JOC The Journal of Organic Chemistry

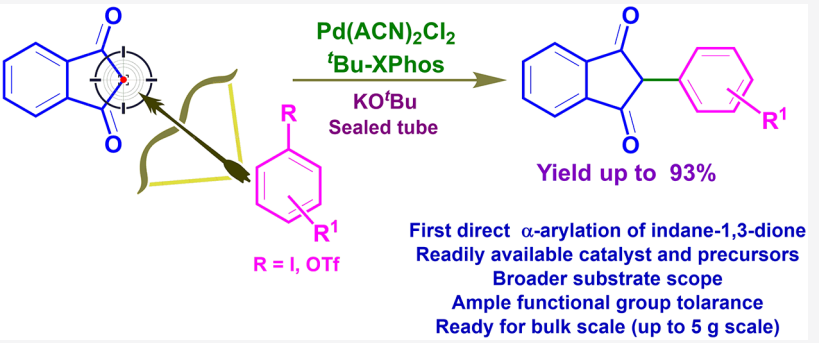
pubs.acs.org/joc Note

Palladium-Catalyzed Direct α-Arylation of Indane-1,3-dione to 2-Substituted Indene-1,3-diones

Natarajan Tamizharasan, Gurulingappa Hallur,* and Palaniswamy Suresh*

Cite This: https://doi.org/10.1021/acs.joc.1c01149 Read Online

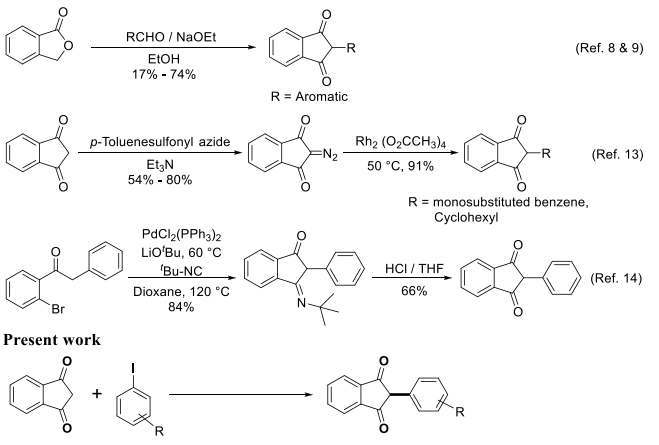
ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A straightforward and feasible palladium-catalyzed direct α-arylation of indane-1,3-dione to 2-substituted aryl/heteroaryl indene-1,3-diones has been disclosed for the first time. Optimization of reaction conditions identified ^{t}Bu-XPhos as a preferred ligand for the bis(acetonitrile)dichloropalladium(II) catalyst. A broad spectrum of aryl iodides and aryl triflates containing electron-donating, electron-withdrawing, and sterically hindered substituents gave an excellent yield for the quick access α-arylated 1,3-diones library.

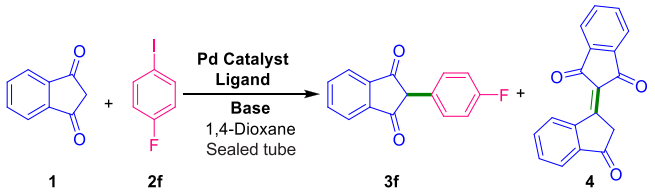
The C−C bonds forming through metal-catalyzed cross-coupling is one of the prime methodologies and widely adopted synthetic tools for constructing distinct organic motifs. α-Arylation is an efficient method for functionalizing the acidic "α-" C−H bond of carbonyl compounds with aryl motifs. Over the decades, the α-arylation of carbonyl compounds emerged as one of the pivotal bond-forming reactions due to their broad scope in natural products and clinical molecules.[1] Transition metals play a vital role, in α-arylation of ketones and various EWG functionalized substrates with alkyl/aryl halides.[2] Although numerous α-arylation reagents have been developed, their applications are limited because they involve different strategies and transmetalation.[3] Furthermore, major efforts toward the α-arylation of aliphatic enolates[4] and cyclic carbonyl compounds have scantly been reported.[5] It reveals that some shortcomings still exist in the direct α-arylation of cyclic carbonyl compounds. Indane-1,3-diones, pivotal cyclic carbonyl compounds, are explored as a key building block for the synthesis of many natural products and pharmaceuticals.[6] Their corresponding α-arylated derivatives 2-aryl indene-1,3-diones serve as the essential synthetic precursor for various bioactive molecules[7] (Figure S1, see Supporting Information (SI)) with a broad spectrum of therapeutic properties.[8−11] Because of their decisive role in organic synthesis, some methodologies for the synthesis of arylated indene-1,3-diones have been reported[8,9,12] (Scheme 1). Alkoxide base-catalyzed condensation of aryl aldehyde with

Scheme 1. Previously Reported Strategies to Access α-Arylated Indene-1,3-diones



Received: May 17, 2021

Table 1. Optimization of Catalyst and Ligand for the Direct α-Arylation of Indane-1,3-dione[a]



entry	ligand	catalyst	base	yield (%)[g] 3f/4
1[a]	L1−L4	$Pd(OAc)_2$	all four bases	-/-
2[b]	S-Phos (L5)	$Pd(OAc)_2$	Na_2CO_3	-/-
3[b]	S-Phos (L5)	$Pd(OAc)_2$	Cs_2CO_3	16/17
4[b]	S-Phos (L5)	$Pd(OAc)_2$	KO^{t}Bu	33/32
5[b]	S-Phos (L5)	$Pd(OAc)_2$	K_2CO_3	25/15
6[c]	S-Phos (L5)	$Pd(OAc)_2$	Cs_2CO_3	17/22
7[c]	S-Phos (L5)	$Pd(OAc)_2$	KO^{t}Bu	53/13
8[c]	S-Phos (L5)	$Pd(OAc)_2$	K_2CO_3	44/12
9[c]	S-Phos (L5)	$Pd(OAc)_2$	K_3PO_4	28/17
10[c]	S-Phos (L5)	$Pd(OAc)_2$	Et_3N	-/-
11[c]	S-Phos (L5)	$Pd_2(dba)_3$	KO^{t}Bu	44/9
12[c]	S-Phos (L5)	$PdCl_2$	KO^{t}Bu	47/8
13[c]	S-Phos (L5)	$(allylPdCl)_2$	KO^{t}Bu	41/11
14[c]	S-Phos (L5)	$Pd(CH_3CN)_2Cl_2$	KO^{t}Bu	64/7
15[d]	^{t}BuMePhos (L6)	$Pd(OAc)_2$	K_3PO_4	20/26
16[e]		$Pd(CH_3CN)_2Cl_2$	KO^{t}Bu	-/-
17[f]	S-Phos (L5)	$Pd(CH_3CN)_2Cl_2$	KO^{t}Bu	-/-

[a]Reaction conditions: Ligands L1−L4 (4 mol %), all four bases (Na_2CO_3, Cs_2CO_3, KO^{t}Bu, and K_2CO_3(2.3 equiv), catalyst (4 mol %), total 16 reactions, 1,4-dioxane, sealed tube; 80 °C, 20 h. [b]Reaction conditions B: Ligand (4 mol %), catalyst (4 mol %), base (2.3 equiv), 1,4-dioxane, 80 °C, 20 h, sealed tube. [c]Reaction conditions C: Ligand (8 mol %), catalyst (4 mol %), base (2.3 equiv), 1,4-dioxane, 110 °C, 12 h, sealed tube. [d]Reaction conditions D: Ligand (2.2 mol %), catalyst (1 mol %), base (2.3 equiv), THF, 80 °C, 23 h, sealed tube (ref 5). [e]Reaction conditions E: Catalyst (4 mol %), base (2.3 equiv), 1,4-dioxane, 110 °C, 12 h, sealed tube. [f]Reaction conditions F: 1-Chloro/1-bromo-4-fluorobenzene (1 equiv), ligand (8 mol %), catalyst (4 mol %), base (2.3 equiv), 1,4-dioxane, 110 °C, 12 h, sealed tube. [g]Isolated yield.

