Scope of Propargyl Alcohols 2b-i[a]

Entry	2	product 3	yield (%)[b]
			
1	**2b**: R^1 = OMe	**3sb**: R^1 = OMe	92
2	**2c**: R^1 = Me	**3sc**: R^1 = Me	75
3	**2d**: R^1 = Br	**3sd**: R^1 = Br	78
4	 **2e**	 **3se**	94

5	 **2f**	 **3sf**	75
6	 **2g**	 **3sg**	92
7	 **2h**	 **3sh**	80
8	 **2i**	 **3si**	90

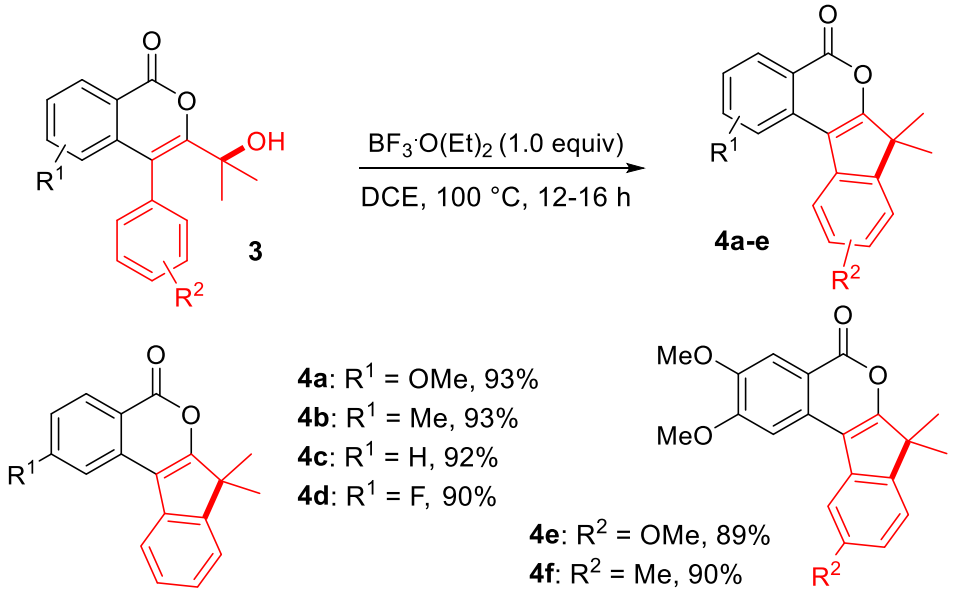
[a]All reactions were carried out using **1s** (0.057 gm, 0.37 mmol), **2b-i** (0.050 gm, 0.3 mmol), $[Cp^*IrCl_2]_2$ (0.007 gm, 0.009 mmol), $LiOAc{\cdot}2H_2O$ (0.032 gm, 0.3 mmol) and Ag_2CO_3 (0.103 gm, 0.37 mmol) in $ClCH_2CH_2Cl$ (2.0 mL) under N_2 at 80 °C for 20 h. [b]Isolated yield.

The scope of cyclization reaction was examined with substituted propargyl alcohols (Table 2). The reaction of OMe, Me, Br substituent on the aryl ring of propargyl alcohols **2b-d** with **1s** gave cyclized products **3sb-3sd** in 92%, 75% and 78% yields, respectively (entries 1-3). *ortho* Bromo substituent on the aryl ring of propargyl alcohol **2e** also efficiently participated in the reaction, giving cyclized product **3se** in 94% yield. Heterocyclic 2-thienyl **2f** and alkyl **2g** substituted propargyl alcohols also efficiently reacted with **1s**, affording cyclized products **3sf** and **3sg** in 75% and 92% yields, respectively. α-Disubstituted propargyl alcohols **2h** and **2i** reacted with **1s**, giving cyclized products **3sh** and **3si** in 80% and 90% yields, respectively. The structure of **3ba** (CCDC 1875730) is confirmed by a single crystal XRD (see SI). However, 3-phenylprop-2-yn-1-ol, but-2-yn-1-ol, α-methyl substituted 4-phenylbut-3-yn-2-ol, (3,3-dimethylbut-1-yn-1-yl)benzene as well as 3,3-dimethylbut-1-yne were not suitable for the reaction.

The isocoumarin derivatives were further converted into biologically active tetracyclic systems indeno[2,1-*c*]isocoumarin by intramolecular Lewis acid mediated cyclization.

Treatment of **3aa** with $BF_3{\cdot}O(Et)_2$ in DCE at 100 °C for 12 h gave tetracyclic product **4a** in excellent 93% yield (Scheme 4). In a similar fashion, products **3aa**, **3ba**, **3ca**, **3ga**, **3sb** and **3sc** were converted into the expected products **4b-f** in excellent 93%, 93%, 92%, 90%, 89% and 90% yields, respectively. This type of tetracyclic molecules shows various biological properties including anticancer and cytotoxic properties.[7] The structure of **4a** (CCDC 1875796) is confirmed by a single crystal XRD (see SI).

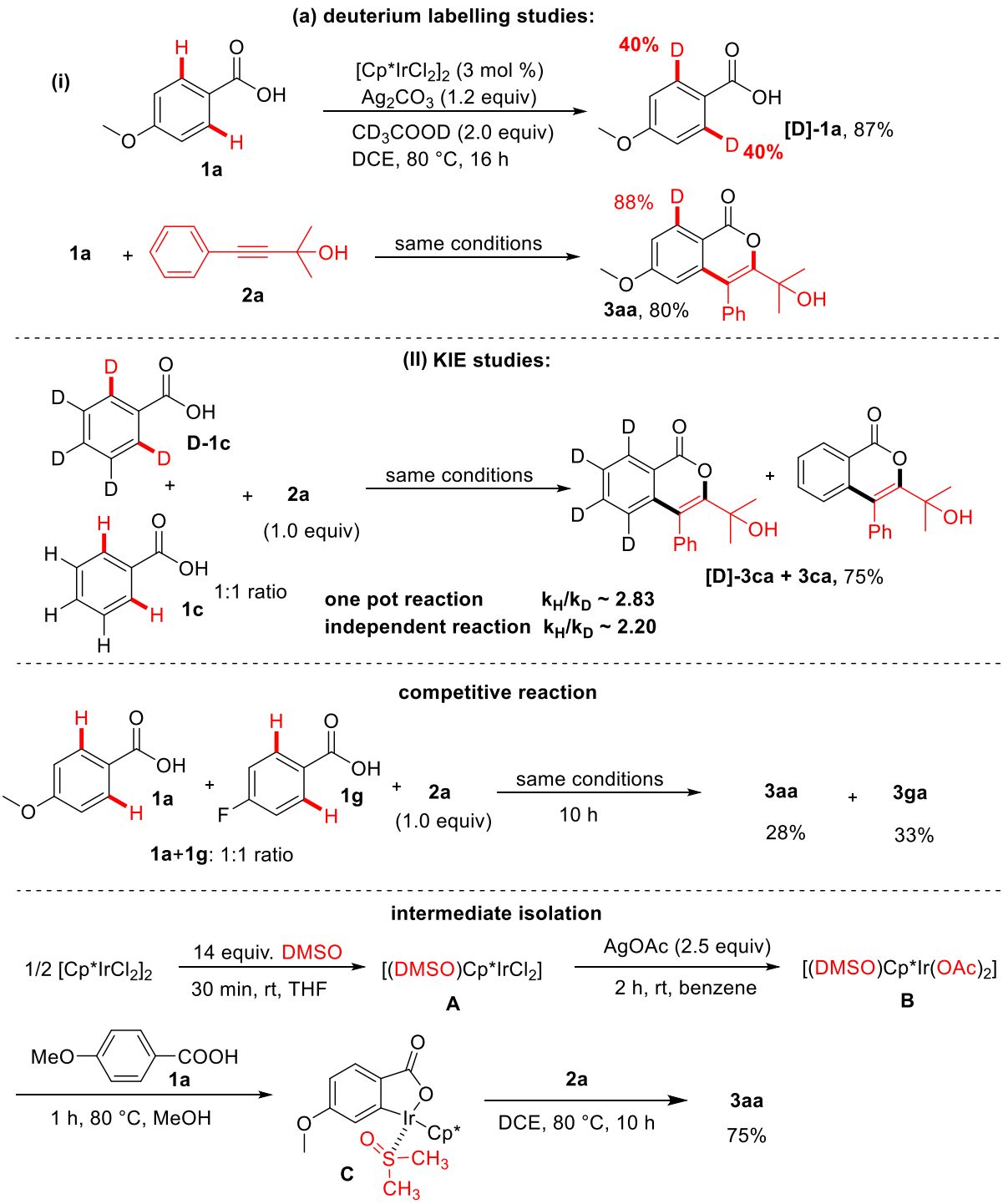
Scheme 4. Preparation of Indeno[2,1-*c*]isocoumarins



