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(71) Applicants: SAUDI ARABIAN OIL COMPANY

[SA/SA]; 1 Eastern Avenue, Dhahran, 31311 (SA). KING

FAHD UNIVERSITY OF PETROLEUM & MINER-

ALS [SA/SA]; KING FAHD UNIVERSITY OF PETRO-

LEUM & MINERALS, Dhahran, 31261 (SA).

(71) Applicant (for AG only): ARAMCO SERVICES COM-

PANY [US/US]; 1200 Smith Street, Two Allen Building,

Houston, Texas 77002 (US).

(72) Inventors: EL ALI, Bassam; King Fahd University of

Petroleum & Minerals, Chemistry Department, Dhahran,

31261 (SA). MANSOUR, Waseem; King Fahd University

of Petroleum & Minerals, Chemistry Department, Dhahran,

31261 (SA). FETTOUHI, Mohammed; King Fahd Uni-

versity of Petroleum & Minerals, Chemistry Department,

Dhahran, 31261 (SA).

(74) Agent: BRUCE, Carl E. et al.; FISH & RICHARDSON

P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022

(US).

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(54) Title: SELECTIVE CYCLOCARBONYLATIVE COUPLING OF 2-IODOPHENOLS WITH TERMINAL ALKYNES CATALYZED BY BRIDGED BIS(NHC)PD(II)BR<sub>2</sub> CATALYSTS

(57) Abstract: Palladium catalysts, methods of synthesizing palladium-carbene catalysts, and methods of producing chromones and aurones using palladium-N-heterocyclic carbene (NHC) catalysts are provided. In some implementations, the palladium catalysts include a bridged palladium catalyst with distorted square planar geometry around the center palladium atom. The catalysts can be used in cyclocarbonylative Sonogashira crosscoupling reactions to produce chromones and aurones at a high yield. The selectivity of the catalysts can be adjusted by adjusting reaction conditions.



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SELECTIVE CYCLOCARBONYLATIVE COUPLING OF 2-  
IODOPHENOLS WITH TERMINAL ALKYNES  
CATALYZED BY BRIDGED BIS(NHC)Pd(II)Br<sub>2</sub>  
CATALYSTS

**CLAIM OF PRIORITY**

[001] This application claims priority to U.S. Patent Application No. 17/094,140, filed on November 10, 2020, the entire contents of which are hereby incorporated by reference.

**TECHNICAL FIELD**

[002] This document relates to palladium-carbenes complexes and cyclocarbonylative Sonogashira cross-coupling reactions.

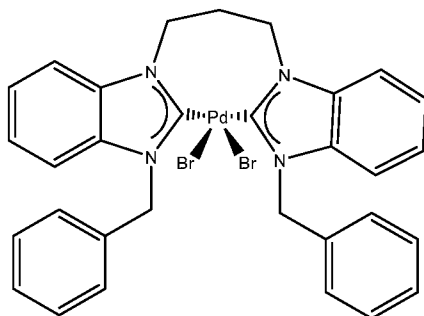
**BACKGROUND**

[003] Chromones and aurones are useful precursors to pharmacological compounds, and new and efficient methods and catalysts for producing chromones and aurones are needed.

**SUMMARY**

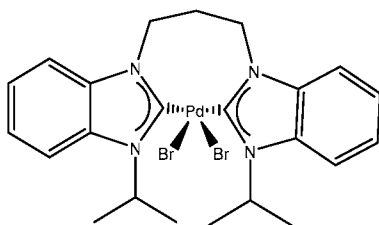
[004] This disclosure describes palladium catalysts, methods of synthesizing palladium-carbene catalysts, and methods of producing chromones and aurones using palladium-N-heterocyclic carbene (NHC) catalysts.

[005] In some implementations, a compound of Formula C3 has the following structure:

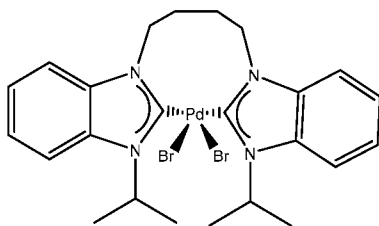


[006] In some implementations, a method of synthesizing a palladium catalyst includes reacting a benzimidazole with a halogenated hydrocarbon in the presence of a base and acetonitrile to produce an alkyl-1*H*-benzo[d]imidazole, reacting the alkyl-1*H*-benzo[d]imidazole with a halogenated crosslinking chain to produce a bridged N-heterocyclic carbene salt precursor, and reacting the bridged N-heterocyclic carbene with palladium acetate.

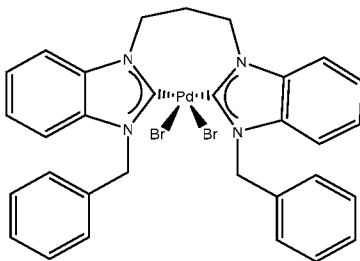
[007] In some implementations, a method of synthesizing chromones or aurones includes reacting a 2-iodophenol and an aryl alkyne in the presence of a palladium catalyst, wherein the palladium catalyst includes at least one of Formula C1, Formula C2, or Formula C3, where Formula C1 has the structure



; Formula C2 has the structure

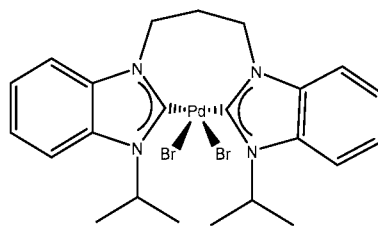


; and

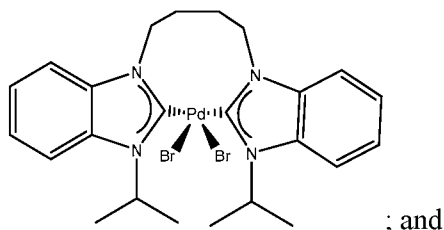


Formula C3 has the structure

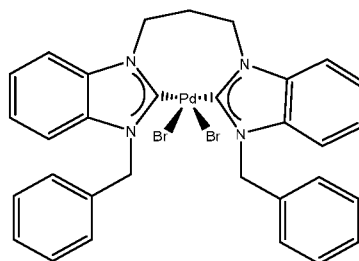
[008] In some implementations, a method of synthesizing chromones or aurones includes reacting a 2-iodophenol and an alkyl alkyne in the presence of a palladium catalyst, wherein the palladium catalyst includes at least one of Formula C1, Formula



C2, or Formula C3, where Formula C1 is



Formula (C2) is



Formula (C3) is

[009] The details of one or more implementations of the disclosure are set forth in the accompanying drawings and the description that follows. Other features, objects, and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

## DESCRIPTION OF DRAWINGS

[010] FIG. 1 shows an example of Sonogashira cross-coupling reaction.

[011] FIG. 2 shows an example of carbonylative Sonogashira cross-coupling reaction.

[012] FIG. 3 shows an example of cyclocarbonylative Sonogashira cross-coupling reaction.

[013] FIG. 4 shows examples of chromones.

[014] FIG. 5 shows a bridged bis(N-Heterocyclic Carbene) palladium(II) [bis(NHC)Pd(II)] catalyst.

[015] FIG. 6 shows the structure of three bis(NHC)Pd(II)Br<sub>2</sub> catalysts.

[016] FIG. 7 is a flow chart of an example method of synthesizing a palladium bridged bis(NHCs) catalyst.

[017] FIG. 8 is a flow chart of an example method of synthesizing chromones or aurones.

[018] FIG. 9 is a flow chart of a second example method of synthesizing chromones or aurones.

[019] FIG. 10 shows an example of a reaction between a benzimidazole and an alkyl halide.

[020] FIG. 11 shows an example of a reaction between a 1-alkyl benzimidazole produced in FIG. 10 and a halogenated crosslinking alkyl chain.

[021] FIG. 12 shows an example reaction of a bridged NHC salt precursor with palladium acetate.

[022] FIG. 13 shows an example ORTEP diagram of the molecular structure of complex C1.

[023] FIG. 14 shows an example ORTEP diagram of the molecular structure of complex C3.

[024] FIG. 15 shows an example reaction between a substituted 2-iodophenol and an aryl alkyne.

[025] FIG. 16 shows an example reaction between a substituted 2-iodophenol and an alkyl alkyne.

[026] Like reference symbols in the various drawings indicate like elements.

### DETAILED DESCRIPTION

[027] Reference will now be made in detail to certain embodiments of the disclosed subject matter, examples of which are illustrated in part in the accompanying drawings. While the disclosed subject matter will be described in conjunction with the enumerated claims, it will be understood that the exemplified subject matter is not intended to limit the claims to the disclosed subject matter.

[028] Provided in this disclosure, in part, are palladium catalysts, methods of synthesizing palladium catalysts, and methods of producing chromones and aurones using palladium bridged bis(NHCs) catalysts.

[029] In some implementations, a catalyst containing palladium is complexed with one or more N-heterocyclic carbenes (NHC). For example, palladium can be complexed with benzimidazole. The palladium-NHC complex (Pd-NHC) can be used to catalyze Sonogashira reactions.

[030] Sonogashira reactions can be exemplified by three types of reactions. In a first type of Sonogashira cross-coupling reaction, a carbon-carbon bond is formed between a terminal alkyne and an aryl or vinyl halide, resulting in an aryl alkyne. This type of reaction uses both a palladium catalyst and a copper catalyst. FIG. 1 shows an example of this type of a Sonogashira cross-coupling reaction.

[031] In a carbonylative Sonogashira cross-coupling reaction, a carbonyl-carbon bond is formed between a terminal alkyne and an aryl halide under carbon monoxide, resulting in an alkynone. Alkynones are known to be bioactive. Carbonylative Sonogashira cross-coupling reactions employ a palladium catalyst and a copper co-catalyst in the presence of carbon monoxide (CO). FIG. 2 shows an example of a carbonylative Sonogashira cross-coupling reaction.

[032] In a cyclocarbonylative Sonogashira cross-coupling reaction, carbonylative coupling reactions occur in the presence of carbon monoxide to form carbonyl-carbon bonds. The reaction products include five- or six-membered ring ketones. Cyclocarbonylative Sonogashira cross-coupling reactions employ palladium catalysts, and can employ copper co-catalysts. The carbonyl-carbon bonds are formed via cyclocarbonylative coupling reactions between a terminal alkyne and a halogenated phenol. Five-membered ring products of this reaction are referred to as aurones, and six-membered ring products are referred to as chromones. FIG. 3 shows an example of a cyclocarbonylative Sonogashira cross-coupling reaction that yields an aurone or a chromone. Chromones and aurones have industrial and pharmaceutical applications, for example as precursor compounds. FIG. 4 illustrates a number of different chromones, which have uses in anticancer, anti-microbial, anti-inflammatory, and anti-viral applications, among others. Accordingly, there is a need for new chromones and new methods of producing chromones.

[033] Pd-NHC complexes can be used for Sonogashira cross-coupling and carbonylative Sonogashira cross-coupling reactions. However, bridged

bis(NHC)Pd(II)Br<sub>2</sub> complexes that include N-heterocyclic carbenes (NHCs) have not previously been used for cyclocarbonylative Sonogashira cross-coupling reactions.

The bridged bis(NHC)Pd(II)Br<sub>2</sub> catalysts described herein can be used in a cyclocarbonylative Sonogashira cross-coupling reaction to yield chromones and aurones. Advantageously, these catalysts can be used for cyclocarbonylative Sonogashira cross-coupling reactions in the absence of phosphines or any other ligands or co-catalysts.

[034] In some implementations, the catalyst for cyclocarbonylative Sonogashira cross-coupling reaction is a bridged palladium complex shown in FIG. 5. The catalyst contains a bridged palladium with specific stereochemistry. As shown by X-ray diffraction analysis, the Pd(II) complexes shown in FIG. 5 can have distorted square planar geometries around the center palladium atom.

[035] The alkyl bridge between N-heterocyclic carbene units can vary in length. The alkyl bridge is shown in FIG. 5 with n number of repeating methylene units. In some implementations, n is 1, 2, or 3.

[036] The N-heterocyclic carbenes can be functionalized with a functional group R. In some implementations, R is a straight or branched alkyl group, for example –CH(CH<sub>3</sub>)<sub>2</sub>. In some implementations, R includes a carbon ring structure or aromatic group, for example –CH<sub>2</sub>Ph. The functional group R can alter the steric hindrance around the palladium center and alter the functionality of the catalyst. FIG. 6 shows the structure of three palladium catalysts C1, C2, and C3, which were used in cyclocarbonylative Sonogashira cross-coupling reactions. The synthesis of these catalysts is discussed in Examples 1-3.

[037] Catalysts C1, C2, and C3 are stable complexes. For example, C1, C2, and C3 are stable at temperatures as high as 120°C. These catalysts are efficient and selective. In addition, the catalysts have low loading requirements, wide substrate applications, and high yields. The geometry and configuration of C1, C2, and C3 yields a specific catalytic activity that is advantageous for cyclocarbonylative Sonogashira cross-coupling reactions. Further, the regioselectivity of the catalysts can be controlled using specific solvents and a base, for example dimethyl formamide (DMF) as a solvent and diethylamine (Et<sub>2</sub>NH) as a base. The selectivity of the

catalysts is shown in Table 6. In addition, the catalysts can be used with catalyst loading as small as 0.50 mol%, and in the absence of phosphines or any co-ligands.

[038] FIG. 7 is a flow chart of an example method 700 of synthesizing palladium catalysts C1, C2, and C3. At 702, a benzimidazole is reacted with a halogenated hydrocarbon to produce an alkyl-1*H*-benzo[d]imidazole. At 704, the alkyl-1*H*-benzo[d]imidazole is reacted with a halogenated crosslinking chain to produce a bridged N-heterocyclic carbene salt precursor. At 706, the bridged N-heterocyclic carbene salt precursor is reacted with acetylated palladium.

[039] FIG. 8 is a flow chart of an example method 800 of synthesizing chromones or aurones. At 802, a 2-iodophenol is reacted with an aryl alkyne in the presence of a palladium catalyst C1, C2, or C3.

[040] FIG. 9 is a flow chart of a second example method 900 of synthesizing chromones or aurones. At 902, a 2-iodophenol is reacted with an alkyl alkyne in the presence of a palladium catalyst C1, C2, or C3.