phthalide gave aryl-substituted indene-1,3-dione in moderate yield.[8,9] Rhodium-catalyzed synthesis of substituted indene-1,3-dione[13] was achieved through the decomposition of diazo derivatives. In another attempt, a multistep approach through oxidative cyclization involving the reaction between 1-(2-bromophenyl)-2-phenylethanone with *tert*-butyl isocyanide formed an intermediate and the arylated indene-1,3-dione which was obtained through consecutive hydrolysis.[14]

Though α-arylated indene-1,3-diones have found potential synthetic applications, however, their access through the traditional synthetic methods requires multistep synthesis with an overall low yield. Existing shortcomings prompted us to develop a reliable methodology to access the 2-aryl indene-1,3-dione through a direct and facile coupling strategy. Herein, we report a direct α-arylation of indane-1,3-dione through intermolecular cross-coupling with aryl iodide using a palladium catalyst. To the best of our knowledge, no method has been attempted for the direct α-arylation of aromatic cyclic 1,3-diketones, using $Pd(CH_3CN)_2Cl_2$ as a catalyst.

To find an optimal reaction condition for the direct α-arylation of indane-1,3-dione (**1**), a model reaction was initially performed with 4-fluoroiodobenzene (**2f**) in 1,4-dioxane medium at 80 °C using a palladium catalyst with a series of ligands (**L1−L14**, see SI, Scheme S1). These reactions were screened with different bases, and the results are summarized in Tables 1 and 2. First, phosphine ligands **L1−L4** were screened with four different bases Cs_2CO_3, Na_2CO_3, KO^{t}Bu, and K_2CO_3 (Table 1, entry 1), where weak bases were chosen owing to the mild acidic nature (pK_a 10) of the indane-1,3-dione (**1**). Ligands (**L1−L4**) screened with four different base

Table 2. Screening of Ligands for Palladium-Catalyzed Direct α-Arylation of Indane-1,3-dione (1)[a]

entry	ligand	yield (%)[b] 3f/4
1	S-Phos (L5)	64/7
2	*t*BuMePhos (L6)	68/21
3	John Phos (L7)	42/15
4	^{t}Bu-XPhos (L8)	93/-
5	*Me*$_4$^{t}Bu- XPhos (L9)	30/11
6	XPhos (L10)	43/-
7	Brett Phos (L11)	56/-
8	Dave Phos (L12)	14/6
9	RuPhos (L13)	36/14
10	CM-Phos (L14)	39/14

[a]Reaction conditions: Ligand (8 mol %), $Pd(CH_3CN)_2Cl_2$ (4 mol %), KO^{t}Bu (2.3 equiv), 1,4-dioxane, 110 °C, 12 h, sealed tube. [b]Isolated yield.

combinations were inactive toward this reaction without any notable conversion. However, under the identical condition, ligand **L5**, screened with the same four bases, gave slightly better yields of **3f** (entries 4 and 5, Table 1) with KO^{t}Bu (33%) and K_2CO_3(25%) along with the quantitative amount (32% and 15%) of condensation product **4**.

From these encouraging results, further optimization was carried to enhance the α-arylated product and suppress or prevent the undesired condensation product (**4**). From the literature, it is known that the 2:1 ligand and catalyst ratio was optimal for the arylation of enolates.[2b,15] On the basis of that, the loading amount of **L5** was increased from 4 mol % to 8 mol

https://doi.org/10.1021/acs.joc.1c01149
J. Org. Chem. XXXX, XXX, XXX−XXX

%, maintaining the same catalyst load (4 mol %). Meanwhile, the reaction temperature was increased to 110 °C and the time was reduced to 12 h. A marginal enhancement in the α-arylated product and concomitant decrease of condensation was observed with KO^{t}Bu (entry 7, Table 1).

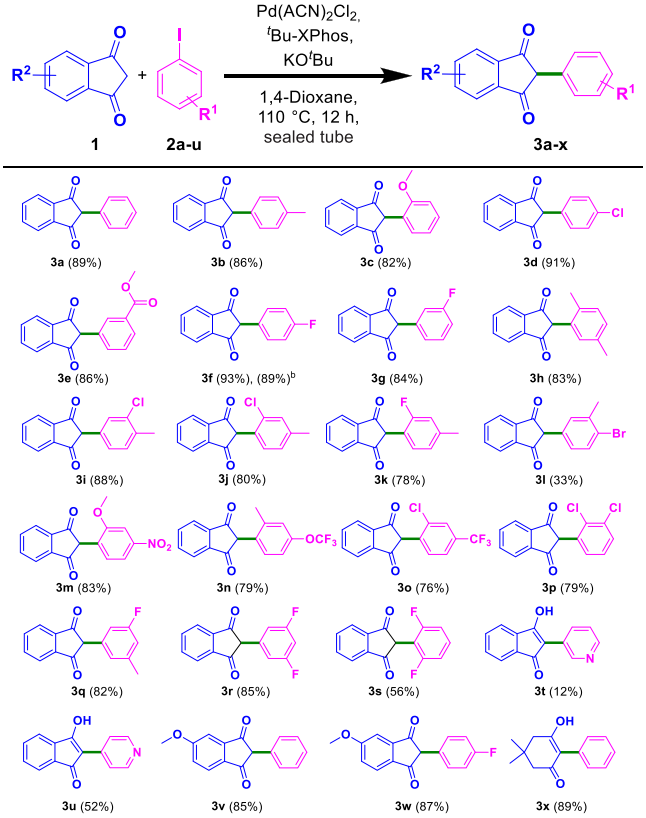
The screening results in Table 1 showed low to a moderate yield of the desired product (**3f**), we speculated this could be due to catalyst's poor activation. In order to address this, we next tried with the direct source of Pd(0) catalyst of $Pd_2(dba)_3$ (entry 11, Table 1). However, the yield remained unchanged. Further, screening with other palladium(II) catalysts, such as $PdCl_2$, $(allylPdCl)_2$, and $Pd(CH_3CN)_2Cl_2$, indicated that the latter one suppressed the formation of the condensation product **4** (entry 14, Table 1) and considerably enhanced the yield (64%) of **3f**. Previously reported conditions were not encouraging for the present arylation (entry 15, Table 1); also, the reaction is highly inert only with a palladium source and without ligand (entry 16, Table 1). This inspiring result encouraged us to screen with other biaryl phosphine ligands to further fine-tune the selectivity toward the desired product (**3f**) without condensation product (**4**). Two sets of readily available ligands such as di-*tert*-butyl biaryl phosphines ligands (**L6**−**L9**) and dicyclohexylbiarylphosphines ligands (**L10**−**L14**) were further screened with $Pd(CH_3CN)_2Cl_2$. Among the screened ligands, **L8**, **L10**, and **L11**, selectively yielded the desired α-arylated product **3f** and without formation of condensation product. The ligand 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (**L8**) gave the α-arylated product **3f** to our delight selectively with the maximum yield 93% (Table 2, entry 4).