The reaction of 4-methoxy benzoic acid (**1a**) with d_4-AcOH provided [**D**]-**1a** in 80% yield in which the deuterium incorporation was observed at the both *ortho* carbons in 40% (Scheme 5). Further, in the reaction of **1a** with **2a** in the presence of d_4-AcOH, product **[D]-3aa** was observed in 87% yield, in which 88% of deuterium incorporation was observed at the *ortho* C-H position. This result reveals that the C-H bond activation is a reversible process. Further, the kinetic isotopic effect study was carried by using deuterated benzoic acid **[D]-1c** and benzoic acid **1c** in the competitive version and independent version. In the competitive reaction, k_H/k_D was observed to be around 2.83. Similarly, in parallel two pot reaction, k_H/k_D was observed around 2.2. This result reveals that the C-H activation could be the rate determining step in the reaction. Next, the competitive reaction was carried out with equal amount of 4-F **1g** and 4-OMe **1a** benzoic acids. In the reaction, **3aa** was observed in 28% and **3ha** in 33% yields, respectively. This indicates that the electrophilic iridiation is unlikely. Further, the metalacycle intermediate **C** was isolated in the reaction of $Cp^*Ir(OAc)_2{\cdot}DMSO$

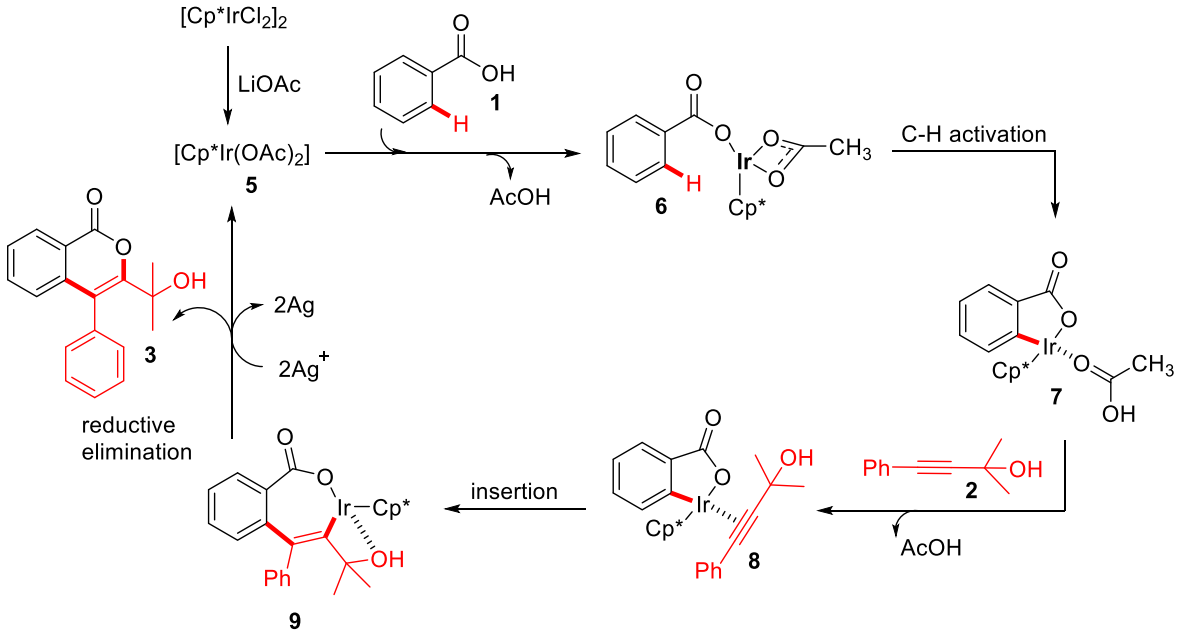
with **1a**. Later, the metalacycle intermediate **C** was treated with **2a** yielding product **3aa** in 75% yield. This result suggests that the metalacycle is key intermediate in the reaction.

Scheme 5. Mechanistic Studies



A plausible mechanism is proposed for the cyclization reaction in Scheme 6. The $[Cp^*IrCl_2]_2$ complex reacted with LiOAc giving the active catalyst $[Cp^*Ir(OAc)_2]$ **5**. The benzoic acid **1** reacted with one of the acetate groups of complex **5** affording benzoate-Ir complex **6**. The *ortho* C-H bond of benzoate is deprotonated by an acetate group in complex **6** provides iridiacycle intermediate **7**. The regioselective coordinative insertion of propargyl alcohol **2** into the Ir-C bond of complex **7** gives a seven membered iridiacycle intermediate **9**. The reductive elimination of intermediate **9** giving product **3** and Ir(I) species. The active Ir(III) species **5** can be regenerated by the reaction of Ir(I) with Ag(I) and AcOH

Scheme 6. Proposed Mechanism



DFT calculations were carried out for understanding the proposed reaction mechanism using M06 density functional theory (Figure 1). The active catalyst $[Cp^*Ir(OAc)_2]$ **5** can be generated by the reaction of $[Cp^*IrCl_2]_2$ with LiOAc. In the first step, lithium benzoate replaces one of the acetate ligand in the active complex **5**, gives **int-6** which has coordination of benzoate through the oxygen atom, one acetate moiety and Cp* ligand. Concerted metalation-deprotonation of the *ortho* C-H bond of benzoate in **int-6** takes place via **TS-1**, forming **int-7**. The *ortho* C-H bond in intermediate **int-6** is activated by an acetate moiety *via* agostic interaction. The overall C-H activation barrier is found to be 16.0 kcal.mol^{-1}. The replacement of acetic acid by propargyl alcohol **2** in **int-7** forms **int-8a**. It involves pre-coordination of the hydroxyl group with an iridium metal centre which may be the reason for

high regioselectivity. In next step, more stable **int-8b** is formed by coordination of Ir to alkyne carbon of propargyl alcohol exergonically (-10.33 kcal.mol^{-1}). It is noted that the formation of isomer **8b** is more favourable than the isomer **8b'** by -2 kcal. mol^{-1}. Meanwhile, the energy calculation for transition states was also performed. It was observed that the **TS-2** (18.4 kcal/mol) has lower energy than the **TS-2'** (21.2 kcal/mol). Both steric as well as weak interaction between Ir-O play an important role for the selectivity. Since the distance between Ir-O is 3.23 Å, there could be very weak interaction between metal and oxygen atom in **TS-2**. Meanwhile, the steric factor may also play the major role in the selective formation of **TS-2**. Further, more stable **TS-2** results in **int-9** exergonically (-42.0 kcal.mol^{-1}). In the next step, **int-9** is rearranged into **int-10a** by absorption of 19.17 kcal.mol^{-1} of energy followed by oxidation with AgOAc providing thermodynamically stable **int-10b**. The **int-10b** dissociates product **3** and further oxidizes with AgOAc giving active catalyst **5**.[5k] It is expected that the pre-coordination of the OH group and steric effect of propargyl alcohol could be important for the selectivity.