[041] Example 1: Synthesis of Benzimidazole Precursors

Bis-NHC-Pd(II) catalysts as shown in FIG. 5 were synthesized using alkylated benzimidazole precursors. FIG. 10 shows an example of a reaction between a benzimidazole with a halogenated alkyl group in the presence of base and acetonitrile to generate alkyl-1*H*-benzo[d]imidazoles. The functional group R can include branched alkyl or aromatic groups. For example, R can be  $-\text{CH}(\text{CH}_3)_2$  or  $-\text{CH}_2\text{Ph}$ .

[042] The synthesis of benzimidazole precursors is described herein. A dry and clean round bottom flask was charged with benzimidazole (10.0 mmol), excess amount of alkyl bromide (12.2 mmol), an appropriate base (20.0 mmol), and 1.00 mmol of tetrabutylammonium bromide (TBAB). For the synthesis of 1-isopropyl-1*H*-benzo[d]imidazole, the alkyl bromide is 2-bromopropane and the base is potassium hydroxide. For the synthesis of 1-benzyl-1*H*-benzo[d]imidazole, the alkyl bromide is benzyl bromide and the base is cesium carbonate. 100 mL of acetonitrile was used to dissolve the prepared mixture with continuous stirring at 80 °C for 24 h. Thin layer chromatography (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 rotary evaporator. The oily products were

collected as residues, and the purification of the products was conducted by extraction twice with 30 mL ethyl acetate and 20 mL distilled water. The aqueous layers were separated then washed with ethyl acetate. The separated organic layers were dried and washed several times with n-hexane.

[043] The synthesized compounds were analyzed by  $^1\text{H}$  NMR (nuclear magnetic resonance) analysis and  $^{13}\text{C}\{^1\text{H}\}$  NMR analysis. For the NMR analyses, 's' denotes a singlet, 'd' denotes a doublet, 'dd' denotes a doublet of doublets, 't' denotes a triplet, 'q' denotes a quartet, 'qui' denotes a quintet, and 'sept' denotes a septet. The coupling constant is given as J.

[044] Synthesis of 1-isopropyl-1H-benzo[d]imidazole resulted in a 77% yield by mass of a sticky brown oil.  $^1\text{H}$  NMR analysis (400 MHz,  $\text{CDCl}_3$ ) yielded the following spectra in  $\delta$  (ppm): 7.85 (s, 1H, NCHN), 7.64-7.62 (1H, m, Ar-H), 7.25-7.22 (1H, m, Ar-H), 7.11-7.08 (2H, m, Ar-H), 4.42 (1H, sept,  $^3J = 6.76$  Hz, NCH), 1.40 (6H, d,  $^3J = 6.76$  Hz,  $\text{NC}(\text{CH}_3)_2$ ).

[045]  $^{13}\text{C}\{^1\text{H}\}$  NMR analysis (500 MHz,  $\text{CDCl}_3$ ) yielded the following spectra in  $\delta$  (ppm): 143.5 (NCN), 139.8, 132.7, 122.1, 121.5, 119.8, 109.7, (Ar-H), 47.2 (NCH), 22.02 [ $\text{NC}(\text{CH}_3)_2$ ].

[046] The theoretical composition calculated for this compound ( $\text{C}_{10}\text{H}_{12}\text{N}_2$ , molecular weight 160) is 74.97% carbon by mass, 7.55% hydrogen by mass, and 17.48% nitrogen by mass. Elemental analysis found 74.84% carbon by mass; 7.23% hydrogen by mass; and 17.23% nitrogen by mass.

[047] Synthesis of 1-benzyl-1H-benzo[d]imidazole resulted in an 87% yield by mass of a light yellow solid.  $^1\text{H}$  NMR analysis (500 MHz,  $\text{CDCl}_3$ ) yielded the following spectra in  $\delta$  (ppm): 7.98 (1H, s, NCHN), 7.83 (1H, d,  $^3J = 7.63$  Hz, Ar-H), 7.34-7.24 (6H, m, Ar-H), 7.18 (2H, d,  $^3J = 7.02$  Hz, Ar-H), 5.36 (2H, m,  $\text{NCH}_2\text{-Ph}$ ).

[048]  $^{13}\text{C}\{^1\text{H}\}$  NMR analysis (500 MHz,  $\text{CDCl}_3$ ) yielded the following spectra in  $\delta$  (ppm): 143.1 (NCN), 135.4, 129, 128.3, 127.06, 123.1, 122.3, 120.3, 110.04 (Ar-H), 48.8 ( $\text{NCH}_2$ ).

[049] The theoretical composition calculated for this compound ( $\text{C}_{14}\text{H}_{12}\text{N}_2$ , molecular weight 208) is 80.74% carbon by mass, 5.81% hydrogen by mass, and

13.45% nitrogen by mass. Elemental analysis found 80.89% carbon by mass, 6.03% hydrogen by mass, and 13.73% nitrogen by mass.

[050] Example 2: Synthesis of Precursors L1, L2, and L3

The alkylated benzimidazoles were reacted with a crosslinking halogenated alkyl chain. The alkyl chain will form the bridge of the bridged palladium catalysts. FIG. 11 shows an example reaction between the benzimidazole produced in FIG. 10 and a halogenated crosslinking alkyl chain to yield a bridged NHC salt precursor. The alkyl chain can vary in length. The alkyl chain can include n number of repeating methylene units, for example where n is 1, 2, or 3.

[051] The 1-alkyl benzimidazoles synthesized in Example 1 (5.0 mmol) and 2.5 mmol of dibromoalkane (1,3-dibromopropane or 1,4-dibromobutane) were introduced into a dried 100 mL round bottom flask. The mixture was refluxed in 35 mL of 1,4-dioxane with stirring at 103 °C for 12 h. The products appeared as white precipitates. The products were collected by filtration and washed three times with 15 mL of 1,4-dioxane and then with 15 mL of toluene to remove any traces of the starting materials. The products were dried under vacuum then collected as a white precipitate. Characterization of the alkylene bridged N-heterocyclic dicarbene salts was conducted with different spectroscopic techniques including <sup>1</sup>H NMR, <sup>13</sup>C NMR, elemental analysis, and electrospray ionization. The resulting NHC salts are precursors L1, L2, and L3 for the palladium catalysts C1, C2, and C3.

[052] **3,3'-(propane-1,3-diyl)-bis(1-isopropyl-1H-benzo[d]imidazole-3-ium) bromide (precursor L1)** was synthesized with 1-isopropyl-1H-benzo[d]imidazole and 1,3-dibromopropane as above. The synthesis resulted in a 91% yield by mass of a white solid. <sup>1</sup>H NMR analysis (500 MHz, DMSO-d<sub>6</sub>) yielded in the following spectra in δ (ppm): 9.83 (2H, s, NCHN), 8.15-8.11 (4H, m, Ar-H), 7.71-7.69 (2H, m, Ar-H), 5.05 (2H, sept, <sup>3</sup>J=6.71 Hz, NCH), 4.67 (4H, t, <sup>3</sup>J=7.01 Hz, CH<sub>2</sub>), 2.67 (2H, qui, <sup>3</sup>J=7.02 Hz, CH<sub>2</sub>), 1.61 (12H, d, <sup>3</sup>J=6.7 Hz, NC(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR analysis (125 MHz, DMSO) yielded the following spectra in δ (ppm): 140.7 (NCN), 131.3, 130.5, 126.7, 126.6, 114.1, 113.7, (Ar-H), 50.7 (NCH), 44.1 (NCH<sub>2</sub>), 28.0 (CH<sub>2</sub>), 21.6 (NC(CH<sub>3</sub>)<sub>2</sub>).

[053] The theoretical composition of precursor L1 ( $C_{23}H_{30}N_4Br_2$ , molecular weight 522.3) is 52.89% carbon by mass, 5.79 % hydrogen by mass, 10.73% nitrogen by mass. Elemental analysis found 52.37% carbon by mass, 5.8% hydrogen by mass, and 10.97% nitrogen by mass. Electrospray ionization analysis revealed a mass-to-charge ratio ( $m/z$ ) of 442 with positive ionization and an  $m/z$  ratio of 441 with negative ionization.

[054] **3,3'-(Butane-1,4-diyl)-bis(1-isopropyl-1H-benzo[d]imidazole-3-ium) bromide (precursor L2)** was synthesized with 1-isopropyl-1H-benzo[d]imidazole and 1,4-dibromobutane, as above. The synthesis resulted in a 76% yield of a white solid.  $^1H$  NMR analysis (500 MHz, DMSO- $d_6$ ) yielded the following spectra in  $\delta$  (ppm): 10.05 (2H, s, NCHN), 8.13-8.11 (4H, m, Ar-H), 7.68 (4H, dd,  $^3J = 6.1$  Hz,  $^3J_2 = 2.75$  Hz, Ar-H), 5.05 (2H, sept,  $^3J = 6.71$  Hz, NCH), 4.58 (4H, m, NCH $_2$ ), 2.04-1.99 (4H, m, CH $_2$ ), 1.62 [12H, d,  $^3J = 6.71$  Hz (CH $_3$ ) $_2$ ].  $^{13}C\{^1H\}$  NMR analysis (125 MHz, DMSO) yielded the following spectra in  $\delta$  (ppm): 140.7 (NCN), 131.3, 130.6, 126.7, 126.6, 114.1, 113.8, (Ar-H), 50.7 (NCH), 46.3 (NCH $_2$ ), 25.6 (CH $_2$ ), 21.64 [NC(CH $_3$ ) $_2$ ].

[055] The theoretical composition of precursor L2 ( $C_{24}H_{32}N_4Br_2$ , molecular weight 536.3) is 53.74% carbon by mass; 6.01 % hydrogen by mass, and 10.45% nitrogen by mass. Elemental analysis found 52.12% carbon by mass, 5.91% hydrogen by mass, and 10.79% nitrogen by mass. Electrospray ionization analysis revealed an  $m/z$  ratio of 456 with positive ionization.

[056] **3,3'-(Propane-1,3-diyl)-bis(1-benzyl-1H-benzo[d]imidazole-3-ium) bromide (precursor L3)** was synthesized with 1-benzyl-1H-benzo[d]imidazole and 1,4-dibromobutane, as above. The synthesis resulted in a 65% yield of a white solid.  $^1H$  NMR analysis (500 MHz, DMSO- $d_6$ ) yielded the following spectra in  $\delta$  (ppm): 10.15 (2H, s, NCHN), 8.14 (2H, d,  $^3J_1 = 7.93$  Hz, Ar-H), 7.96 (2H, d,  $^3J_1 = 7.32$  Hz, Ar-H), 7.66-7.62 (4H, m, Ar-H), 7.53 (4H, d,  $^3J_1 = 7.02$  Hz, Ar-H), 7.39-7.36 (4H, m, Ar-H), 5.80 (4H, s, NCH $_2$ Ph), 4.62 (4H, m, NCH $_2$ CH $_2$ ), 2.06 (2H, m, CH $_2$ ).  $^{13}C\{^1H\}$  NMR analysis yielded (125 MHz, CDCl $_3$ ) yielded the following spectra in  $\delta$  (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 $_2$ ), 51.37 (NCH $_2$ ), 22.44 2(CH $_2$ CH).

[057] The theoretical composition of precursor L3 ( $C_{31}H_{30}N_4Br_2$ , molecular weight 618.4) is 60.61% carbon by mass; 4.89 % hydrogen by mass, 9.06% nitrogen by mass. Elemental analysis found 60.83% carbon, 5.11% hydrogen, and 9.79% nitrogen. Electrospray ionization analysis revealed an  $m/z$  ratio of 538.5 with positive ionization.

[058] Example 3: Synthesis of bis-NHC-Pd(II) complexes C1, C2, and C3

FIG. 12 shows an example reaction of an NHC salt precursor with palladium acetate to yield the bis-NHC-Pd(II) complexes C1, C2, and C3.

[059] A round bottom flask (50 mL) was charged with 0.50 mmol of a bridged N-heterocyclic dicarbene ligand precursor (L1, L2 or L3), and 0.50 mmol of palladium(II) acetate. 15 mL of dimethyl sulfoxide was used as a solvent. The resulting orange solutions were heated to 70 °C for 24 h under stirring. The products were obtained as white precipitates. The precipitates were collected by filtration and washed twice with 15 mL of distilled water and then 15 mL of hexane. The residues were purified by extraction three times with dichloromethane/ $H_2O$  (5 mL/5 mL). Finally, the dichloromethane extracts were evaporated under vacuum and the products were obtained as crystalline solids. Full characterization of the three complexes was accomplished by different physical and spectroscopic techniques such as  $^1H$  and  $^{13}C$  NMR, electrospray ionization – mass spectrometry, elemental analysis, and single crystal X-ray diffraction analysis.

[060] **Synthesis of Dibromido(1,1'-diisopropyl-3,3'-propylenedibenzimidazoline-2,2-diylidene)palladium(II) (complex C1)** was performed as described above, with a 92% yield by mass of a white solid. Single crystals for complex C1 were obtained by slow crystallization procedure using a saturated solution of dichloromethane/acetonitrile (10:1 v/v).  $^1H$  NMR analysis (500 MHz,  $DMF-d_7$ ) yielded the following spectra in  $\delta$  (ppm): 8.08 (2H, d,  $^3J=8.24$  Hz, Ar-H, (the signals of aromatic protons overlap with solvent signal), 7.97 (2H, d,  $^3J=8.24$  Hz, Ar-H), 7.45-7.37 (4H, m, Ar-H), 5.99 (2H, m, NCH), 5.43 (2H, m,  $CH_2$ ), 5.11 (2H, m,  $CH_2$ ), 2.19 (2H, m,  $CH_2CH_2CH_2$ ), 1.94 [6H, d,  $^3J=6.71$  Hz,  $NC(CH_3)_2$ ], 1.78 [6H, d,  $^3J=5.80$  Hz,  $NC(CH_3)_2$ ].  $^{13}C\{^1H\}$  NMR analysis (125 MHz,  $CD_2Cl_2$ ) yielded the following spectra in  $\delta$  (ppm): 181 (Pd-C)[carbene signal ( $NC_{binim}N$ )], 135.2, 133.3,

132.3, 123.8, 123.7, 123.4, 123.1, 122.9, 113.2, 113, 110.7, 110.5 (Ar-H), 55.4 (NCH), 53.4 (NCH), 49.5 (NCH<sub>2</sub>), 47.8 (NCH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 22.1, 21.7, 21.3 [NC(CH<sub>3</sub>)<sub>2</sub>].

[061] The theoretical composition for complex C1 (C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>Br<sub>2</sub>Pd, molecular weight 626.74) is 44.08% carbon; 4.50% hydrogen; and 8.94% nitrogen. Elemental analysis found 43.86% carbon, 4.25% hydrogen, and 8.63% nitrogen. Electrospray ionization yielded an m/z ratio of 547 with positive ionization.