The ligand screening results revealed that the substituents present on the ^{t}Bu-XPhos (**L8**) have played a crucial role than the substituents of dicyclohexyl biaryl phosphine ligands (**L10** and **L11**). The enhanced reactivity and selectivity of the palladium catalyst were rationalized through the boom in the electron density at the metal center, which fastened the oxidative addition and reductive elimination step, also strongly influenced the side reactions, and eliminated the condensation product. Finally, in the screening studies, the role of solvents (Table S1, see SI) was also examined and 1,4-dioxane was chosen as an appropriate solvent under the screened conditions for both selectivity and yield. From the above-screened parameters, the optimum reaction condition for the smooth α-arylation of indane-1,3-dione was found to be using $Pd(CH_3CN)_2Cl_2$ as a catalyst with ligand ^{t}Bu-XPhos in 1,4-dioxane at 110 °C for 12 h.

With the optimized reaction condition for α-arylation of indane-1,3-dione (**1**) in hand, we then probed the substrate scope using the $Pd(CH_3CN)_2Cl_2$ and ^{t}Bu-XPhos catalytic system. We studied a wide range of activated and non-activated aryl iodides, and the results are shown in Table 3. The electron neutral (4-H) and electron-rich (4-Me, 2,5-diMe, and 2-OMe) substituted aryl iodides had undergone α-arylation with **1** to the corresponding product in good to excellent yield (82−89%, Table 3, **3a**−**3c** and **3h**). Aryl iodides with electron-withdrawing substituents such as chloro (**3d**), ester (**3e**), 4-fluoro (**3f**), and 3-fluoro (**3g**) were also compatible with current reaction conditions with good yield (84−93%).

Further, spectra of aryl iodides with disubstituent (**3i**−**3s**) were also tested. 4-Methyliodobenzene having 2-chloro, 3-chloro, and 2-fluoro substitutes yielded the corresponding α-arylated products **3i**−**3k** with good yield without any electronic and steric influences from the halo substituents.

Table 3. Palladium-Catalyzed α-Arylation of Indane-1,3-dione with Aryl Iodides[a]



[a]Reaction conditions: Indane-1,3-dione (1.0 equiv), aryl iodide (1.0 equiv), KO^{t}Bu (2.3 equiv), ^{t}Bu-XPhos (0.08 equiv), $Pd(CH_3CN)_2Cl_2$ (0.04 equiv), 1,4-dioxane, 110 °C, 12 h, sealed tube. All are isolated yields. [b]5 g scale reaction.

Conversely, in the case of 1-bromo-4-iodo-2-methylbenzene (**2l**), the yield was drastically decreased to 33% (Table 3, **3l**) owing to the electronic reinforcement between bromo and methyl substituents present *ortho* to each other, which decreased the leaving nature of the iodo group and decreased the reactivity toward the oxidative addition. Notably, the iodo coupling's selectivity was specifically favored than bromo coupling and no traces of bromo coupled product was observed. Disubstituted aryl iodide with both electron-releasing and electron-withdrawing substitutes had undergone the arylation (**3m**−**3o** and **3q**) with a mild drop in the yield.

However, the electronic reinforcement between the substitutes did not affect the yield. Similarly, the dihalo substituents on aryl iodides gave good yield (**3p** and **3r**) irrespective of their electronic nature. 1,3-Difluoro-2-iodobenzene (**2s**) gave a relatively moderate yield for **3s** (56%) compared to **3r** (85%) owing to the steric hindrance of both *ortho*-substituted fluoro groups. Finally, the scope of heteroaryl iodide was also attempted with iodopyridines. 3-Iodopyridine (**2t**) gave a low yield (**3t**, 12%); meanwhile, with another heteroaryl iodide, 4-iodo pyridine (**2u**) gave a moderate yield (**3u**, 52%). From the NMR analysis, both were confirmed that they existed as their corresponding enol form. Next, a substituted, 5-methoxy indane-1,3-dione also gave the corresponding products (**3v** and **3w**) with good yields. Further, the scope of this reaction extended to one more

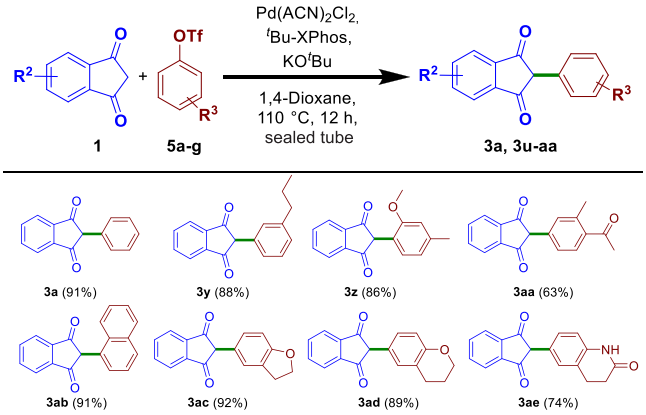
https://doi.org/10.1021/acs.joc.1c01149
J. Org. Chem. XXXX, XXX, XXX−XXX

diketo compound dimedone, which reacted smoothly with aryl iodide and gave the arylated product (**3x**, 89%) in good yield.

Indeed, from the wide reactivity of aryl iodides, it clearly demonstrates that, in the palladium-catalyzed α-arylation of indane-1,3-dione, substituents' electronic nature and the steric factors were not more influenced in the reaction conversion. Furthermore, the optimized conditions strongly favored the smooth and selective formation of the α-arylated products. Furthermore, the present catalytic system's scope was also extended with the other electrophiles such as aryl chlorides and bromide and aryl triflates under the optimized reaction conditions. As observed in the above substrate scope (Table 3, entries **3d** and **3l**), aryl chlorides and aryl bromides were highly inert even after an extended reaction time and temperature.

On the contrary, electrophile phenyl triflate (**5a**) smoothly underwent the coupling with **1** under a similar reaction condition and yielded **3a** (Table 4) in excellent yield (91%).

Table 4. Palladium-Catalyzed α-Arylation of Indane-1,3-dione with Aryl Triflates[a]

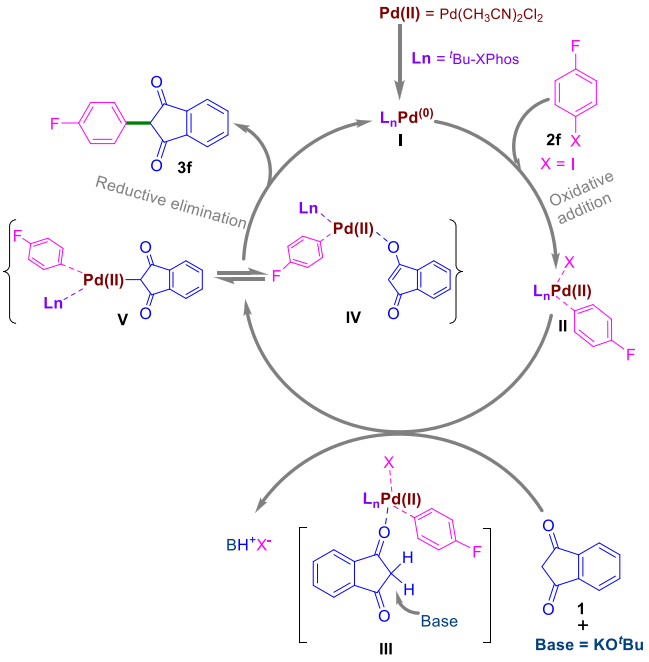


[a]Reaction conditions: Indane-1,3-dione (1.0 equiv), aryl triflate (1.0 equiv), KO^{t}Bu (2.3 equiv), ^{t}Bu-XPhos (0.08 equiv), $Pd(CH_3CN)_2Cl_2$ (0.04 equiv), 1,4-dioxane, 110 °C, 12 h, sealed tube. All are isolated yields.