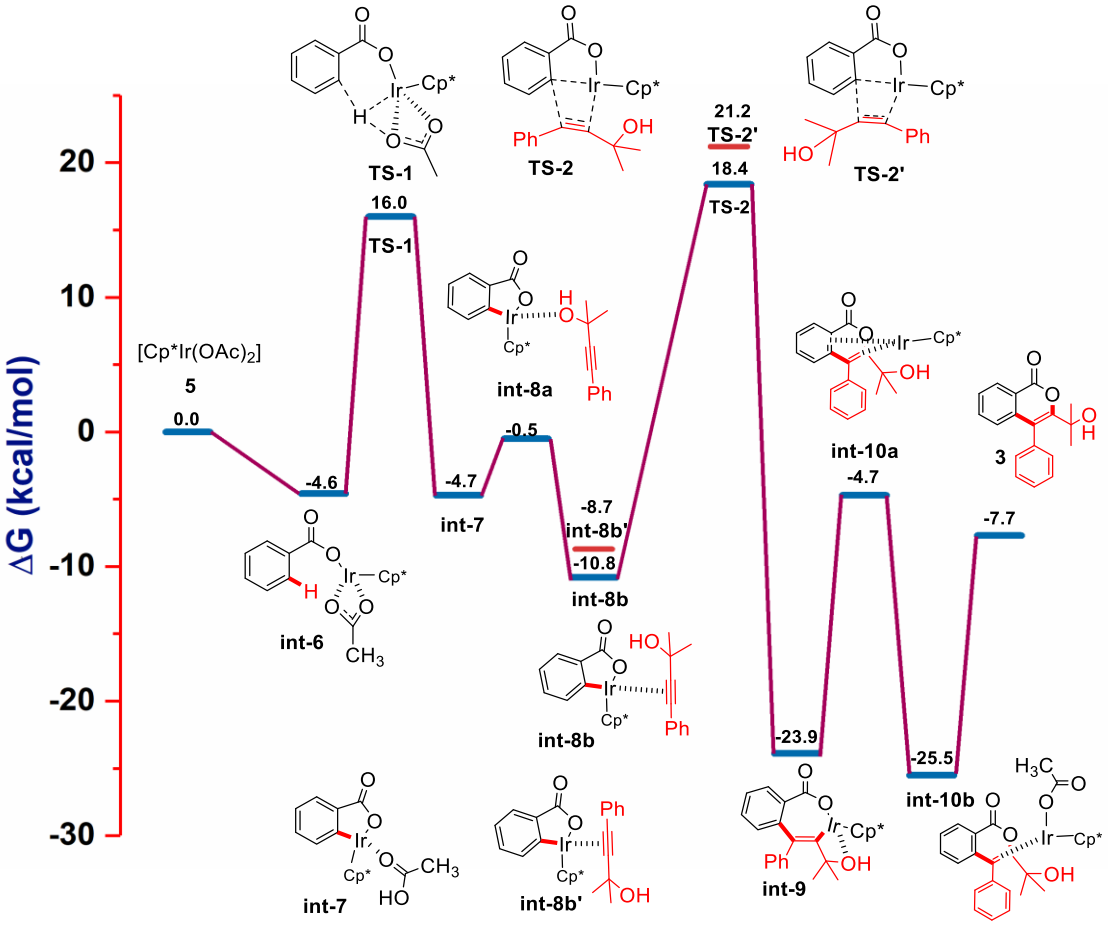


Figure 1. DFT-computed energy profiles.

Conclusion

In conclusion, we have demonstrated an iridium-catalyzed cyclization of benzoic acids with propargyl alcohols. The reaction provides isocoumarins in a highly regioselective manner. The hydroxyl group of propargyl alcohol plays crucial role for the high selectivity. The observed isocoumarins were converted into tetracyclic indeno[2,1-*c*]isocoumarins by Lewis acid mediated cyclization. A possible reaction mechanism was proposed and strongly supported by the detailed mechanistic investigation and DFT studies.

Experimental Section

General information: All reactions were carried out under the N_2 atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use (three times). Dry solvents are used for the reaction. Column chromatographical purifications were performed using SiO_2 (120- 200 mesh ASTM) from Merck if not indicated otherwise. Abbrevations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The starting materials, propargyl alcohols **2a-i**, were prepared according to the literature procedures.[8] Commercially available metal salts and acids were purchased from Sigma-Aldrich and Spectrochem. Pvt. Ltd., India and used without further purification.

General Procedure 1 for the Synthesis of Isocoumarins.

A 15 ml schlenk tube with septum containing propargyl alcohol **2a** (0.050 gm, 0.3 mmol), 4-methoxy benzoic acid **1a** (0.057 gm, 0.37 mmol), $LiOAc{\cdot}2H_2O$ (0.032 gm, 0.3 mmol), Ag_2CO_3 (0.103 gm, 0.37 mmol) and $[Cp^*IrCl_2]_2$ (0.007 gm, 0.009 mmol) was evacuated and purged with nitrogen gas three times. Followed by 1,2-Dichloroethane (2 mL) was added *via* syringe and the reaction mixture was evacuated and purged with nitrogen gas three times. Then rubber septum was taken out and screw cap was used to cover the tube. The reaction mixture was allowed to stir at 80 $^{\circ}$C for 20 h. Then the reaction mixture was allowed to reach ambient temperature and diluted with CH_2Cl_2, followed by filteration through celite and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent to give pure **3aa** in 86% isolated yield. The yield of product was calculated based on propargyl alcohol **2a.**

General Procedure 2 for the Synthesis of Indeno[2,1-*c*] isocoumarins.

A 15 ml schlenk tube with septum containing isocoumarin **3aa** (0.050 gm, 0.2 mmol) was dissolved in 2 mL of 1,2-Dichloroethane. Then, $BF_3.O(C_2H_5)_2$ (0.02 mL, 0.16 mmol) was added *via* syringe. Then, rubber septum was taken out and screw cap was used to cover the tube. The reaction mixture was allowed to stir at 100 $^{\circ}$C for 12 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent to give pure **4a** in 93% isolated yield.

Mechanistic Studies

Deuterium labelling studies:

(i) Preparation of *ortho*-deuterated 4-OMe benzoic acid [D]-1a:

A 15 mL schlenk tube with septum containing **1a** (0.050 gm, 0.3 mmol), $[Cp^*IrCl_2]_2$ (0.009 gm, 0.009 mmol), Ag_2CO_3 (0.108 gm, 0.4 mmol). was evacuated and purged with nitrogen gas three times. Followed by solvent $ClCH_2CH_2Cl$ (2 mL) and CD_3COOH (1 mL) were added *via* syringe and again the reaction mixture was evacuated and purged with nitrogen gas three times. Then rubber septum was taken out and screw cap was used to cover the tube. The reaction mixture was allowed to stir at 80 ^oC for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through celite and the filtrate was concentrated and product [**D]-1a** was observed in 87% yield with 40% of deuterium incorporation at both ortho carbons, respectively.

Reaction of *ortho*-deuterated 4-OMe benzoic acid [D]-1a with 2a:

A 15 mL schlenk tube with septum containing propargyl alcohol **2a** (0.050 gm, 0.3 mmol), [**D]-1a** (0.049 gm, 0.4 mmol), $LiOAc.2H_2O$ (0.032 gm, 0.3 mmol) and $[Cp^*IrCl_2]_2$ (0.007 gm, 0.009 mmol) was evacuated and purged with nitrogen gas three times. Followed $ClCH_2CH_2Cl$ (2 mL) was added *via* syringe and again the reaction mixture was evacuated and purged with nitrogen gas three times. Then rubber septum was taken out and screw cap was used to cover the tube. The reaction mixture was allowed to stir at 80 ^oC for 20 h. After cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2, filtered through celite and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent to give pure **[D]-3aa** product was observed in 80% yield with 88% of deuterium incorporation at ortho hydrogen.