[062] **Dibromido(1,1'-diisopropyl-3,3'-butylenedibenzimidazoline-2,2-diylidene)palladium(II) (complex C2)** was synthesized as above, with a 68% yield by mass of an orange solid. <sup>1</sup>H NMR analysis (400 MHz, CDCl<sub>3</sub>) yielded the following spectra in δ (ppm): 8.49 (2H, d, <sup>3</sup>J=7.28 Hz, Ar-H), 7.30 (2H, d, <sup>3</sup>J=7.44 Hz, Ar-H), 7.17-7.14 (4H, m, Ar-H), (the signals of aromatic protons overlap with solvent signal), 6.00-5.96 (2H, m, NCH), 5.75-5.71 (2H, m, NCH<sub>2</sub>), 4.45-4.41 (2H, m, NCH<sub>2</sub>), 1.80-1.45 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>) (the signals of methylene protons were not assigned due to overlap with the isopropyl methyl signals), 1.74 [6H, d, <sup>3</sup>J=6.56 Hz (CH<sub>3</sub>)<sub>2</sub>], 1.69 [6H, d, <sup>3</sup>J=7.16 Hz (CH<sub>3</sub>)<sub>2</sub>]. <sup>13</sup>C{<sup>1</sup>H} NMR analysis (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>) yielded the following spectra in δ (ppm): 181.1 (Pd-C)/Carbene signal (NC<sub>binim</sub>N), 135.9, 132.9, 122.9, 122.8, 112.9, 111.0, (Ar-H), 48.2 (NCH), 30.1 (NCH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 21.2 [NC(CH<sub>3</sub>)<sub>2</sub>].

[063] The theoretical composition for this compound (C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>Br<sub>2</sub>Pd, molecular weight 640.7) is 44.99% carbon, 4.72% hydrogen, and 8.74% nitrogen. Elemental analysis found 44.78% carbon, 4.89% hydrogen, and 8.53% nitrogen. Electrospray ionization yielded an m/z ratio of 561.00 with positive ionization.

[064] **Dibromido(1,1'-dibenzyl-3,3'-propylenedibenzimidazoline-2,2-diylidene)palladium(II) (complex C3)** was synthesized as above, with a 73% yield by mass of white crystals. <sup>1</sup>H NMR analysis (400 MHz, CDCl<sub>3</sub>) yielded the following spectra in δ (ppm): 7.10-7.69 (m, 2H, C-H-*pyr*), 7.48 (m, 4H, C-H-*arom*), 7.45-7.41 (m, 6H, C-H-*arom*), 7.35-7.29 [m, 6H, C-H-(*phenyl*)], 5.87 (s, 4H, CH<sub>2</sub>-Ph), 5.25 (m, 4H, NCH<sub>2</sub>), 1.67 (m, 2H, NC(CH<sub>2</sub>)). <sup>13</sup>C NMR analysis (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>) yielded the following spectra in δ (ppm): 176.39 (Pd-C), 135.14, 134.96, 133.86, 129.08.

[065] Example 4: X-ray crystallography of complexes C1 and C3:

Single crystal X-ray data collection for complexes C1 and C3 were performed at 298 K on a Bruker D8 Quest diffractometer (MoK $\alpha$  radiation  $\lambda = 0.71073$  Angstroms (Å)). Data were collected and integrated using Bruker APEX3 software package. Multi-scan absorption correction was performed using SADABS. The structures were solved by direct methods with SHELXS using SHELXTL package and refined using full-matrix least squares procedures on F<sup>2</sup> via the program SHELXL-2014. ORTEP3 software was used for molecular graphics. The molecular structures of complexes C1 and C3 are depicted in example ORTEP diagrams in FIG. 13 and FIG. 14, respectively. All hydrogen atoms were included at calculated positions using a riding model. The thermal ellipsoids in FIGS. 13 and 14 are drawn at 30% probability level, with a symmetry code where  $i = x, -y+1/2, z$ . The crystal data and refinement details for C1 and C3 are given in Table 1. Selected bond lengths and bond angles are given in Table 2.

[066] Complex C1 crystallized with one molecule, located on a mirror plane, in the asymmetric unit, as a dimethylformamide solvate while complex C3 crystallized with one molecule in the asymmetric unit as mixed hydrate/dichloromethane solvate. In both complexes the Pd(II) ion is coordinated by the chelating bridged bis-carbene ligand and two bromide ions at *cis* positions, in a distorted square planar geometry. The *cis* bond angles are in the ranges of 88.66(17) - 92.97(2)° and 87.4(3)° - 97.01(4)° in C1 and C3 respectively. The former is 1.997(3) Å in C1 and in the range of (1.964(8) Å - 1.985(8) Å) in C3 while the latter is 2.4906(4) Å in C1 and in the range of (2.4659(11) Å - 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.

[067] Table 1: Crystal and structure refinement data of complexes C1 and C3

|                                                 | C1                                                                 | C3                                                                                 |
|-------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------|
| CCDC Deposition #                               | 1961539                                                            | 1950067                                                                            |
| Empirical formula                               | C <sub>26</sub> H <sub>35</sub> Br <sub>2</sub> N <sub>5</sub> OPd | C <sub>32</sub> H <sub>32</sub> Br <sub>2</sub> Cl <sub>2</sub> N <sub>4</sub> OPd |
| Formula weight                                  | 699.81                                                             | 825.73                                                                             |
| Temperature (K)                                 | 298(2)                                                             | 298(2)                                                                             |
| Wavelength(Å)                                   | 0.71073                                                            | 0.71073                                                                            |
| Crystal system                                  | Orthorhombic                                                       | Monoclinic                                                                         |
| Space group                                     | P nma                                                              | P 2 <sub>1</sub> /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)                                                                        |
| $\alpha(^{\circ})$                              | 90                                                                 | 90                                                                                 |
| $\beta(^{\circ})$                               | 90                                                                 | 92.033(2)                                                                          |
| $\gamma(^{\circ})$                              | 90                                                                 | 90                                                                                 |
| Volume(Å <sup>3</sup> )                         | 2742.63(19)                                                        | 3374.0(5)                                                                          |
| Z                                               | 4                                                                  | 4                                                                                  |
| Density (calculated, g/cm <sup>3</sup> )        | 1.695                                                              | 1.626                                                                              |
| Absorption coefficient (mm <sup>-1</sup> )      | 3.619                                                              | 3.108                                                                              |
| F(000)                                          | 1400                                                               | 1640                                                                               |
| Theta range data collect. (°)                   | 2.512 to 28.371                                                    | 2.564 to 28.367                                                                    |
| Index ranges                                    | -21 ≤ h ≤ 21, -24 ≤ k ≤ 24, 12 ≤ l ≤ 12                            | -14 ≤ h ≤ 14, -31 ≤ k ≤ 32, -17 ≤ l ≤ 17                                           |
| Reflections collected                           | 76298                                                              | 123299                                                                             |
| Independent reflections                         | 3528 [R(int) = 0.0387]                                             | 8604 [R(int) = 0.1448]                                                             |
| Absorption correction                           | Semi-empirical from equivalents                                    | Semi-empirical from equivalents                                                    |
| Refinement method                               | Full-matrix least-squares on F <sup>2</sup>                        | Full-matrix least-squares on F <sup>2</sup>                                        |
| Data / restraints / parameters                  | 3528 / 18 / 173                                                    | 8604 / 6 / 399                                                                     |
| Goodness-of-fit on F <sup>2</sup>               | 0.989                                                              | 1.112                                                                              |
| Final R indices [I > 2sigma(I)]                 | R1 = 0.0342, wR2 = 0.1080                                          | R1 = 0.0716, wR2 = 0.1905                                                          |
| R indices (all data)                            | R1 = 0.0473, wR2 = 0.1299                                          | R1 = 0.1308, wR2 = 0.2298                                                          |
| Largest diff. peak and hole (e.Å <sup>3</sup> ) | 1.039 and -0.978                                                   | 1.673 and -1.585                                                                   |

[068] **Table 2: Selected Bond lengths [Å] and bond angles [°] for complexes C1 and C3**

| C1                   |           | C3                  |            |
|----------------------|-----------|---------------------|------------|
| Pd(1)-C(1)#2         | 1.997(3)  | Pd(1)-C(1)          | 1.964(8)   |
| Pd(1)-C(1)           | 1.997(3)  | Pd(1)-Br(1)         | 2.4659(11) |
| Pd(1)-Br(1)          | 2.4906(4) | Pd(2)-C(17)         | 1.985(8)   |
| Pd(1)-Br(1)#2        | 2.4906(4) | Pd(2)-Br(2)         | 2.4704(11) |
| C(1)-N(2)            | 1.344(4)  | N(1)-C(1)           | 1.352(10)  |
| C(1)-N(1)            | 1.350(4)  | N(1)-C(9)           | 1.395(10)  |
| C(2)-N(1)            | 1.397(4)  | N(2)-C(1)           | 1.355(9)   |
| C(7)-N(2)            | 1.388(4)  | N(2)-C(14)          | 1.372(9)   |
| C(8)-N(1)            | 1.475(4)  | N(2)-C(15)          | 1.458(9)   |
| C(11)-N(2)           | 1.469(4)  | N(3)-C(17)          | 1.339(10)  |
|                      |           | N(3)-C(25)          | 1.373(9)   |
|                      |           | N(3)-C(18)          | 1.463(9)   |
|                      |           | N(4)-C(17)          | 1.339(8)   |
|                      |           | N(4)-C(30)          | 1.401(9)   |
|                      |           | N(4)-C(31)          | 1.452(9)   |
| C(1)#2-Pd(1)-C(1)    | 88.66(17) | C(1)-Pd1-C(1)#1     | 87.4(3)    |
| C(1)#2-Pd(1)-Br(1)   | 177.48(8) | C(1)-Pd(1)-Br(1)    | 175.0(2)   |
| 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-Pd1-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)   | 97.01(4)   |
|                      |           | C(17)-Pd(2)-Br(2)   | 175.2(2)   |
|                      |           | C(17)#2-Pd(2)-Br(2) | 87.6(2)    |

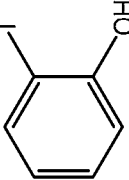
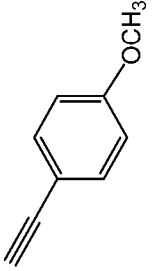
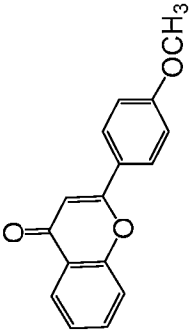
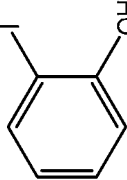
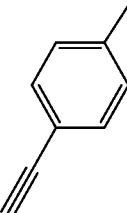
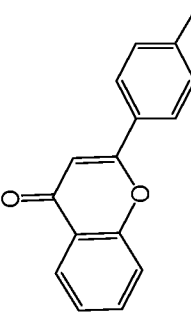
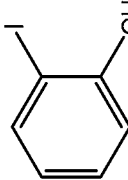
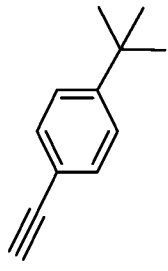
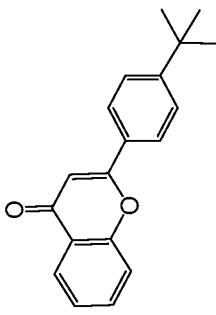
Symmetry codes: #1= x,-y+3/2,z #2= x,-y+1/2,z

[069] Example 5: Cyclocarbonylative Sonogashira cross-coupling reaction with bis(NHC)Pd(II)Br<sub>2</sub> complexes C1, C2, or C3

The bis(NHC)Pd(II)Br<sub>2</sub> complexes C1, C2, and C3 can catalyze a reaction between 2-iodophenols and aryl alkynes. For example, FIG. 15 shows an example reaction between a functionalized 2-iodophenol, for example functionalized 4'-hydroxy-3'-iodoaryl, and an aryl alkyne. The functional groups R<sub>1</sub> and R<sub>2</sub> can be electron withdrawing or electron donating functional groups, for example methoxy, hydrogen, nitro, methyl, tertiary butyl, phenyl or acetyl functional groups. Advantageously, the catalysts C1, C2, and C3 can be used with as little as 0.5 mol% in the reaction. The catalyzed reactions between a functionalized 2-iodophenol and an aryl alkyne were conducted with 0.50 mmol of functionalized 2-iodophenol, 0.55 mmol of an aryl alkyne, 1.00 mmol of diethylamine (Et<sub>2</sub>NH), 3 mL of dimethylformamide (DMF), and 0.50 mol% of complex C1, C2, or C3.

The reactants were added to a 45 mL stainless steel autoclave equipped with a glass liner, gas inlet valve and pressure gauge. The reaction was run for 16 hours at 100 °C under 100 psi of carbon monoxide gas. After the reaction, the autoclave was cooled to room temperature and excess carbon monoxide gas was discharged. The reaction products were 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 in a 7:1 v/v ratio). Chromones and flavones (a type of aurone) were produced at high yields, between 86-91% isolated yield by mass percent. Table 3 shows example reactants and products for cyclocarbonylative Sonogashira coupling reactions catalyzed by complex C1, and the percent yield for these reactions.  $^1\text{H}$  NMR spectra were taken at 300 MHz in  $\text{CDCl}_3$  at 24°C.  $^{13}\text{C}\{^1\text{H}\}$  spectra were taken at 75 MHz in  $\text{CDCl}_3$  at 24°C.