Then it was extended with diverse aryl triflates **5a**−**5g** (Table 4). Electron neutral aryl triflates gave the corresponding coupled products **3a** and **3ab** in excellent yield. Similar behavior was also observed with electron-releasing (**3y**−**3z**) substitutes; conversely, electron-withdrawing substituents (**3aa**) gave moderate yield (63%). Heteroaryl-substituted bicyclic systems underwent the coupling with **1** and gave the α-arylated product **3ac**−**3ae** from good to excellent (74−92%) yield.

With the help of the observed experimental results and from the previous literature report, a possible mechanism could be proposed for the first palladium-catalyzed direct α-arylation of indane-1,3-dione (**1**). As shown in Scheme 2, initially, the palladium catalyst $Pd(CH_3CN)_2Cl_2$ forms a Pd^0 (**I**) complex with ^{t}Bu-XPhos. Then, it undergoes oxidative addition with aryl iodide to form the complex **II**. Meanwhile, the diketone **1** gets deprotonated by the base KO^{t}Bu, and the resulting carbanion coordinates with **II** and forms complex **III**. Owing to the presence of two carbonyl groups at 1,3-positions in compound **1**, it undergoes keto-enol tautomerism, and there exists a possibility of two types of complexes **IV** and **V**. In the next step, either **IV** or **V** undergoes reductive elimination, to

Scheme 2. Plausible Mechanism for Palladium-Catalyzed Direct α-Arylation of Indane-1,3-dione



give the desired coupling product and regenerates the Pd(0) complex for the next catalytic cycle.

In summary, we have demonstrated the first palladium-catalyzed direct α-arylation of indane-1,3-dione (**1**) using aryl iodides as electrophiles. The combination of the Pd-$(CH_3CN)_2Cl_2$ and ^{t}Bu-XPhos as a suitable catalytic system for the present α-arylation exhibited excellent product selectivity. The above combination selectively yields only the coupling product over the other ligands and palladium catalyst combinations and avoids formation of the condensation product. This catalytic system is highly compatible with a wide range of aryl iodides and aryl triflates bearing electron-rich, electron-neutral, and electron-poor substituents, which are smoothly coupled with the indane-1,3-dione and other cyclic 1,3-dione systems. Further, the optimized catalytic system is feasible with a gram-scale reaction. Further investigation on the arylation of other sterically hindered diverse 1,3-diones using the present catalytic system is now underway.

GENERAL PROCEDURE FOR PALLADIUM-CATALYZED DIRECT α-ARYLATION OF INDANE-1,3-DIONE

To a stirred solution of 1*H*-indene-1,3(2*H*)-dione derivative (0.68 mmol) in dry dioxane (4 mL) were added substituted iodobenzene (0.68 mmol), ^{t}Bu-XPhos (0.054 mmol), and $Pd(CH_3CN)_2Cl_2$ (0.027 mmol). The resulting mixture was purged with argon gas for 15 min. Potassium *tert*-butoxide (1.57 mmol) was added into the reaction mixture and stirred at 110 °C (preheated oil bath) for 12 h in a sealed tube. The reaction was monitored by TLC. The reaction mixture was cooled to room temperature, filtered through a Celite bed, and washed with 1,4-dioxane (10 mL), and the filtrate was removed. All the nonpolar impurities and volatiles are removed. The Celite bed was washed with methanol (50 mL). The filtrate was concentrated under high vacuum to get a crude compound. The crude residue was purified through combi-flash column chromatography using silica gel cartridges (0−20% MeOH in EtOAc) which afforded the α-arylated substituted indane-1,3-dione derivatives.

https://doi.org/10.1021/acs.joc.1c01149
J. Org. Chem. XXXX, XXX, XXX−XXX

2-Phenyl-1*H*-indene-1,3(2*H*)-dione: (3a).[8] White solid (0.135 g, 89%); m.p.: 148−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.06 (m, 2H), 7.91−7.90 (m, 2H), 7.36−7.28 (m, 3H), 7.20−7.18 (m, 2H), 4.26 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 142.7, 135.9, 133.2, 128.9, 128.7, 127.8, 123.7, 59.8. Mass (ESI): 221.0 (M − 1).

2-(*p*-Tolyl)-1*H*-indene-1,3(2*H*)-dione: (3b).[9] White solid (0.139 g, 86%); m.p.: 143−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.05 (m, 2H), 7.90−7.89 (m, 2H), 7.15 (d, 2H, J = 7.6 Hz), 7.06 (d, 2H, J = 7.6 Hz), 4.22 (s, 1H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.5, 142.7, 137.6, 135.9, 130.1, 129.7, 128.6, 123.7, 59.6, 21.1. Mass (ESI): 235.0 (M − 1).

2-(2-Methoxyphenyl)-1*H*-indene-1,3(2*H*)-dione: (3c).[9] White solid (0.142 g, 82%); m.p.: 178−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.01 (m, 2H), 7.87−7.85 (m, 2H), 7.32−7.28 (m, 2H), 7.00 (t, 1H, J = 7.6 Hz), 6.79 (d, 1H, J = 8 Hz), 4.16 (s, 1H), 3.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.1, 156.5, 141.7, 135.3, 132.7, 129.7, 123.1, 122.9, 121.3, 110.9, 58.7, 55.3. Mass (ESI): 253.0 (M + 1).

2-(4-Chlorophenyl)-1*H*-indene-1,3(2*H*)-dione: (3d).[9] Yellow solid (0.160 g, 91%); m.p.: 145−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.93−7.90 (m, 2H), 7.29−7.28 (m, 2H), 7.19 (s, 1H), 7.10 (s, 1H), 4.23 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.7, 142.5, 136.1, 133.9, 131.4, 130.1, 129.2, 123.8, 58.9. Mass (ESI): 255.0 (M − 1).

Methyl 3-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-yl)benzoate: (3e). Pale brown solid (0.164 g, 86%); m.p.: 131−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 2H), 8.00 (d, 1H, J = 7.2 Hz), 7.93−7.91 (m, 2H), 7.85 (s, 1H), 7.47−7.40 (m, 2H), 4.33 (s, 1H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 166.5, 142.5, 136.2, 133.6, 133.4, 130.9, 129.6, 129.9, 129.1, 123.9, 59.5, 52.2. HRMS (ESI) m/z: $[M - H]^-$ calculated for $C_{17}H_{12}O_4$, 279.0651; found 279.0675.

2-(4-Fluorophenyl)-1*H*-indene-1,3(2*H*)-dione: (3f).[8] Yellow solid (0.153 g, 93%), m.p.: 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.92−7.91 (m, 2H), 7.19−7.16 (m, 2H), 7.07−7.02 (m, 2H), 4.25 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 162.4 (J_{CF} = 246.4 Hz), 142.4, 135.9 (J_{CF} = 24.8 Hz), 130.4 (J_{CF} = 7.7 Hz), 128.7 (J_{CF} = 3.1 Hz), 123.8, 115.9 (J_{CF} = 21.7 Hz), 58.9. Mass (ESI): 241.0 (M + 1).

2-(3-Fluorophenyl)-1*H*-indene-1,3(2*H*)-dione: (3g).[9] White solid (0.138 g, 84%); m.p.: 158−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.06 (m, 2H), 7.92−7.90 (m, 2H), 7.35−7.31 (m, 1H), 7.03−6.99 (m, 2H), 6.94−6.92 (m, 1H), 4.26 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.4, 162.9 (J_{CF} = 245.6 Hz), 142.5, 136.1, 134.9 (J_{CF} = 7.7 Hz), 130.4 (J_{CF} = 8.5 Hz), 124.5 (J_{CF} = 3.1 Hz), 123.9, 115.9 (J_{CF} = 22.5 Hz), 114.9 (J_{CF} = 20.9 Hz), 59.2. Mass (ESI): 239.0 (M − 1).

