Regioselective Synthesis of Chromones via Cyclocarbonylative Sonogashira Coupling Catalyzed by Highly Active Bridged-Bis(N-Heterocyclic Carbene)Palladium(II) Complexes

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ABSTRACT: The one-pot regioselective and catalytic synthesis of bioactive chromones and flavones was achieved via phosphine-free cyclocarbonylative Sonogashira coupling reactions of 2-iodophenols with aryl alkynes, alkyl alkynes, and dialkynes. The reactions are catalyzed by new dibromide(NHC)palladium(II) complexes. The new bridged N,N'-substituted benzimidazolium salts (L1, L2, and L3) and their palladium complexes C1, C2, and C3 were designed, prepared, and fully characterized using different physical and spectroscopic techniques. The molecular structures of complexes C1 and C3 were determined by single-crystal X-ray diffraction analysis. They showed a distorted square planar geometry, where the Pd(II) ion is bonded to the carbon atoms of two cis NHC carbene ligands and two cis bromido anions. These complexes displayed a high catalytic activity in cyclocarbonylative Sonogashira coupling reactions with low catalyst loadings. The regioselectivity of these reactions was controlled by using diethylyamine as the base and DMF as the solvent.

INTRODUCTION

Chromones are valuable compounds that have attracted the attention of researchers because of their multiple uses and their utmost importance in the medical and pharmaceutical fields.\(^1\)–\(^3\) These bioactive compounds comprise important structural moieties that showed activity in the treatment of various diseases such as anticancer,\(^4\)–\(^6\) anti-HIV,\(^7\) asthma,\(^8\) anti-inflammatory,\(^9\) antianagelse,\(^10\) antimicrobial,\(^11\) anti-diabetic,\(^12\) and antioxidant\(^13\) agents (Figure 1).

Moreover, the chromones and flavones are interesting moieties in agrochemicals, insecticides, and natural products.\(^1\)–\(^3\),\(^12\),\(^13\) They were extracted from different plant sources such as citrus lemon, sweet oranges, mandarin, grapefruit, ginger, Casimiroa edulis, and others.\(^1\)

The synthesis of chromones and flavones by traditional methods usually requires several step reactions.\(^2\),\(^13\),\(^19\),\(^20\) For example, alkyl lithium reagents were used for ortho-directed metalation of methoxymethyl aryl ethers followed by the reaction with a conjugatated unsaturated aldehyde; then, the allylic alcohol intermediate was oxidized with "periodinane".\(^2\) The obtained ortho-allylic ketone product was heated with acetic acid to yield the corresponding chromanone that was dehydrogenated with pyrrolidone hydrotribromide in dimethyl sulfoxide.\(^2\) This method and other similar methods have drawbacks including abundant side reactions, low yields, and difficulty in separation.\(^19\)–\(^21\) Friedel–Crafts acylation of suitably substituted benzoyl chlorides with alkynes was reported for chromone and flavone synthesis,\(^22\),\(^23\) but this method is associated with the use of large quantities of hazardous soluble Lewis acids (e.g., AlCl\(_3\), FeCl\(_3\), and TiCl\(_4\)), which made this method as one of the most challenges for green chemistry.\(^24\),\(^25\) Copper(II)-catalyzed cyclization of 1-(2-hydroxyaryl)-3-aryl-1,3-propanedione under microwave irradiation was reported for the synthesis of functionalized flavones and chromones.\(^26\),\(^27\) Other synthetic protocols were developed in recent years such as the tandem acyl transfer-cyclization reactions catalyzed by Lewis base,\(^28\) the carbonylative coupling of p-hydroxyacetophenones with aryl bromides\(^29\) and the annulation of salicylaldehydes with benzaldehydes or alkynes.\(^30\) Recently, a new improved method for the single-step synthesis of chromones and flavones was the palladium-catalyzed cyclocarbonylative Sonogashira coupling reaction of 2-halophenols with terminal alkynes.\(^31\)–\(^33\) Different palladium complexes and protocols were evaluated in the catalytic cyclocarbonylative Sonogashira coupling reactions of different alkynes with 2-iodophenols.\(^31\)–\(^33\) Nevertheless, these methods were associated with some shortcomings such as the high loading of palladium catalysts and the need for the phosphine ligands.\(^32\)–\(^35\),\(^36\) Researchers have continued the investigation for the synthesis and development of efficient palladium catalysts for the cyclocarbonylative Sonogashira coupling reactions in order to overcome the problems of low catalyst activity, high loading of catalyst, long reaction time, high

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temperature, and high CO pressure. A catalytic system including palladium complexes with mixed “phosphines” or “nitrogen-based ligands such as pyridines, pyrroles, or imidazoles showed high activity in the synthesis of flavones and less efficacy in the production of alkyl-functionalized chromones. The difficulty was in the control of the regioselectivity of the reaction between six-membered ring “chromones” and five-membered ring “aurones” products. There are numerous publications that report the control of the selectivity through the type of the base, catalyst, or solvent. However, most of these protocols have considered high loading of both catalysts and phosphine ligands and also led to low yields of the corresponding chromones when terminal alkyl alkynes reacted with 2-iodophenols in the presence of carbon monoxide. Recently, the focus on the use of N-heterocyclic carbene (NHC)–metal complexes has increased. This field made a significant revolution in organometallic chemistry because of the catalytic applications in different organic transformations.

The NHC ligands are known as strong σ-electrons donors, which enable them to form strong bonds with metals and to stabilize the metal complexes. Another important feature of NHCs as ligands is the flexibility to design their structures for different catalytic purposes. For instance, the electronic and steric properties can be tailored for special applications in catalysis. An interesting approach is the use of chelating bridged bis(N-heterocyclic carbene) ligands. The resulting complexes are expected to have more electron-rich centers and have higher thermodynamic stability by the chelate effect, as compared to the mono NHC counterparts. This would favor the oxidative addition step of the aryl halide substrate to the palladium(0) active species. Additionally, the steric properties can be controlled by varying the N-substituents. These bridged NHC–palladium complexes showed high activity in different applications. There are limited publications that consider Pd–NHC complexes for the synthesis of chromones and flavones via catalytic cyclocarbonylation of ortho-functionalized aryl halides with terminal alkynes. Nevertheless, these palladium complexes were active with aryl alkynes but showed lower catalytic activity with terminal alkyl alkynes. Previously, we have reported the synthesis and characterization of new mixed ligand dibromido and diiodido-palladium(II)–NHCs–pyridine (Br2–Pd–NHC–Py) and (I2–Pd–NHC–Py) complexes and their catalytic applications in the carbonylative Sonogashira coupling reactions and carbonylative Suzuki–Miyaura coupling reactions of aryl iodides with different alkynes or boronic acids in the presence of CO.

In this work, we report the results of the regioselective synthesis of chromones via the one-pot cyclocarbonylative Sonogashira coupling reactions of 2-iodophenols with aryl alkynes, alkyl alkynes, and dialkynes catalyzed by the active-bridged bis(NHC)–palladium(II) catalysts C1, C2, and C3. We have succeeded to crystallize the new palladium complexes C1 and C3 and characterize them by single-crystal X-ray diffraction analysis. Also, the study of the steric and electronic effects was conducted using various benzimidazole N-substituents. In addition, we report the catalytic synthesis of the new compound, 2,2′-(1,4-phenylene)-bis(6-acetyl-4H-chromen-4-one) (8c).

### RESULTS AND DISCUSSION

**Synthesis.** N-alkylation reactions of benzimidazole with alkyl bromides (2-bromopropane, benzyl bromides) using potassium hydroxide as the base were conducted efficiently to produce 1-alkyl benzimidazoles (S1 and S2) in very good yields (Scheme 1). Further, bridged bis-benzimidazolium bromide salts (L1, L2, and L3) were prepared in good to very good yields.
by direct alkylation of the 1-alkyl benzimidazoles (S1 and S2) with dibromoalkanes (1,3-dibromopropane and 1,4-dibromobutane) (Scheme 2). The proton NMR spectra showed downfield singlet peaks at 9.83 ppm (L1), 10.05 ppm (L2), and 10.15 ppm (L3), which are assigned to C-2 protons of the benzimidazole rings. These singlet peaks confirm the formation of the benzimidazolium bromides.