[070] Table 3: Cyclocarbonylative Sonogashira coupling reactions of 4'-hydroxy-3'-iodoaryls with aryl alkynes catalyzed by complex C1

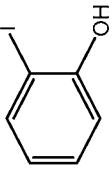
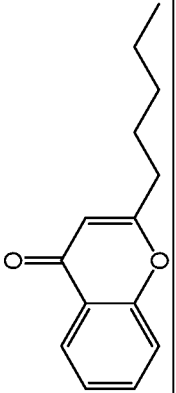
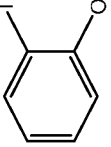
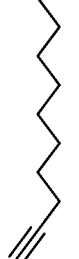
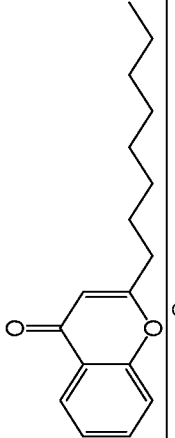
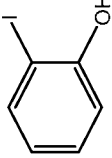
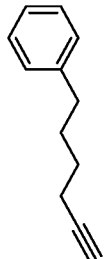
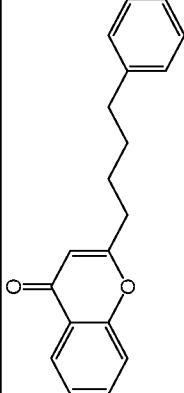
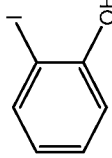
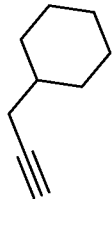
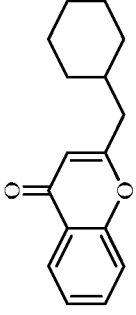
| Example Reaction No. | 4'-Hydroxy-3'-iodoaryl                                                               | Aryl Alkyne                                                                          | Product                                                                            | Yield (% by mass) |
|----------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------|
| 1                    |   |   |   | 91                |
| 2                    |   |   |   | 86                |
| 3                    |  |  |  | 88                |

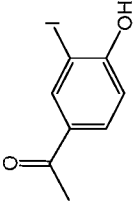
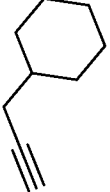
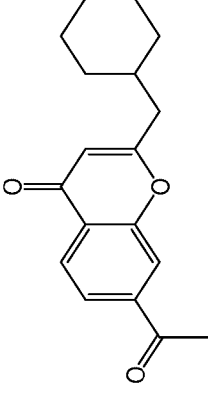
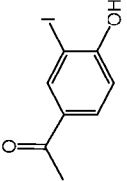
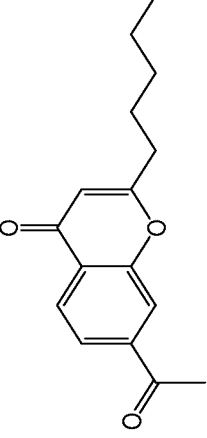
| Example Reaction No. | 4'-Hydroxy-3'-iodoaryl | Aryl Alkyne | Product | Yield (% by mass) |
|----------------------|------------------------|-------------|---------|-------------------|
| 4                    |                        |             |         | 93                |
| 5                    |                        |             |         | 98                |
| 6                    |                        |             |         | 95                |
| 7                    |                        |             |         | 91                |
| 8                    |                        |             |         | 93                |

[071] Example 6: Cyclocarbonylative Sonogashira cross-coupling reaction with Pd-bis(NHC)Br<sub>2</sub> complexes C1, C2, or C3

The bis(NHC)Pd(II)Br<sub>2</sub> complexes C1, C2, and C3 can each catalyze the reaction between 2-iodophenols and an alkyl alkyne. For example, FIG. 16 shows an example reaction between a functionalized 2-iodophenol and an alkyl alkyne. The functional groups R<sub>1</sub> and R'' can be electron withdrawing or electron donating functional groups, for example methoxy, hydrogen, nitro, methyl, tertiary butyl, phenyl or acetyl functional groups. Advantageously, the catalysts C1, C2, and C3 can be used with as little as 0.5 mol% in the reaction. The catalyzed reactions between a functionalized 2-iodophenol and an alkyl alkyne were conducted with 0.50 mmol of functionalized 2-iodophenol, 0.60 mmol of an alkyl alkyne, 1.00 mmol of Et<sub>3</sub>NH, 2.5 mL of DMF, and 0.50 mol% of complex C1. The reactants were added to a 45 mL stainless steel autoclave equipped with a glass liner, gas inlet valve and pressure gauge. The reaction was run for 24 hours at 110 °C under 100 psi of carbon monoxide. After the reaction, the autoclave was cooled to room temperature and excess carbon monoxide gas was discharged. The reaction products were 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 in a 7:1 v/v ratio). Chromones and flavones were produced at high yields, between 53-90% by mass. Table 4 shows example reactants and products for cyclocarbonylative Sonogashira coupling reactions catalyzed by complex C1, and the percent yield for these reactions.

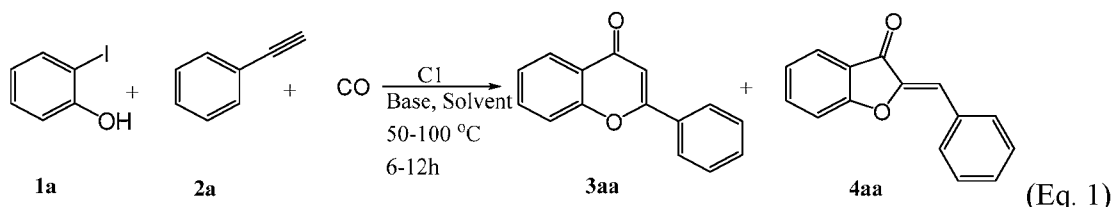
[072] Table 4: Cyclocarbonylative Sonogashira coupling reactions of 4'-hydroxy-3'-iodoaryls with alkyl alkynes catalyzed by complex C1.

| Example Reaction No. | 4'-Hydroxy-3'-iodoaryl                                                                | Alkyl Alkyne                                                                          | Product                                                                             | Yield (% by mass) |
|----------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------|
| 9                    |    |    |   | 81                |
| 10                   |    |    |   | 68                |
| 11                   |    |    |  | 53                |
| 12                   |  |  |  | 71                |

| Example<br>Reaction<br>No. | 4'-Hydroxy-3'-<br>iodoaryl                                                          | Alkyl<br>Alkyne                                                                     | Product                                                                            | Yield<br>(% by<br>mass) |
|----------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------|
| 13                         |  |  |  | 77                      |
| 14                         |  |  |  | 90                      |

[073] Example 6: Regioselectivity of Complexes C1, C2, and C3:

Cyclocarbonylative Sonogashira coupling reactions of a 2-iodophenol with phenylacetylene can illustrate the selectivity of the complexes C1, C2, and C3. An example reaction of 2-iodophenol (compound 1a) and phenylacetylene (compound 2a) under carbon monoxide in the presence of a catalytic amount of C1 was analyzed (Eq. 1). Table 5 shows the selectivity of the complexes under these conditions.



[074] **Table 5: Cyclocarbonylative Sonogashira coupling reactions of 2-iodophenol (1a) with phenylacetylene (2a).**

| Catalyst<br>(mol%)  | Conversion<br>(%) <sup>b</sup> | Selectivity<br>% <sup>b</sup> |                         |
|---------------------|--------------------------------|-------------------------------|-------------------------|
|                     |                                | 3aa<br>(%) <sup>c</sup>       | 4aa<br>(%) <sup>c</sup> |
| <b>C1</b><br>(0.5%) | 98                             | 96<br>(92)                    | 4                       |
| <b>C2</b><br>(0.5%) | 88                             | 96<br>(85)                    | 4                       |
| <b>C3</b><br>(0.5%) | 84                             | 95<br>(79)                    | 5                       |

- a. Reaction conditions: [Pd] (mol%), 2-iodophenol (0.5 mmol), phenylacetylene (0.6 mmol), Et<sub>2</sub>NH (1.0 mmol), DMF (2.5 mL), CO (100 psi), 100 °C, 16 h.
- b. Determined by gas chromatography (GC) and gas chromatography – mass spectrometry (GC-MS).
- c. Isolated yield.
- d. THF was used as a solvent.

[075] The selectivity of the complexes is dependent on the reaction conditions. Table 6 shows varied conditions for the reaction in Equation 1, catalyzed by complex C1. For example, the reactions were conducted at room temperature, 80°C, or 100°C, and the base

and solvent were varied. The results of these reactions are summarized in Table 6. Only traces of 2-phenyl-4H-chromen-4-one (compound 3aa) were obtained when a neat reaction was conducted using 1.0% mol of C1 as a catalyst and diethylamine ( $\text{Et}_2\text{NH}$ ) as a base at room temperature for 16 hours (Table 6, Example Reaction 15). However, a conversion of 59.5% was obtained at 80 °C and a high conversion (85.5%) was achieved at 100 °C. These reactions produced 2-phenyl-4H-chromen-4-one (compound 3aa) as a major compound. The isolated yield of compound 3aa gradually increased by increasing the temperature (Table 6, Example Reactions 16-17). When diethylamine ( $\text{Et}_2\text{NH}$ ) in the neat reaction was replaced by trimethylamine ( $\text{Et}_3\text{N}$ ) at 80°C and 100°C using C1, the cyclocarbonylative reaction of 2-iodophenols with phenylacetylene led to a six member ring product flavone (compound 3aa) and five membered ring product aurone (compound 4aa). Moreover, the increase of the temperature from 80 °C to 100 °C increased the conversion from 85% to 100% and favored the formation of the aurone product compound 4aa (57% and 66%) (Table 6, Example Reactions 18-19). However, when tetrahydrofuran (THF) was used as a solvent at 80 °C and 100 °C, with triethylamine as a solvent, the conversions dropped to 69% and 93%, respectively, with only small changes in the regioselectivity (Table 6, Example Reactions 20 and 21). Nevertheless, the use of  $\text{Et}_2\text{NH}$  as a base with THF as solvent at 80°C and 100°C led to higher conversions (68% and 84.5%) (Table 6, Example Reactions 22 and 23). Accordingly, under the same experimental conditions, triethylamine oriented the cyclocarbonylative Sonogashira reactions towards the production of aurone compound 4aa as the major product. In addition, diethylamine in THF produced flavone compound 3aa in high isolated yields. When potassium carbonate was used as a base in THF at 100 °C (Table 6, Example Reaction 24), a full conversion was observed to produce flavone compound 3aa and aurone compound 4aa (38/62). In toluene as a solvent, the cyclocarbonylative Sonogashira reaction of 2-iodophenol with phenylacetylene under the conditions in Example Reaction 25 ( $\text{Et}_2\text{NH}$  / 1.0% mol of C1 / 100 °C / 16 h) was converted (97%) and led to the two products flavone compound 3aa and aurone compound 4aa with a ratio of 93/7. In THF as a solvent and  $\text{Et}_2\text{NH}$  as a base, the catalyst's C1 loading can be decreased from 1.0 mol% to 0.5 mol% of C1 leading to high conversion (80%) to produce

flavone compound 3aa as the only product of the reaction (Table 6, Example Reaction 26). An isolated yield of 2-phenyl-4H-chromen-4-one (compound 3aa, 96%) was achieved with 98% conversion of 2-iodophenol when the DMF was used as solvent under the conditions in Example Reaction 27 [Et<sub>2</sub>NH / C1 (0.5 mol%) / 100 °C / 16 h]. Small amounts of aurone compound 4aa were also obtained (compound 3aa / compound 4aa = 96/4). A decrease in the temperature from 100°C to 80 °C and 50 °C [DMF / Et<sub>2</sub>NH / 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 compound 3aa were 81% at 80 °C and 35% at 50 °C (Table 6, Example Reactions 28 and 29). Therefore, 100 °C can be considered as an optimized temperature for the subsequent catalytic reactions. The effect of the reaction time was also studied. After 16 h, 12 h and 6 h the isolated yields of the flavone compound 3aa decreased from 92% to 72% and 46%, respectively (Table 6, Example Reactions 27, 30, 31). When DMF was replaced by other solvents such as THF, toluene and in the neat Et<sub>2</sub>NH [Et<sub>2</sub>NH / C1 (0.5mol%) / 100 °C / 16 h], a significant decrease in the conversions and isolated yields in flavone were observed (Table 6, Example Reactions 32-34).

[076] Additionally, the study of the role of the base on the regioselectivity was also conducted using Et<sub>3</sub>N and K<sub>2</sub>CO<sub>3</sub> as bases with DMF as solvent [C1 (0.5 mol%) / 100 °C / 16 h]. For example, the use of K<sub>2</sub>CO<sub>3</sub> as a base produced a mixture of flavone compound 3aa and aurone compound 4aa (70/30) (Table 6, Example Reaction 35). Similarly, the use of trimethylamine gave lower regioselectivity, producing a mixture of flavone compound 3aa and aurone compound 4aa (60/40) (Table 6, Example Reaction 36). When Et<sub>3</sub>N was used with THF as a solvent, the isolated yield in flavone compound 3aa dropped to 30% (Table 6, Example Reaction 21) and increased with DMF to 54% (Table 6, Example Reaction 37). These results showed the importance of Et<sub>2</sub>NH and DMF as regioselective factors in the production of flavones.