2-(2,5-Dimethylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3h).[16a] White solid (0.142 g, 83%); m.p.: 156−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.91−7.89 (m, 2H), 7.11 (d, 1H, J = 7.6 Hz), 7.01 (d, 1H, J = 7.2 Hz), 6.68 (s, 1H), 4.46 (s, 1H), 2.26 (s, 3H), 2.22 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.8, 142.5, 137.1, 135.8, 134.2, 132.1, 130.8, 129.9, 128.9, 123.6, 59.0, 20.8, 19.8. Mass (ESI): 251.1 (M + 1).

2-(3-Chloro-4-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3i). Brown solid (0.162 g, 88%); m.p.: 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.92−7.90 (m, 2H), 7.20 (d, 1H, J = 7.6 Hz), 7.17 (s, 1H), 7.00 (d, 1H, J = 8 Hz), 4.20 (s, 1H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.7, 142.5, 136.1, 135.8, 134.8, 131.9, 131.4, 129.2, 127.1, 123.8, 58.9, 19.7. HRMS (ESI) m/z: $[M - H]^-$ calculated for $C_{16}H_{11}ClO_2$, 269.0363; found 269.0378.

2-(2-Chloro-4-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3j). Pale yellow solid (0.147 g, 80%); m.p.: 203−204 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.93−7.91 (m, 2H), 7.18−7.17 (m, 2H), 6.86 (s, 1H), 4.47 (s, 1H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 142.3, 136.1, 133.9, 132.9, 132.1, 131.8, 129.0, 128.1, 123.74, 58.6, 19.8. HRMS (ESI) m/z: $[M - H]^-$ calculated for $C_{16}H_{11}ClO_2$, 269.0363; found 269.0362.

2-(2-Fluoro-4-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3k). White solid (0.135 g, 78%); m.p.: 180−181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.92−7.90 (m, 2H), 6.82 (d, 1H, J = 9.6 Hz), 6.78 (s, 1H), 6.71 (d, 1H, J = 9.2 Hz), 4.2 (s, 1H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 162.9 (J_{CF} = 244.8 Hz), 142.6, 141.1 (J_{CF} = 8.5 Hz), 136.1, 134.7 (J_{CF} = 8.5 Hz), 125.2 (J_{CF} = 2.4 Hz), 123.8, 115.6 (J_{CF} = 20.9 Hz), 112.9 (J_{CF} = 22.4 Hz), 59.3, 21.3. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{11}FO_2 + H^+$, 255.0815; found 255.0815.

2-(4-Bromo-3-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3l). Pale yellow solid (0.071 g, 33%); m.p.: 201−203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.92−7.90 (m, 2H), 7.50 (d, 1H, J = 8.4 Hz), 7.05 (s, 1H), 6.87 (d, 1H, J = 7.6 Hz), 4.19 (s, 1H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 142.5, 139.3, 138.6, 136.1, 132.9, 132.2, 131.1, 127.7, 123.8, 59.2, 22.9. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{11}BrO_2 + H^+$, 315.0015; found 315.0014.

2-(2-Methoxy-4-nitrophenyl)-1*H*-indene-1,3(2*H*)-dione: (3m). Pale yellow color solid (0.169 g, 83%); m.p.: 125−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.04 (m, 2H), 7.92−7.91 (m, 3H), 7.66 (s, 1H), 7.42 (d, 1H, J = 8 Hz), 4.33 (s, 1H), 3.58 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.3, 157.0, 149.1, 141.6, 135.8, 133.1, 130.1, 123.4, 116.4, 105.9, 58.5, 56.0. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{12}NO_5 + H^+$, 298.0709; found 298.0707.

2-(2-Methyl-4-(trifluoromethoxy)phenyl)-1*H*-indene-1,3(2*H*)-dione: (3n). Gray color solid (0.174 g, 79%); m.p.: 209−211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.93−7.91 (m, 2H), 7.10 (s, 1H), 6.98 (d, 1H, J = 8.4 Hz), 6.91 (d, 1H, J = 8.4 Hz), 4.51 (s, 1H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 142.7, 142.3, 139.9, 136.1, 130.9, 130.4, 123.7, 123.2, 120.4 (J_{CF} = 255.7 Hz), 118.56, 58.27, 20.36. HRMS (ESI) m/z: $[M - H]^-$ calculated for $C_{17}H_{11}F_3O_3$, 319.0577; found 319.0578.

2-(2-Chloro-4-(trifluoromethyl)phenyl)-1*H*-indene-1,3(2*H*)-dione: (3o). Off-white solid (0.169 g, 76%); m.p.: 145−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.93−7.91 (m, 2H), 7.67 (s, 1H), 7.54 (d, 1H, J = 8 Hz), 7.32 (d, 1H, J = 8 Hz), 4.65 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.9, 141.8, 136.1, 135.8, 134.9, 133.1, 132.1 (J_{CF} = 33.3 Hz), 126.9, 124.3 (J_{CF} = 31 Hz), 123.8, 120.5 (J_{CF} = 251.2 Hz), 60.4. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_8ClF_3O_2 + H^+$, 325.0238; found 325.0238.

2-(2,3-Dichlorophenyl)-1*H*-indene-1,3(2*H*)-dione: (3p). Pale yellow color solid (0.158 g, 79%); m.p.: 213−214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.92−7.90 (m, 2H), 7.47 (d, 1H, J = 8 Hz), 7.22 (d, 1H, J = 8 Hz), 7.12 (d, 1H, J = 6.8 Hz), 4.60 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.5, 141.7, 135.9, 134.0, 133.8, 131.1, 130.5, 130.4, 127.7, 123.7, 61.3. HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{15}H_8Cl_2O_2 + H^+$, 290.9974; found 290.9976.

2-(3-Fluoro-5-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3q).[16b] Pale yellow solid (0.142 g, 82%); m.p.: 182−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.92−7.90 (m, 2H), 6.82 (d, 1H, J = 9.2 Hz), 6.78 (s, 1H), 6.71 (d, 1H, J = 9.2 Hz), 4.20 (s, 1H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 162.9 (J_{CF} = 245.6 Hz), 142.6, 141.1 (J_{CF} = 7.7 Hz), 136.1, 134.7 (J_{CF} = 8.5 Hz), 125.2 (J_{CF} = 2.4 Hz), 123.8, 115.6 (J_{CF} = 20.9 Hz), 112.9 (J_{CF} = 22.5 Hz), 59.3, 21.3. Mass (ESI): 253.1 (M − 1).

2-(3,5-Difluorophenyl)-1*H*-indene-1,3(2*H*)-dione: (3r).[16b] White solid (0.15 g, 85%); m.p.: 135−137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 2H), 7.94−7.91 (m, 2H), 6.80−6.74 (m, 3H), 4.24 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 185.7, 162.8 (J_{CF} = 240.9 Hz), 162.7 (J_{CF} = 241.7 Hz), 137.2, 137.1, 136.9, 136.7, 132.1, 120.3, 108.5, 104.5, 100.1. Mass (ESI): 257.0 (M − 1).