The bridged N-heterocyclic biscarbene palladium(II) complex-bridged-bis(NHC)PdBr2 (C1, C2, and C3) were synthesized in very good yields by reacting palladium acetate with 1.0 equiv of the appropriate ligand precursor (L1, L2, or L3) (Scheme 3). The absence of the singlet peaks for the acidic C-2 protons in 1H NMR spectra confirmed the formation of the new palladium complexes. Furthermore, 13C NMR spectra for the palladium–NHC complexes showed new signals assigned to C–Pd at 181.7, 181.1, and 176.3 ppm for C1, C2, and C3, respectively. The ESI mass spectra of the three complexes showed peaks at 546.8 (C1), 560.8 (C2), and 642.8 (C3) that confirm the formation of the Pd–carbene complexes.

The molecular structures of complexes C1 and C3 are depicted in (Figures 2 and 3), respectively. Selected bond distances and bond angles are given in (Table 7). The cis bond angles are in the ranges 88.66(17)° and 97.01(4)° in C1 and C3, respectively. The Pd–C and Pd–Br bond distances are within the range reported in the literature.35,40 The former is 1.997(3) Å in C1 and in the range [1.964(8)–1.985(8) Å] in C3, while the latter is 2.4906(4) Å in C1 and in the range [2.4659(11)–2.4704(11) Å] in C3. The chelate C–Pd–C bite angle values are 88.66(17)° and [87.4(3), 87.7(3)°] in C1 and C3, respectively. The larger bond distances in C1 are consistent with the larger steric hindrance of the isopropyl group opposing the formation of the chelate complex.

There are various catalytic systems used for the synthesis of chromones and flavones reported in the literature. However, they suffer from significant shortcomings such as high catalyst loading, long reaction time, the use of phosphines, and the low selectivity.32–37 Recently, NHC–Pd(II) complexes were evaluated in various cross coupling reactions,53–56 but their applications in cyclocarbonylative Sonogashira coupling reactions of 2-iodophenols with terminal alkynes are still limited, where the catalytic system is prepared in situ by mixing the palladium(II) precursors with the NHC ligands.38

In this work, we have examined the application of the newly synthesized bridged-bis(NHC)PdBr2 complexes (C1, C2, and C3) in the cyclocarbonylative Sonogashira coupling reactions of various 2-iodophenols with aryl and alkyl alkynes. The optimization of the reactions was conducted by using the bridged-bis(NHC)PdBr2 complex C1. For this purpose, a model reaction of 2-iodophenol and phenylacetylene under pressurized CO in the presence of a catalytic amount of C1 was adopted (eq 1). The results of the optimization of the reactions are summarized in (Table 1). Only traces of 2-phenyl-4H-chromen-4-one (3aa) were observed when a neat reaction was conducted using 1.0% mol of C1 as the catalyst and diethylamine as the base at room temperature for 16 h (Table 1, entry 1). However, a conversion of 59.5% was obtained at 80 °C, and a higher conversion (85.5%) was achieved at 100 °C. These reactions produced 2-phenyl-4H-chromen-4-one (3aa) as a major compound. The isolated yield of 3aa gradually increased by increasing the temperature (Table 1, entries 2–3). When diethylamine in the neat reaction was replaced by triethylamine at 80 and 100 °C using C1, the cyclocarbonylative of 2-iodophenols with phenylacetylene via a 6-endo cyclization mode leading to six-membered ring product “flavone” (3aa) and 5-exo cyclized five-membered ring product “aurone” (4aa) was formed. Moreover, the increase of the temperature from 80 to 100 °C increased the conversion from 85% to 100% and favors the formation of the aurone product 4aa (57 and 66%) (Table 1, entries 6–7). Nevertheless, the use of Et3NH as the base with THF as the solvent at 80 and 100 °C with triethylamine as the solvent, the conversions dropped to 69 and 93%, respectively, with no significant change in the regioselectivity (Table 1, entries 6–7). Consequently, under the same experimental conditions, triethylamine oriented the cyclocarbonylative Sonogashira reactions toward the production of aurone 4aa as the major product. In addition, diethylamine in THF produced flavone 3aa in high isolated yields. When potassium carbonate was used as the base in THF at 100 °C (Table 1, entry 10), a full conversion was observed to produce flavone 3aa and aurone 4aa (38%/62%). In toluene as a solvent, the cyclocarbonylative Sonogashira reaction of 2-iodophenol with phenylacetylene under the optimized conditions (Et3NH/1.0% mol of C1/100 °C/16 h) was converted (97%) which led to the formation of

Scheme 2. Synthesis of Bridged NHC Salt Ligand Precursors
two products flavone "3aa" and aurone "4aa" with a ratio of 93/7 (Table 1, entry 11). We have also observed that in THF as the solvent and Et₂NH as the base, the catalyst’s C1 loading can be decreased from 1.0 to 0.5 mol % of C1 leading to high conversion (80%) to produce flavone 3aa as the only product of the reaction (Table 1, entry 12). An excellent isolated yield of 2-phenyl-4H-chromen-4-one (3aa) (96%) was achieved with 98% conversion of 2-iodophenol when the DMF was used as solvent under optimized conditions [Et₂NH/C1 (0.5 mol %)/100 °C/16 h] (Table 1, entry 13); small amounts of aurone 4aa were obtained (3aa/4aa = 96:4). A decrease in the temperature from 100 to 80 and 50 °C under the optimized conditions [DMF/Et₂NH/C1 (0.5 mol %)/16 h] demonstrated a gradual decline in the conversion of 2-iodophenol (83% at 80 °C and 38% at 50 °C) and the isolated yields of the flavone 3aa were 81% at 80 °C and 35% at 50 °C (Table 1, entries 14, 15). Therefore, 100 °C was considered as the optimized temperature for the subsequent reactions. The effect of the reaction time was also studied. After 16, 12, and 6 h, the isolated yields of the flavone 3aa decreased from 92 to 72 and 46%, respectively (Table 1, entries 13, 16, 17). When DMF was replaced by other solvents such as THF, toluene, and in the neat Et₂NH under the optimized conditions [Et₂NH/C1 (0.5 mol %)/100 °C/16 h], a significant decrease in the conversions and isolated yields in flavone was observed (Table 1, entries 18–20).

Additionally, the study of the role of the base on the regioselectivity was also conducted using Et₃N and K₂CO₃ as bases with DMF as solvent under optimized conditions [C1 (0.5 mol %)/100 °C/16 h]. For instance, the use of K₂CO₃ as the base produced a mixture of flavone 3aa and aurone 4aa (70%/30%) (Table 1, entry 21). Similarly, the use of trimethylamine gave lower regioselectivity producing a mixture of flavone 3aa and aurone 4aa (60%/40%) (Table 1, entry 22). On the other hand, when Et₃N was used with THF as a solvent, the isolated yield in flavone 3aa dropped to 30% (Table 1, entry 7) and increased with DMF to 54%. These results showed the importance of Et₂NH and DMF as regioselective factors in the production of flavones.

Based on the above results, the subsequent reactions of the scope of substrates were carried out using 0.5 mol % of C1, Et₂NH as the base, and DMF as the solvent at 100 °C for 16 h. The catalytic reactions using C1 under the optimized conditions were highly regioselective. The reactions resulted in the
formation of the flavone "2-phenyl-4H-chromen-4-one" (3aa) as the major product; only traces of the aurone "2-benzylidenbenzofuran-3(2H)-one" (4aa) were detected. It is important to note that because of the use of an excess of Et₂NH as compared to phenylacetylene, small amounts of benzylidenebenzofuran as a side product from the carbonylative coupling of phenylacetylene with Et₂NH.

The catalytic activity of the other synthesized bridged-NHC PdBr₂ catalysts (C2 and C3) were also evaluated under the same optimized conditions (CO/Et₂NH/DMF/100 °C/16 h). Their catalytic efficiency in the cyclocarbonylative Sonogashira coupling reactions was slightly less than C1 (Table 2). The conversions with C2 and C3 were 88 and 84%, respectively. The isolated yields of the flavone 3aa were 85 and 79%, respectively (Table 2, entries 2, 3).