(ii) Kinetic isotopic effect studies (KIE):

For one pot reaction:

In 15 mL schlenk tube, **1c** (0.038 gm, 0.3 mmol), **[D]-1c** (0.040 gm, 0.3 mmol), **2a** (1.0 equiv, 0.3 mmol), $[Cp^*IrCl_2]_2$ (0.007gm, 0.009 mmol), Ag_2CO_3 (0.103 gm, 0.4 mmol), $LiOAc{\cdot}2H_2O$ (0.032 gm, 0.3 mmol), was added and then purged with nitrogen gas three times. Then 2 mL of $ClCH_2CH_2Cl$ was added *via* syringe. After that, the tube was purged and evacuated with N_2 gas three times and screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 80 ^oC for 10 h. Then the reaction mixture was allowed to reach ambient temperature and diluted with CH_2Cl_2, followed by filteration through celite

and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent to give combined products **3ca** and **[D]-3ca** with 75% yield. From ^{1}H-NMR, the KIE value was found to be 2.83.

For independent reaction:

In separate 15 mL schlenk tubes, **1c** (0.076 gm, 0.6 mmol), **[D]-1c** (0.079 gm, 0.6 mmol), **2a** (0.100 gm, 0.6 mmol), $[Cp^*IrCl_2]_2$ (0.014 gm, 0.009 mmol), Ag_2CO_3 (0.103 gm, 0.4 mmol), $LiOAc{\cdot}2H_2O$ (0.032 gm, 0.3 mmol), was added. 1,3,5-trimethoxybenzene(0.105gm, 0.625 mmol) was also added as internal reference.Then 3 mL of $ClCH_2CH_2Cl$ was added *via* syringe. After that, the tube was purged and evacuated with N_2 gas three times and screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 80 °C. After 60 minutes, an aliquot (0.1 mL) was removed by a syringe every 20 min for 1 hour,filtered and concentrated under reduced pressure. Yields of products were determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal reference. Data from independent kinetic isotope studies are collected in **Table S2** (see SI) and using plot, KIE was found to be $k_H/k_D \approx 2.2$.

Procedure for Competitive reaction between 1a and 1c:

In 15 mL schlenk tube, **1a** (0.048 gm, 0.3mmol), **1g** (0.044 gm, 0.3mmol), **2a** (0.050 gm 0.3 mmol), $[Cp^*IrCl_2]_2$ (0.007 gm, 0.009 mmol), Ag_2CO_3 (0.103 gm, 0.4 mmol), $LiOAc{\cdot}2H_2O$ (0.032 gm, 0.3 mmol), was added and then purged with nitrogen gas three times. Then 2 mL of $ClCH_2CH_2Cl$ solvent was added using syringe. After that, the tube was purged and evacuated with N_2 gas three times and screw cap was used to cover the tube. Then, the reaction mixture was allowed to stir at 80 ^{o}C for 20 h. Then the reaction mixture was allowed to reach ambient temperature and diluted with CH_2Cl_2, followed by filteration through celite and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexane and ethyl acetate as eluent to get product **3aa** and **3ga** in 28% and 33%.

Procedure for Intermediate Isolation.

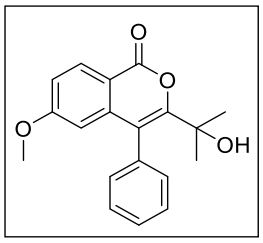
Intermediate **C** was isolated according to literature procedure.[5m] Followed by its reaction with **2a** taking equal equivalents of both in a 15 mL schlenk tube at 80 ^{o}C for 16 h and product was isolated with 75% yield.

Computational Details.

DFT computations were carried out using the Gaussian 09 program (revision A.02).[9] The model systems have been fully optimized using the B3LYP density functional theory *via* vibrational frequency calculations as either minima (all positive frequency) or transition states (one negative frequency) obtained the zero-point energy (ZPE), and thermal correction. The valence orbitals of iridium were described using the SDD basis set, non-metal centers were described using the 6-31G* basis set. IRC calculations and subsequent geometry optimizations were used to confirm the minima linked by each transition state. A solvent correction (for DCE) was performed using the polarized continuum model (PCM).[10] The M06 functional has been used to improve the treatment of non-covalent interactions in the model systems.[11] Single point energies including solvent effects were evaluated at the PCM (in DCE)/M06/6-31G(d), SDD(Ir). The energy profile diagram of the reaction pathway is presented as Gibbs free energy changes (ΔG's) involving zero-point vibrational energy (ZPVE) and thermal corrections obtained at 298.15 K and 1 atm pressure. To estimate the Gibbs free energies of M06 calculations, the ZPVE and thermal corrections obtained from the B3LYP calculations have been used.

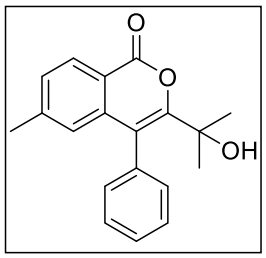
Spectral Data of All Compounds:

3-(2-Hydroxypropan-2-yl)-6-methoxy-4-phenyl-1*H*-isochromen-1-one (3aa)



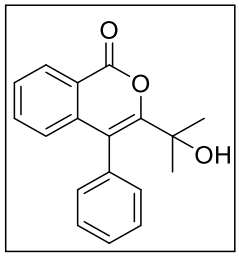
Prepared according to **GP 1;** white solid. 84 mg, 86% yield, eluent (10 % ethyl acetate in hexane), mp: 124-125 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.27 (dd, *J* = 8.8, 3.6Hz, 1H), 7.68 – 7.41 (m, 3H), 7.43 – 7.19 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.18 (d, *J* = 1.6 Hz, 1H), 3.69 (s, 3H), 1.47 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 164.8, 161.6, 157.6, 142.2, 134.5, 131.8, 130.8, 129.1, 128.6, 115.6, 114.3, 113.4, 108.8, 73.6, 55.5, 30.4. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{19}O_4$ 311.1283; Found 311.1271.

3-(2-Hydroxypropan-2-yl)-6-methyl-4-phenyl-1*H*-isochromen-1-one (3ba)



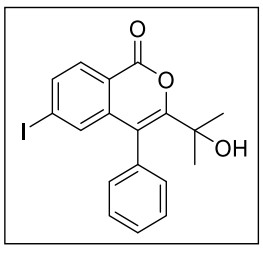
Prepared according to **GP 1**; white solid. 82 % yield, 75 mg, eluent (8 % ethyl acetate in hexane), mp: 164-165 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.22 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.32 – 7.27 (m, 3H), 6.56 (s, 1H), 2.31 (s, 3H), 1.98 (s, 1H), 1.46 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 161.7, 156.8, 145.8, 139.6, 134.4, 130.7, 129.3, 129.2, 128.8, 128.3, 125.3, 117.5, 114.2, 73.4, 29.8, 22.1. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{19}O_3$ 295.1334; Found 295.1331.

3-(2-Hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3ca)



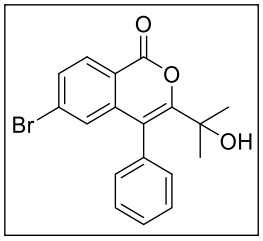
Prepared according to **GP 1**; white solid. 81 mg, 92 % yield, eluent (8 % ethyl acetate in hexane), mp: 100-101 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.34 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.52 – 7.45 (m, 4H), 7.32 – 7.28 (m, 2H), 6.81 (d, *J* = 8 Hz, 1H), 1.90 (s, 1H), 1.48 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.7, 156.8, 139.6, 134.6, 134.3, 130.7, 129.2, 128.9, 128.4, 127.9, 125.3, 119.9, 114.3, 73.6, 29.9. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{17}O_3$ 281.1178; Found 281.1172.

