(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
05 January 2023 (05.01.2023)

WIPO | PCT

(10) **International Publication Number**
WO 2023/278766 A1

(51) **International Patent Classification:**
C25B 3/29 (2021.01) *C25B 3/20* (2021.01)
C25B 3/00 (2021.01) *C07C 51/00* (2006.01)

(21) **International Application Number:**
PCT/US2022/035816

(22) **International Filing Date:**
30 June 2022 (30.06.2022)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
63/216,700 30 June 2021 (30.06.2021) US

(71) **Applicant: WISCONSIN ALUMNI RESEARCH FOUNDATION** [US/US]; 614 Walnut Street, Madison, Wisconsin 53726 (US).

(72) **Inventors: STAHL, Shannon**; 943 Pontiac Trl, Madison, Wisconsin 53711 (US). **SU, Zhiming**; 1101 University Avenue, Madison, Wisconsin 53706 (US). **TWILTON, Jack**; 1101 University Avenue, Madison, Wisconsin 53706 (US).

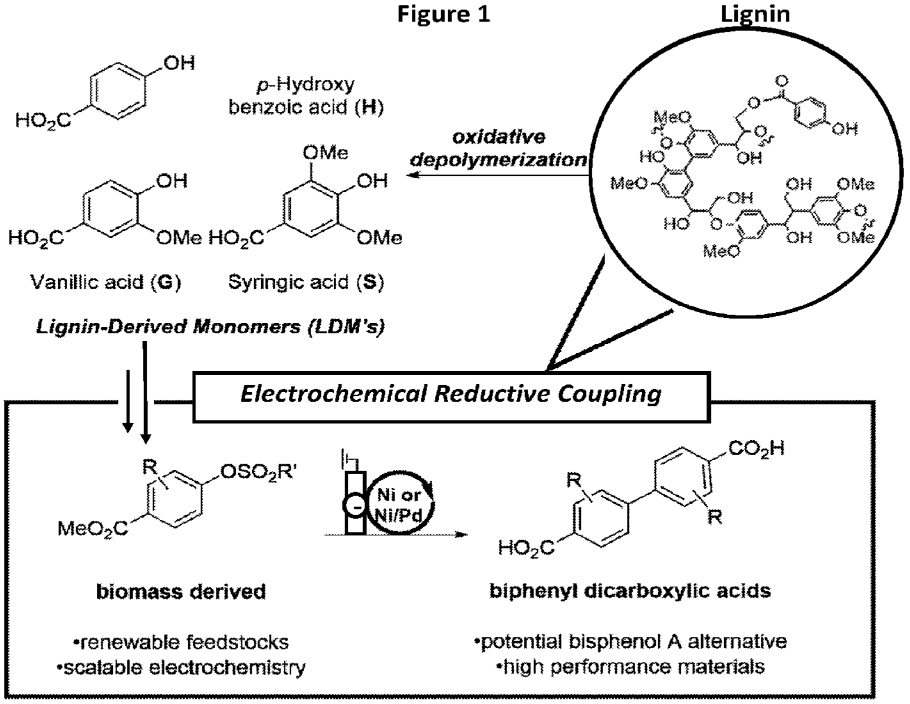
(74) **Agent: GULMEN, Tolga S.** et al.; QUARLES & BRADY LLP, 33 East Main Street, Suite 900, Madison, Wisconsin 53703 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

(54) **Title:** ELECTROCHEMICAL REDUCTIVE COUPLING OF PHENOL DERIVATIVES

Figure 1



(57) **Abstract:** A scalable Ni- or Ni/Pd-catalyzed electrochemical reductive coupling method is disclosed, affording biaryls in good to excellent yield via the electrolysis of lignin-derived aryl sulfonate esters. This method features the enhanced reactivity provided by the combination of transition metal catalysis and electrochemistry and the high selectivity for desired biaryls over other side products. The biaryls find applications in building blocks for high-performance polyesters or PVC plasticizers.

[Continued on next page]

MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

ELECTROCHEMICAL REDUCTIVE COUPLING OF PHENOL DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of United States Provisional Patent Application Ser. No. 63/216,700, filed June 30, 2021, the contents of which is incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH/DEVELOPMENT

[0002] This invention was made with government support under GM134929 awarded by the National Institutes of Health and under DE-SC0018409 awarded by the US Department of Energy. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The present disclosure relates to methods and systems for the electrochemical reductive homo-coupling and/or electrochemical reductive cross-coupling of substituted phenol derivatives to form the corresponding substituted biphenyls.

BACKGROUND OF THE INVENTION

[0004] Biphenyl-4,4'-dicarboxylic acid (BPDA) and its derivatives represent an important class of compounds in material science. BPDAs are potential precursors, either alone or as modifiers for polyethylene terephthalate (PET) or novel designer analogues. These polymers are utilized in the production of polyester fibers, engineering plastics, liquid crystal polymers for electronic and mechanical devices, and films with high heat resistance and strength. It has been reported that polyesters derived from biphenyl-4,4'-dicarboxylic acids and various aliphatic diols, including ethylene glycol, 1,4-butanediol and 1,6-hexanediol, can be readily manufactured. Such polyesters exhibit unique properties, including high stiffness and tensile strength. BPDAs also find applications in the manufacturing of plastics as plasticizers, they are readily converted to these important additives by esterification with an aliphatic alcohol.

[0005] Contemporary methods for the production of biphenyl-4,4'-dicarboxylic acid mainly rely on oxidation of 4,4'-dialkyl-biphenyls prepared via a separate oxidative coupling of aromatics derived from petroleum. For instance, 4,4'-diisopropylbiphenyl can be oxidized to biphenyl-4,4'-

dicarboxylic acid utilizing O_2, in the presence of metal catalysts, such as Co or Mn, at temperatures from 100 °C to 240 °C (see, e.g., U.S. Patent No. 4,970,338). Oxidation of other 4,4'-dialkyl-biphenyls can also be utilized to generate BPDAs (see., e.g., U.S. Patent Publication No. 2020/0290945).

[0006] However, these existing methods often generate substantial quantities of undesired byproducts of incomplete oxidation, such as formylbiphenylcarboxylic acid (FBCA) and 4-isopropylbiphenyl-4-carboxylic acid (BPMC). These byproducts can inhibit polymer growth and cause undesirable decolorization of the resultant polymer. Additionally, undesired 2,x' (x' is 2', 3', or 4') BPDA isomers are also generated during the production of the 4,4' isomers as a result of poor chemoselectivity in the initial oxidation coupling of the petroleum derived aromatics. To partially address these challenges, Bokis et al. have recently disclosed a process for purifying a BPDA product containing one or more impurities by esterifying the biphenyldicarboxylic acids (U.S. Patent Publication No. 2020/0290945).

[0007] There is a need in the art for an alternate approach to generate the BPDA monomers in high chemical purity. Ideally the precursors for production of BPDAs should come from renewable feedstocks, to reduce the reliance of the manufacturing of plastics on finite petroleum resources.

[0008] Lignin, a major component of biomass, is the only renewable feedstock composed of aromatic building blocks; successful depolymerization of lignin and repurposing of the monomers would provide a bio-renewable supply of aromatics for chemical manufacturing. Stahl et al. have developed a strategy for lignin depolymerization that is initiated via structural modification by selective oxidation, and subsequent base-promoted depolymerization delivering 4-carboxylic acid phenols as the major monomer products (see, e.g., Rafiee, M.; Alherech, M.; Karlen, S. D.; Stahl, S. S. Electrochemical Aminoxyl-Mediated Oxidation of Primary Alcohols in Lignin to Carboxylic Acids: Polymer Modification and Depolymerization. *J. Am. Chem. Soc.* **2019**, *141*, 15266-15276; Rahimi, A.; Ulbrich, A.; Coon, J. J.; Stahl S. S. Formic-acid-induced depolymerization of oxidized lignin to aromatics. *Nature* **2014**, *515*, 249–252). The inherent incorporation of the carboxylic acid group renders 4-hydroxybenzoic acid (H), syringic acid (S) and vanillic acid (G) ideal renewable precursors to biphenyl-4,4'-dicarboxylic acid (BPDA) derivatives for use in improved methods of BPDA synthesis.

BRIEF SUMMARY

[0009] We disclose herein a new approach for electrochemical reductive coupling of these lignin derived monomers in the presence of Ni or Ni/Pd catalysis, in batch or flow electrolytic cells, using dimethylforamide (DMF), dimethylacetamine (DMA) or dimethyl sulfoxide (DMSO) as a solvent. A simple sequential esterification and phenol activation of lignin-derived monomers leads to appropriate substrates for reductive coupling, whereby the biphenyl motifs will be delivered. Under Ni-mediated conditions, the homo-coupled products are smoothly delivered in good to near quantitative yields.

[0010] Of special interest, biphenyl-4,4’-dicarboxylic acid, a known monomer employed in specialty polymer synthesis, is prepared in 97% yield under batch conditions and 87% yield via flow electrolysis, using only 1 mol% catalyst. The cross-couplings of the abovementioned lignin derived monomers via Ni/Pd co-catalysis also delivered the corresponding products in good yields and selectivity.

[0011] Differential methoxyl substitution patterns on the aromatic products will likely modify the structural properties of derived polyesters, affecting the rigidity, thermal stability, and other characteristics. The tunable nature of the properties of the homo-coupled and cross-coupled products makes them promising precursors for plasticizers and monomers in high-performance plastics.