2-(2,6-Difluorophenyl)-1*H*-indene-1,3(2*H*)-dione: (3s).[16c] White solid (0.099 g, 56%); m.p.: 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.91 (s, 2H), 7.31 (t, 1H, J = 7.2 Hz), 6.93 (s, 2H), 4.70 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.32, 161.50 (J_{CF} = 250 Hz), 141.76, 135.91, 130.15 (J_{CF} = 20.2 Hz), 123.66, 111.38 (J_{CF} = 2.6 Hz), 110.09 (J_{CF} = 38.8 Hz), 50.63. Mass (ESI): 257.1 (M − 1).

https://doi.org/10.1021/acs.joc.1c01149
J. Org. Chem. XXXX, XXX, XXX−XXX

3-Hydroxy-2-(pyridin-3-yl)-1*H*-inden-1-one: (3t).[16b] Orange color solid (0.018 g, 12%); m.p.: 259−260 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.01 (br, 1H), 9.71 (s, 1H), 9.44 (d, 1H, J = 8.4 Hz), 8.20 (d, 1H, J = 5.2 Hz), 7.78 (q, 1H, J = 8.4 Hz), 7.38 (dd, 2H, J = 5.2 Hz, 4.8 Hz), 7.30 (dd, 2H, J = 4.8 Hz, 5.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 189.9, 140.5, 139.9, 138.18, 137.7, 136.0, 133.5, 131.9, 131.3, 126.8, 125.7, 124.8, 119.1, 97.7. Mass (ESI): 222.0 (M − 1).

3-Hydroxy-2-(pyridin-4-yl)-1*H*-inden-1-one (3u).[16d] Orange color solid (0.079 g, 52%); m.p.: >280 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (br, 1H), 8.72 (d, 2H, J = 7.2 Hz), 8.17 (d, 2H, J = 6.8 Hz), 7.54−7.46 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 191.4, 151.2, 140.1, 138.4, 132.3, 119.9, 115.2, 101.8. Mass (ESI): 223.0 (M + 1).

5-Methoxy-2-phenyl-1*H*-indene-1,3(2*H*)-dione (3v).[16e] Pale yellow solid (0.122 g, 85%); m.p.: 182−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 8.4 Hz), 7.41−7.29 (m, 5H), 7.18 (d, 2H, J = 6.8 Hz), 4.24 (s, 1H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.4, 196.5, 166.2, 145.4, 136.2, 133.5, 128.9, 128.6, 127.7, 125.4, 124.8, 104.9, 60.1, 56.2. Mass (ESI): 253.1 (M + 1).

2-(4-Fluorophenyl)-5-methoxy-1*H*-indene-1,3(2*H*)-dione (3w). Pale pink solid (0.134 g, 87.5%); m.p.: 148−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 7.6 Hz), 7.41 (s, 2H), 7.18−7.15 (m, 2H), 7.03 (t, 2H, J = 8.4 Hz), 4.22 (s, 1H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.2, 196.3, 166.3, 162.3 (J_{CF} = 245 Hz), 145.2, 136.0, 130.2 (J_{CF} = 8 Hz), 129.07 (J_{CF} = 4 Hz), 125.51, 124.99, 116.0 (J_{CF} = 22 Hz), 105.0, 59.2, 56.2. HRMS (ESI) m/z: [M + H]$^+$ calculated for $C_{16}H_{11}FO_3$ + H$^+$, 271.0765; found 271.0759.

6-Hydroxy-4,4-dimethyl-4,5-dihydro-[1,1′-biphenyl]-2(3*H*)-one (3x).[16f] Off-white solid (0.137 g, 89%); m.p.: 195−197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, 2H, J = 8 Hz), 7.36 (t, 1H, J = 4 Hz), 7.20 (d, 2H, J = 4 Hz), 5.99 (br, 1H), 2.49 (s, 2H), 2.38 (s, 2H), 1.17 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 204.8, 130.8, 130.6, 129.7, 129.2, 128.1, 127.0, 116.8, 53.8, 52.2, 31.7, 28.3. Mass (ESI): 217.0 (M + 1).

2-(3-Propylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3y). Red color solid (0.16 g, 88%); m.p.: 68−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.91−7.89 (m, 2H), 7.22 (s, 1H), 7.12−7.10 (m, 1H), 6.99−6.96 (m, 2H), 4.22 (s, 1H), 2.55 (t, 2H, J = 7.6 Hz), 1.66−1.60 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.5, 143.5, 142.7, 135.9, 132.9, 128.9, 128.8, 128.0, 125.9, 123.8, 59.9, 37.9, 24.4, 13.8. HRMS (ESI) m/z: [M + H]$^+$ calculated for $C_{18}H_{17}O_2$, 265.1223; found 265.1223.

2-(2-Methoxy-4-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3z). Yellow solid (0.157 g, 86%); m.p.: 212−213 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.01 (m, 2H), 7.86−7.84 (m, 2H), 7.13 (d, 1H, J = 7.2 Hz), 6.81 (d, 1H, J = 7.2 Hz), 6.61 (s, 1H), 4.12 (s, 1H), 3.42 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 156.3, 141.7, 139.9, 135.2, 132.4, 123.1, 121.9, 119.9, 111.9, 58.4, 55.2, 21.6. HRMS (ESI) m/z: [M + Na]$^+$ calculated for $C_{17}H_{14}O_3$ + Na$^+$, 289.0835; found 289.0836.

2-(4-Acetyl-3-methylphenyl)-1*H*-indene-1,3(2*H*)-dione: (3aa). Red color solid (0.123 g, 63%); m.p.: 209−211 °C. ^{1}H NMR (400 MHz, $CDCl_3$and drop of DMSO-d_6) δ 8.01 (s, 1H), 7.87 (s, 2H), 7.62 (d, 1H, J = 8.4 Hz), 7.04 (d, 1H, J = 8 Hz), 6.99 (s, 1H), 4.23 (s, 1H), 2.48 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 200.7, 185.5, 137.7, 136.8, 133.6, 131.9, 130.4, 129.8, 124.1, 122.7, 120.1, 119.5, 116.3, 106.2, 29.7, 22.3. HRMS (ESI) m/z: [M + H]$^+$ calculated for $C_{18}H_{14}O_3$ + H$^+$, 279.1015; found 279.1019.

2-(Naphthalen-1-yl)-1*H*-indene-1,3(2*H*)-dione: (3ab).[7e] Pale yellow solid (0.170 g, 91%); m.p.: 217−218 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.95 (s, 2H), 7.88−7.83 (m, 2H), 7.75 (s, 1H), 7.48−7.41 (m, 3H), 7.19 (s, 1H), 4.98 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.3, 142.3, 136.0, 134.3, 132.1, 130.1, 128.9, 128.8, 127.7, 126.7, 126.0, 125.3, 123.9, 123.8, 58.5. Mass (ESI): 271.1 (M − 1).

2-(2,3-Dihydrobenzofuran-5-yl)-1*H*-indene-1,3(2*H*)-dione: (3ac). White solid (0.166 g, 92%); m.p.: 147−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.06 (m, 2H), 7.91−7.90 (m, 2H), 6.99 (s, 1H), 6.90 (d, 1H, J = 8.4 Hz), 6.75 (d, 1H, J = 8 Hz), 4.55 (t, 2H, J = 8.8 Hz), 4.18 (s, 1H), 3.17 (t, 2H, J = 8.8 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.8, 159.9, 142.6, 135.9, 128.6, 127.9, 125.3, 125.0, 123.7, 109.8, 71.3, 59.4, 29.7. HRMS (ESI) m/z: [M + Na]$^+$ calculated for $C_{17}H_{12}O_3$ + Na$^+$, 287.0679; found 287.0688.