3-(2-Hydroxypropan-2-yl)-6-iodo-4-phenyl-1*H*-isochromen-1-one (3da)



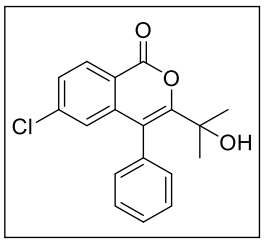
Prepared according to **GP 1**; white solid.76 mg, 60% yield, eluent (8 % ethyl acetate in hexanes), mp: 170-171 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.30 – 7.25 (m, 2H), 7.14 (d, *J* = 1.5 Hz, 1H), 1.84 (s, 1H), 1.46 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.3, 158.1, 140.8, 137.3, 134.3, 133.4, 130.5, 130.4, 129.1, 128.7, 119.1, 113.2, 103.6, 3.5, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}IO_3$ 407.0144; Found 407.0138.

6-Bromo-3-(2-hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3ea)



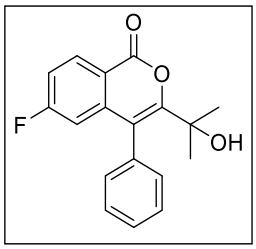
Prepared according to **GP 1**; white solid. 86 mg, 60% yield, eluent (8 % ethyl acetate in hexane), mp: 176-177 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):**δ 8.17 (d, *J* = 8 Hz, 1H), 7.60 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.30 – 7.27 (m, 2H), 6.93 (d, *J* = 1.8 Hz, 1H), 1.87 (s, 1H), 1.47 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**:δ 161.0, 158.3, 141.1, 133.4, 131.4, 130.8, 130.5, 130.5, 129.1, 128.7, 128.1, 128.1, 118.6, 113.7,73.5, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}BrO_3$ 359.0283; Found 359.0277.

6-Chloro-3-(2-hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3fa)



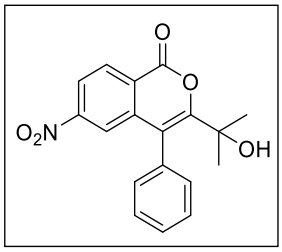
Prepared according to **GP 1**; white solid. 75 mg, 87% yield, eluent (8 % ethyl acetate in hexane), mp: 178-179 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.25 (d, *J* = 8.5 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.44 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.76 (d, *J* = 1.9 Hz, 1H), 1.91 (s, 1H), 1.47 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 160.9, 158.3, 141.6, 141.1, 133.5, 130.8, 130.5, 129.1, 128.7, 128.5, 125.0, 118.2, 113.6, 73.5, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}ClO_3$ 315.0788; Found 315.0785.

6-Fluoro-3-(2-hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3ga)



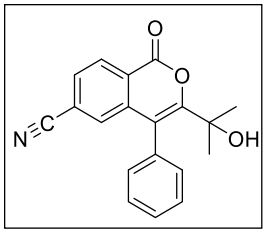
Prepared according to **GP 1**; white solid. 75 mg, 81 % yield, eluent (8 % ethyl acetate in hexanes), mp: 148-149 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.34 (dd, *J* = 8.7, 5.8 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.29 (dd, *J* = 8.0, 2 Hz, 2H), 7.17 (td, *J* = 8.0, 2.5 Hz, 1H), 6.44 (dd, *J* = 10.1, 2.5 Hz, 1H), 1.96 (s, 1H), 1.48 (s, 6H). **^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 167.8, 165.7 (d, ^{1}J=256 Hz), 160.7, 158.2, 142.,142.6(d, ^{3}J=10Hz), 133.7, 132.5 ,132.4 (d, ^{3}J =10Hz), 130.5, 129.1, 128.6, 116.4,116.2 (d, ^{2}J=23.5Hz), 113.9, 111.5 ,111.28(d, ^{2}J=24.0Hz), 73.4, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}FO_3$ 299.1083; Found 299.1077.

3-(2-Hydroxypropan-2-yl)-6-nitro-4-phenyl-1*H*-isochromen-1-one (3ha)



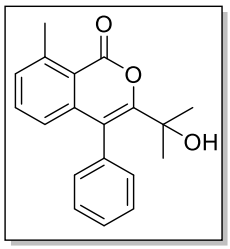
Prepared according to **GP 1**; yellow solid. 43 mg, 42% yield, eluent (15 % ethyl acetate in hexane), mp: 126-127 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.44 (d, *J* = 8.5 Hz, 1H), 8.18 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.25 – 7.21 (m, 2H), 1.44 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 159.9, 159.4, 151.8, 141.0, 132.8, 131.2, 130.4, 129.45, 129.2, 123.8, 121.9, 120.5, 113.9, 73.6, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}NO_5$ 326.1028; Found 326.1013.

3-(2-Hydroxypropan-2-yl)-1-oxo-4-phenyl-1*H*-isochromene-6-carbonitrile (3ia)



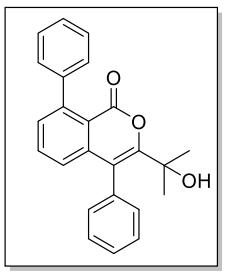
Prepared according to **GP 1**; yellow solid. 30 mg, 32% yield, eluent (15 % ethyl acetate in hexane), mp: 124-125 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.36 – 8.33 (m, 1H), 7.64 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.24 – 7.20 (m, 2H), 7.04 (d, *J* = 1.0 Hz, 1H), 1.42 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 160.2, 159.1, 140.2, 132.9, 130.4, 130.2, 129.7, 129.4, 129.1, 122.6, 118.2, 117.5, 113.6, 113.3, 73.6, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{16}NO_3$ 306.1130; Found 306.1115.

3-(2-Hydroxypropan-2-yl)-8-methyl-4-phenyl-1*H*-isochromen-1-one (3ja)



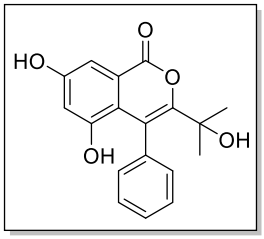
Prepared according to **GP 1**; white solid. 72 mg, 82% yield, eluent (8% ethyl acetate in hexane), mp: 110-111 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.51 – 7.43 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.27 (ddd, *J* = 8.5, 5.0, 1.5 Hz, 3H), 6.63 (d, *J* = 8.0 Hz, 1H), 2.86 (s, 3H), 1.96 (s, 1H), 1.45 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 160.9, 156.4, 143.2, 141.1, 134.9, 133.7, 130.9, 130.8, 128.9, 128.3, 123.5, 118.5, 114.2, 73.2, 29.8, 23.4. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{19}O_3$ 295.1334; Found 295.1330.

3-(2-Hydroxypropan-2-yl)-4,8-diphenyl-1*H*-isochromen-1-one (3ka)



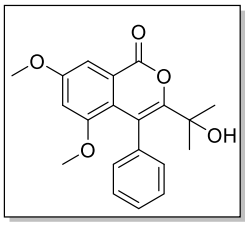
Prepared according to **GP 1**; white solid. 75 mg, 56% yield, eluent (10 % ethyl acetate in hexane) mp: 140-141 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.43 (m, 4H), 7.38 – 7.30 (m, 3H), 7.30 – 7.21 (m, 6H), 6.74 (d, *J* = 10 Hz, 1H), 1.36 (s, 1H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**: δ 159.8, 157.0, 145.7, 141.6, 141.1, 134.7, 133.4, 131.2, 130.9, 129.0, 128.4, 127.7, 127.3, 125.0, 117.2, 114.0, 73.3, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{24}H_{21}O_3$ 357.1491; Found 357.1515.