In order to rationalize the relative activity of the three complexes, one can consider the relative sigma donation effects of the ligand precursors L1, L2, and L3 that can be probed by the proton NMR chemical shift of the C-2 protons of the benzimidazole rings, observed at 9.83, 10.05, and 10.15 ppm for L1, L2, and L3 respectively. The most downfield signals were consistent with the highest electron donating effect of the isopropyl group in L1 and L2 relatively to the benzyl group in L3. The results of the comparative catalytic evaluation of the corresponding palladium−NHC complexes C1, C2, and C3 are in agreement with the strong electron donating effect of the ligand in C1 and the stability of the corresponding 8-membered ring chelate.

In addition, the catalytic activity for the mono NHC palladium(II) complexes was also evaluated under the optimized reaction conditions. In fact, the two heteroleptic (NHC)−pyridine palladium(II) complexes, which were previously reported, Pd−NHC−Py1 (1-isopropyl,3-dihydro-2H-benzo[d]imidazole-2-ylidene)(pyridin-1(2H)-yl) palladium(II) bromide" and Pd−NHC−Py2 (1(3-disopropyl,1,3-dihydro-2H-benzo[d]imidazole-2-ylidene)(pyridin-1(2H)-yl)palladium(II) bromide” (Figure 4), were evaluated in the cyclocarbonylative Sonogashira [Pd−NHC−Py (0.5 mol %)/Et₂NH/DMF/100 psi/100 °C/16 h] (Table 2, entries 4−5). These complexes catalyzed the carbonylation reaction with very good conversions (83 and 79%, respectively) of 2-iodophenol and high selectivity (89 and 86%) toward the flavone. However, the conversion and the isolated yield of

Table 1. Cyclocarbonylative Sonogashira Coupling Reactions of 2-Iodophenol (1a) with Phenylacetylene (2a) by C1a, b

| No. | C1 mol % | base | solvent | T (°C) | time (h) | conv. (%) | 3aa (%)c | 4aa (%)d |
|-----|----------|------|---------|--------|----------|-----------|-----------|-----------|
| 1   | 1.0      | Et₂NH | Et₂NH   | RT     | 16       | traces    | traces    | traces    |
| 2   | 1.0      | Et₂NH | Et₂NH   | 80     | 16       | 59.5      | 100 (55)  |           |
| 3   | 1.0      | Et₂NH | Et₂NH   | 100    | 16       | 85.5      | 100 (82)  |           |
| 4   | 1.0      | Et₂N  | Et₂N    | 80     | 16       | 85        | 43 (34)   | 57 (45)   |
| 5   | 1.0      | Et₂N  | Et₂N    | 100    | 16       | 69        | 40 (25)   | 60 (38)   |
| 6   | 1.0      | Et₂N  | THF     | 80     | 16       | 93        | 36 (30)   | 64 (56)   |
| 7   | 1.0      | Et₂N  | THF     | 100    | 16       | 68        | 100 (64)  |           |
| 8   | 1.0      | Et₂NH | THF     | 100    | 16       | 84.5      | 100 (81)  |           |
| 9   | 1.0      | Et₂NH | THF     | 100    | 16       | 96        | 38 (33)   | 62 (57)   |
| 10  | 1.0      | K₂CO₃ | THF     | 100    | 16       | 97        | 93 (88)   | 7         |
| 11  | 1.0      | Et₂NH | Toluene | 100    | 16       | 80        | 100 (77)  |           |
| 12  | 0.5      | Et₂NH | THF     | 100    | 16       | 98        | 96 (92)   | 4         |
| 13  | 0.5      | Et₂NH | DMF     | 100    | 16       | 83        | 100 (81)  |           |
| 14  | 0.5      | Et₂NH | DMF     | 80     | 16       | 38        | 100 (35)  |           |
| 15  | 0.5      | Et₂NH | DMF     | 50     | 16       | 76        | 100 (72)  |           |
| 16  | 0.5      | Et₂NH | DMF     | 100    | 16       | 6         | 100 (46)  |           |
| 17  | 0.5      | Et₂NH | DMF     | 100    | 16       | 72        | 100 (70)  |           |
| 18  | 0.5      | Et₂NH | Toluene | 100    | 16       | 82        | 95 (76)   | 5         |
| 19  | 0.5      | Et₂NH | Toluene | 100    | 16       | 79        | 100 (76)  |           |
| 20  | 0.5      | Et₂NH | Et₂NH   | 100    | 16       | 97        | 70 (65)   | 30 (27)   |
| 21  | 0.5      | K₂CO₃ | DMF     | 100    | 16       | 95        | 60 (54)   | 40 (35)   |
| 22  | 0.5      | Et₂N  | DMF     | 100    | 16       | 95        | 60 (54)   | 40 (35)   |

aOptimization of reaction conditions. bReaction conditions: C1 (mol %), 2-iodophenol (0.5 mmol), phenylacetylene (0.6 mmol), base (1.0 mmol), solvent (2.5 mL), and CO (100 psi), 100 °C. Determined by GC and GC−MS. cIsolated yield.
flavone are lower than those obtained with the bridged-bis(NHC)PdBr₂ complexes.

Furthermore, Pd(OAc)₂ was used with an equal amount of the ligand L₁ in the cyclocarbonylative Sonogashira coupling reaction under the optimized conditions. The conversion was lower (81%) with high selectivity (94%) for the flavone 3aa (Table 2, entry 6). This result confirms the superiority of the catalytic activity of C₁ as compared to the “in situ”-formed palladium complex.

For comparison, commercially available palladium complexes were also considered (Table 2, entries 7–12) under different protocols in the presence of other ligands, such as 1,1’-bis(diphenylphosphino)ferrocene (DPPF), and using a higher catalyst loading. The results of the catalytic evaluation confirmed again the high catalytic efficiency and selectivity of the bridged-bis(NHC)PdBr₂ catalysts C₁, C₂, and C₃.

The model cyclocarbonylative Sonogashira coupling reactions under optimized conditions showed high catalytic activity and selectivity with the newly synthesized bridged-bis(NHC)PdBr₂ complexes (C₁, C₂, and C₃). The catalyst C₁ was considered in the study of the scope of substrates. The reactions were conducted under the optimized experimental conditions [C₁ (0.5 mol %), 2.0 equiv of Et₃NH, 3 mL of DMF, 100 psi CO, 100 °C, 16 h]. Different 2-iodophenols were reacted with various aryl alkynes (eq 2, Table 3). Numerous chromones and flavones were produced in excellent yields via cyclocarbonylative Sonogashira coupling reactions of various aryl alkynes with different electron-withdrawing-substituted 2-iodophenols (4’-hydroxy-3’-iodoaryl). The carbonylation reaction of 2-iodophenol with alkynes that have activating electron releasing substituents with deactivated 2-iodophenols were also very successful with excellent isolated yields (91–98%) (Table 3, entries 5–8). On the other hand, a decrease in the isolated yield of the corresponding chromone to 74% was obtained when the cyclocarbonylative Sonogashira coupling reaction was carried out with 2-iodophenol and 2-ethynylanisole (Table 3, entry 9), probably because of the steric hindrance of the methoxy substituent in the ortho position of an alkyne substrate.

Cyclocarbonylative Sonogashira Coupling Reactions of 2-Iodophenol (1a–b) with Alkyl Alkynes (5a–e) Catalyzed by the Bridged-Bis(NHC)PdBr₂ Complex C₁. The research studies of the cyclocarbonylative Sonogashira coupling reactions of 2-iodophenols with alkyl alkynes are still very limited, where low yields of chromones were produced in the presence of palladium–phosphine or palladium-mixed ligand complexes. Interestingly, various chromones were produced in good yields via the cyclocarbonylative coupling reactions of different 2-iodophenols with various alkyl alkynes catalyzed efficiently by the complex C₁ under the optimized conditions (Et₃NH/DMF/110 °C/24 h) (eq 3) (Table 4). For instance, the cyclocarbonylative coupling reaction of 2-iodophenol with 1-heptyne (Table 4, entry 1), 1-decynye (Table 4, entry 2), 6-phenyl-1-hexyne (Table 4, entry 3), and 3-cyclohexyl-1-propyne (Table 4, entry 4) was accomplished successfully to produce the corresponding chromones 6 in good to excellent yields (53–90%). These results showed a relation between the chain lengths on the alkyl alkynes and the yields of corresponding chromones. Alkynes with shorter alkyl chain, such as 1-heptyne (Table 4, entry 1), were more reactive than the alkyl alkynes having longer alkyl chains such as 1-decynye (Table 4, entry 2). The cyclocarbonylative Sonogashira coupling reactions of 2-iodophenol with either 6-phenyl-1-hexyne or 3-cyclohexyl-1-propyne led to good and very good yields (53 and 71%) of their corresponding chromones (Table 4, entries 3–4). The reactivity 2-iodophenols were improved with 4’-hydroxy-3’-iodoacetophenone (1b) having an electron-withdrawing substituent. The reaction of 1b with 3-cyclohexyl-1-propyne and 1-heptyne catalyzed by C₁ gave very good to excellent isolated yields of the corresponding chromones (77–90%) (Table 4, entries 5–6). In conclusion, useful chromones were produced in high yields by the cyclocarbonylative coupling of different 2-iodophenols with various alkyl alkynes in the presence of bridged-bis(NHC)PdBr₂ as the catalyst.