[0012] Our approach provides a superior alternative to generate biphenyl-4,4’-dicarboxylic acids and derivatives from lignin derived monomers, under electrochemical conditions. The resultant products are generated in high purity, and are easily isolated, due to the excellent yields and the lack of the isomeric byproducts. By employing lignin as the source of these aromatic monomers, this approach has the potential to decrease reliance on petroleum for chemical manufacturing and provides a sustainable method for the continued production of plastics and other high-performance materials.

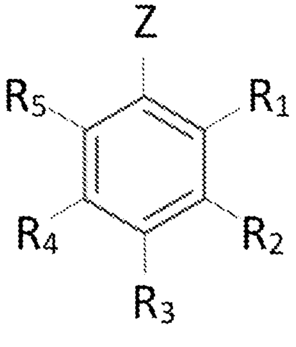
[0013] In a first aspect, this disclosure encompasses a method of producing one or more desired substituted biaryl products from one or more substituted aryl sulfonate reactants by electrochemical reductive coupling. The method includes the step of applying an external electromotive force to add electrons to a cathode electrode of an electrosynthetic cell and to simultaneously remove electrons from an anode electrode of the electrosynthetic cell. The cathode electrode is in contact with a liquid phase solution that includes the one or more substituted aryl sulfonate reactants. As a result of performing the method, the one or more substituted aryl sulfonate reactants are reductively coupled to produce the one or more desired substituted biaryl products.

[0014] In some embodiments, a single substituted aryl sulfonate reactant is homo-coupled to make the desired substituted biaryl product. In some such embodiments, the liquid phase solution includes a catalyst that contains Ni. In some such embodiments, the catalyst contains a nickel salt.

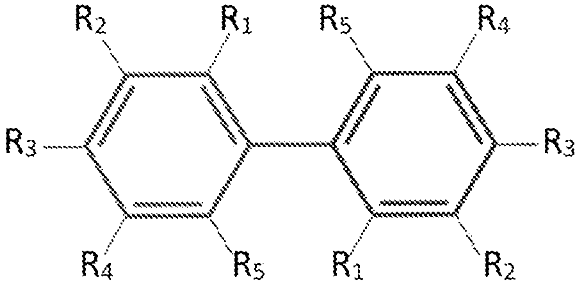
[0015] In other embodiments, two different substituted aryl sulfonate reactants are cross-coupled to make the desired substituted biaryl product. In some such embodiments, the liquid phase solution includes a catalyst or a combination of catalysts that together contain both Ni and Pd. In some such embodiments, the one or more catalysts contain a nickel salt and/or a palladium salt.

[0016] In some embodiments, the one or more substituted aryl sulfonate reactants are derived from one or more substituted phenols by converting the phenolic –OH to a sulfonate. In some such embodiments, the one or more substituted phenols are derived from lignin. In some embodiments, the one or more substituted phenols are derived from lignin by depolymerization of the lignin. In some such embodiments, the lignin is depolymerized by structurally modifying the lignin via selective oxidation, followed by base-promoted depolymerization of the structurally modified lignin.

[0017] In some embodiments, the substituted aryl sulfonate reactant has the chemical formula:



, where Z includes a sulfonate ester. The desired substituted biaryl product then has the chemical formula:



.

[0018] R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

[0019] In some embodiments, Z includes a sulfonate having the formula $-SO_2X$, where X is OR_{11}, and where R_{11} is a cation, an alkyl, a haloalkyl, an aryl, or a silyl.

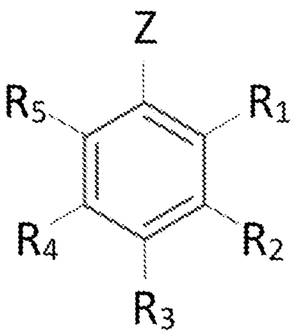
[0020] In some embodiments, Z is a mesylate, a tosylate or a triflate.

[0021] In some embodiments, R_2 and R_4 are hydrogen.

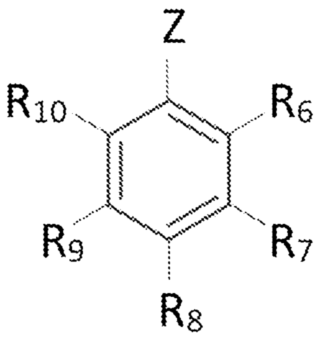
[0022] In some embodiments, R_1 and R_5 are each independently an alkoxy or hydrogen. In some such embodiments, the alkoxy is methoxy.

[0023] In some embodiments, R_3 is a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

[0024] In some embodiments, the substituted aryl sulfonate reactants have the chemical formulas:

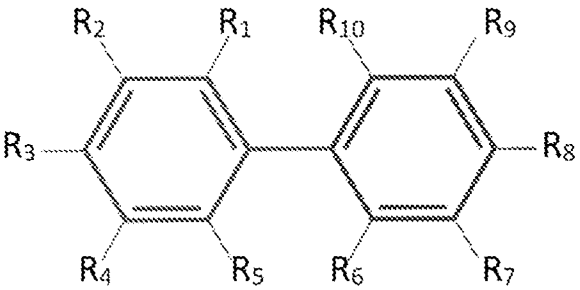


and



, where Z includes a sulfonate ester.

The desired substituted biaryl product then has the chemical formula:



.

[0025] R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

[0026] In some embodiments, Z includes the sulfonate having the formula $-SO_2X$, where X is OR_{11}, and where R_{11} is a cation, an alkyl, a haloalkyl, an aryl, or a silyl.

[0027] In some embodiments, Z is a mesylate, a tosylate or a triflate.

[0028] In some embodiments, R_2, R_4, R_7 and R_9 are hydrogen.

[0029] In some embodiments, R_1, R_5, R_6 and R_{10} are each independently an alkoxy or hydrogen. In some such embodiments, the alkoxy is methoxy.

[0030] In some embodiments, R_3 and R_8 are each independently a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

[0031] In some embodiments, the method is performed by batch electrolysis. In other embodiments, the method is performed by flow electrolysis.

[0032] In some embodiments, the electrosynthetic cell is a divided cell. In other embodiments, the electrosynthetic cell is an undivided cell.

[0033] In some embodiments, the liquid phase further includes one or more organic solvents. Non-limiting examples of organic solvents that could be used include acetone, acetonitrile, benzene, 1-butanol, 2-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethane, dimethyl carbonate, diethyl carbonate, diethylene glycol, diethyl ether, diglyme (diethylene glycol dimethyl ether), 1,2-dimethoxy-ethane (glyme, DME), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-1,3-diazinan-2-one (DMPU), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethanol, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), 1-propanol, 2-propanol, propylene carbonate, pyridine, sulfolane, tetrahydrofuran (THF), 2-methyl tetrahydrofuran toluene, triethyl amine, o-xylene, m-xylene, or p-xylene.

[0034] In a second aspect, this disclosure encompasses an electrosynthetic cell for use in producing one or more desired substituted biaryl products from one or more substituted aryl sulfonate reactants by electrochemical reductive coupling. The electrosynthetic cell includes a cathode electrode and an anode electrode. The cathode electrode is in contact with a liquid phase solution that includes the one or more substituted aryl sulfonate reactants.

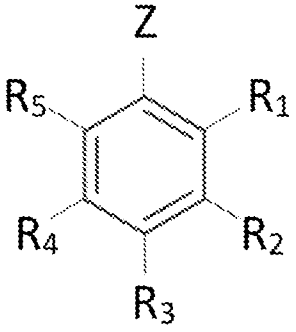
[0035] In some embodiments, the electrosynthetic cell further includes a device configured to externally apply an electromotive force to add electrons to the cathode electrode and to simultaneously remove electrons from the anode electrode. When the electromotive force is applied, the one more substituted aryl sulfonate reactants are reductively coupled to produce the one or more desired substituted biaryl products.

[0036] In some embodiments, the cell is configured to homo-couple a substituted aryl sulfonate reactant to make the desired substituted biaryl product. In some such embodiments, the liquid phase solution includes a catalyst that contains Ni. In some such embodiments, the catalyst contains a nickel salt.

[0037] In other embodiments, the cell is configured to cross-couple two different substituted aryl sulfonate reactants to make the desired substituted biaryl product. In some such embodiments, the liquid phase solution includes a catalyst or a combination of catalysts that together contain both Ni and Pd. In some embodiments, the catalysts include a nickel salt and/or a palladium salt.

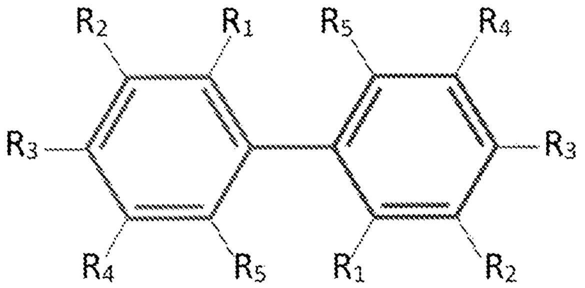
[0038] In some embodiments, the one or more substituted aryl sulfonate reactants are derived from one or more substituted phenols by converting the phenolic –OH to a sulfonate. In some such embodiments, the one or more substituted phenols are derived from lignin. In some such embodiments, the one or more substituted phenols are derived from lignin by depolymerization of the lignin. In some such embodiments, the lignin is depolymerized by structurally modifying the lignin via selective oxidation, followed by base-promoted depolymerization of the structurally modified lignin.