5,7-Dihydroxy-3-(2-hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3la)



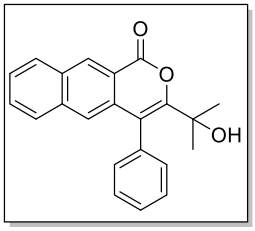
Prepared according to **GP 1**; white solid. 52 mg, 53% yield, eluent (20 % ethyl acetate in hexane), mp: 128-129 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 11.09 (s, 1H), 7.42 – 7.33 (m, 3H), 7.19 (s, 2H), 6.35 (s, 1H), 5.54 (s, 1H), 1.37 (s, 13H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**: δ 165.1, 163.8, 163.7, 156.5, 142.3, 134.0, 130.4, 129.9, 128.5, 115.2, 103.6, 102.3, 99.7, 73.5, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{17}O_5$ 313.1076 ; Found 313.1070.

3-(2-Hydroxypropan-2-yl)-5,7-dimethoxy-4-phenyl-1*H*-isochromen-1-one (3ma)



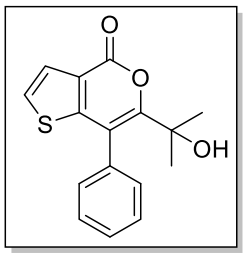
Prepared according to **GP 1**; white solid. 78 mg, 75% yield, eluent (20 % ethyl acetate in hexane), mp: 134-135 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.33 (d, *J* = 2.0 Hz, 1H), 7.27 (m, 3H), 7.24 – 7.19 (m, 2H), 6.54 (d, *J* = 3 Hz, 1H), 3.82 (s, 3H), 3.14 (s, 3H), 1.36 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**: δ 161.7, 160.1, 157.6, 154.1, 137.2, 130.2, 127.4, 127.2, 122.4, 122.2, 112.9, 107.0, 101.8, 73.9, 55.8, 55.7, 30.1. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{21}O_5$ 341.1389; Found 341.1393.

3-(2-Hydroxypropan-2-yl)-4-phenyl-1*H*-benzo[*g*]isochromen-1-one (3na)



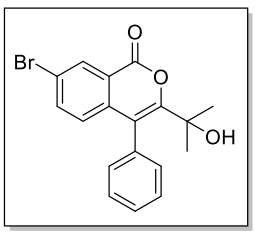
Prepared according to **GP 1**; white solid. 32 mg, 31% yield, eluent (15 % ethyl acetate in hexane), mp: 180-181 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 9.72 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.72 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.48 – 7.40 (m, 3H), 7.29 – 7.25 (m, 2H), 6.83 (d, *J* = 8.9 Hz, 1H), 1.45 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 160.9, 158.6, 141.9, 135.9, 134.7, 132.5, 131.3, 131.0, 129.5, 129.0, 128.5, 128.5, 127.0, 126.9, 122.5, 73.5, 30.0. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{19}O_3$ 331.1334; Found 331.1317.

6-(2-Hydroxypropan-2-yl)-7-phenyl-4*H*-thieno[3,2-c]pyran-4-one (3oa)



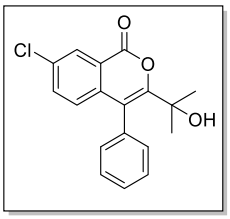
Prepared according to **GP 1**; white solid. 36 mg, 40% yield, eluent (15 % ethyl acetate in hexane), mp: 138-139 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.61 (d, *J* = 5.5 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.26 – 7.22 (m, 2H), 6.49 – 6.46 (m, 1H), 1.87 (s, 1H), 1.43 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 159.5, 157.6, 150.5, 136.1, 135.0, 129.9, 128.8, 128.4, 125.1, 121.7, 113.8, 73.5, 30.1. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{16}H_{15}O_3S$ 287.0742 ; Found 287.0751.

7-Bromo-3-(2-hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3pa)



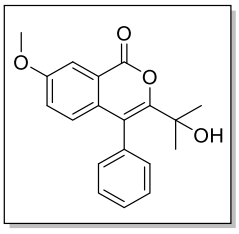
Prepared according to **GP 1**; white solid. 70 mg, 63% yield, eluent (15 % ethyl acetate in hexane), mp: 168-169 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.45 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.30 – 7.26 (m, 2H), 6.68 (d, *J* = 8.5 Hz, 1H), 1.88 (s, 1H), 1.47 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 160.4, 157.4, 138.3, 137.7, 133.7, 131.6, 130.5, 129.0, 128.6, 127.1, 121.8, 121.3, 113.9, 73.5, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}BrO_3$ 359.0283; Found 359.0274.

7-Chloro-3-(2-hydroxypropan-2-yl)-4-phenyl-1*H*-isochromen-1-one (3qa)



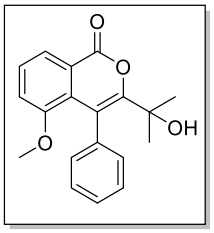
Prepared according to **GP 1**; white solid. 48 mg, 50% yield, eluent (15 % ethyl acetate in hexane) mp: 152-153 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.22 (d, *J* = 2.5 Hz, 1H), 7.44 – 7.40 (m, 4H), 7.21 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 1H), 1.40 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 160.6, 157.2, 138.0, 135.0, 134.1, 133.9, 130.6, 129.0, 128.5, 127.0, 121.1, 113.8, 73.5, 29.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{16}ClO_3$ 315.0788 ; Found 315.0770.

3-(2-Hydroxypropan-2-yl)-7-methoxy-4-phenyl-1*H*-isochromen-1-one (3ra)



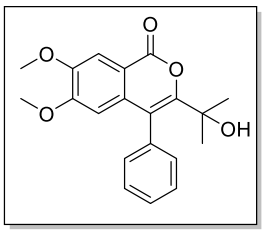
Prepared according to **GP 1**; white solid. 42 mg, 43% yield, eluent (10 % ethyl acetate in hexane) mp: 140-141 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.74 (d, *J* = 3.0 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.31 – 7.27 (m, 2H), 7.15 (dd, *J* = 9.0, 2.0 Hz, 1H), 6.75 – 6.72 (d,J=9.0Hz, 1H), 3.90 (s, 3H), 1.47 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 161.8, 159.4, 154.8, 134.5, 133.2, 130.6, 128.9, 128.3, 127.0, 124.2, 121.0, 114.1, 109.6, 73.3, 55.8, 29.9. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{19}O_4$ 311.1283; Found 311.1276.

3-(2-Hydroxypropan-2-yl)-5-methoxy-4-phenyl-1*H*-isochromen-1-one (3ra')



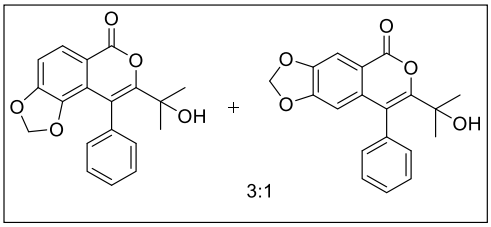
Prepared according to **GP 1**; white solid. 42 mg, 43% yield, eluent (10 % ethyl acetate in hexane) mp: 120-121 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.26 – 7.22 (m, 2H), 6.99 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.18 (s, 3H), 1.71 (s, 1H), 1.38 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 161.6, 156.3, 156.2, 137.3, 130.2, 129.0, 127.9, 127.5, 127.3, 121.7, 121.6, 117.7, 113.0, 74.1, 56.0, 30.1. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{19}O_4$ 311.1283,measured 311.1284.

3-(2-Hydroxypropan-2-yl)-6,7-dimethoxy-4-phenyl-1*H*-isochromen-1-one (3sa)



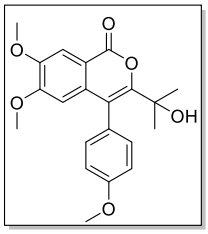
Prepared according to **GP 1**; white solid. 98 mg, 92% yield, eluent (15 % ethyl acetate in hexane), mp: 128-129 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.61 (s, 1H), 7.44 – 7.36 (m, 3H), 7.23 (m, 2H), 6.06 (s, 1H), 3.91 (s, 3H), 3.56 (s, 3H), 1.39 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.5, 155.8, 154.8, 149.5, 135.3, 134.6, 130.6, 128.8, 128.4, 114.0, 113.1, 109.0, 106.1, 73.3, 56.3, 55.7, 29.9. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{21}O_5$ 341.1389 ; Found 341.1381.