Cyclocarbonylative Sonogashira Coupling Reaction of 2-Iodophenol with Dialkynes Catalyzed by Complex C₁. Considering the high efficiency of the newly synthesized complexes C₁, C₂, and C₃, we have investigated the cyclocarbonylative Sonogashira coupling reaction of 2-iodophenol with dialkynes. Remarkably, these reactions successfully proceeded to obtain symmetrical di flavones in very good to excellent isolated yields. For instance, the cyclocarbonylative coupling reactions of 1,4-diethynylbenzene and 1,3-diethynylbenzene with 2 equiv of 2-iodophenol or 4-hydroxy-3-iodoacetophenone proceeded smoothly to yield the corresponding para-diflavones (8a) and (8c) (eq 4) and (eq 4) in 86 and
Furthermore, meta-diflavone was obtained in 74% (8b) (eq 4).

The excellent results obtained with the catalytic cyclocarbonylative coupling of 2-iodophenols with alkynes and diarylalkynes showed the high catalytic activity of the newly synthesized bridged-N-heterocyclic carbene palladium complexes C1, C2, and C3. The complex C1 exhibited superior catalytic efficiency with much lower loading in the absence of additional phosphine ligands as compared to other reported catalytic systems in the literature (Table 5).

Table 3. Cyclocarbonylative Sonogashira Coupling Reactions of 4′-Hydroxy-3′-iodoaryls (1a–d) with Aryl Alkynes (2a–e) Catalyzed by the C1

| Entry | 4′-Hydroxy-3′-iodoaryl 1 | Aryl Alkyne 2 | Product 3 | Yield (%) \(^b\) |
|-------|--------------------------|---------------|-----------|------------------|
| 1     | ![image](image1.png) 1a  | ![image](image2.png) 2b | ![image](image3.png) 3ab | 91 |
| 2     | ![image](image4.png) 1a  | ![image](image5.png) 2c | ![image](image6.png) 3ac | 86 |
| 3     | ![image](image7.png) 1a  | ![image](image8.png) 2d | ![image](image9.png) 3ad | 88 |
| 4     | ![image](image10.png) 1a | ![image](image11.png) 2e | ![image](image12.png) 3ae | 93 |
| 5     | ![image](image13.png) 1b  | ![image](image14.png) 2a | ![image](image15.png) 3ba | 98 |
| 6     | ![image](image16.png) 1c  | ![image](image17.png) 2a | ![image](image18.png) 3ca | 95 |
| 7     | ![image](image19.png) 1d  | ![image](image20.png) 2a | ![image](image21.png) 3da | 91 |
| 8     | ![image](image22.png) 1b  | ![image](image23.png) 2d | ![image](image24.png) 3bd | 93 |
| 9     | ![image](image25.png) 1a  | ![image](image26.png) 2f | ![image](image27.png) 3af | 74 |

\(^a\)Reaction conditions: C1 (0.50 mol %), 4′-hydroxy, 3′-iodoaryl (0.50 mmol), aryl alkyne (0.60 mmol), Et₂NH (1.0 mmol), DMF (2.5 mL), CO (100 psi), 100 °C, 16 h. \(^b\)Isolated yield.
Plausible Mechanisms for the Cyclocarbonylative Sonogashira Coupling Reactions. Chromones and aurones were produced via carbonylative Sonogashira coupling reactions followed by the cyclization reactions. Initially, in the presence of the base, alkynes are deprotonated and the palladium(II) precatalyst (II) undergoes a substitution of the bromides by the

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Table 4. Cyclocarbonylative Sonogashira Coupling Reactions of 4′-Hydroxy-3′-iodoaryls (1a–d) with Alkyl Alkynes (5a–e) Catalyzed by C1

| Entry | 4′-Hydroxy-3′-iodoaryl 1 | Alkyl Alkyne 5 | Product 6 | Yield (%)a |
|-------|--------------------------|----------------|-----------|------------|
| 1     | 1a                       | 5a             | 6aa       | 81         |
| 2     | 1a                       | 5b             | 6ab       | 68         |
| 3     | 1a                       | 5c             | 6ac       | 53         |
| 4     | 1a                       | 5d             | 6ad       | 71         |
| 5     | 1b                       | 5a             | 6a       | 90         |

aReaction conditions: C1 (1.0 mol %), 4′-hydroxy, 3′-iodoaryl (0.50 mmol), alkyl alkyne (0.60 mmol), Et2NH (1.0 mmol), DMF (2.5 mL), CO (100 psi), 110 °C, 24 h. aIsolated yield.

Table 5. Comparison of the Activity of the New Catalytic System Including Bridged-Bis(NHC)PdBr2 (C1) in Cyclocarbonylative Sonogashira Coupling Reactions of 2-Iodophenol and Alkynes with Literature Data

| refs | catalyst | co-catalyst/ligand/additive | base | time (h) | yield (%) |
|------|----------|----------------------------|------|----------|-----------|
| 33   | PdCL2 (5 mol %) | (H3C)5P=C(C6H4Br)2- (1.5 g) | Et2N | 24       | 64–95     |
| 31   | PdCL2 (5 mol %) | PPh3 (10 mol %) | Et2N | 24       | 35–95     |
| 35   | Pd(OAc)2 (5 mol %) | DPPF (5 mol %) | Et2N | 24       | 30–95     |
| 32   | Pd2(dba)3 (1.5 mol %) | 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (3 mol %) | DBU | 0.5 MW | 62–95     |
| 40   | Pd(PPh3)4 (3 mol %) | Ac2O (6 mol %) | Et2N | 24       | 51–82     |
| 38   | Pd–NHC–Py (0.5 mol %) | imidazole (0.5 mol %) pyridine (0.5 mol %) | Et2NH | 24 | 25–98     |
| 49   | Pd/C (1 mol %) | | Et2NH | 20 | 74–98     |
| this work | bridged-bis(NHC)PdBr2 (0.5 mol %) | | Et2NH | 16 | 53–98     |
Acetylides to produce the palladium(II) intermediate (III), which undergoes reductive elimination of the dialkynes to generate the Pd(0) (IV) as the active catalytic species (Scheme 4, pathway A). The palladium(II) intermediate (Ar\(-\)Pd\(\rightarrow\)) (V) is then formed via the oxidative addition of 2-iodophenol to the Pd(0). The acyl palladium intermediate (VI) is formed by the insertion of carbon monoxide (CO) into the Ar--Pd bond. Then, the iodide is substituted by the acetylide to produce the palladium intermediate VII. The reductive elimination in the presence of the base yields the carbonylative Sonogashira product VIII with the subsequent regeneration of the Pd(0) catalyst.58,61 The production of aurones or chromones depends on the type of base used in the reaction.

In the presence of diethylamine, the favored Michael addition to the intermediate VIII forms the Michael adduct IX (Scheme 4, pathway B), which is usually stabilized in DMF as an ideal solvent in these reactions.62,63 This Michael adduct (IX) was detected and identified in the reaction mixture by gas chromatography–mass spectrometry (GC–MS) \[m/z = 296.5; C_{19}H_{22}NO_2 (MH^+)\]. The diethylamine is then eliminated to produce the cyclic enolate X, which is converted into the corresponding chromone.

When triethylamine was used as a base, no reaction was observed in the absence of the palladium catalyst. Furthermore, the palladium catalyzed reaction in the presence of triethylamine led to the formation of a mixture of aurones and chromones (Table 3, entries 4–7). In this case, it is suggested that the oxidative addition of O--H to the Pd(0) species generates the palladium intermediate XI (Scheme 4, pathway C). The subsequent insertion of the alkynie into Pd--H proceeds following two pathways to generate either the seven-membered metallacycle XII (pathway D) or the six-membered metallacycle XIII (pathway E) as intermediates. These undergo further reductive elimination to produce chromones and aurones, respectively.