[0039] In some embodiments, the substituted aryl sulfonate reactant has the chemical formula:



, where Z includes a sulfonate ester.

The desired substituted biaryl product then has the chemical formula:



.

[0040] R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

[0041] In some embodiments, Z includes a sulfonate having the formula $-SO_2X$, where X is OR_{11}, and where R_{11} is a cation, an alkyl, a haloalkyl, an aryl, or a silyl.

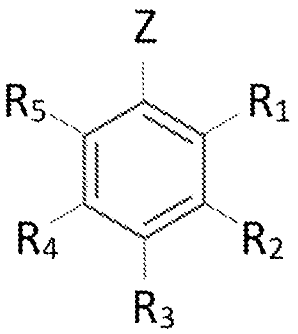
[0042] In some embodiments, Z is a mesylate, a tosylate or a triflate.

[0043] In some embodiments, R_2 and R_4 are hydrogen.

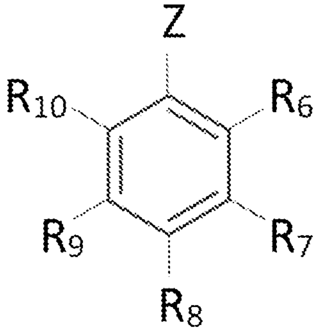
[0044] In some embodiments, R_1 and R_5 are each independently an alkoxy or hydrogen. In some such embodiments, the alkoxy is methoxy.

[0045] In some embodiments, R_3 is a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

[0046] In some embodiments, the substituted aryl sulfonate reactants have the chemical formulas:

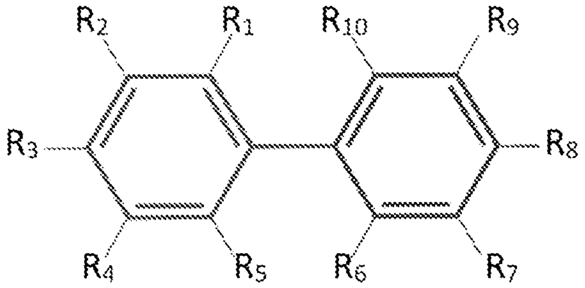


and



, where Z includes a sulfonate ester.

The desired substituted biaryl product then has the chemical formula:



.

[0047] R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

[0048] In some embodiments, Z includes a sulfonate having the formula $-SO_2X$, where X is OR_{11}, and where R_{11} is a cation, an alkyl, a haloalkyl, an aryl, or a silyl.

[0049] In some embodiments, Z is a mesylate, a tosylate or a triflate.

[0050] In some embodiments, R_2, R_4, R_7 and R_9 are hydrogen.

[0051] In some embodiments, R_1, R_5, R_6 and R_{10} are each independently an alkoxy or hydrogen. In some such embodiments, the alkoxy is methoxy.

[0052] In some embodiments, R_3 and R_8 are each independently a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

[0053] In some embodiments, the cell is configured for batch electrolysis. In other embodiments, the cell is configured for flow electrolysis.

[0054] In some embodiments, the cell is a divided cell. In other embodiments, the cell is an undivided cell.

[0055] In some embodiments, the liquid phase further includes one or more organic solvents. Non-limiting examples of organic solvents that could be used include acetone, acetonitrile, benzene, 1-butanol, 2-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethane, dimethyl carbonate, diethyl carbonate, diethylene glycol, diethyl ether, diglyme (diethylene glycol dimethyl ether), 1,2-dimethoxy-ethane (glyme, DME), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-1,3-diazinan-2-one (DMPU), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethanol, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), 1-propanol, 2-propanol, propylene carbonate, pyridine, sulfolane, tetrahydrofuran (THF), 2-methyl tetrahydrofuran toluene, triethyl amine, o-xylene, m-xylene, or p-xylene.

[0056] The above and still other advantages of the present disclosure will be apparent from the description that follows. However, the following description is merely of specific non-limiting exemplary embodiments. The full scope of the invention is described in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] Figure 1 depicts a general scheme for the electrochemical reductive coupling of lignin-derived monomers.

[0058] Figure 2 illustrates results for electrochemical homo-coupling.

[0059] Figure 3 shows cyclic voltammograms recorded with glassy carbon as working electrode (~7.0 mm^2) and a platinum wire (1.0 cm, spiral wire) as counter electrode at 100 mV/s. From top to bottom: traces a) to d). a). DMF containing 0.4 M of LiBr and 5 mM of $Ni(bpy)_3Br_2$. b). Solution (a) with 10 mM H-OMs added. c). Solution (a) with 25 mM H-OMs added. d). Solution (a) with 50 mM H-OMs added.

[0060] Figure 4 illustrates results for electrochemical cross-coupling.

[0061] Figure 5 is a graphic illustration of the components of the divided flow cell reactor.

[0062] Figure 6 illustrates a plausible catalytic cycle.

[0063] Figure 7 is a graphic illustration of the divided cell before (left) and after (right) assembly.

[0064] Figure 8 is a graphic illustration of the undivided cell before (left) and after (right) assembly.

[0065] Figure 9 is a graphic illustration of the undivided flow cell for 12 mmol (left) and 48 mmol (right) scale-up.

[0066] Figure 10 depicts optimization of thermochemical Ni-catalyzed reductive homo-coupling of G-Oms. [a] Yields were determined by ^1H NMR using mesitylene as internal standard. [b] New batch of Zn dust. [c] < 5% yield was obtained with 8 more bpy derivatives (shown is with 2,2'-bipyridine). [d] With 1,10-Phen as ligand. [e] With 2,9-dimethyl-1,10-Phen as ligand.

[0067] Figure 11 depicts conditions screening focused on nitrogen-based ligands. Yields were determined by ^1H NMR using mesitylene as internal standard.

[0068] Figure 12 depicts conditions screening focused on phosphine-based ligands. Yields were determined by ^1H NMR using mesitylene as internal standard.

[0069] Figure 13 depicts conditions screening focused on ligand loading and additives. Yields were determined by ^1H NMR using mesitylene as internal standard. [a] LiBr instead of LiCl. [b] $^nBu_4NBr$ instead of LiCl. [c] $^nBu_4NCl$ instead of LiCl. [d] $^nBu_4NI$ instead of LiCl.

[0070] Figure 14 shows conditions screening focused on temperature and solvents. Yields were determined by ^1H NMR using mesitylene as internal standard.

[0071] Figure 15 shows conditions screening focused on additive loadings. Yields were determined by ^1H NMR using mesitylene as internal standard.

[0072] Figure 16 demonstrates conditions screening focused on molecular sieves and solvents. Yields were determined by UPLC-MS using 2,4,6-trimothoxybenzene as internal standard.

[0073] Figure 17 shows the structures of the ligands in the separate stock solutions for addition to the 96-well plate.

[0074] Figure 18 demonstrates ligand screening. Yields were determined by UPLC using 2,4,6-trimothoxybenzene as internal standard. AY = array yield.

[0075] Figure 19 depicts ligand and solvent screening. Yields were determined by UPLC using 2,4,6-trimothoxybenzene as internal standard. AY = array yield.

[0076] Figure 20 shows screening for catalyst loading, solvent, and substrate ratio. Yields were determined by UPLC using 2,4,6-trimothoxybenzene as internal standard. Circle size corresponds to conversion – full conversion was observed with 10 mol% Ni. 65% was the highest yield.

DETAILED DESCRIPTION

[0077] The disclosed devices and methods are not limited to the particular methodology, protocols, materials, and reagents described, as these may vary. Furthermore, the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is limited only by the pending claims.

[0078] As used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural reference, unless the context clearly dictates otherwise. Accordingly, the terms “a” (or “an”), “one or more” and “at least one” can be used interchangeably. The terms “comprising,” “including,” and “having” can also be used interchangeably.

[0079] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods and materials of exemplary non-limiting embodiments are now described. All publications and patents specifically mentioned herein are incorporated by reference in their entirety for all purposes.

[0080] This disclosure is based on the inventors' systems and methods for reductive electrochemical coupling of aryl sulfonate esters to form the corresponding biaryls. The reductive electrochemical coupling occurs when an external electromotive force is applied to an electrosynthetic cell, pushing electrons into the cathode electrode and withdrawing electrons from the anode electrode. The cathode electrode is in contact with a liquid phase solution that includes the aryl sulfonate esters and a Ni-containing catalyst (for homo-coupling) or a Ni/Pd-containing catalyst (for cross-coupling). The electromotive force and the catalyst together facilitate the reductive electrochemical coupling reaction.

[0081] In some embodiments, the Ni- or Ni/Pd-containing catalyst is not affixed to the cathode electrode. Thus, the cathode electrode itself need not act as a catalyst. Accordingly, the type of cathode electrode used is not limited, and may comprise any electrode material that is typically used in the art.

[0082] In operation, the cathode half-cell may be paired with any anode half-cell that is configured to allow the reductive coupling to occur within the cathode half-cell. Accordingly, the oxidation reaction occurring within the anode half-cell is not limited, and can include any oxidation reaction that can occur under the given reaction conditions and EMF application. In one exemplary embodiment, the anode half-cell may be a hydrogen anode half-cell, where H_2 is oxidized to H^+.