[077] Table 6: Cyclocarbonylative Sonogashira coupling reactions of 2-iodophenol (compound 1a) with phenylacetylene (compound 2a) by complex C1.

| Example Reaction No. | C1 mol % | Base                           | Solvent            | T (°C) | Time (h) | Conv. (%) <sup>b</sup> | Selectivity (%) <sup>b</sup> |                      |
|----------------------|----------|--------------------------------|--------------------|--------|----------|------------------------|------------------------------|----------------------|
|                      |          |                                |                    |        |          |                        | 3aa (%) <sup>c</sup>         | 4aa (%) <sup>c</sup> |
| 15                   | 1.0      | Et <sub>2</sub> NH             | Et <sub>2</sub> NH | RT     | 16       | traces                 | traces                       | traces               |
| 16                   | 1.0      | Et <sub>2</sub> NH             | Et <sub>2</sub> NH | 80     | 16       | 59.5                   | 100 (55)                     | -                    |
| 17                   | 1.0      | Et <sub>2</sub> NH             | Et <sub>2</sub> NH | 100    | 16       | 85.5                   | 100 (82)                     | -                    |
| 18                   | 1.0      | Et <sub>3</sub> N              | Et <sub>3</sub> N  | 80     | 16       | 85                     | 43 (34)                      | 57 (45)              |
| 19                   | 1.0      | Et <sub>3</sub> N              | Et <sub>3</sub> N  | 100    | 16       | 100                    | 34 (30)                      | 66 (63)              |
| 20                   | 1.0      | Et <sub>3</sub> N              | THF                | 80     | 16       | 69                     | 40 (25)                      | 60 (38)              |
| 21                   | 1.0      | Et <sub>3</sub> N              | THF                | 100    | 16       | 93                     | 36 (30)                      | 64 (56)              |
| 22                   | 1.0      | Et <sub>2</sub> NH             | THF                | 80     | 16       | 68                     | 100 (64)                     | -                    |
| 23                   | 1.0      | Et <sub>2</sub> NH             | THF                | 100    | 16       | 84.5                   | 100 (81)                     | -                    |
| 24                   | 1.0      | K <sub>2</sub> CO <sub>3</sub> | THF                | 100    | 16       | 96                     | 38 (33)                      | 62 (57)              |
| 25                   | 1.0      | Et <sub>2</sub> NH             | Toluene            | 100    | 16       | 97                     | 93 (88)                      | 7                    |
| 26                   | 0.5      | Et <sub>2</sub> NH             | THF                | 100    | 16       | 80                     | 100 (77)                     | -                    |
| 27                   | 0.5      | Et <sub>2</sub> NH             | DMF                | 100    | 16       | 98                     | 96 (92)                      | 4                    |
| 28                   | 0.5      | Et <sub>2</sub> NH             | DMF                | 80     | 16       | 83                     | 100 (81)                     | -                    |

| Example Reaction No. | C1 mol % | Base                           | Solvent            | T (°C) | Time (h) | Conv. (%) <sup>b</sup> | Selectivity (%) <sup>b</sup> |                      |
|----------------------|----------|--------------------------------|--------------------|--------|----------|------------------------|------------------------------|----------------------|
|                      |          |                                |                    |        |          |                        | 3aa (%) <sup>c</sup>         | 4aa (%) <sup>c</sup> |
| 29                   | 0.5      | Et <sub>2</sub> NH             | DMF                | 50     | 16       | 38                     | 100 (35)                     | -                    |
| 30                   | 0.5      | Et <sub>2</sub> NH             | DMF                | 100    | 12       | 76                     | 100 (72)                     | -                    |
| 31                   | 0.5      | Et <sub>2</sub> NH             | DMF                | 100    | 6        | 49                     | 100 (46)                     | -                    |
| 32                   | 0.5      | Et <sub>2</sub> NH             | THF                | 100    | 16       | 72                     | 100 (70)                     | -                    |
| 33                   | 0.5      | Et <sub>2</sub> NH             | Toluene            | 100    | 16       | 82                     | 95 (76)                      | 5                    |
| 34                   | 0.5      | Et <sub>2</sub> NH             | Et <sub>2</sub> NH | 100    | 16       | 79                     | 100 (76)                     | -                    |
| 35                   | 0.5      | K <sub>2</sub> CO <sub>3</sub> | DMF                | 100    | 16       | 97                     | 70 (65)                      | 30 (27)              |
| 36                   | 0.5      | Et <sub>3</sub> N              | DMF                | 100    | 16       | 95                     | 60 (54)                      | 40 (35)              |

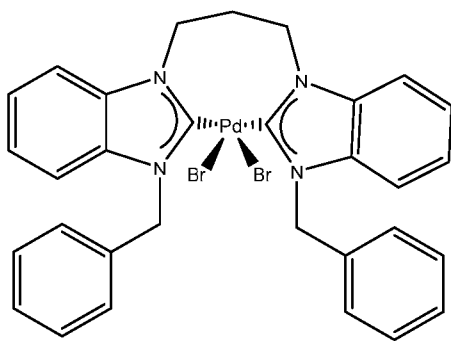
- a. Reaction conditions: complex C1 (mol%), 2-iodophenol (0.5 mmol), phenylacetylene (0.6 mmol), base (1.0 mmol), solvent (2.5 mL), CO (100 psi), 100 °C.
- b. Determined by GC and GC-MS.
- c. Isolated yield.

[078] The following units of measure have been mentioned in this disclosure:

| Unit of Measure | Full form                                              |
|-----------------|--------------------------------------------------------|
| hr              | hour                                                   |
| °C              | degree Celsius                                         |
| mol             | mole                                                   |
| mol%            | catalytic loading, (mol catalyst / mol reactant) x 100 |
| mmol            | milimole                                               |
| psi             | pounds per square inch                                 |
| Å               | Angstrom                                               |
| g               | gram                                                   |

| Unit of Measure | Full form        |
|-----------------|------------------|
| cm <sup>3</sup> | cubic centimeter |
| mm              | milimeter        |

[079] In some implementations, a compound of Formula C3 has the following structure:



[080] In some implementations, a method of synthesizing a palladium catalyst includes reacting a benzimidazole with a halogenated hydrocarbon in the presence of a base and acetonitrile to produce an alkyl-*1H*-benzo[d]imidazole, reacting the alkyl-*1H*-benzo[d]imidazole with a halogenated crosslinking chain to produce a bridged N-heterocyclic carbene salt precursor, and reacting the bridged N-heterocyclic carbene with palladium acetate.

[081] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting a benzimidazole with a halogenated hydrocarbon includes reacting at 80 °C for 24 hours.

[082] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting the alkyl-*1H*-benzo[d]imidazole with a halogenated crosslinking chain includes reacting at 103 °C for 24 hours in 1,4-dioxane.

[083] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting the N-heterocyclic carbene with palladium acetate includes reacting at 70 °C for 24 hours in dimethyl sulfoxide.

[084] This aspect, taken alone or combinable with any other aspect, can include the following features. The halogenated hydrocarbon is a branched halogenated alkyl group.

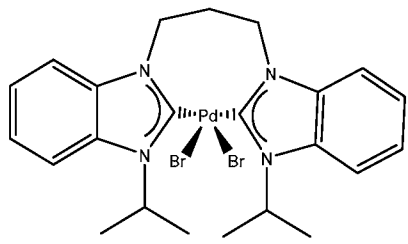
[085] This aspect, taken alone or combinable with any other aspect, can include the following features. The branched halogenated alkyl group is isopropyl bromide.

[086] This aspect, taken alone or combinable with any other aspect, can include the following features. The halogenated hydrocarbon is benzyl bromide.

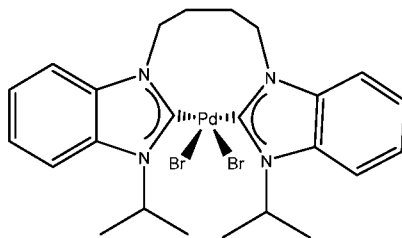
[087] This aspect, taken alone or combinable with any other aspect, can include the following features. The halogenated crosslinking chain is a di-halido unbranched alkyl chain.

[088] This aspect, taken alone or combinable with any other aspect, can include the following features. The di-halido unbranched alkyl chain is 1,3-dibromopropane, 1,4-dibromobutane, or 1,5-dibromopentane.

[089] In some implementations, a method of synthesizing chromones or aurones includes reacting a 2-iodophenol and an aryl alkyne in the presence of a palladium catalyst, wherein the palladium catalyst includes at least one of Formula C1, Formula C2,

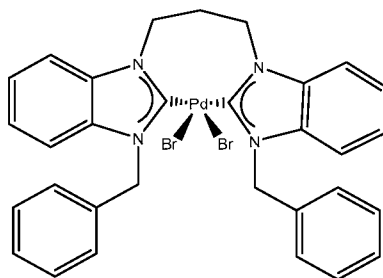


or Formula C3, where Formula C1 has the structure



Formula C2 has the structure

; and



Formula C3 has the structure

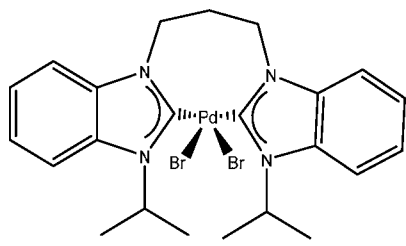
[090] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting the 2-iodophenol and the aryl alkyne in the presence of a palladium catalyst includes reacting the 2-iodophenol and the aryl alkyne in the presence of 0.5 mol% of the palladium catalyst.

[091] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting the 2-iodophenol and the aryl alkyne in the presence of a palladium catalyst includes reacting the 2-iodophenol and the aryl alkyne with 2 equivalents diethylamine in dimethylformamide, and the reaction takes place under carbon monoxide at 100 psi for 16 hours at 100 °C.

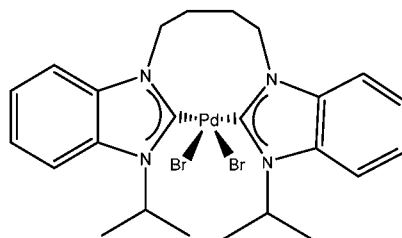
[092] This aspect, taken alone or combinable with any other aspect, can include the following features. The 2-iodophenol is functionalized with an electron withdrawing group.

[093] This aspect, taken alone or combinable with any other aspect, can include the following features. The aryl alkyne is functionalized with an electron withdrawing group.

[094] In some implementations, a method of synthesizing chromones or aurones includes reacting a 2-iodophenol and an alkyl alkyne in the presence of a palladium catalyst, wherein the palladium catalyst includes at least one of Formula C1, Formula C2,

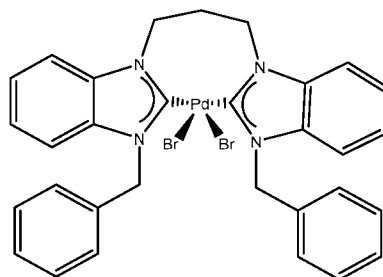


or Formula C3, where Formula C1 is



Formula (C2) is

; and



Formula (C3) is

[095] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting the 2-iodophenol and the alkyl alkyne in the presence of a palladium catalyst includes reacting the 2-iodophenol and the alkyl alkyne in the presence of 0.5 mol% of the palladium catalyst.

[096] This aspect, taken alone or combinable with any other aspect, can include the following features. Reacting the 2-iodophenol and the alkyl alkyne in the presence of a palladium catalyst includes reacting the 2-iodophenol and the alkyl alkyne with 2 equivalents diethylamine in dimethylformamide, and wherein the reaction takes place under carbon monoxide at 100 psi for 24 hours at 110 °C.

[097] This aspect, taken alone or combinable with any other aspect, can include the following features. The 2-iodophenol is functionalized with an electron withdrawing group.

[098] This aspect, taken alone or combinable with any other aspect, can include the following features. The alkyl alkyne is functionalized with an electron withdrawing group.

[099] The term "about" as used in this disclosure can allow for a degree of variability in a value or range, for example, within 10%, within 5%, or within 1% of a stated value or of a stated limit of a range.

[0100] The term "solvent" as used in this disclosure refers to a liquid that can dissolve a solid, another liquid, or a gas to form a solution. Non-limiting examples of solvents are silicones, organic compounds, water, alcohols, ionic liquids, and supercritical fluids.

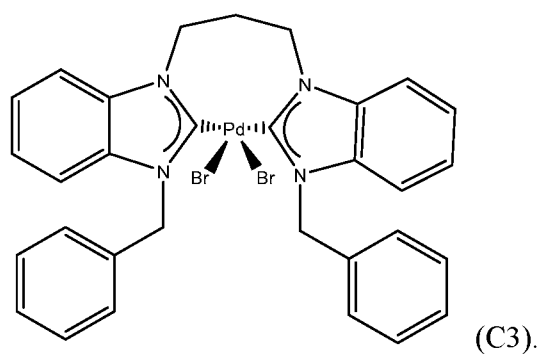
[0101] As used in this disclosure, "weight percent" (wt %) can be considered a mass fraction or a mass ratio of a substance to the total mixture or composition. Weight percent can be a weight-to-weight ratio or mass-to-mass ratio, unless indicated otherwise.

[0102] A number of implementations of the disclosure have been described.

Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the disclosure.

**WHAT IS CLAIMED IS:**

1. A compound of Formula (C3):



2. A method of synthesizing a palladium catalyst, comprising:

reacting a benzimidazole with a halogenated hydrocarbon in the presence of a base and acetonitrile to produce an alkyl-*1H*-benzo[d]imidazole;

reacting the alkyl-*1H*-benzo[d]imidazole with a halogenated crosslinking chain to produce a bridged N-heterocyclic carbene salt precursor; and

reacting the bridged N-heterocyclic carbene with palladium acetate.

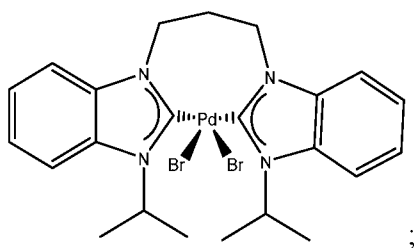
3. The method of claim 2, wherein reacting a benzimidazole with a halogenated hydrocarbon further comprises reacting at 80 °C for 24 hours.

4. The method of claim 2, wherein reacting the alkyl-*1H*-benzo[d]imidazole with a halogenated crosslinking chain comprises reacting at 103 °C for 24 hours in 1,4-dioxane.

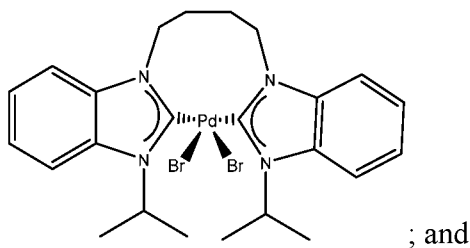
5. The method of claim 2, wherein reacting the N-heterocyclic carbene with palladium acetate comprises reacting at 70 °C for 24 hours in dimethyl sulfoxide.

6. The method of claim 2, wherein the halogenated hydrocarbon is a branched halogenated alkyl group.
7. The method of claim 6, wherein the branched halogenated alkyl group is isopropyl bromide.
8. The method of claim 2, wherein the halogenated hydrocarbon is benzyl bromide.
9. The method of claim 2, wherein the halogenated crosslinking chain is a di-halido unbranched alkyl chain.
10. The method of claim 9, wherein the di-halido unbranched alkyl chain is 1,3-dibromopropane, 1,4-dibromobutane, or 1,5-dibromopentane.
11. A method of synthesizing chromones or aurones comprising reacting a 2-iodophenol and an aryl alkyne in the presence of a palladium catalyst, wherein the palladium catalyst comprises at least one of Formula (C1), Formula (C2), or Formula (C3), wherein

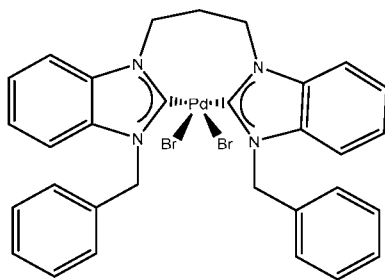
Formula (C1) is



Formula (C2) is



Formula (C3) is



12. The method of claim 11, wherein reacting the 2-iodophenol and the aryl alkyne in the presence of a palladium catalyst comprises reacting the 2-iodophenol and the aryl alkyne in the presence of 0.5 mol% of the palladium catalyst.