7-(2-Hydroxypropan-2-yl)-8-phenyl-*5H*-[1,3]dioxolo[4,5-*g*]isochromen-5-one (3ta)



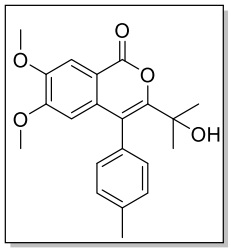
Prepared according to **GP 1**; white solid. 74 mg for inseparable mixture of two regioisomers in the ratio (3:1), 73 % yield, eluent (15 % ethyl acetate in hexane), mp: 130-131 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 0.24H), 7.48 – 7.36 (m, 1H), 7.31 (m, 3H), 7.25 (m, 2H), 7.20 (d, *J* = 4.0Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.08 (s, 0.26H), 5.96 (s, 0.59H), 5.62 (s, 2H), 1.37 (s, 8H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**:δ 161.0, 156.7, 153.2, 142.7, 134.8, 130.6, 130.5, 128.9, 128.4, 128.2, 128.1, 125.8, 125.8, 122.2, 114.4, 111.0, 109.4, 107.0, 104.2, 102.2, 101.9, 73.7, 29.3. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{17}O_5$ 325.1071; Found 325.1068.

3-(2-Hydroxypropan-2-yl)-6,7-dimethoxy-4-(4-methoxyphenyl)-1*H*-isochromen-1-one (3sb)



Prepared according to **GP 1**; white solid.93 mg, 92% yield, eluent (25 % ethyl acetate in hexanes); mp: 160-161 ºC.**^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.61 (s, 1H), 7.16 – 7.11 (dd, J=8.5, 1.5 Hz, 2H), 6.98 – 6.92 (m, 2H), 6.13 (s, 1H), 3.91 (s, 3H), 3.81 (s,, 3H), 3.59 (s, 3H), 1.39 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.6, 159.5, 156.2, 154.9, 149.5, 135.7, 131.8, 126.2, 114.3, 113.7, 113.1, 109.1, 106.2, 73.4, 56.3, 55.9, 55.3, 30.0. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $[M+H]^+$ $C_{21}H_{22}O_6$ 371.1495 ; Found 371.1504.

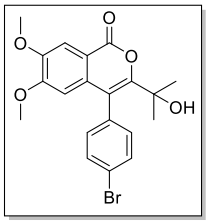
3-(2-Hydroxypropan-2-yl)-6,7-dimethoxy-4-(p-tolyl)-1*H*-isochromen-1-one (3sc)



Prepared according to **GP 1**; white solid. 114 mg, 75% yield, eluent (20 % ethyl acetate in hexane) mp: 140-141 ºC. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62 (s, 1H), 7.19 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.11 (s, 1H), 3.91 (s, 3H), 3.58 (s, 3H), 2.37 (s, 3H), 1.90

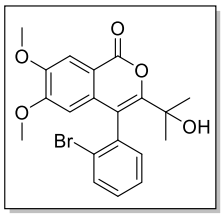
(s, 1H), 1.39 (s, 6H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 161.6, 156.0, 154.9, 149.5, 138.2, 135.5, 131.3, 130.4, 129.6, 114.0, 113.1, 109.1, 106.2, 73.4, 56.3, 55.9, 29.9, 21.3. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{21}H_{23}O_5$ 355.1545 ; Found 355.1540.

4-(4-Bromophenyl)-3-(2-hydroxypropan-2-yl)-6,7-dimethoxy-1*H*-isochromen-1-one(3sd)



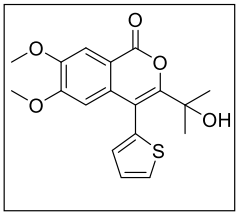
Prepared according to **GP 1**; white solid. 86 mg, 78% yield, eluent (15 % ethyl acetate in hexane) mp: 142-143 ºC. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.05 (s, 1H), 3.91 (s, 3H), 3.60 (s, 3H), 1.80 (s, 1H), 1.40 (s, 6H). **$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$):** δ 161.3, 157.0, 155.0, 149.7, 134.8, 133.8, 132.3, 132.0, 122.5, 113.1, 113.0, 109.2, 105.9, 73.3, 56.4, 55.9, 30.0. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{20}BrO_5$ 419.0494; Found 419.0483.

4-(2-Bromophenyl)-3-(2-hydroxypropan-2-yl)-6,7-dimethoxy-1*H*-isochromen-1-one(3se)



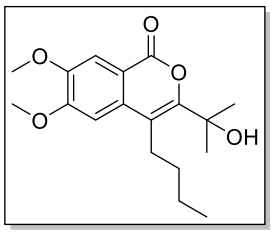
Prepared according to **GP 1** (2a is taken as 0.5 mmol); white solid. 104 mg, 94% yield, eluent (15 % ethyl acetate in hexane) mp: 142-143 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.65 (m, 1H), 7.63 (s, 1H), 7.39 – 7.34 (m, 1H), 7.27 – 7.23 (m, 2H), 5.96 (s, 1H), 3.91 (s, 3H), 3.58 (s, 3H), 1.75 (s, 1H), 1.44 (d, *J* = 7.0 Hz, 6H). **$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):** δ 161.5, 156.1, 155.1, 149.7, 136.3, 133.9, 133.0, 132.2, 129.9, 127.7, 125.4, 113.5, 113.2, 109.3, 73.4, 56.4, 55.8, 29.4, 29.04. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{20}H_{20}BrO_5$ 419.0494 ; Found 419.0480.

3-(2-Hydroxypropan-2-yl)-6,7-dimethoxy-4-(thiophen-2-yl)-1*H*-isochromen-1-one (3sf)



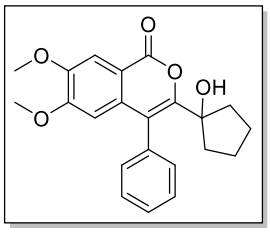
Prepared according to **GP 1**; 75 mg, 72% yield, eluent (15 % ethyl acetate in hexane), mp: 114-115 ºC.**^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58 (s, 1H), 7.45 (s, 1H), 7.09 (s, 1H), 6.99 (s, 1H), 6.27 (s, 1H), 3.91 (s, 3H), 3.65 (s, 3H), 2.24 (s, 1H), 1.46 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**: δ 161.1, 158.5, 155.1, 149.7, 135.5, 134.6, 129.7, 127.7, 127.3, 112.7, 108.9, 106.8, 105.7, 73.5, 56.3, 55.8, 29.4. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{19}O_5S$ 347.0953 ; Found 347.0950.

4-Butyl-3-(1-hydroxycyclopentyl)-6,7-dimethoxy-1*H*-isochromen-1-one (3sg)



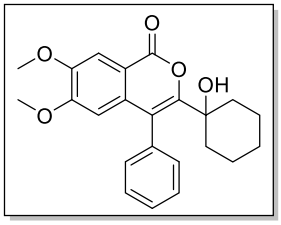
Prepared according to **GP 1**; white solid. 105 mg, 92% yield, eluent (15 % ethyl acetate in hexane), mp: 106-107 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**:δ 7.65 (s, 1H), 6.92 (s, 1H), 4.00 (d, *J* = 5.6 Hz, 6H), 3.05 – 2.94 (m, 2H), 2.32 (d, *J* = 10.6 Hz, 1H), 1.67 (s, 6H), 1.63 – 1.56 (m, 2H), 1.51 (dt, *J* = 14.4, 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.8, 155.4, 154.9, 149.2, 134.5, 114.1, 113.1, 109.5, 104.1,73.9, 56.2, 56.0, 32.5, 30.0, 25.2, 23.1, 13.9. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{25}O_5$ 321.1702 ; Found 321.1695.