[0083] The anode and cathode half-cells may be separated by a permeable or semi-permeable membrane or a glass frit, or may be combined in an undivided cell. The semi-permeable membrane may be a proton-exchange membrane, an anion-exchange membrane, or a membrane designed to facilitate transfer of a specific cation, anion, group of ions, solvent, or group of solvents, depending on the specific species movement desired between half-cells.

A. Use of Biomass Feedstocks and Scalability

[0084] The disclosed systems and methods provide an alternative to petroleum-based production of BPDA and related substituted derivatives. Instead, the methods may use renewable feedstocks, such as lignin, and electrochemistry to produce these valuable intermediates at high yields.

[0085] In such embodiments, lignin-derived monomers, such as 4-carboxylic acid phenols, may be protected by esterification, and the phenol –OH group may be activated by sulfonate ester formation. The resulting substituted aryl sulfonates are the substrates for electrochemical reductive coupling in the presence of Ni or Ni/Pd catalysis, which produces the corresponding substituted biphenyl products. Non-limiting examples of such products include value-added intermediates, such as BPDA.

[0086] The disclosed systems and methods can be implemented in batch or flow electrolytical cells, and are compatible with various organic solvents (e.g., DMF, DMA and DMSO). The method is based on sequential esterification and phenol activation of lignin monomers to produce substrates for reductive coupling. The method results in excellent to near quantitative yields, and is readily scalable via flow electrolysis. If implemented on a commercial scale, the disclosed method could dramatically reduce costs while providing sustainability advantages over petroleum-based solutions.

B. Commercial Applications

[0087] In a non-limiting example, the disclosed systems and methods could be used in biomass upgrading and polymer manufacture. The resultant products are easily purified and are promising monomeric precursors for high-performance polymers, including polyester fibers, engineered plastics, liquid crystal polymers for electronic and mechanical devices, and films with high heat resistance and strength. Polyesters from BPDA have been shown to exhibit unique properties including high stiffness and tensile strength. BPDAs also find applications as plasticizers, as they are readily converted via esterification with an aliphatic alcohol.

C. Exemplary Organic Solvents

[0088] The liquid phase (i.e., electrolyte solution) of the cathode half-cell (i.e., the catholyte), the anode half-cell (i.e., the anolyte), or both (i.e., of the electrosynthetic cell as a whole) may include water and/or one or more organic solvents. The solvent mix may be tuned to optimize the desired solubility of the substrate, the catalyst(s), and/or the one or more desired chemical products.

[0089] Non-limiting examples of organic solvents that could be used in the anolyte or catholyte include acetone, acetonitrile, benzene, 1-butanol, 2-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethane, dimethyl carbonate, diethyl carbonate, diethylene glycol, diethyl ether, diglyme (diethylene glycol dimethyl ether), 1,2-dimethoxy-ethane (glyme, DME), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-1,3-diazinan-2-one (DMPU), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethanol, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), 1-propanol, 2-propanol, propylene carbonate, pyridine, sulfolane, tetrahydrofuran (THF), 2-methyl tetrahydrofuran toluene, triethyl amine, o-xylene, m-xylene, or p-xylene.

D. Supporting Electrolytes

[0090] In some embodiments the anolyte and/or catholyte contain a supporting electrolyte. Non-limiting examples of supporting electrolytes include lithium chloride, lithium bromide, lithium iodide, lithium hexafluorophosphate, lithium tetrafluoroborate, lithium hexafluoroantinomate, lithium perchlorate, sodium chloride, sodium bromide, sodium iodide, sodium hexafluorophosphate, sodium tetrafluoroborate, sodium hexafluoroantinomate, sodium perchlorate, potassium chloride, potassium bromide, potassium iodide, potassium hexafluorophosphate, potassium tetrafluoroborate, potassium hexafluoroantinomate, potassium perchlorate, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, tetrabutylammonium hexafluorophosphate, tetrabutylammonium tetrafluoroborate, tetrabutylammonium hexafluoroantinomate, tetrabutylammonium perchlorate, pyridinium chloride, pyridinium bromide, pyridinium iodide, pyridinium hexafluorophosphate, pyridinium tetrafluoroborate, pyridinium hexafluoroantinomate, pyridinium perchlorate, 2,6-lutidinium chloride, 2,6-lutidinium bromide, 2,6-lutidinium iodide, 2,6-lutidinium hexafluorophosphate, 2,6-lutidinium tetrafluoroborate, 2,6-lutidinium hexafluoroantinomate, 2,6-lutidinium perchlorate.

DEFINITIONS

[0091] The term "biaryl" refers to a compound containing two aryl groups. The term "aryl" refers to a carbocyclic aromatic group that is monocyclic or fused (*e.g.* bicyclic, tricyclic, polycyclic, etc.) containing up to 14 carbon atoms (*e.g.* C_6-C_{14}-aryl). Examples of aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like. “Aryl” also contemplates an aryl ring that is part of a fused polycyclic system, such as aryl fused to cycloalkyl as defined herein. An exemplary aryl is phenyl. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein (*e.g.* alkyl).

[0092] The term “alkyl” as used herein, means a saturated, straight or branched hydrocarbon chain radical. In some instances, the number of carbon atoms in an alkyl moiety is indicated by the prefix “C_{x-y}”, wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, “C_{1-6} alkyl” means an alkyl substituent containing from 1 to 6 carbon atoms and “C_{1-4} alkyl” means an alkyl substituent containing from 1 to 4 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, n-hexyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 3,3-dimethylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-methylpropyl, 2-methylpropyl, 1-ethylpropyl, and 1,2,2-trimethylpropyl.

[0093] The term "haloalkyl" refers to an alkyl group, as defined herein, substituted with one or more halogens. The term "halogen" or "halo," as used herein, refers to -F or fluoro, -Cl or chloro, -Br or bromo, or -I or iodo.

[0094] The term "alkoxy" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy. In some instances, the number of carbon atoms in an alkoxy moiety is indicated by the prefix "$C_{x\text{-}y}$", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "$C_{1\text{-}6}$ alkoxy" means an alkoxy substituent containing from 1 to 6 carbon atoms and "$C_{1\text{-}4}$ alkoxy" means an alkoxy substituent containing from 1 to 4 carbon atoms.

[0095] The term "cycloalkyl" as used herein, refers to a saturated monocyclic, bicyclic, tricyclic, or polycyclic, 3- to 14-membered ring system, such as a C_3-C_8-cycloalkyl. The cycloalkyl may be attached via any atom. Representative examples of cycloalkyl include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Polycyclic cycloalkyl includes rings that can be fused, bridged, and/or spiro-fused. A cycloalkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein.

[0096] "Heteroaryl" as defined herein, refers to a monocyclic aromatic ring structure containing 5 to 10, such as 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or heteroatom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. A heteroaryl group can be unsubstituted or optionally substituted with one or more substituents as described herein.

[0097] "Heterocycloalkyl" as used herein, refers to a saturated or partially unsaturated non-aromatic monocyclic, bicyclic, tricyclic or polycyclic ring system that has from 3 to 14, such as 3 to 6, atoms in which 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N. Polycyclic heterocycloalkyl includes rings that can be fused, bridged, and/or spiro-fused. In addition, a heterocycloalkyl is optionally fused with aryl or heteroaryl of 5-6 ring members, and includes oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment of the heterocycloalkyl ring is at a carbon or heteroatom such that a stable ring is retained. Examples of heterocycloalkyl groups include without limitation morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl. A heterocycloalkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein.

[0098] The term "carboxylic acid" refers to a group of the formula -C(O)OH.

[0099] The term "carboxylate ester" refers to a group of the formula -C(O)OR, wherein the R group is an organic group such as aryl, alkyl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl etc., as defined herein.

[00100] The term "aldehyde" refers to a group of the formula -C(O)H.

[00101] The term "ketone" refers to a group of the formula -C(O)R, wherein the R group is an organic group such as aryl, alkyl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl etc., as defined herein.

[00102] The term "dione" refers to a compound containing two ketone groups as defined herein.

[00103] The term "silyl" as used herein, refers to a group of the formula $-Si(R)_3$, wherein each R group is independently selected from an organic group such as aryl, alkyl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl etc., as defined herein.

[00104] The term "sulfonate" as used herein, refers to a salt or an ester of a sulfonic acid $R-S(O)_2OH$, wherein the R group is an organic group such as aryl, alkyl, cycloalkyl, etc., as defined herein. When the term "sulfonate" refers to a salt, the "sulfonate" has a formula of $-SO_2OR_{11}$, wherein the counteraction R_{11} is a cation. In some embodiments, the cation of a Group 1A, 2A, or 3A metal. For example, R_{11} may be a Na^+ cation or a Mg^{2+} cation.

[00105] As used herein, the term "mesylate" refers to a group having the formula $CH_3-S(O)_2O^-$.

[00106] As used herein, the term "tosylate" refers to a group having the formula p-$CH_3-C_6H_4-S(O)_2O^-$.

[00107] As used herein, the term "triflate" refers to a group having the formula $CF_3-S(O)_2O^-$.