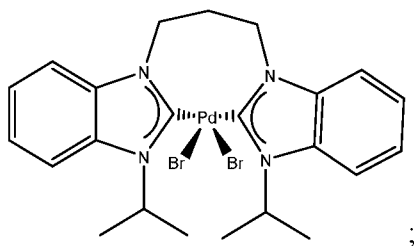
13. The method of claim 11, wherein reacting the 2-iodophenol and the aryl alkyne in the presence of a palladium catalyst comprises reacting the 2-iodophenol and the aryl alkyne with 2 equivalents diethylamine in dimethylformamide, and wherein the reacting takes place under carbon monoxide at 100 psi for 16 hours at 100 °C.

14. The method of claim 11, wherein the 2-iodophenol is functionalized with an electron withdrawing group.

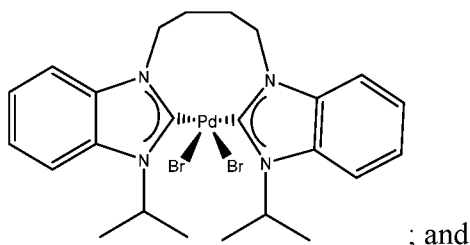
15. The method of claim 11, wherein the aryl alkyne is functionalized with an electron withdrawing group.

16. A method of synthesizing chromones or aurones comprising reacting a 2-iodophenol and an alkyl alkyne in the presence of a palladium catalyst, wherein the palladium catalyst comprises at least one of Formula (C1), Formula (C2), or Formula (C3), wherein

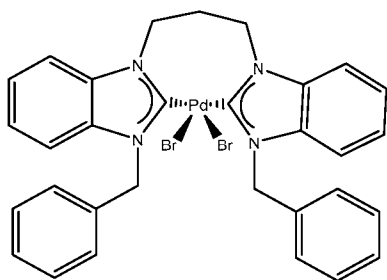
Formula (C1) is



Formula (C2) is



Formula (C3) is



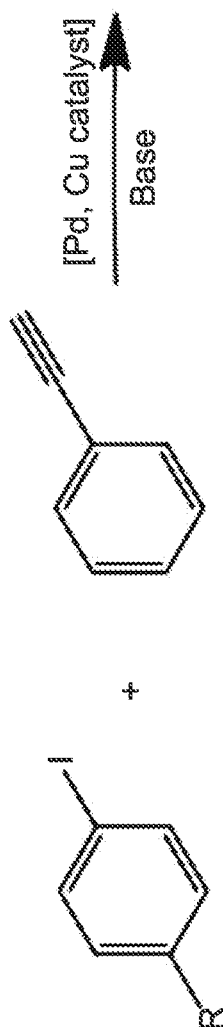
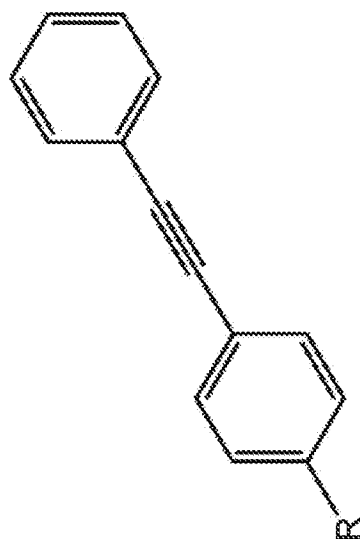
17. The method of claim 16, wherein reacting the 2-iodophenol and the alkyl alkyne in the presence of a palladium catalyst comprises reacting the 2-iodophenol and the alkyl alkyne in the presence of 0.5 mol% of the palladium catalyst.

18. The method of claim 16, wherein reacting the 2-iodophenol and the alkyl alkyne in the presence of a palladium catalyst comprises reacting the 2-iodophenol and the alkyl alkyne with 2 equivalents diethylamine in dimethylformamide, and wherein the reacting takes place under carbon monoxide at 100 psi for 24 hours at 110 °C.

19. The method of claim 16, wherein the 2-iodophenol is functionalized with an electron withdrawing group.

20. The method of claim 16, wherein the alkyl alkyne is functionalized with an electron withdrawing group.

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[Pd, Cu catalyst]  
Base

FIG. 1

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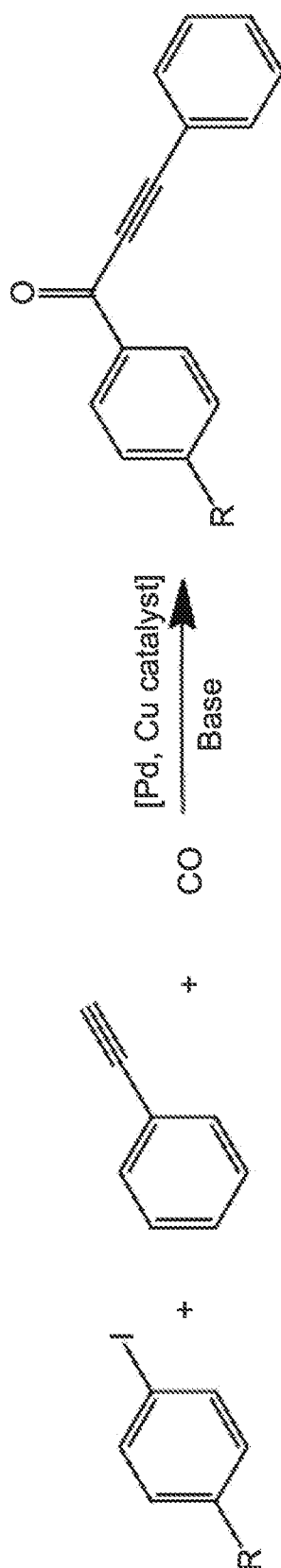


FIG. 2

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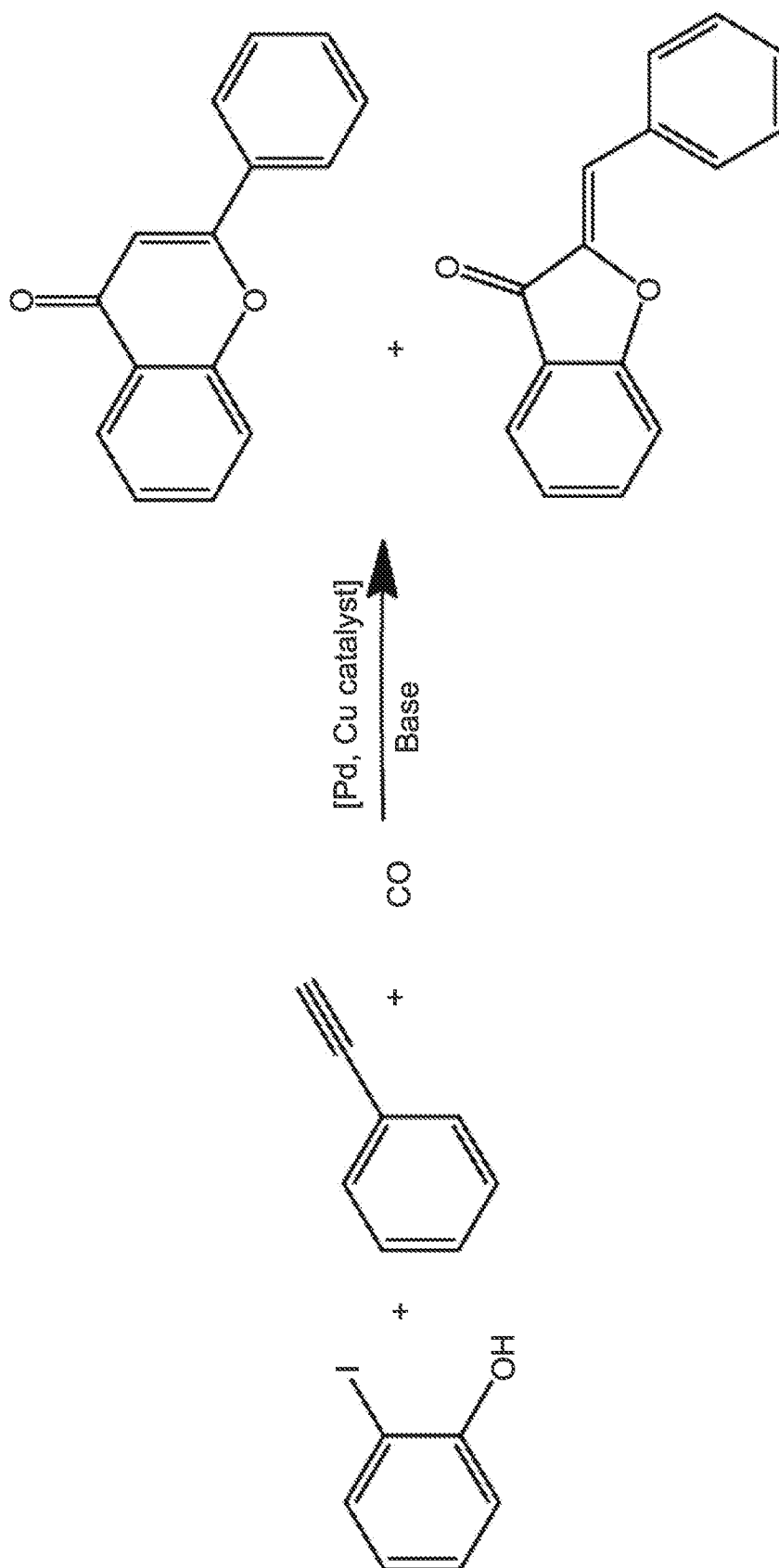


FIG. 3

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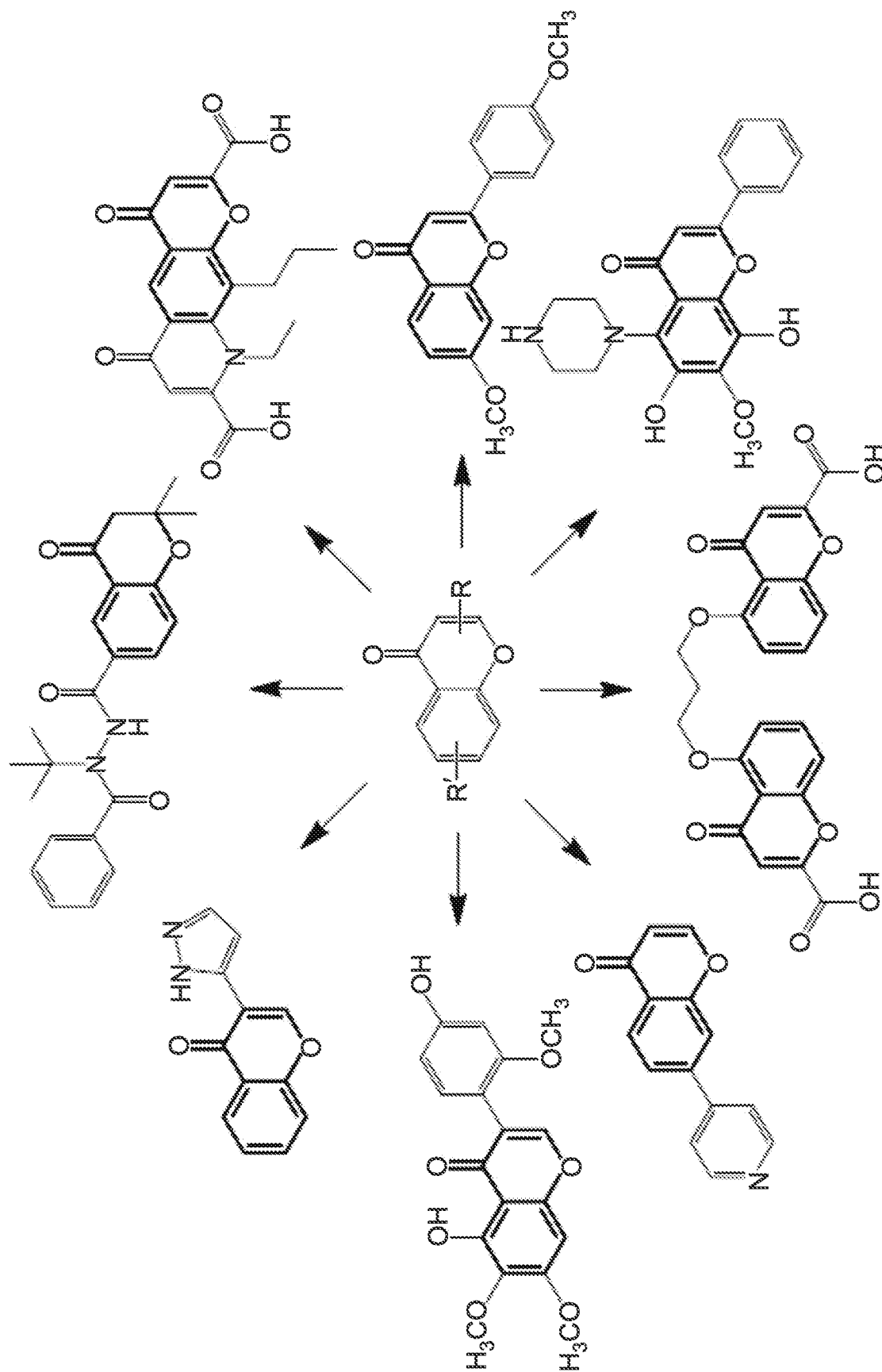