3-(1-Hydroxycyclopentyl)-6,7-dimethoxy-4-phenyl-1*H*-isochromen-1-one (3sh)



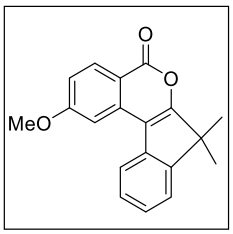
Prepared according to **GP 1**; white solid. 78 mg, 80% yield, eluent (20 % ethyl acetate in hexane) mp: 130-131 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.70 (s, 1H), 7.47 (m, 3H), 7.38 – 7.26 (m, 2H), 6.35 – 6.12 (m, 1H), 3.98 (s, 3H), 3.66 (s, 3H), 2.34 (s, 1H), 2.02 (m, 2H), 1.72 (m, 5H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.7, 154.8, 154.7, 149.5, 135.2, 134.6, 130.7, 128.8, 128.3, 115.2, 113.2 109.1, 106.1, 83.5, 56.3, 55.7, 40.0, 23.3. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{22}H_{23}O_5$ 367.1545 ; Found 367.1543.

3-(1-Hydroxycyclohexyl)-6,7-dimethoxy-4-phenyl-1*H*-isochromen-1-one (3si)



Prepared according to **GP 1**; white solid. 86 mg, 90% yield, eluent (20 % ethyl acetate in hexane) mp: 158-159 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.69 (s, 1H), 7.52 – 7.43 (m, 3H), 7.31 (m, 2H), 6.12 (s, 1H), 3.98 (s, 3H), 3.63 (s, 3H), 2.02 (td, *J* = 13.2, 4.9 Hz, 2H), 1.71 (d, *J* = 12.7 Hz, 2H), 1.63 – 1.48 (m, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 161.7, 156.5, 154.7, 149.4, 135.5, 134.9, 130.5, 128.8, 128.2, 114.4, 113.0, 109.0, 106.0, 74.9, 56.3, 55.7, 36.5, 24.9, 21.2. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{23}H_{25}O_5$ 381.1702 ; Found 381.1693.

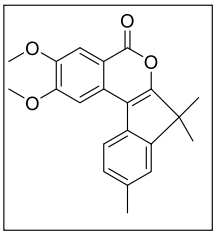
2-Methoxy-7,7-dimethylindeno[2,1-c]isochromen-5(7*H*)-one (4a)



Prepared according to **GP 2**; white solid. 44 mg, 93 % yield, eluent (2 % ethyl acetate in hexane), mp: 146-147 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.27 (d, *J* = 8.9 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 2.5 Hz, 1H), 7.31 (dd, *J* = 14.8, 7.5 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.2 Hz, 1H), 3.93 (s, 3H), 1.42 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 167.9, 165.0, 162.4, 148.3, 137.0, 136.6, 133.5, 127.2, 125.5, 121.9, 120.4, 114.6,

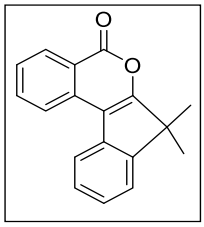
113.3, 110.8, 106.1, 55.7, 46.1, 23.5. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{16}O_3$ 293.1178 ; Found 293.1176.

2,3-Dimethoxy-7,7,9-trimethylindeno[2,1-c]isochromen-5(7*H*)-one (4b)



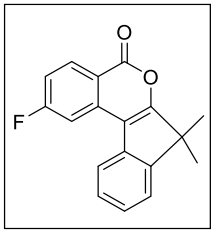
Prepared according to **GP 2**; white solid. 44 mg, 90% yield, eluent (2 % ethyl acetate in hexane) mp: 150-151 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.73 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.16 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 4.06 (s, 3H), 3.94 (s, 3H), 1.42 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)**: δ 165.6, 162.8, 155.3, 148.9, 148.7, 135.4, 133.8, 130.7, 127.7, 127.7, 123.0, 119.9, 113.4, 111.2, 110.9, 103.7, 56.3, 45.9, 23.6. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{21}H_{21}O_4$ 337.1440 ; Found 337.1421.

7,7-Dimethylindeno[2,1-c]isochromen-5(7*H*)-one (4c)



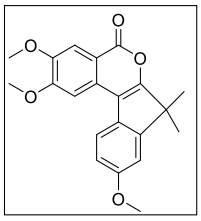
Prepared according to **GP 2**; white solid. 34 mg, 92% yield, eluent (2 % ethyl acetate in hexane) mp: 110-111 ºC. **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 8.35 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.80 (d,*J* = 7.5 Hz, 1H), 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.36 – 7.29 (m, 2H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 1.43 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)**: δ 167.1, 162.7, 148.3, 135.1, 134.9, 131.3, 127.5, 127.3, 125.6, 122.5, 121.9, 120.7, 120.3, 111.0, 46.1, 23.5. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{15}O_2$ 263.1072 ; Found 263.1064.

2-Fluoro-7,7-dimethylindeno[2,1-c]isochromen-5(7*H*)-one (4d)



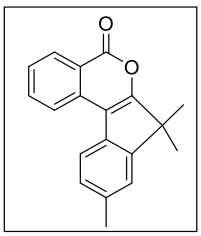
Prepared according to **GP 2**; white solid. 43 mg, 90% yield, eluent (2 % ethyl acetate in hexane), mp: 172-173 ºC. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.37 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.35 – 7.30 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.18 – 7.13 (m, 1H), 1.43 (s, 6H). **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):** δ 168.4, 168.0, 166.0 (d, ^{1}J=257 Hz), 161.8, 148.0, 137.4, 137.3(d, ^{3}J=10.8 Hz), 136.0, 134.54, 134.5(d, ^{3}J=10.5 Hz), 127.4, 125.8, 122.0, 120.4, 116.7, 115.7, 115.5 (d, ^{2}J=23.9 Hz), 110.7, 110.6 (d, ^{4}J=2.9 Hz), 109.0, 108.8 (d, ^{2}J=23.9 Hz), 46.2, 23.4. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{18}H_{14}FO_2$ 281.0978 ; Found 281.0973.

2,3,9-Trimethoxy-7,7-dimethylindeno[2,1-c]isochromen-5(7*H*)-one (4e)



Prepared according to **GP 2**; white solid. 46 mg, 90% yield, eluent (3 % ethyl acetate in hexane), mp: 247-249 ºC. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.73 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.39 (s, 1H), 6.92 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.06 (s, 3H), 3.94 (s, 3H), 3.81 (s, 3H), 1.42 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 164.7, 162.7, 158.2, 155.3 150.5, 148.9, 130.6, 129.3, 120.7, 113.5, 111.7, 111.3, 110.8, 109.3, 103.5, 56.3, 55.6, 46.1, 23.8. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{21}H_{21}O_5$ 353.1358 ; Found 353.1384.

7,7,9-Trimethylindeno[2,1-*c*]isochromen-5(7*H*)-one (4f)



Prepared according to **GP 2**; white solid. 43 mg, 90% yield, eluent (2 % ethyl acetate in hexane), mp: 262-264 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.83 (d, *J* = 7.4 Hz,1H), 7.31 (m, 3H), 7.21 (m, 1H), 2.51 (s, 3H), 1.43 (s, 6H). **^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$):** δ 167.3, 148.3, 146.3, 136.7, 135.0, 131.2, 128.8, 127.2, 125.5, 122.7, 121.9, 120.8, 117.8, 110.9, 46.0,23.5, 22.4. **HRMS (ESI-TOF) m/z:** $[M+H]^+$ Calcd for $C_{19}H_{17}O_2$ 277.1229; Found 277.1226.

ACKNOWLEDGMENT

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ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra data of all compounds, CIF information and Cartesian coordinate of all molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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