2-(Chroman-6-yl)-1*H*-indene-1,3(2*H*)-dione: (3ad). Red color solid (0.170 g, 89%); m.p.: 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.90−7.88 (m, 2H), 6.90−6.81 (m, 2H), 6.75 (d, 1H, J = 8.4 Hz), 4.16−4.14 (m, 3H), 2.74 (t, 2H, J = 6 Hz), 2.00−1.94 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.8, 154.7, 142.7, 135.9, 130.1, 127.5, 124.6, 123.7, 122.8, 117.4, 66.5, 59.3, 25.0, 22.2. HRMS (ESI) m/z: [M + Na]$^+$ calculated for $C_{18}H_{14}O_3$ + Na$^+$, 301.0835; found 301.0832.

2-(2-Oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1*H*-indene-1,3(2*H*)-dione: (3ae). Pale yellow color solid (0.147 g, 74%); m.p.: 288−289 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 7.93 (d, 4H, J = 3.6 Hz), 6.79−6.74 (m, 3H), 2.74−2.72 (m, 2H), 2.39 (t, 2H, J = 7.6 Hz). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.6, 139.2, 137.2, 129.7, 129.2, 124.2, 123.3, 123.1, 114.7, 64.0, 30.7, 25.4. HRMS (ESI) m/z: [M − H]$^-$ calculated for $C_{18}H_{13}NO_3$, 290.0811; found 290.0832.

[1,2′-Biindenylidene]-1′,3,3′(2*H*)-trione: (4).[16g] Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, J = 8.4 Hz, 1H), 8.04−8.02 (m, 1H), 7.99−7.94 (m, 2H), 7.88−7.79 (m, 3H), 7.75 (t, 1H, J = 14.8 Hz), 4.17 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.9, 191.0, 189.3. 155.4, 145.9, 141.7, 141.3, 140.4, 135.4, 135.3, 131.7, 125.9, 123.5, 123.4, 123.1, 43.4. Mass (ESI): 273.0 (M − 1).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01149.

Experimental details and spectral characterization of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Gurulingappa Hallur − *Medicinal Chemistry Department, Jubilant Biosys Ltd., Bangalore 560022 Karnataka, India*; Phone: +91-8066628642; Email: Gurulingappa.hallur@jubilantbiosys.com

Palaniswamy Suresh − *Supramolecular and Catalysis Lab, Department of Natural Products Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625021 Tamil Nadu, India*; orcid.org/0000-0002-2827-8552; Phone: +91-9790296673; Email: ghemistry@gmail.com, suresh.chem@mkuniversity.ac.in

Author

Natarajan Tamizharasan − *Supramolecular and Catalysis Lab, Department of Natural Products Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625021 Tamil Nadu, India; Medicinal Chemistry Department, Jubilant Biosys Ltd., Bangalore 560022 Karnataka, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01149

Author Contributions

These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Jubilant Biosys Ltd., Bangalore for supporting and funding in completion of this work. Dr. P. S. gratefully

acknowledges SERB, CSIR, and DST-FIST (SR/FST/CS-II/2017/35(C)) for financial and instrument (LC-MS and NMR) support.

REFERENCES

(1) Abramovitch, R. A.; Barton, D. H.R.; Finet, J.-P. Newer methods of arylation. *Tetrahedron* **1988**, *44* (11), 3039−3071.

(2) (a) Vogl, E. M.; Buchwald, S. L. Palladium-Catalyzed Monoarylation of Nitroalkanes. *J. Org. Chem.* **2002**, *67*, 106−111. (b) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. Efficient Palladium-Catalyzed Cross Coupling of Highly Acidic Substrates, Nitroacetates. *Org. Lett.* **2012**, *14* (3), 760−763. (c) Beare, N. A.; Hartwig, J. F. Palladium-catalyzed arylation of malonates and cyanoesters using sterically hindered trialkyl- and ferrocenyldialkylphosphine ligands. *J. Org. Chem.* **2002**, *67*, 541−555. (d) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. Palladium-catalyzed α-arylation of esters and amides under more neutral conditions. *J. Am. Chem. Soc.* **2003**, *125*, 11176−11177. (e) Mitin, A. V.; Kashin, A. N.; Beletskaya. Palladium-catalyzed arylation of sulfones. *Russ. J. Org. Chem.* **2004**, *40*, 802−812. (f) de Filippis, A.; Pardo, D. G.; Cossy, J. Palladium-catalyzed α-arylation of N-protected 2-piperidinones. *Tetrahedron* **2004**, *60*, 9757−9767. (g) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. Pd-Catalyzed α-Arylation of Nitriles and Esters and γ-Arylation of Unsaturated Nitriles with TMPZnCl. LiCl. *Org. Lett.* **2011**, *13* (7), 1690−1693. (h) Moradi, W. A.; Buchwald, S. L. Palladium-Catalyzed α-Arylation of Esters. *J. Am. Chem. Soc.* **2001**, *123*, 7996−8002.

(3) (a) Morgan, J.; Pinhey, J. T.; Rowe, B. A. α-Arylation of ketones by aryl lead triacetates. Effect of methyl and phenyl substitution at the α position. *J. Chem. Soc., Perkin Trans. 1* **1997**, *1*, 1005−1008. (b) Ryan, J. H.; Stang, P. J. Direct α-Arylation of Ketones: The Reaction of Cyclic Ketone Enolates with Diphenyliodonium Triflate. *Tetrahedron Lett.* **1997**, *38* (28), 5061−5064. (c) Palucki, M.; Buchwald, S. L. Palladium-Catalyzed α-Arylation of Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (d) Mino, T.; Matsuda, T.; Maruhashi, K.; Yamashita, M. Arylation of Ketone *N*,*N*-Dimethylhydrazones with (π-Chlorobenzene)chromium Tricarbonyl. *Organometallics* **1997**, *16*, 3241−3242. (e) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. α-Arylation *vs.* α-Arylhydrazonylation of Alkyl Aryl Ketones with Arylazo *tert*-Butyl Sulfides. *Tetrahedron* **1993**, *49* (1), 235−242. (f) Rathke, M. W.; Vogiazoglou, D. α-Phenylation of Ketones. Reaction of Bromo Enamines with Phenylcopper Reagents. *J. Org. Chem.* **1987**, *52*, 3697−3698. (g) Lee, H.-E.; Kim, D.; You, A.; Park, M. H.; Kim, M.; Kim, C. Transition Metal-Catalyzed α-Position Carbon-Carbon Bond Formations of Carbonyl Derivatives. *Catalysts* **2020**, *10*, 861. (h) Bellina, F.; Rossi, R. Transition Metal-Catalyzed Direct Arylation of Substrates with Activated sp^3-Hybridized C-H Bonds and Some of Their Synthetic Equivalents with Aryl Halides and Pseudohalides. *Chem. Rev.* **2010**, *110*, 1082−1146. (i) Johansson, C. C. C.; Colacot, T. J. Metal-Catalyzed α-Arylation of Carbonyl and Related Molecules: Novel Trends in C-C Bond Formation by C-H Bond Functionalization. *Angew. Chem., Int. Ed.* **2010**, *49*, 676−707. (j) Novák, P.; Martin, R. Pd-catalyzed α-Arylation of Carbonyl and Related Compounds: Recent Developments and Perspectives. *Curr. Org. Chem.* **2011**, *15*, 3233−3262. (k) Potukuchi, H. K.; Spork, A. P.; Donohoe, T. J. Palladium-catalyzed α-arylation of carbonyls in the de novo synthesis of aromatic heterocycles. *Org. Biomol. Chem.* **2015**, *13*, 4367−4373. (l) Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Seechurn, C. C. C. J.; Colacot, T. J. Palladium-Catalyzed α-Arylation Reactions in Total Synthesis. *Eur. J. Org. Chem.* **2015**, *2015* (1), 38−49.