**CONCLUSIONS**

High regioselectivity of phosphine-free cyclocarbonylative Sonogashira coupling reactions of 2-iodophenols with alkynes toward chromones was achieved using new bridged-bis(NHC)-PdBr\(_2\) chelate catalysts. The preligands and the corresponding complexes C1, C2, and C3 were synthesized and fully characterized using various physical, analytical, and spectroscopic techniques including single-crystal X-ray diffraction. The catalytic efficiency was evaluated in the cyclocarbonylative Sonogashira coupling reactions of various 2-iodophenols with aryl and alkyl alkynes including the dialkynes under CO pressure and in the absence of any additional phosphine ligands. The palladium complex C1 was more active as compared to C2 and C3 complexes. In general, C1, C2, and C3 showed high catalytic activity with lower catalyst loading as compared to other known...
catalytic systems. Excellent isolated yields of the expected chromones and flavones were obtained for the cyclocarbonylative Sonogashira coupling reactions of 2-iodophenols with the aryl alkynes and good to very good yields with alkyl alkynes or aryl dialkynes. The regioselectivity of these reactions toward the chromones was favored with diethylamine as a base and in DMF as a solvent. It is worth noting the synthesis of a new compound, 2,2′-(1,4-phenylene) bis(6-acetyl-4H-chromen-4-one) (8c), by the one-pot cyclocarbonylative Sonogashira coupling reaction of 4-hydroxy-3-iodoacetophenone with 1,4-diethynylbenzene catalyzed by C1.

## EXPERIMENTAL SECTION

**Materials and Instrumentation.** All precursors used for the synthesis of NHCs, palladium complexes, 2-iodophenols, and alkynes were purchased from Sigma-Aldrich and used directly as received unless specified otherwise. Flash column chromatography (packed with 60 F Silica gel from Fluka Chemie AG, Buchs, Switzerland) was used to purify the products. 

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker EQUINSS (400 MHz for $^1$H; 101 MHz for $^{13}$C) and JOEL 1500 MODEL (500 MHz for $^1$H; 125 MHz for $^{13}$C) NMR spectrometer in different deuterated solvents like CDCl$_3$, CD$_2$Cl$_2$, DMSO-d$_6$, and DMF-d$_7$. Chemical shifts were reported in ppm downfield of tetramethylsilane, used as the internal standard. The collected data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), and coupling constant in Hz. $^{13}$C NMR spectra were obtained with complete proton decoupling.

The products were analyzed by GC−MS (Agilent GC−MS; GC 6890N and MS 5975B; 30 m HP-5 capillary column). A separate GC (Agilent 6890) was used to monitor the reactions and analyze the products. Mass spectra were obtained using the Fisher ESI-TOF/MS spectrometer with the ESI scan (0.104−0.499 min, 17 scans) Frag = 180.0 V. Elemental analyses for the ligand precursors, corresponding complexes, and products were performed on PerkinElmer Series 11 (CHNS/O) Analyzer 2400. Merck 60 F$_{254}$ silica gel plates (250 μm layer thickness) were used for thin-layer chromatography (TLC) analyses.

Single-crystal X-ray data collection for complexes C1 and C3 was performed at 298 K on a Bruker D8 Quest diffractometer (Mo Kα radiation $\lambda$ = 0.71073 Å). Data were collected and integrated using the Bruker APEX3 software package. Multiscan absorption correction was performed using SA-DABS. The structures were solved by direct methods with SHELXS using the SHELXTL package and refined using full-matrix least squares procedures on $F^2$ via the program SHELXL-2014. ORTEP3 was used for molecular graphics. All hydrogen atoms were included at calculated positions using a riding model. The crystal data and refinement details for C1 and C3 are given in (Table 6). Selected bond lengths and bond angles are given in (Table 7).

### Synthesis of 1-Alkyl Benzimidazole (S1 and S2).

A dry and clean round-bottom flask was charged with benzimidazole

![Scheme 4. Plausible Mechanism for the Cyclocarbonylative Sonogashira Coupling Reaction Catalyzed by Bridged-Bis(NHC)PdBr$_2$ Complexes; Production of Chromone [Pathway B or (C,D)], and Aurone (Pathway C−E)](https://dx.doi.org/10.1021/acsomega.0c04706)
Table 6. Crystal and Structure Refinement Data of Compounds C1 and C3

|   | C1       | C2       |
|---|----------|----------|
| CCDC deposition # | 1961539 | 1950067  |
| empirical formula | C6H6Br2N2OPd | C6H6Br2CL2N2OPd |
| formula weight      | 699.81  | 825.73   |
| temperature (K)     | 298(2)  | 298(2)   |
| wavelength (Å)      | 0.71073 | 0.71073  |
| crystal system      | orthorhombic | monoclinic |
| space group         | Pnma    | P21/m    |
| unit cell dimensions|         |          |
| a (Å)               | 16.2158(6) | 10.5561(8) |
| b (Å)               | 18.1879(7) | 23.972(2)  |
| c (Å)               | 9.2992(4)  | 13.3418(11) |
| α (deg)             | 90       | 90       |
| β (deg)             | 90       | 90       |
| γ (deg)             | 90       | 90       |
| volume (Å³)         | 2742.63(19) | 3374.0(5)  |
| Z                    | 4        | 4        |
| density (calculated, g/cm³) | 1.695  | 1.626   |
| absorption coefficient (mm⁻¹) | 3.619  | 3.108   |
| F(000)              | 1400    | 1640     |
| θ range data collect. (deg) | 2.512−28.371 | 2.564−28.367 |
| index ranges        | −21 ≤ h ≤ 21, −14 ≤ k ≤ 14, −24 ≤ l ≤ 24, −31 ≤ k ≤ 32, −11 ≤ l ≤ 17 |
| reflections collected | 76,298 | 123,299 |
| independent reflections | 3528  | 3860(4)|
| absorption correction | semiempirical from equivalents | semiempirical from equivalents |
| refinement method   | full-matrix least-squares on F² | full-matrix least-squares on F² |
| data/restraints/parameters | 3528/18/173 | 8604/6/399 |
| goodness-of-fit on F² | 0.989  | 1.112    |
| ginal R indices [1 > 2σ(f)] | R₁ = 0.0342, wR₁ = 0.1080 | R₁ = 0.0716, wR₁ = 0.1905 |
| R indices (all data) | R₁ = 0.0473, wR₁ = 0.1299 | R₁ = 0.1308, wR₁ = 0.2298 |
| largest diff. peak and hole (e Å⁻³) | 1.039 and −0.978 | 1.673 and −1.585 |

(10.0 mmol), excess amount of alkyl bromide (12.2 mmol), 2-bromopropane or benzyl bromide, and an appropriate base, potassium hydroxide (20.0 mmol) with 2-bromopropane or cesium carbonate (20.0 mmol) with benzyl bromide, and 1.00 mmol of tetrabutylammonium bromide. 100 mL of acetonitrile was used to dissolve the prepared mixture with continuous stirring at 80 °C for 24 h. TLC (1:1 = hexane/ethyl acetate) was used for monitoring the reaction until no free benzimidazole was observed. After the completion of the reactions, the solvents were removed under vacuum by the rotary evaporator. The oily products were used as crude ingredients for 1H NMR and 13C{1H} NMR. The products appeared as white precipitates. They were filtered and washed three times with 15 mL of 1,4-dioxane and then by 15 mL of toluene to remove any traces of the starting materials. The products were dried under vacuum and then collected as a white precipitate. Characterization of the alkylidenated N-heterocyclic dicarbene salts was conducted with different spectroscopic techniques including 1H NMR, 13C NMR, elemental analysis, and ESI.