[00108] As used herein, the term "electrochemical reductive coupling" refers to a coupling reaction of two molecular entities through a reductive process, wherein the reaction is performed electrochemically.

[00109] As used herein, the term "electromotive force" refers to the maximum potential difference between two electrodes of a cell.

[00110] As used herein, the term "homo-couple" refers to the formation of a new carbon-carbon bond in the product from two identical molecules, with the aid of a metal catalyst.

[00111] As used herein, the term "cross-couple" refers to the formation of a new carbon-carbon bond in the product from two fragments that are attached to different groups, with the aid of a metal catalyst.

[00112] The following example is offered for illustrative purposes only, and does not limit the scope of the present invention in any way. Indeed, various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and the following example, and fall within the scope of the appended claims.

Example: Ni- or Ni/Pd-Catalyzed Electrochemical Reductive Coupling of Phenol Derivatives from Lignin Depolymerization

1. General Summary

[00113] Lignin represents the largest renewable feedstock of bio-mass derived aromatics and the phenol derivatives from lignin polymerization are promising precursors to replace petroleum-based monomers for continued production of plastics and high-performance polymers. A scalable Ni- or Ni/Pd-catalyzed electrochemical reductive coupling method has been developed, affording biaryls from lignin-derived aryl sulfonate esters in good to excellent yield. This method features the enhanced reactivity provided by the combination of transition metal catalysis and electrochemistry and the high selectivity for desired biaryls over other side products. The biaryls find applications in building blocks for high-performance polyesters or PVC plasticizers.

2. Specific Objectives

[00114] Polymers, which are macromolecules composed of multiple repeating subunits (monomers), play essential and ubiquitous roles in everyday life[1]. Biphenyl-4,4'-dicarboxylic acid (BPDA) and its derivatives are a class of monomers that have found broad utility in polymer science[2-5]. Contemporary methods to produce BPDAs often require harsh reaction conditions such as high temperatures or pressures and fail to deliver BPDAs as the sole product[2,6]. An effective and efficient approach to generate BPDA derivatives in high chemical purity at mild conditions is highly desirable. This example discloses new methods for electrochemical reductive coupling of phenol derivatives from lignin depolymerization to generate biaryls in the presence of Ni- or Ni/Pd- catalysis. The specific objectives are summarized as follows:

[00115] *Specific Objective 1*: Achieving electrochemical Ni-catalyzed reductive homo-coupling of lignin-derived phenol derivatives.

[00116] Various reaction parameters, such as catalysts, solvents, additives, electrodes, etc., were evaluated to obtain conditions for electrochemical Ni-catalyzed reductive homo-coupling. In addition, multigram scale synthesis of homo-coupled lignin monomers has been demonstrated via batch/flow electrolysis.

[00117] *Specific Objective 2*: Achieving electrochemical Ni/Pd-catalyzed reductive cross-coupling of lignin-derived phenol derivatives.

High-throughput techniques were used to aid the condition screening and optimization, and multigram scale synthesis of hetero-coupled lignin monomers has been demonstrated via batch/flow electrolysis.

3. Background and Significance

[00118] Biaryls represent an important class of compounds in material science. Biphenyl-4,4'-dicarboxylic acids (BPDAs) are potential precursors, either alone or as modifiers for polyethylene terephthalate (PET) or novel designer analogues. These polymers are utilized in the production of polyester fibers, engineering plastics, liquid crystal polymers for electronic and mechanical devices, and films with high heat resistance and strength[6]. It has been reported that polyesters derived from biphenyl-4,4'-dicarboxylic acids and various aliphatic diols, including ethylene glycol, 1,4-butanediol and 1,6-hexanediol, can be readily manufactured[7,8]. Such polyesters exhibit unique properties including high stiffness and tensile strength. BPDAs also find potential applications in the manufacturing of plastics[9] since they are readily converted to ester plasticizers by esterification with an aliphatic long chain alcohol.

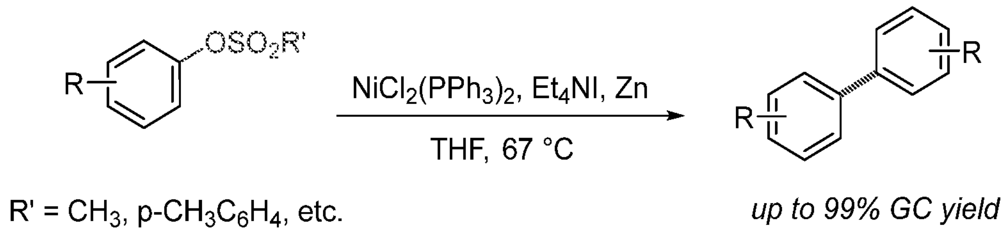
[00119] Contemporary methods to produce BPDAs mainly rely on the oxidation of 4,4'-dialkyl-biphenyls prepared via a separate oxidative coupling of aromatics derived from petroleum. For instance, 4,4'-diisopropylbiphenyl can be oxidized to biphenyl-4,4'-dicarboxylic acid utilizing O_2, in the presence of metal catalysts, such as Co or Mn, at temperatures from 100 °C to 240 °C[2]. Oxidation of other 4,4'-dialkyl-biphenyls can also be utilized to generate BPDAs[6].

[00120] Despite the high operating temperature, the existing methods often generate substantial quantities of undesired byproducts from incomplete oxidation, such as formylbiphenylcarboxylic acid (FBCA) and 4-isopropylbiphenyl-4-carboxylic acid (BPMC). These byproducts can (a) inhibit polymer growth by chain termination when the BPDA is subsequently polymerized and (b) cause undesirable decolorization of the resultant polymer. Additionally, undesired 2,x'- (x' is 2', 3', or 4') BPDA isomers are also generated during the production of the 4,4' isomers as a result of poor chemoselectivity in the initial oxidation coupling of the petroleum derived aromatics. To partially address these challenges, Bokis et al.[6] have recently disclosed a process for purifying a BPDA product containing one or more impurities by esterifying the biphenyldicarboxylic acids. However, this process still involves harsh reaction conditions such as highly pressurized H_2 atmosphere and only separates out the FBCA byproduct.

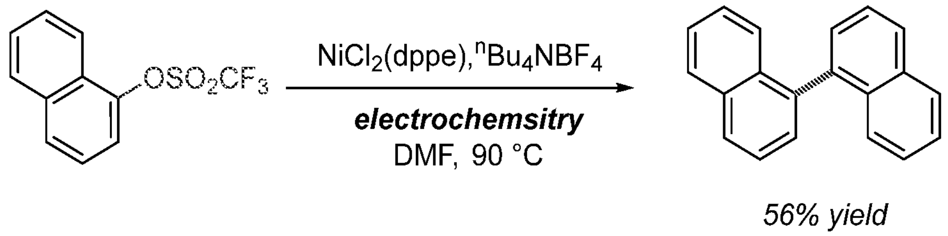
[00121] Transition-metal-catalyzed reductive coupling has been recognized as one of the synthetic approach to afford biaryls[10]. Since the seminal report of the classic Ullmann reaction[11], where homo-coupling between two aryl iodides delivered the biaryl products, this transformation has been extensively studied and developed to access a broad spectrum of biaryl molecules[12,13]. Common conditions often involve aryl halides as substrates, nickel- or palladium- based catalysts, and stoichiometric metals such as Zn or Mn as terminal reductants. Phenol derivatives, which are ubiquitous in nature[14], are also explored as starting materials for reductive coupling[15]. For instance, Percec et al.[16] demonstrated that biaryls were smoothly delivered using 10 mol% Ni catalyst in THF (**Scheme 1**).

Scheme 1: Ni-catalyzed reductive coupling of aryl sulfonates

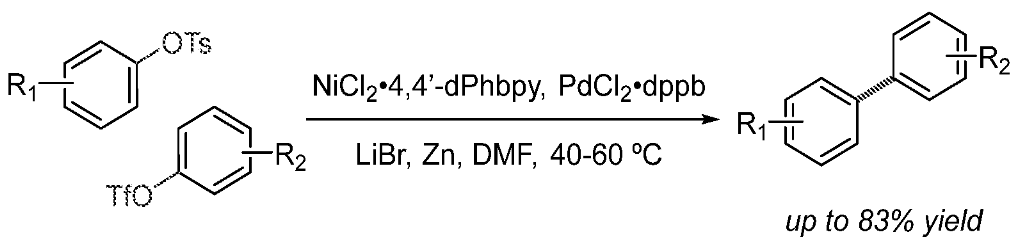
Percec 1995: Ni-catalyzed reductive homo-coupling of aryl sulfonates with Zn



Jutand 1997: Electrochemical Ni-catalyzed reductive homo-coupling of aryl sulfonates



Weix 2020: Ni/Pd-catalyzed reductive hetero-coupling of aryl sulfonates with Zn



[00122] However, these coupling reactions usually feature the use of super-stoichiometric amounts of external metal-based reductants for catalyst turnover, which results in undesirable metal waste.[17] Additionally, inconsistencies in the purity and surface morphology of commercial metal reductants could lead to reproducibility problems.[18]

[00123] Electrochemical synthesis has undergone a renaissance in recent years,[19] and the merger of electrochemistry and transition-metal catalysis has received increasing attention from synthetic organic chemists since it represents a powerful, attractive, and environmentally benign strategy toward sustainable synthesis, featuring electricity as a waste-free and renewable oxidant or reductant. Electrochemical reductive coupling of aryl halides has been studied by several groups and proven to be a successful alternative to access biaryls.[13f,13h,13i] A singular precedent for electrochemical reductive coupling of phenol derivatives was reported by Jutand et al,[20] where aryl triflates were coupled to give biaryls in moderate yields via controlled potential electrolysis (**Scheme 1**). In addition, most of the reported methods focused on reductive homo-coupling to construct symmetrical biaryls,[13,15] leaving unsymmetrical biaryl formation less explored, especially for cross-coupling between two different phenol derivatives.[21] In 2020, Weix and co-workers[21] reported the first example of a cross-electrophile coupling reaction between two different aryl sulfonate esters to afford the hetero-coupling products (**Scheme 1**). New electrosynthetic methods for reductive coupling of phenol derivatives, either in a homo-coupled or hetero-coupled manner, are thus highly desired.