FIG. 4

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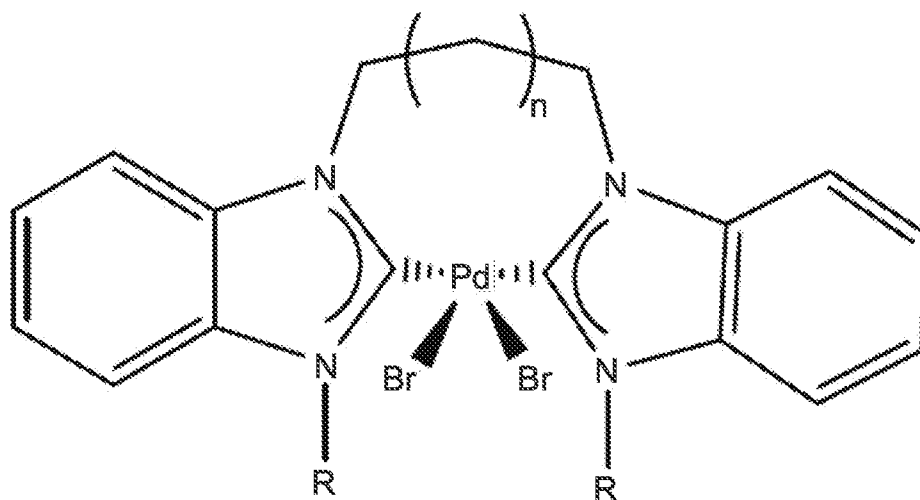
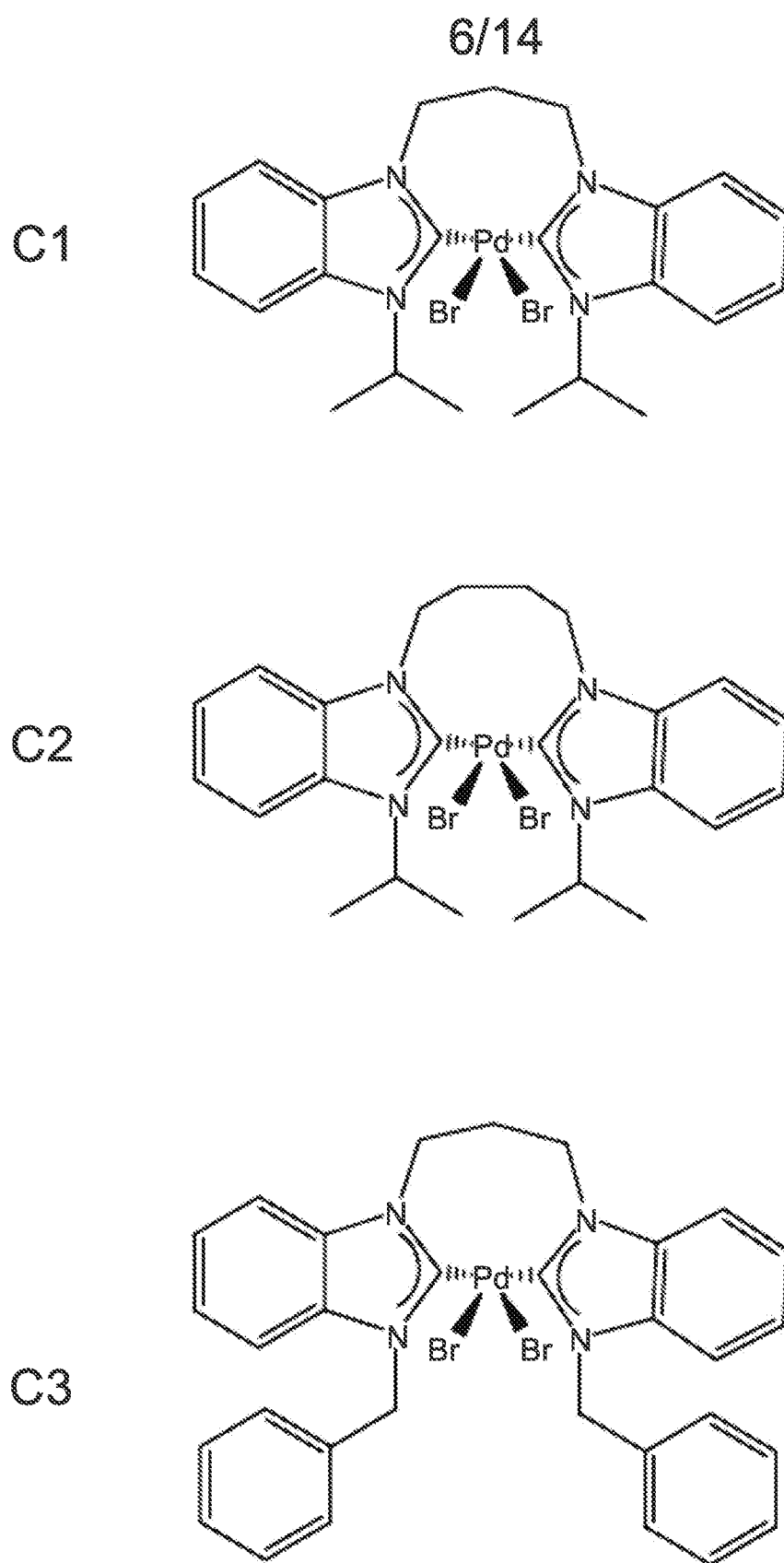
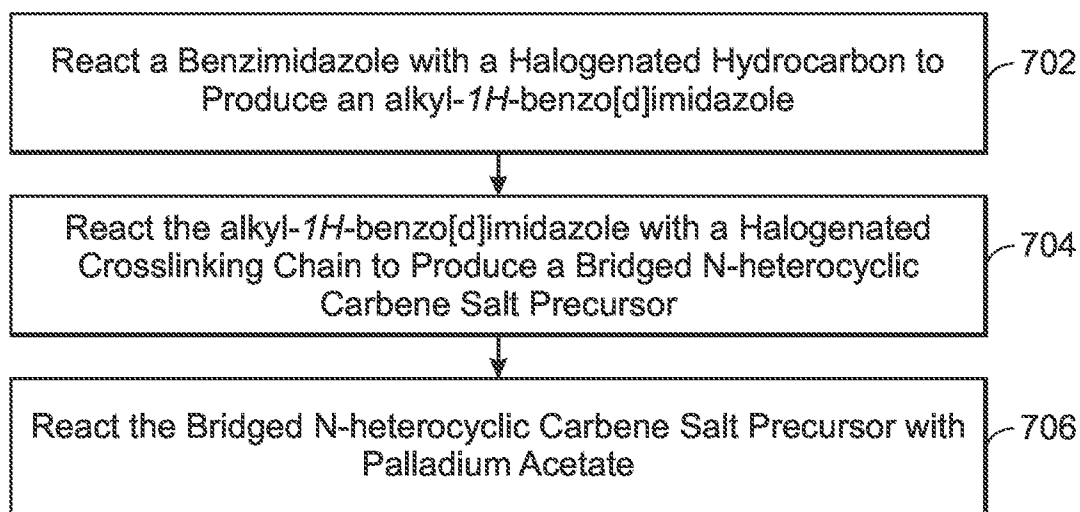


FIG. 5

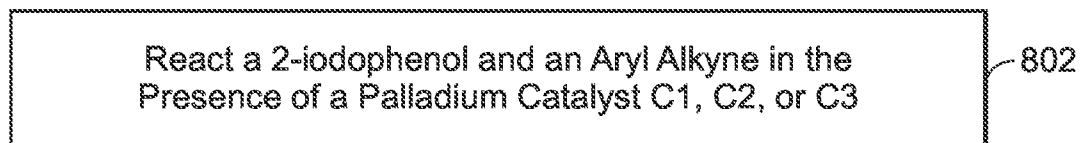


7/14



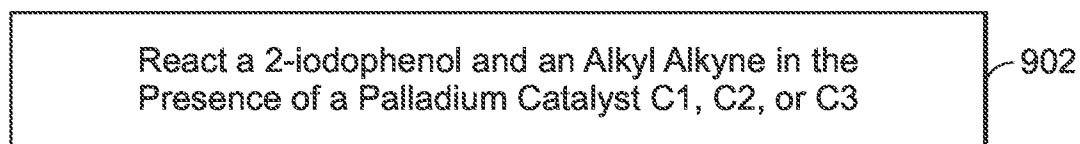
700

FIG. 7



800

FIG. 8



900

FIG. 9

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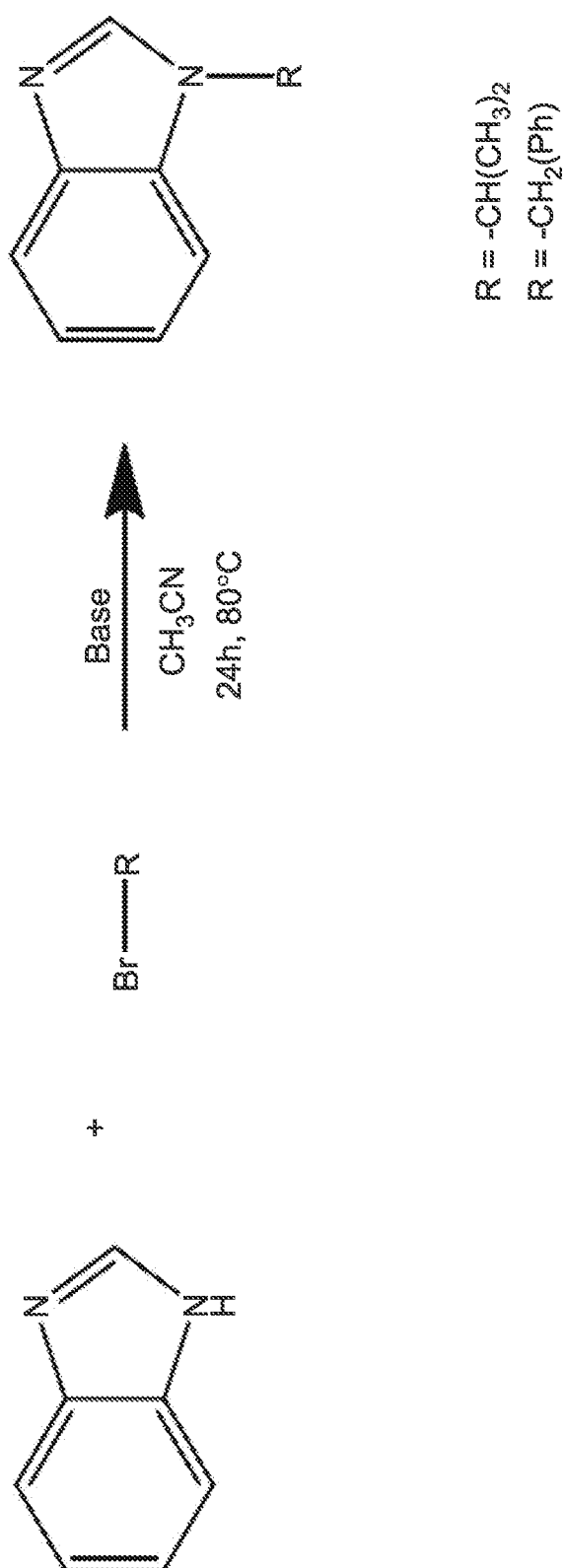


FIG. 10

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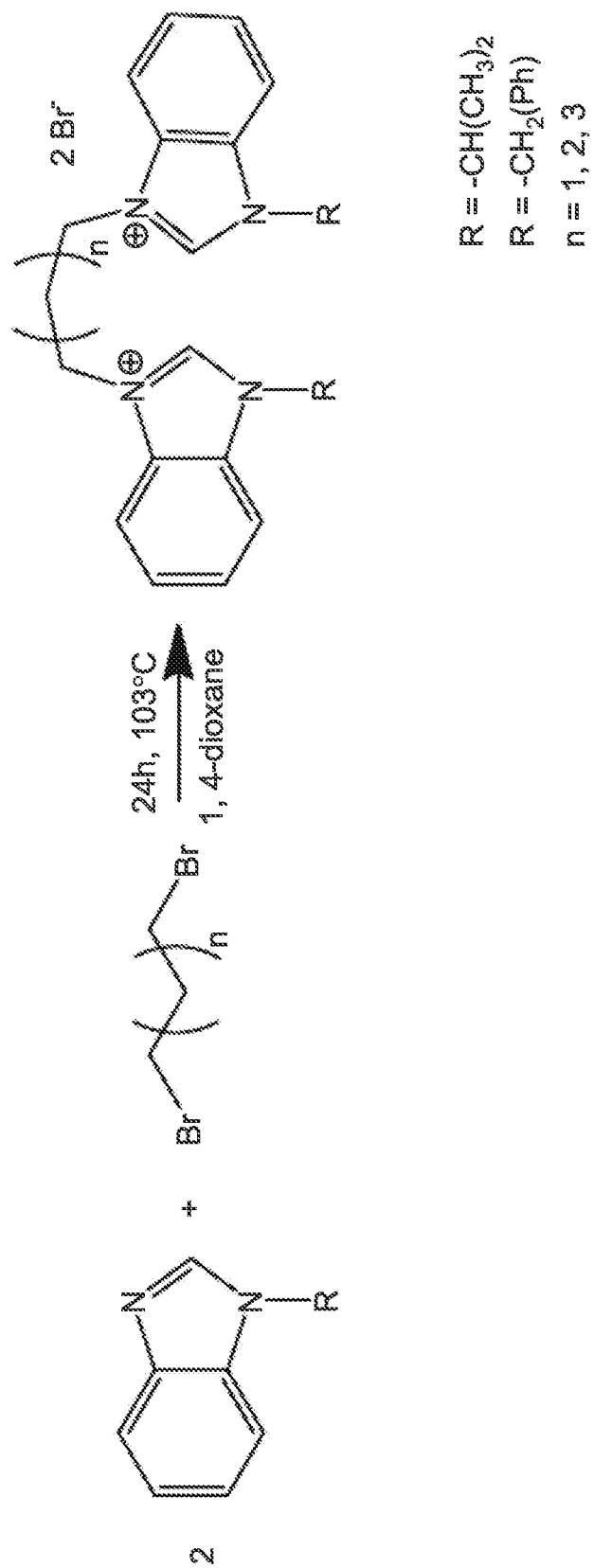


FIG. 11

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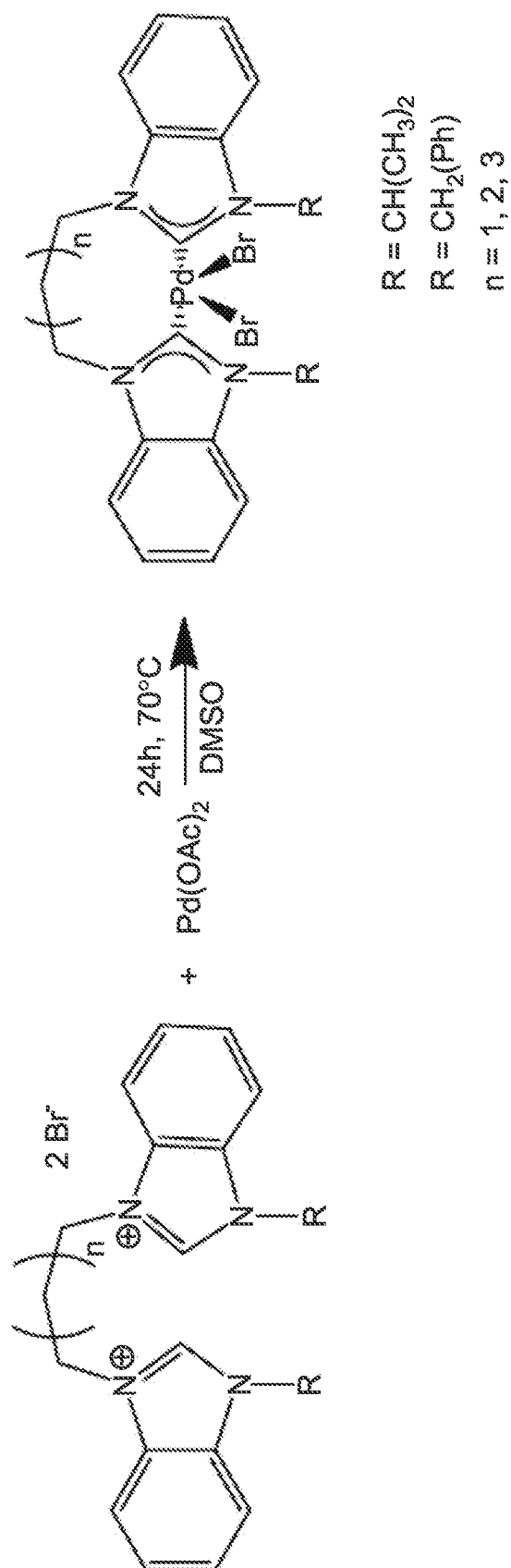