3,3′-(Propane-1,3-diyl)-bis(1-isopropyl-1H-benzo[d]imidazole-3-ium) Bromide (L1). Yield = 91%. White solid. 1H NMR (500 MHz, DMSO-d₆): δ (ppm) 9.83 (2H, s, NCH-N), 8.15−8.11 (4H, m, Ar-H), 7.71−7.69 (2H, m, Ar-H), 5.05 (2H, sep, J = 6.71 Hz, NCH), 4.67 (4H, t, J = 7.01 Hz, CH₂), 2.67 (2H, qu, J = 7.02 Hz, CH₂), 1.61 (12H, d, J = 6.7 Hz, NC(CH₃)₂); 13C{1H} NMR (125 MHz, DMSO): δ (ppm) 140.07 (NCN), 131.3, 130.5, 126.7, 126.6, 114.1, 113.7, (Ar-H), 50.7 (NCH), 44.1 (NCH₂), 28.0 (CH₂), 21.6 (NC(CH₃)₂). Anal. Calcd for C₂₆H₃₅Br₂N₅O₃Pd: C, 74.84%; H, 7.23%; N, 17.23%. Found: C, 74.84%; H, 7.23%; N, 17.23%.

3,3′-(Butane-1,4-diyl)-bis(1-isopropyl-1H-benzo[d]imidazole-3-ium) Bromide (L2). Yield = 76%. White solid. 1H NMR (500 MHz, DMSO-d₆): δ (ppm) 10.05 (2H, s, NCH-N), 8.13−8.11 (4H, m, Ar-H), 7.68 (4H, dd, J = 6.1 Hz, J = 2.75 Hz, Ar-H), 5.05 (2H, sept, J = 6.71 Hz, NCH), 4.58 (4H, m, NCH₂), 2.04−1.99 (4H, m, CH₂), 1.62 (12H, d, J = 6.71 Hz (CH₂)); 13C{1H} NMR (125 MHz, DMSO): δ (ppm) 140.07 (NCN), 131.3, 130.6, 126.7, 126.6, 114.1, 113.8, (Ar-H), 50.7 (NCH), 46.3 (NCH₂), 25.6 (CH₂), 21.64 (NC(CH₃)₂). Anal. Calcd for C₃₂H₃₅Br₂N₅: C, 73.84%; H, 6.01%; N, 10.73%. Found: C, 72.37%, H, 5.8%, N, 10.97%. ESI m/z: 442 [M − Br]⁺, m/z: 441 [M − Br⁺ (−H⁺)].

3,3′-(Propane-1,3-diyl)-bis(1-benzyl-1H-benzo[d]imidazole-3-ium) Bromide (L3). Yield = 65%. White solid. 1H NMR (500 MHz, DMSO-d₆): δ (ppm) 10.15 (2H, s, NCH-N), 8.14 (2H, d, J = 7.93 Hz, Ar-H), 7.96 (2H, d, J = 7.32 Hz, Ar-H), 7.66−7.62 (4H, m, Ar-H), 7.53 (4H, d, J = 7.02 Hz, Ar-H), 7.39−7.36 (4H, m, Ar-H), 5.80 (4H, s, NCH₂Ph), 4.62 (4H, m, NCH₂CH₃), 2.06 (2H, m, CH₂). 13C{1H} NMR (125 MHz, CDCl₃): δ (ppm) 141.31, 132.99, 131.51, 130.77, 129.27, 129.10, 128.52, 127.26, 127.14, 114.08, 113.64 (C-arom), 51.95 (NCH), 51.37 (NCH₂), 22.44 2(CH₂CH₂). Anal. Calcd for C₃₇H₃₇Br₂N₅ (618.4): C, 60.61%; H, 4.89%; N, 9.06%. Found: C, 60.83%; H, 5.11%; N, 9.79%. ESI m/z: 538.5 [M − Br⁺].

Synthesis of Palladium-Bridged N-Heterocyclic Dicarbene Complexes (C₁, C₂, and C₃). A round-bottom flask (50
solid. 1H NMR (500 MHz, DMF-d6) (ppm): 8.08 (2H, d, J = 8.24 Hz, Ar-H), (the signals of aromatic protons overlap with the solvent signal), 7.97 (2H, d, J = 8.24 Hz, Ar-H), 7.45—7.37 (4H, m, Ar-H), 5.99 (2H, m, NCCH), 5.43 (2H, m, CH2), 5.11 (2H, m, CH2), 5.11 (2H, m, CH2), 2.19 (2H, m, CH2), 1.94 (6H, s), 1.71 Hz, NC(CH2)2, 1.78 [6H, d, J = 5.80 Hz, NC(CH2)2]. 13C{1H} NMR (125 MHz, CD2Cl2): δ (ppm) 181 (Pd−C)[carbene signal (N(N=C(N=N))], 135.2, 133.3, 132.8, 132.8, 132.7, 132.4, 132.1, 129.2, 122.9, 121.3, 113.2, 110.7, 110.5 (Ar-H), 55.4 (NCH), 53.4 (NCH), 49.5 (NCH2), 47.8 (NCH2), 30.0 (CH2), 28.5 (CH2), 22.1, 21.7, 21.3 [N(C=C)H2]; Anal. Calcd for C36H36N2Br2Pd, (626.74): C, 44.08%; H, 4.50%; N, 8.94%. Found: C, 43.86%; H, 4.25%; N, 8.63%. ESI m/z: $460.82 [M – Br]^+$.

**Dibromido (1,1′-Disopropyl-3,3′-propylenedibenzimidazoline-2,2-diydilenedipalladium(II) (C3)**. Yield = 73%. White crystals. 1H NMR (400 MHz, CDCl3): δ (ppm) 7.71—7.69 (m, 2H, C–H-ary), 7.48 (4H, m, 4H, C–H-arom), 7.45—7.41 (m, 6H, C–H aron), 7.35—7.29 (m, 6H, C–H-(phenyl)), 5.87 (m, 4H, CH2-Ph), 5.25 (m, 4H, NCH2), 1.67 (m, 2H, NC(CH2)2). 13C NMR (125 MHz, CD2CL2): δ (ppm) 176.39 (Pd−C), 135.14, 134.96, 133.86, 129.08, 128.38, 127.58, 127.42, 127.29, 124.11, 123.86, 112.27 (C-aron), 52.39 NCH2, 49.01 NCH, 31.93 NCH2, 29.90 NCH2, 23.00 CH2. Anal. Calcd for C36H36N2Br2Pd, (722.8): C, 51.51%; H, 3.90%; N, 7.75%. Found: C, 50.82; H, 4.03; N, 7.93. ESI m/z: 642.90 [M − Br]^+$.

**Procedure for the Cyclocarbonylative Sonogashira Coupling Reactions.** Chromones and flavones were synthesized via cyclocarbonylative Sonogashira coupling reactions that were carried out in a 45 mL stainless steel autoclave equipped with a glass liner, gas inlet valve, and pressure gauge. Palladium–bis(NHC) complex (0.50 mol %), functionalized 2-iodophenol (0.50 mmol), alkylene (0.55 mmol), base (1.00 mmol) and an anhydrous solvent (2 mL) were charged into the glass liner of the autoclave. Then, the autoclave was vented carefully three times with carbon monoxide and then pressurized to 100 psi of

| Table 7. Selected Bond Lengths [Å] and Bond Angles [deg] for Compounds C1 and C3** |
|---------------------------------|----------------|----------------|
| C1                              | C3             | **                        |
| Pd(1)—C(1)                     | Pd(1)—C(1)     | 1.997(3)                  |
| Pd(1)—C(1)                     | Pd(1)—C(1)     | 1.997(3)                  |
| Pd(1)—Br(1)                    | 2.4906(4)      | 1.964(8)                  |
| Pd(1)—Br(1)#2                  | 2.4906(4)      | 1.964(8)                  |
| C(1)—N(2)                      | 1.344(4)       | 1.352(10)                 |
| C(1)—N(1)                      | 1.350(4)       | 1.395(10)                 |
| C(2)—N(1)                      | 1.397(4)       | 1.355(9)                  |
| C(7)—N(2)                      | 1.388(4)       | 1.372(9)                  |
| C(8)—N(1)                      | 1.475(4)       | 1.458(9)                  |
| C(11)—N(2)                     | 1.469(4)       | 1.339(10)                 |
| C(1)#2—Pd(1)—C(1)              | 88.66(17)      | C(1)—Pd1—C(1)#1          | 87.03 |
| C(1)#2—Pd(1)—Br(1)             | 177.48(8)      | C(1)—Pd1—Br(1)           | 175.02 |
| C(1)—Pd(1)—Br(1)               | 89.17(8)       | C(1)#1—Pd(1)—Br(1)       | 88.5(2) |
| C(1)#2—Pd(1)—Br(1)#2           | 89.17(8)       | Br1−Pd−Br1#1              | 95.49(4) |
| C(1)—Pd(1)—Br(1)#2             | 177.48(8)      | C(17)#2—Pd(2)—C(17)      | 87.7(3) |
| Br(1)—Pd(1)—Br(1)#2            | 92.97(2)       | Br2#2—Pd(2)—Br(2)        | 97.0(4) |
|                                  |                | C(17)#2—Pd(2)—Br(2)      | 175.2 |
|                                  |                | C(17)#2—Pd(2)—Br(2)      | 86.2(6) |