[00124] Lignin, a major component of biomass, is the only renewable feedstock composed of aromatic building blocks. Successful depolymerization of lignin and repurposing of the monomers would provide a bio-renewable supply of aromatics for chemical manufacturing.[22] However, strategies to convert lignin into value-added chemicals remain underdeveloped.[23] Stahl and co-workers[24] have developed a strategy for lignin depolymerization that is initiated via structural modification by selective oxidation, and subsequent base-promoted depolymerization delivering 4-carboxylic acid phenols as the major monomer products. The inherent incorporation of carboxylic acid group renders 4-hydroxybenzoic acid (H), syringic acid (S) and vanillic acid (G) ideal renewable precursors to BPDA derivatives.

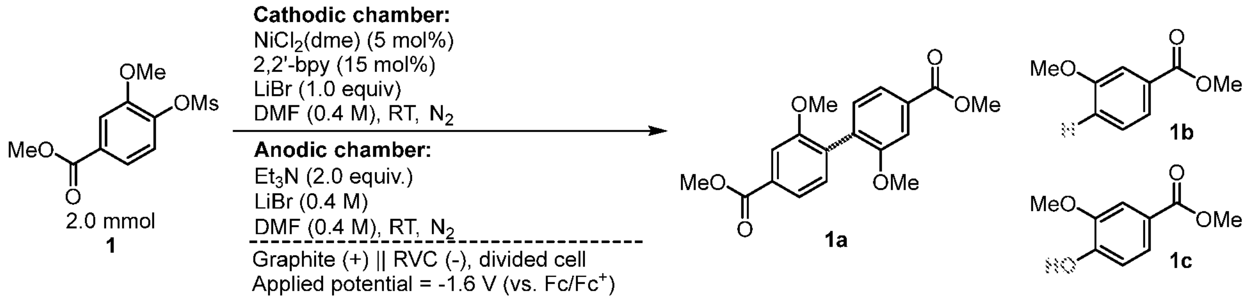
[00125] The research disclosed in this example focuses on the electrochemical reductive coupling of phenol derivatives from lignin depolymerization (**Figure 1**). A simple sequential esterification and phenol activation of lignin monomers leads to appropriate substrates for electrochemical reductive coupling. By strategic evaluation and optimization of the reaction parameters (e.g., catalysts, solvents, additives, electrodes), the resultant products are generated in good to excellent yields with little or no isomeric byproducts, thus making the desired products easily isolated. The tunable nature of the properties of the homo-coupled and cross-coupled products makes them promising precursors for plasticizers and monomers in high-performance plastics[25]. By employing lignin as the source of the starting materials, the proposed method has the potential to decrease reliance on petroleum for chemical manufacturing and provides a sustainable method for the continued production of plastics and other high-performance materials.

4. Experiments and Results

[00126] *Specific Objective 1*: Achieving electrochemical Ni-catalyzed reductive homo-coupling of lignin-derived phenol derivatives.

[00127] The 4-carboxylic acid phenols obtained from lignin oxidative depolymerization process could serve as ideal precursors for reductive coupling. The carboxylic acid functional group are readily converted to the corresponding methyl ester by esterification with methanol, and the phenols are readily converted to sulfonate esters, thus becoming potent electrophiles. Aryl sulfonate esters commonly employed in transitional metal mediated coupling include aryl mesylates (Ar-OMs), aryl tosylates (Ar-OTs), and aryl triflates (Ar-OTf). Initial optimization studies were carried out for the homo-coupling of methyl 3-methoxy-4-((methylsulfonyl)oxy)benzoate (G-OMs) (**1**, 2 mmol scale) in a divided cell, with $NiCl_2$(dme) as the precatalyst, 2,2'-bipyridyl as the ligand, and LiBr as the supporting electrolyte. (**Table 1**).

Table 1. Optimization of electrochemical Ni-catalyzed reductive homo-coupling



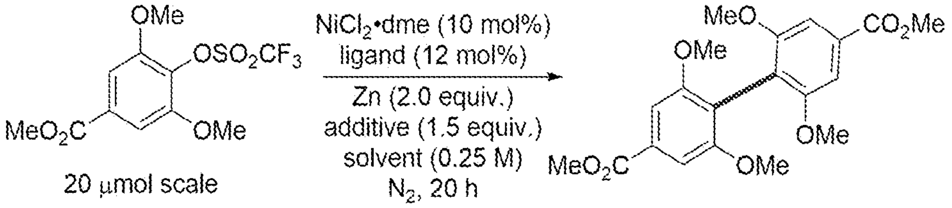
Entry	Variation from above conditions	1b (%)	1c (%)	1a[a] (%)
1	None	6	4	72
2	NaBr instead of LiBr, 6 mol% 2,2'-bpy	8	6	53
3	NaBr instead of LiBr, 10 mol% 2,2'-bpy	5	5	56
4	NaBr instead of LiBr	4	6	64
5	NaBr instead of LiBr, 65 °C	4	6	32
6	KI instead of LiBr	14	8	29
7	$^{n}Bu_4NBr$ instead of LiBr	8	3	56
8	Undivided cell, Mg instead of graphite, no Et_3N	7	37	4
9	Undivided cell, stainless steel instead of graphite, no Et_3N	27	0	72
10	Divided cell, Mg instead of graphite, no Et_3N	8	0	92 (90)[b]
11	Without electrical current	n.d.	n.d.	n.d.
12[c]	Zn instead of electrical current	38	0	59

[a] Yields were determined by ^{1}H NMR using mesitylene as internal standard. [b] Isolated yield. [c] Reaction conditions: 4.0 equiv. KBr, 2.5 mol% $NiCl_2$(dme), 3 mol% 2,2'-bpy, 2.0 equiv. Zn, DMF, RT, N_2.

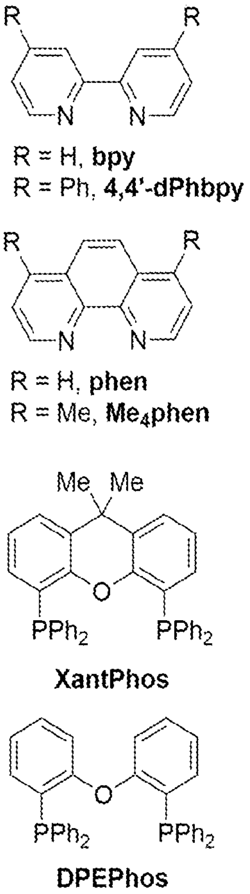
[00128] The applied potential was chosen to be the peak potential of the Ni(II) reduction peak. The metal-to-ligand ratio was crucial for this reaction, as less than 3 equivalents of the ligand (compared to the amount of Ni precatalyst) resulted in decreased yields (entries 2-4). A variety of halide additives were tested as supporting electrolytes, although all led to diminished yields compared with LiBr (entries 4-7). The practically easier set-up, i.e., an undivided cell with a sacrificial anode, failed to further improve the yield (entries 8-9). We suspected that the generated metal salts from direct anode oxidation were detrimental to the homo-coupling and resulted in more byproduct formation. To that end, we intentionally replaced the graphite with a magnesium anode and eliminated the sacrificial chemical reductant Et_3N. The desired product **1a** was formed in 92% NMR yield and 90% isolated yield (entry 10). Finally, no reaction occurred when no electrical current was passed, with full recovery of the starting materials (entry 11). To further demonstrate the advantage of the electrochemical method, we carried out a separate screening for the thermochemical method using Zn powder as the reductant (see Figure 10 for details), and the optimized condition was shown in entry 12. The same transformation using Zn powder instead of electrical current as the reductant resulted in lower yields.