(4) (a) Culkin, D. A.; Hartwig, J. F. Palladium-catalyzed α-arylation of carbonyl compounds and nitriles. *Acc. Chem. Res.* **2003**, *36*, 234−245. (b) Tcyrulnikov, S.; Kozlowski, M. C. Accounting for Strong Ligand Sensitivity in Pd-Catalyzed α-Arylation of Enolates from Ketones, Esters, and Nitroalkanes. *J. Org. Chem.* **2020**, *85* (5), 3465−3472.

(5) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. Highly active and selective catalysts for the formation of α-aryl ketones. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.

(6) (a) Partridge, B. M.; Gonzalez, J. S.; Lam, H. W. Iridium-Catalyzed Arylative Cyclization of Alkynones by 1,4-Iridium Migration. *Angew. Chem., Int. Ed.* **2014**, *53*, 6523−6527. (b) Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. A Dinuclear Palladium Catalyst for α-Hydroxylation of Carbonyls with O_2. *J. Am. Chem. Soc.* **2011**, *133*, 1760−1762. (c) Schroder, S. P.; Taylor, N. J.; Jackson, P.; Franckevicius, V. Catalytic Decarboxylative Alkenylation of Enolates. *Org. Lett.* **2013**, *15* (14), 3778−3781. (d) Lemke, T. L.; Abebe, E.; Moore, P. F.; Carty, T. J. Indeno[l,2-*c*]pyrazoloneAcetic Acids as Semirigid Analogues of the Nonsteroidal Anti-inflammatory Drugs. *J. Pharm. Sci.* **1989**, *78* (4), 343−347.

(7) (a) Cugnon de Servricourt, M. P.; Dacquet, C. G.; Finet, M. A.; Le Marquer, F. J.; Robba, M. F.; Tembo, N. O.; Yannic-Arnoult, S. J.; Torregrosa, J.-L. Derivatives of Indane-1,3-dione and Indane-1,2,3-trione, methods of preparing them and therapeutic use thereof. US 5648381 A, 1997. (b) Thomson, C. G.; Duncan, K.; Fletcher, S. R.; Huscroft, I. T.; Pillai, G.; Raubo, P.; Smith, A. J.; Stead, D. Sarcosine based indane dione hGlyT1 inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1388−1391. (c) Mitka, K.; Sulko, J.; Wozniak, M. 2-(4-Alkylthio-1-Naphthyl)-Indane-1,3-dione and their oxidation products. *Acta. Polon. Pharm. Drug. Res.* **1999**, *56* (6), 443−451. (d) Mitka, K.; Kawalski, P.; Pawelec, D.; Majka, Z. Synthesis of Novel Indane-1,3-dione Derivatives and Their Biological Evaluation as Anticoagulant Agents. *Croat. Chem. Acta.* **2009**, *82* (3), 613−618. (e) Mitka, K.; Kawalski, P.; Sulko, J.; Wozniak, M.; Kloc, J.; Chodkowska, A.; Jagiello-Wojtowicz, E. Synthesis and Pharmacological Properties of Sulfur derivatives of Indane-1,3-dione. *Acta. Polon. Pharm. Drug. Res.* **2002**, *59* (5), 387−393. (f) Holland, G. F.; Lambardino, J. G. Novel 2-Aryl-1,3-indanediones and 2-Aryl-2,3-dihydrobenz[F]Indane-1,3-diones. US 3622632 A, 1971.

(8) Shapiro, S. L.; Geiger, K.; Freedman, L. Indandione Anticoagulants. *J. Org. Chem.* **1960**, *25* (11), 1860−1865.

(9) Lombardino, J. G.; Wiseman, E. H. Antinflammatory 2-aryl-1,3-indandiones. *J. Med. Chem.* **1968**, *11* (2), 342−347.

(10) Murthy, A. R.; Wyrick, S. D.; Hall, I. H. Hypolipidemic activity of indan-1,3-dione derivatives in rodents. *J. Med. Chem.* **1985**, *28* (11), 1591−1596.

(11) Bianchi, C.; Franceschini, J. Experimental observations on Haffner's Method for Testing Analgesic Drugs. *Br. J. Pharmacol. Chemother.* **1954**, *9*, 280−284.

(12) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. Synthesis of 1,3-Diketones Using α-Diazo Ketones and Aldehydes in the Presence of Tin(II)Chloride. *J. Org. Chem.* **1990**, *55*, 5297−5299.

(13) Rosenfeld, M. J.; Ravi Shankar, B. K.; Shechter, H. Rhodium (II) Acetate Catalyzed Reactions of 2-Diazo-1,3-indandione and 2-Diazo-1-indanone with Various Substrates. *J. Org. Chem.* **1988**, *53*, 2699−2705.

(14) Duan, H.; Chen, Z.; Han, L.; Feng, Y.; Zhu, Y.; Yang, S. Palladium-catalyzed chemoselective synthesis of indane-1,3-dione derivatives via *tert*-butyl isocyanide insertion. *Org. Biomol. Chem.* **2015**, *13*, 6782−6788.

(15) Muratake, H.; Nakai, H. Intramolecular Cyclization Using Palladium-Catalyzed Arylation toward Formyl and Nitro Groups. *Tetrahedron Lett.* **1999**, *40*, 2355−2358.

(16) (a) Van Den Berg, G.; Nauta, W. T. Effects of Anti-inflammatory 2-Aryl-1,3-Indandiones on Oxidative Phosphorylation in Rat Liver Mitochondria. *Biochem. Pharmacol.* **1975**, *24* (7), 815−821. (b) Heinz, F.; John, G.; Markus, I.; Thierry, K.; Ralf, K.; Isabelle, L.; Lucile, M.; Julien, P.; Anja, V. Indanone and Indandione derivatives and heterocyclic analogs. WO 068785 A1, 2013. (c) Inoue, K.; Urushibara, K.; Kanai, M.; Yura, K.; Fujii, S.; Ishigami-Yuasa, M.; Hashimoto, Y.; Mori, S.; Kawachi, E.; Matsumura, M.; Hirano, T.; Kagechika, H.; Tanatani, A. Design and synthesis of 4-benzyl-1-(2H)-phthalazinone derivatives as novel androgen receptor antagonists. *Eur. J. Med. Chem.* **2015**, *102*, 310−319. (d) Stadlbauer, W.; Fischer, M. Thermal Cyclization of 3-Azido-

https://doi.org/10.1021/acs.joc.1c01149
J. Org. Chem. XXXX, XXX, XXX−XXX

2-phenyl-indan-1-one to 5H-Indeno[1,2-b]indol-10-one. *J. Heterocycl. Chem.* **2002**, *39*, 131−135. (e) Kayaleh, N. E.; Gupta, R. C.; Johnson, F. Enolate Ions as *β*-Activators of Ortho-Metalation: Direct Synthesis of 3-Aminoindenones. *J. Org. Chem.* **2000**, *65*, 4515−4522. (f) Ye, F.; Ma, P.; Zhai, Y.; Yang, F.; Gao, S.; Zhao, L.-X.; Fu, Y. Design, microwave-assisted synthesis, bioactivity and SAR of novel substituted 2-phenyl-2- cyclohexanedione enol ester derivatives. *RSC Adv.* **2018**, *8*, 19883−19893. (g) Lv, N.; Chen, Z.; Liu, Y.; Liu, Z.; Zhang, Y. Synthesis of Functionalized Indenones via Rh-Catalyzed C-H Activation Cascade Reaction. *Org. Lett.* **2017**, *19*, 2588−2591.

https://doi.org/10.1021/acs.joc.1c01149
J. Org. Chem. XXXX, XXX, XXX−XXX