**Symmetry codes: #1 = x, −y + 3/2, z #2 = x, −y + 1/2, z.**
carbon monoxide. The mixture was stirred and heated to the required temperature for a specific period of time. At the end of the reaction period, the autoclave was cooled down to room temperature and the excess of CO was discharged carefully under the fume hood. The reaction was extracted three times with 5 mL of distilled water and 10 mL of ethyl acetate. The ethyl acetate extracts were combined and concentrated in a rotary evaporator under reduced pressure. Flash chromatography was used to purify the reaction mixture using silica gel and an eluent (pentane/ethyl acetate = 7:1) to afford the corresponding chromones or flavones. Various physical and spectroscopic techniques such as $^1$H and $^{13}$C NMR, GC, and GC–MS were used to fully characterize the products. The spectral data of the chromones and flavones prepared in this study were in full agreement with those reported in the literature.33,35

Analytical and Spectroscopic Data of the New Compound [2,2′-(1,4-Phenylene) bis(6-acetyl-4H-chromen-4-one)] (8c). Yiled = 92%. Yellowish green solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 8.81 (2H, s, C–H–arom), 8.38 (2H, d, J = 9.2 Hz, C–H–arom), 8.15 (4H, s, C–H–arom), 7.68 (2H, d, J = 8.38 Hz, C–H–arom), 6.96 (2H, s, C–H–arom), 3.89 (6H, s, O=C–CH$_3$)$_2$. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) 196.58 (C=O), 177.91 (C=O), 163.84, 158.85, 133.99, 132.91, 127.26, 126.39, 123.45, 118.95, 107.89 (C–arom), 6.37 (O=C–CH$_3$)$_2$. IR ($\nu$, cm$^{-1}$), para aromatic overtone at 1900 (2000–1700), 1766, 1689, 1626, 1591, 1505, 1459, 1253, 1157. GC–MS m/z: 449.44 (M$^+$). Anal. Calcd for C$_{28}$H$_{22}$O$_6$: C, 74.66%; H, 4.04%; Found: C, 75.12; H, 4.11.

**REFERENCES**

1. Harvey, R. G.; Hahn, J. T.; Bukowska, M.; Jackson, H. A new chromone and flavone synthesis and its utilization for the synthesis of potentially antimutagenic polycyclic chromones and flavones. J. Org. Chem. 1990, 55, 6161.

2. Ferreira, A.; Pousinho, S.; Fortuna, A.; et al. Flavonoid compounds as reversal agents of the P-glycoprotein-mediated multidrug resistance: biology, chemistry and pharmacology. Phytochemistry. 2015, 14, 233–272.

3. Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. Chromones as a privileged scaffold in drug discovery: A review. Eur. J. Med. Chem. 2014, 78, 340.

4. Imaish, K. A.; Abd El Aziz, T. Synthesis and biological evaluation of some novel 4H-benzopyran-4-one derivatives as nonsteroidal antiinflammatory agents. Eur. J. Med. Chem. 2001, 36, 243.

5. Maiti, A.; Cuenedt, M.; Konadtryuk, T.; Croy, V. L.; Pezzuto, J. M.; Cushman, M. Synthesis and Biological Evaluation of (+/-)-abysinone II and Its Analogues as Aromatase Inhibitors for Chemoprevention of Breast Cancer. J. Med. Chem. 2007, 50, 350.

6. Babu, T. H.; Subba Rao, V. R.; Tiwari, A. K.; Suresh Babu, K.; Srinivas, P. V.; Ali, A. Z.; Rao, J. M. Synthesis and biological evaluation of novel 8-aminoethylated oroxylin A analogues as α-glucosidase inhibitors. Bioorg. Med. Chem. Lett. 2008, 18, 1659.

7. Netzer, N. C.; Küpper, T.; Voss, H. W.; Eliaison, A. H. The actual role of sodium cromoglicate in the treatment of asthma–a critical review, Sleep Breath. 2012, 16, 1027.

8. Rowe, B. H.; Kelly, K.; Spooner, C. H. Early Emergency Department Treatment of Acute Asthma With Systemic Corticosteroids. Cochrane Database Syst. Rev. 2000, 4, 2731.

9. Musthafa, T. N. M.; Siddiqui, Z. N.; Husain, F. M.; Ahmad, I. Microwave-assisted solvent-free synthesis of biologically active novel heterocycles from 3-formylchromones. Med. Chem. Res. 2012, 20, 1473.

10. Islam, M. N.; Jung, H. A.; Sohn, H. S.; Kim, H. M.; Choi, J. S. Potent α-glucosidase and protein tyrosine phosphatase 1B inhibitors from Artemisia capillaris. Arch. Pharm. Res. 2013, 36, 542.

11. Kuroda, M.; Uchida, S.; Watanabe, K.; Mimaki, Y. Chromones from the tubers of Eranthis cilicica and their antioxidant activity. Phytochemistry 2009, 70, 288.

12. Zhao, P.-L.; Li, J.; Yang, G.-F. Synthesis and insecticidal activity of chromanone and chrome analogues of diacylhydrazines. Bioorg. Med. Chem. 2007, 15, 1888.

13. Lei, J.; Li, Y.; He, L.-J.; Luo, Y.-F.; Tang, D.-Y.; Yan, W.; Lin, H.-K.; Li, H.-Y.; Chen, Z.-Z.; Xu, Z.-G. Expeditious access of chromone analogues via a Michael addition-driven multicomponent reaction. Org. Chem. Front. 2020, 7, 987.

14. Gentili, B.; Horowitz, R. M. Flavonoids of citrus VII: Limoicarol and isolimocarol. Tetrahedron 1964, 20, 2313.

15. Ranganna, S.; Govindarajan, V. S.; Ramana, K. V. R.; Kefford, J. F. Citrus fruits — Varieties, chemistry, technology, and quality evaluation. Part II. Chemistry, technology, and quality evaluation. A. Chemistry. Crit. Rev. Food Sci. Nutr. 1983, 18, 313.

16. Govindarajan, V. S.; Connell, D. W. Ginger-chemistry, Technology, and Quality Evaluation: Part 2. Crit. Rev. Food Sci. Nutr. 1992, 17, 189.

17. Govindarajan, V. S. Ginger — chemistry, technology, and quality evaluation: Part I. Crit. Rev. Food Sci. Nutr. 1982, 17, 11.

18. Hostetler, G. L.; Ralston, R. A.; Schwartz, S. J. Flavones: Food Sources, Bioavailability, Metabolism, and Bioactivity. Adv. Nutr. 2017, 8, 423.

19. Brimble, M. A.; Gibson, J. S.; Sperry, J. Pyrans and their Benzo Derivatives: Synthesis. Compr. Heterocycl. Chem. II 2008, 7, 419.

20. Zhong, Y.-L.; Boruta, D. T.; Gauthier, D. R.; Askin, D. An efficient synthesis of 4-chromanones. Tetrahedron Lett. 2011, 52, 4824.

21. Demirayak, S.; Yurttas, L.; Gundogdu-Karaburun, N.; Karaburun, A. C.; Kayagil, I. New chroman-4-one/thiochroman-4-one derivatives as potential anticancer agents. Saudi Pharm. J. 2017, 26, 1063.

22. Ham, R.; Chalifoux, W. A. One-Pot Domino Friedel–Crafts Acylation/Annulation between Alkynes and 2-Methoxybenzoyl
Chlorides: Synthesis of 2,3-Disubstituted Chromen-4-one Derivatives.
J. Org. Chem. 2018, 83, 9929.