FIG. 12

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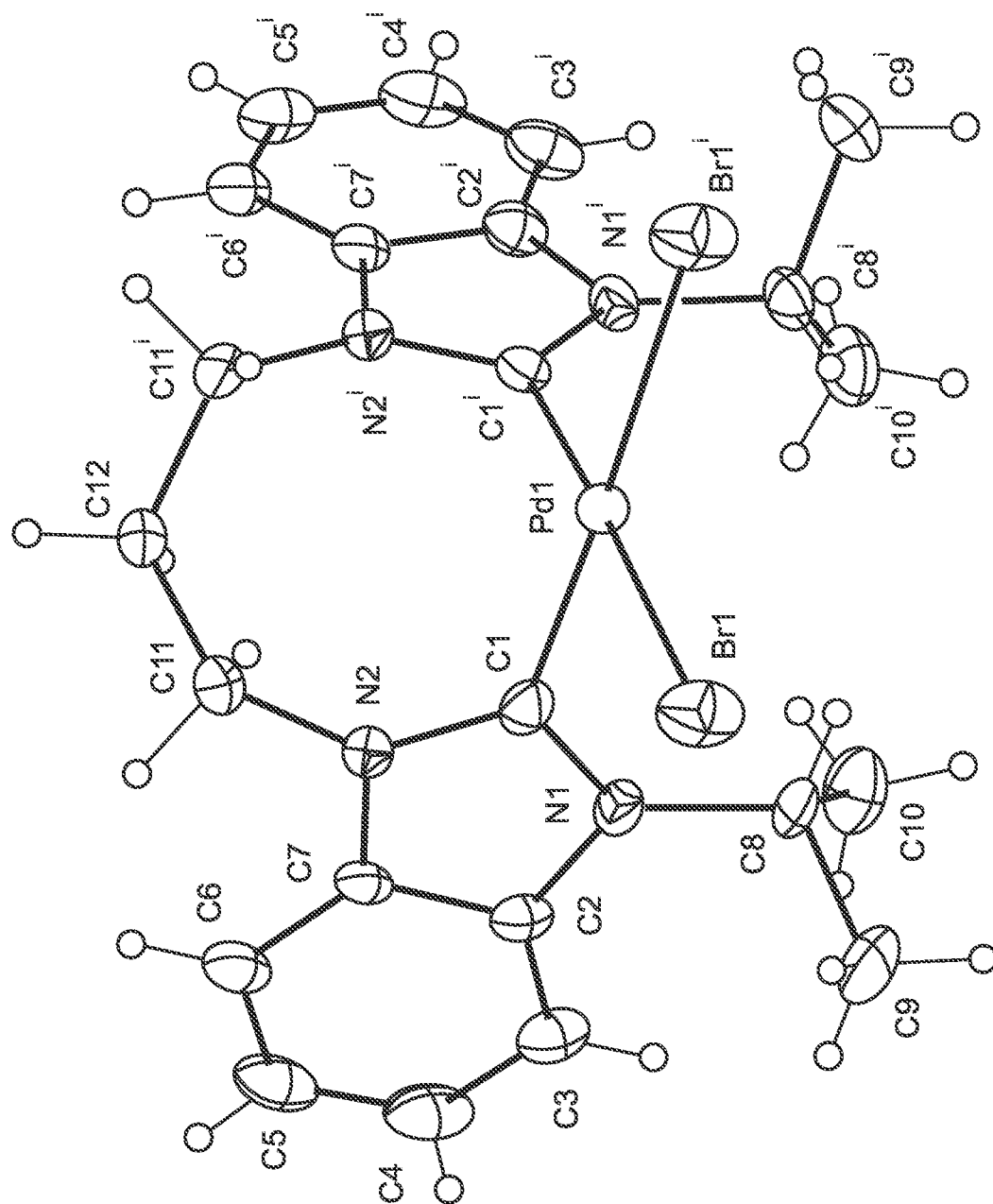


FIG. 13

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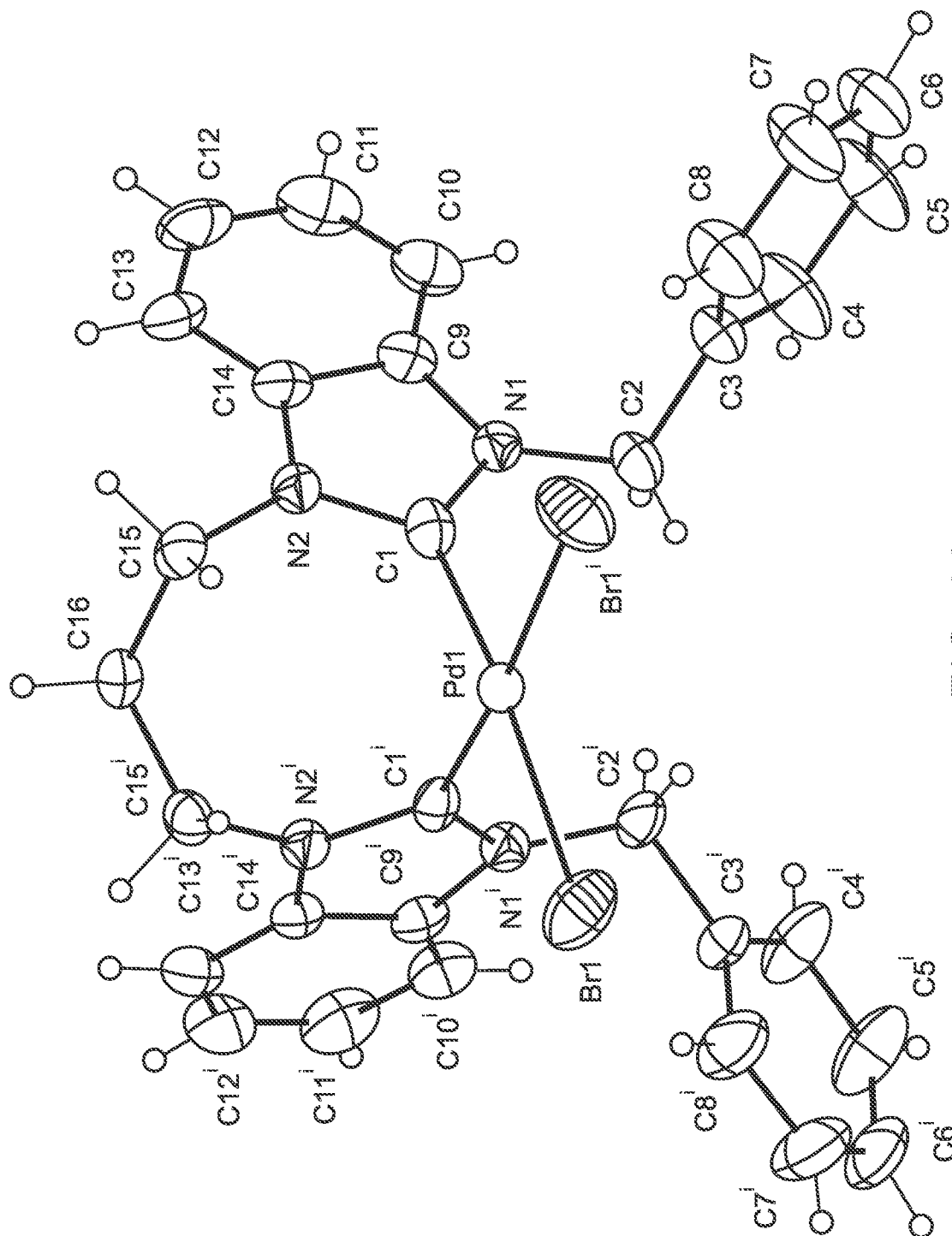


FIG. 14

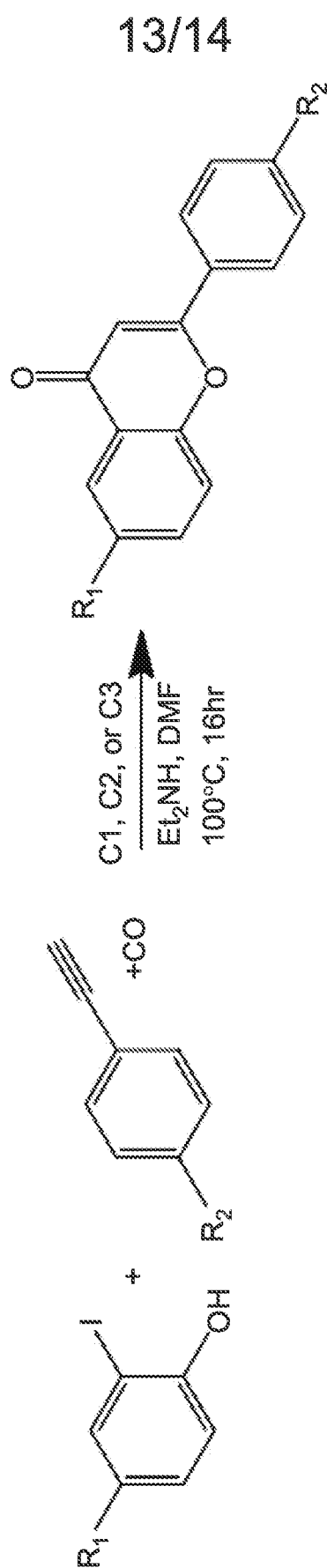
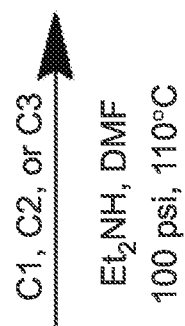
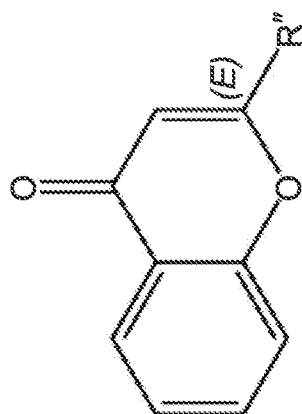


FIG. 15

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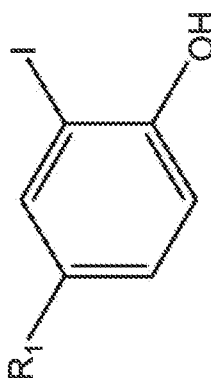


FIG. 16

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2021/058733

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br><b>INV.</b> C07F15/00 B01J31/22 C07D311/22 C07D307/83<br><b>ADD.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br><b>C07F B01J C07D</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br><b>EPO-Internal, CHEM ABS Data, WPI Data</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                             | Relevant to claim No.                              |
| <b>A</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>KALOGLU MURAT ET AL: "The first used butylene linked bis(N-heterocyclic carbene)-palladium-PEPPSI complexes in the direct arylation of furan and pyrrole", JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 915, 19 March 2020 (2020-03-19), page 121236, XP055885062, AMSTERDAM, NL ISSN: 0022-328X, DOI: 10.1016/j.jorganchem.2020.121236 page 3 scheme 1 complex 2a</b><br><div style="text-align: center;">-----<br/>-/-</div> | <b>1-20</b>                                        |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| * Special categories of cited documents :<br><div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> </div> </div> |                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                    |
| Date of the actual completion of the international search                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                | Date of mailing of the international search report |
| <b>31 January 2022</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>09/02/2022</b>                                  |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                | Authorized officer<br><br><b>Bourghida, E</b>      |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2021/058733

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                                      | Relevant to claim No. |
| Y                                                    | <p>LIU QING-XIANG ET AL: "NHC Pd II Complex Bearing 1,6-Hexylene Linker: Synthesis and Catalytic Activity in the Suzuki-Miyaura and Heck-Mizoroki Reactions : Applications of NHC Pd II Complex Bearing 1,6-Hexylene Linker", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2013, no. 7, 21 January 2013 (2013-01-21), pages 1253-1261, XP055885090, DE<br/>ISSN: 1434-193X, DOI: 10.1002/ejoc.201200954<br/>page 1254 scheme 2</p> <p>-----</p>                                                                          | 2-10                  |
| Y                                                    | <p>GUPTA SUMANTA ET AL: "Benzimidazole-based palladium-N-heterocyclic carbene: a useful catalyst for C-C cross-coupling reaction at ambient condition", TETRAHEDRON, vol. 69, no. 1, 1 January 2013 (2013-01-01), pages 122-128, XP055885088, AMSTERDAM, NL<br/>ISSN: 0040-4020, DOI: 10.1016/j.tet.2012.10.055<br/>point 4.2 page 126</p> <p>-----</p>                                                                                                                                                                 | 2-10                  |
| A                                                    | <p>YADAV SEEMA ET AL: "Well-Defined N-Heterocyclic Carbene-Palladium Complexes as Efficient Catalysts for Domino Sonogashira Coupling/Cyclization Reaction and C-H bond Arylation of Benzothiazole", APPLIED ORGANOMETALLIC CHEMISTRY, vol. 33, no. 7, 8 May 2019 (2019-05-08), XP055884933, ISSN: 0268-2605, DOI: 10.1002/aoc.4936<br/>Retrieved from the Internet:<br/>URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1002/aoc.4936&gt;<br/>complex Pd-PEPPSI 2a and 2b page 2, table 2 page 11</p> <p>-----</p> | 1-20                  |