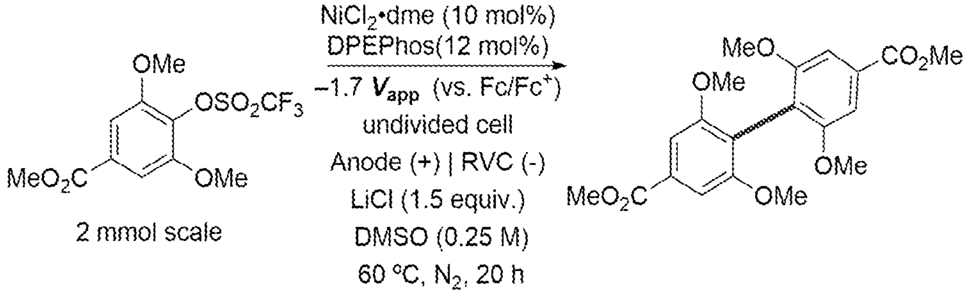
[00129] These reaction conditions can be utilized to affect the homo-coupling of other lignin derived monomers. Methyl 4-((methylsulfonyl)oxy)benzoate (H-OMs) can be successfully coupled to deliver the product in near quantitative yield. It is worth noting that the catalyst loading can be decreased to 1 mol% without diminishing the yield. However, the homo-coupling of the most sterically hindered monomer (S monomer) failed to give any conversion under the previously optimized conditions. More reactive aryl sulfonate esters such as S-tosylates (S-OTs) and S-triflates (S-OTf) were tested as the starting materials, but only zero to trace amount of product was observed. We hypothesized that the catalyst $Ni(bpy)_3Cl_2$ was not effective for the homo-coupling of a heavily sterically hindered substrate. Due to the lack of high throughput electrochemical reaction condition screening techniques, we initiated a rigorous screening using Zn powder as the reductant and S-OTf as the substrate (**Table 2**).

Table 2. Optimization of Ni-catalyzed reductive homo-coupling of S-OTf



Entry	Ligand	Temp (°C)	Additive	Solvent	Conversion (%)	Yield (%)
1	bpy	22	LiCl	DMF	75	8
2	phen	22	LiCl	DMF	74	6
3	4,4'-dPhbpy	22	LiCl	DMF	82	10
4	Me_4Phen	22	LiCl	DMF	81	9
5	dpePhos	22	LiCl	DMF	82	16
6	XantPhos	22	LiCl	DMF	62	0
7	dpePhos	60	LiCl	DMF	98	38
8	dpePhos	70	LiCl	DMF	91	32
9	dpePhos	60	LiCl	DMSO	100	55
10	dpePhos	60	LiBr	DMSO	100	35
11	dpePhos	60	NaCl	DMSO	100	39
12[b]	dpePhos	60	LiCl	DMSO	100	**58**





Entry	Catalyst Loading (mol %)	Sacrificial Anode	Conversion (%)	Yield (%)
13	10	Mg	0	0
14	10	Fe, divided cell	29	12
15	10	Fe	100	65
16	5	stainless steel	100	75 (72)[c]
17[d]	**2.5**	**stainless steel**	**100**	**78**

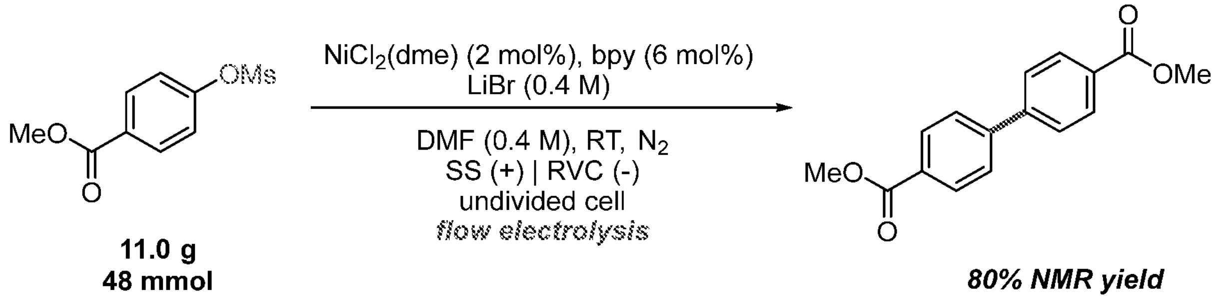
[a] Yields were determined by UPLC with 2,4,6-trimethoxybenzene as the internal standard. [b] 4 Å mol sieves were added. [c] Isolated yield. [d] 30 h.

[00130] The information gained from this effort was leverage to facilitate further electrochemical condition optimization. Various nitrogen-based or phosphine-based ligands (entries 1-6, see Figures 11 and 12 for details) were evaluated. The bidentate phosphine ligand

Bis[(2-diphenylphosphine)phenyl] ether (DPEPhos) was found to give the highest yield of the ligands tested. The bite angle of the ligands was crucial to the reaction, as no product formation was observed when XantPhos was used as ligand (entry 6). The reaction was carried out at elevated temperatures with the intent to improve the substrate conversion. The reaction yield was enhanced significantly to 36% by reacting at 60 °C, then decreased to 32% when the temperature was further raised to 70 °C (entries 7, 8), with more substrates converted to side products.

[00131] Solvents also played a role in this reaction, as DMSO as solvent gave an obvious increase in the reaction yield, by suppressing the formation of side products (entry 9). Electrolytes such as LiBr and NaCl resulted in diminished yields (entries 10, 11). Molecular sieves were added to the reaction mixture to exclude any adventitious water, since the desulfonation byproduct could be derived from hydrolysis of the [ArNi] species. However, no significant improvement was observed (entry 12) (see Figures 13-16for details). We then shifted our focus on achieving the same reaction using electrochemistry. Mg as the sacrificial anode in an undivided cell led to no product formation (entry 13). A divided cell set-up was also tested with an iron rod as the anode, giving a poor conversion of the starting material and drastically decreased yield (entry 14). To our surprise, simply changing the set-up to an undivided cell with the same iron anode gave 65% yield of the homo-coupled product, which was higher than the previous thermochemical counterpart (entry 15). Changing the anode material to stainless steel and decreasing the catalyst loading were beneficial for this reaction (entry 16, 17). The optimized reaction conditions and results are summarized in **Figure 2**.

Scheme 2. Pilot scale-up via flow electrolysis



[00132] The reaction was carried out in an undivided flow cell, using RVC as the cathode and stainless steel as the anode. The current method can be adapted to accommodate large-scale synthesis employing a flow system, with minor modifications needed. As depicted in **Scheme 2**, the homo-coupling of methyl 4-((methylsulfonyl)oxy)benzoate was carried out on a decagram scale using two sequentially attached micro-flow cells, delivering 80% NMR yield.

[00133] During the reaction development, we have conducted a series of cyclic voltammetry (CV) experiments to probe the mechanism of Ni-catalyzed electrochemical reductive coupling reaction (**Figure 3**). Given that in the presence of a large excess amount of LiBr electrolyte, the counter ion to the Ni catalyst will eventually be replaced by the bromide anion, and it is practically easy enough to synthesize the pre-ligated catalyst $Ni(bpy)_3Br_2$, we initiated the CV analysis with $Ni(bpy)_3Br_2$. The catalyst exhibited a reversible reductive peak at -1.58 V versus $Ag/AgNO_3$ in DMF, which may be attributed to the reduction potential of Ni(II)/Ni(0). Catalytic currents were observed when the substrate was added into the solution containing nickel catalyst. With more substrates added to the solution, the catalytic current increased more significantly. This is evidence for the oxidative addition of the substrate to the Ni(0) species, generating an ArNi(II)X ($X = Br^-$ or OMs^-).

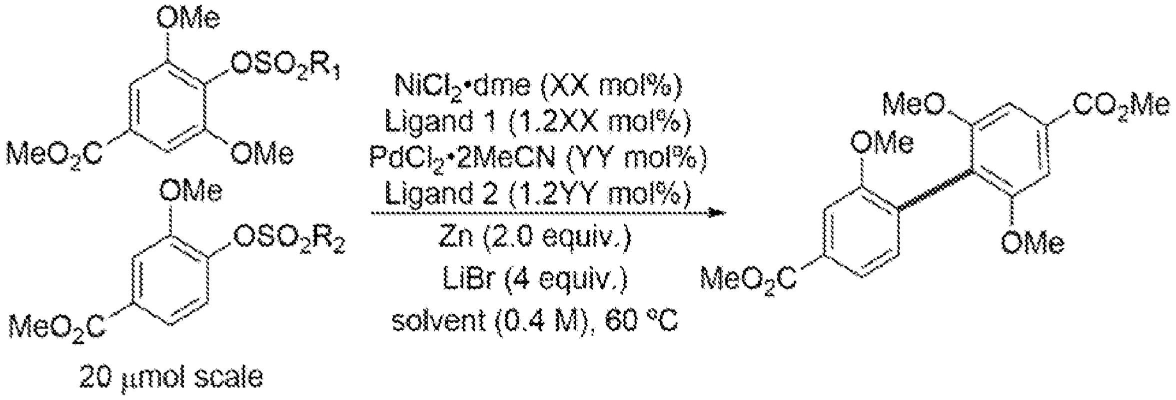
[00134] Two new reductive peaks were observed when substrates were added, at -1.71 V and -1.86 V (vs. $Ag/AgNO_3$), respectively. Based on literature reports (and without being bound by any theory)[26], we attributed the peak at -1.71 V to the reduction of the [ArNi(II)L]X ($X = Br^-$ or OMs^-) species to [ArNi(I)L]. A second oxidative addition of the substrate onto the [ArNi(I)L] species generates the $[Ar_2Ni(III)L]X$ intermediate. The reductive peak at -1.86 V is attributed to the reduction of $[Ar_2Ni(II)]L$ to its radical anion, with the negative charge mostly located on the ligand. A plausible mechanism is presented for the Ni-catalyzed electrochemical reductive coupling (**Figure 6**).