(23) Kim, H. Y.; Song, E.; Oh, K. Unified Approach to (Thio)-chromones via One-Pot Friedel–Crafts Acylation/Cyclization: Distinctive Mechanistic Pathways of β-Chlorovinyl Ketones. Org. Lett. 2017, 19, 312.

(24) Rueping, M.; Nachtshelm, B. J. A review of new developments in the Friedel–Crafts alkylation — From green chemistry to asymmetric catalysis. Beilstein J. Org. Chem. 2010, 6, 6.

(25) Sartori, G.; Maggi, R. Advances in Friedel–Crafts Acylation Reactions: Catalytic and Green Processes; CRC Press: Boca Raton, 2009.

(26) Kabalka, G. W.; Mereddy, A. R. Microwave-assisted synthesis of functionalized flavones and chromones. Tetrahedron Lett. 2005, 46, 6315.

(27) Wen, L.-R.; Jin, X.-J.; Niu, X.-D.; Li, M. Copper-Catalyzed Tandem Reactions for Synthesis of Pyrazolo[5,1-a]isoquinolines with Heterocyclic Ketene Aminals as Ligands. J. Org. Chem. 2015, 80, 90.

(28) Yoshida, M.; Saito, K.; Fujino, Y.; Doi, T. A concise total synthesis of biologically active frutinones via tributylphosphine-nones to Form Flavones. Tetrahedron Lett. 2009, 50, 6852.

(29) Ozin, G. A.; Huynh, H. V. stereoelectronic profiling of expanded-ring N-heterocyclic carbones. Inorg. Chem. 2019, 58, 7545.

(30) Baruah, S.; Kaishap, P. P.; Gogoi, S. Palladium-Catalyzed Carbonylation Reaction of Aryl Bromides with 2-Hydroxyacetophenones to Form Flavones. Chem.–Eur. J. 2012, 18, 12595.

(31) Li, Y.; Jin, A. Y.; Fan, X. Z.; Liu, X.-X.; Li, X.; Hahn, Y. Y.; Wang, Y.-Y.; Han, Y.-F. Strategy for the Construction of Diverse Poly-NHC-Derived Assemblies and Their Photoinduced Transformations. Angew. Chem., Int. Ed. 2020, 59, 10073–10080.

(32) Tao, W.; Wang, X.; Ito, S.; Nozaki, K. Palladium complexes bearing an N-heterocyclic carbene–sulfonamide ligand for cool-ignimerization of ethylene and polypropylene monomers. J. Polym. Sci., Part A: Polym. Chem. 2019, 57, 474.

(33) Xue, L.; Shi, L.; Han, Y.; Xia, C.; Huynh, H. V.; Li, F. Pd–carbene superactive esters as organometallic catalysts for bioorthogonal cross-coupling reactions. J. Org. Chem. 2019, 84, 73.

(34) Liu, J.; Liu, M.; Yue, Y.; Zhang, N.; Zhang, Y.; Zhuo, K. Construction of the flavones and aurones through regioselective carbonylation of 2-bromophenols and terminal alkynes. Tetrahedron Lett. 2013, 54, 1802.

(35) Zhou, B.; Wu, Z.; Ma, D.; Ji, X.; Zhang, Y. Synthesis of indoles through Palladium-catalyzed three-component reaction of aryl iodides, ketones and flavones by Using Water as a Solvent. J. Org. Chem. 2005, 70, 6097.

(36) Guo, M.; Wei, Z.; Yang, J.; Xie, Z.; Zhang, W. β-Alkynylaccelerated Pd(II) dimerization of aryl iodides with Alkynes for the Synthesis of Alkynyl Ketones and Flavones. Chem. Commun. 2016, 52, 13004.

(37) Lang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Lu, R.; Fathi, R.; Chen, J.; Yang, Z. Pd-Catalyzed Copper-Free Carbonylative Sonogashira Reaction of Aryl Iodides with Alkynes for the Synthesis of Aryl Ketones and Flavones by Using Water as a Solvent. J. Org. Chem. 2005, 70, 6097.

(38) Xue, L.; Shi, L.; Han, Y.; Xia, C.; Huynh, H. V.; Li, F. Pd–carbene cross-coupling reactions of “superactive esters” and terminal alkynes. Angew. Chem., Int. Ed. 2008, 47, 9326.

(39) Huynh, H. V.; Johibasu, R. Syntheses and catalytic activities of Pd(II) dicarbene and hetero-dicarbene complexes. J. Organomet. Chem. 2011, 696, 3369.

(40) Mansour, W.; Fettouhi, M.; El Ali, B. Novel and efficient bridged bis(N-heterocyclic carbene)Pd(II) catalysts for selective carbonylative Suzuki–Miyaura coupling reactions to biaryl ketones and biaryl diketones. Appl. Organomet. Chem. 2020, 34, No. e6536.

(41) Sakaguchi, S.; Yoo, K. S.; O’Neill, J. L.; Lee, J. H.; Stewart, T.; Jung, K. W. Chiral Palladium(II) complexes possessing a tridentate N-heterocyclic carbene amidate alkoxide ligand: access to oxygen-bridging dimer structures. Org. Lett. 2011, 13, 3652.

(42) Ibrahim, M.; Malik, I.; Mansour, W.; Sharif, M.; Fettouhi, M.; El Ali, B. Efficient N-heterocyclic carbene palladium(II) catalysts for carbonylative Suzuki–Miyaura coupling reactions leading to aryl ketones and diketones. J. Organomet. Chem. 2018, 859, 44.

(43) Ibrahim, M.; Malik, I.; Mansour, W.; Sharif, M.; Fettouhi, M.; El Ali, B. Novel (N-heterocyclic carbene)Pd(II)Br2 complexes for carbonylative Sonogashira coupling reactions: Catalytic efficiency and scope for arylalkynes, alkylalkynes and dialkynes. Appl. Organomet. Chem. 2018, 32, No. e4280.

(44) Mansour, W.; Suleiman, R.; Fettouhi, M.; El Ali, B. Soft N,C,N-tridentate N-heterocyclic carbene amidate alkoxide ligand: access to oxygen-bridging dimer structures. Angew. Chem., Int. Ed. 2008, 47, 9326.

(45) El Ali, B. Novel (N-heterocyclic carbene)Pd(pyridine)Br2 complexes possessing a tridentate N-heterocyclic carbene amidate alkoxide ligand: access to oxygen-bridging dimer structures. Angew. Chem., Int. Ed. 2008, 47, 9326.

(46) Gardiner, M. G.; McGuinness, D. S.; Vanston, C. R. Chelated phosphorus ligands: structural authentication and facile ligand fragmentation. Dalton Trans. 2017, 46, 3051.

(47) Hao, W.; Sha, J. C.; Sheng, S. R.; Cai, M. Z. The first heterogeneous carbonylative Sonogashira coupling reaction catalyzed...
by MCM-41-supported bidentate phosphine palladium(0) complex. *J. Mol. Catal. A: Chem.* 2009, 298, 94.
(62) Mohapatra, S.; Baral, N.; Mishra, N. P.; Panda, P.; Nayak, S. Michael Addition of Imidazole to \(\alpha,\beta\)-Unsaturated Carbonyl/Cyano Compound. *Open Chem.* 2018, 5, 18.
(63) Boncel, S.; Saletra, K.; Hefczyc, B.; Walczak, K. Z. Michael-type addition of azoles of broad-scale acidity to methyl acrylate. *Beilstein J. Org. Chem.* 2011, 7, 173.
(64) Bruker. *Apex3 v2017.3-0, SAINT V8.38A;* Bruker AXS Inc.: Madison (WI), USA, 2017.
(65) Krause, L.; Herbst-Irmer, R.; Sheldrick, G. M.; Stalke, D. Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *J. Appl. Crystallogr.* 2015, 48, 3.
(66) Sheldrick, G. M. SHELXT - Integrated space-group and crystal-structure determination. *Acta Crystallogr., Sect. A: Found. Adv.* 2015, 71, 3.
(67) Farrugia, L. J. ORTEP-3 for Windows - a version of ORTEP-III with a Graphical User Interface (GUI). *J. Appl. Crystallogr.* 1997, 30, 565.
(68) Zhao, X.; Zhou, J.; Lin, S.; Jin, X.; Liu, R. C−H functionalization via remote hydride elimination: Palladium catalyzed dehydrogenation of ortho-acyl phenols to flavonoids. *Org. Lett.* 2017, 19, 976.