[00135] First, the Ni(II) catalyst is reduced to Ni(0) (**I**) by cathodic reduction. Then, after oxidative addition of an aryl sulfonate to Ni(0), the aryl Ni^{II} species **II** is formed. After cathodic reduction of **II**, the resulting ArNi(I) (**III**) species can react with another equivalent of Ar-X to generate a di-aryl Ni(III) intermediate (**IV**). Direct reductive elimination of **IV** will lead to the desired product and generate a Ni(I)X (**V**) species. Upon cathodic reduction, the active Ni(0) is then regenerated. However, other possible pathways, in which Ni(II)/Ni(0) catalysis is involved, cannot be ruled out at this stage[15,27].

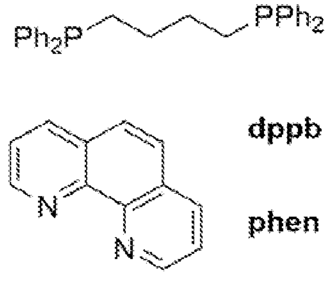
[00136] *Specific Objective 2:* Achieving electrochemical Ni/Pd-catalyzed reductive cross-coupling of lignin-derived phenol derivatives.

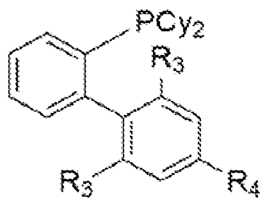
[00137] Our strategy of screening the reductive coupling reaction using Zn as the reductant was proven informative for the later screening using electrochemistry, since the reaction conditions could be well adapted. Therefore, we initiated a series of screening for reductive cross-coupling with Zn reductant and various aryl sulfonate esters as starting materials (**Table 3**, see Figures 18-20 for details).

Table 3. Optimization of Ni/Pd-catalyzed reductive cross-coupling of aryl sulfonate esters



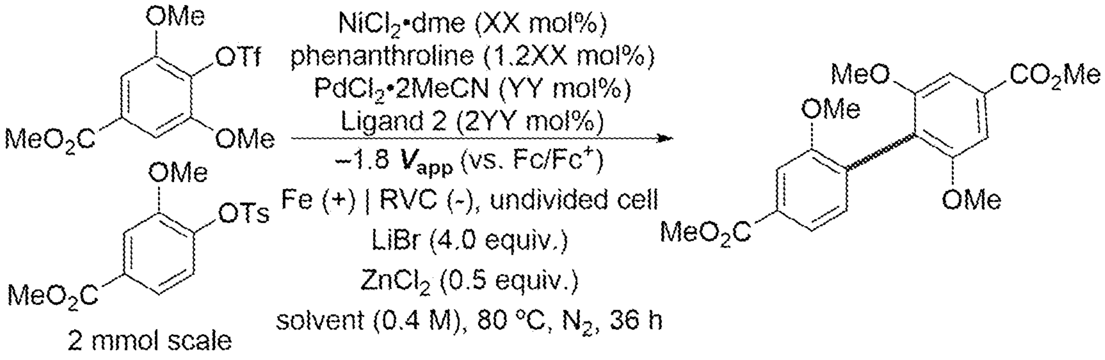
Entry	R_1	R_2	XX (mol%)	Ligand 1	YY (mol%)	Ligand 2	Solvent	Yield (%)	SG:homo
1	CF_3	CF_3	5	phen	5	dppb	DMSO	24	1:1
2	4-MeC_6H_4	4-MeC_6H_4	5	phen	5	dppb	DMSO	14	1:1
3	4-MeC_6H_4	CF_3	5	phen	5	dppb	DMSO	2	1:10
4	CF_3	4-MeC_6H_4	5	phen	5	dppb	DMSO	44	4:1
5	CF_3	4-MeC_6H_4	5	phen	5	RuPhos	DMSO	53	2.4:1
6	CF_3	4-MeC_6H_4	5	phen	5	XPhos	DMSO	9	10:1
7	CF_3	4-MeC_6H_4	5	phen	5	CyJohnPhos	DMSO	56	3.2:1
8	CF_3	4-MeC_6H_4	5	phen	5	SPhos	DMSO	54	2.5:1





$R_3 = R_4 = H$, **CyJohnPhos**
$R_3 = OMe$, $R_4 = H$, **SPhos**
$R_3 = O$*i*-Pr, $R_4 = H$, **RuPhos**
$R_3 = R_4 =$ *i*-Pr, **XPhos**

Table 3. Continued



Entry	XX (mol%)	YY (mol%)	Ligand 2	G-OTs:S-OTf	Yield (%)	SG:homo
9[a,b]	5	5	RuPhos	1:1	26	3.7:1
10[a,c]	5	5	RuPhos	1:1	34	1.5:1
11[a]	5	5	RuPhos	1:1	50	1.6:1
12	5	5	RuPhos	1:1	44	1.6:1
13	5	5	CyJohnPhos	1:1	14	9.4:1
14	5	5	SPhos	1:1	54	2.5:1
15	10	5	SPhos	1:1	50	3.6:1
16	10	5	SPhos	1.25:1	62	2.7:1
17	10	3	SPhos	1.25:1	65	3.8:1
18[d]	**10**	**3**	**SPhos**	**1.25:1**	**75 (70)[e]**	**4.5:1**
19[a]	10	3	SPhos	1.25:1	11	4.7:1

Yields were determined by UPLC with 2,4,6-trimethoxybenzene as the internal standard. [a] Divided cell, Mg anode. [b] 6 mol% Ligand 2, without $ZnCl_2$. [c] Without $ZnCl_2$. [d] Ni foam cathode. [e] Isolated yield.

Since multiple reaction condition variables are involved in catalysis, it is likely that the optimal results come from the interplay of two or more variables, which could not be easily found without a comprehensive screening. In this regard, high-throughput experimentation (HTE) appears to be an advantageous method[28]. The screening was conducted using 96-well plate as the reactor and Ultra Performance Liquid Chromatography (UPLC) analysis to determine yields. Based on the literature report[21], the cross-Ullmann reaction enabled by nickel and palladium co-catalysis is most effective when the appropriate aryl triflates and aryl tosylates are matched. We first evaluated this reaction with different combinations of the aryl triflates and tosylates, under otherwise similar conditions as indicated in the Weix work[21] (entries 1-4). When the more electrophilic C-OTf was installed on the more sterically hindered substrate, the resultant S-OTf effectively cross-coupled with G-OTs to give 44% UPLC yield. Good selectivity of hetero-coupling over homo-coupling was achieved (4:1), proving the effectiveness of this multimetallic strategy.

[00138] A ligand screening was then conducted, revealing that a series of Buchwald ligands on Pd catalyst led to an increased yield (entries 5-8). The transition to electrochemical cross-coupling was not straightforward. Conducting the reaction in a divided cell with the same conditions as in entry 8, except that no Zn powder was present, led to a drastically decreased yield (entry 9). From the UPLC analysis, we discovered that part of the phosphine ligand was oxidized to phosphine oxide, which no longer served as an effective ligand. Further increasing the loading of the phosphine gave a higher yield (entry 10), although still worse than the thermochemical counterpart.

[00139] Mechanistic studies in the literature[21] show that the aryl transfer between nickel and palladium catalysts is mediated by Zn, meaning Zn is not solely a terminal reductant in this reaction. Indeed, with 50 mol% zinc salts deliberately added in reaction mixture, the electrochemical cross-coupling was improved to 50% yield (entry 11). Changing to a practically easier undivided cell set-up caused a slight decrease in the yield (entry 12). Other equally potent phosphine ligands, i.e., CyJohnPhos and SPhos, were tested (entries 13, 14). SPhos was found to be a more effective ligand on Pd under electrochemical conditions, while CyJohnPhos showed the opposite effect. It is suspected that CyJohnPhos was more susceptible to oxidation, as only the oxidized form of CyJohnPhos was detected in UPLC analysis.

[00140] The ratios of the two catalysts and the two substrates were varied, respectively, to better match the rates of the two catalysis processes (entries 15-17). A higher Ni catalyst loading with an excess amount of G-OTs led to 65% yield, without compromising the chemoselectivity. Replacing the RVC cathode with a piece of Ni foam further increased the UPLC yield to 75%, giving 70% isolated yield (entry 18). Simply changing to an undivided cell set-up drastically diminished the yield (entry 19), under otherwise identical conditions as in entry 18.

[00141] Applying the optimized conditions to the cross-coupling of other lignin monomers is not straightforward. For instance, we found that the cross-coupling between H-OTs and G-OTf was more effective with RVC cathode, instead of Ni foam, and less Pd catalyst was needed (2 mol%) to achieve a higher yield. The optimization of the cross-coupling between H and G monomers is still ongoing, but the current results suggested that the optimized catalytic system

($NiCl_2$•Phen with$PdCl_2$•SPhos) were less effective for H-G coupling. To our delight, the cross-coupled products are smoothly delivered in good yields, with a remarkable selectivity over the homo-coupled side products.

5. Materials and Methods

[00142] Solvents and reagents

[00143] All solvents (anhydrous) and reagents were purchased from commercial sources and used as received without further purification. Substrates were purchased from Aldrich, Alfa Aesar, and Combi-Blocks. Nickel salts, Palladium salts, and ligands were purchased from Aldrich. Anhydrous solvents were purchased from Aldrich and handled in a nitrogen-filled glove box.

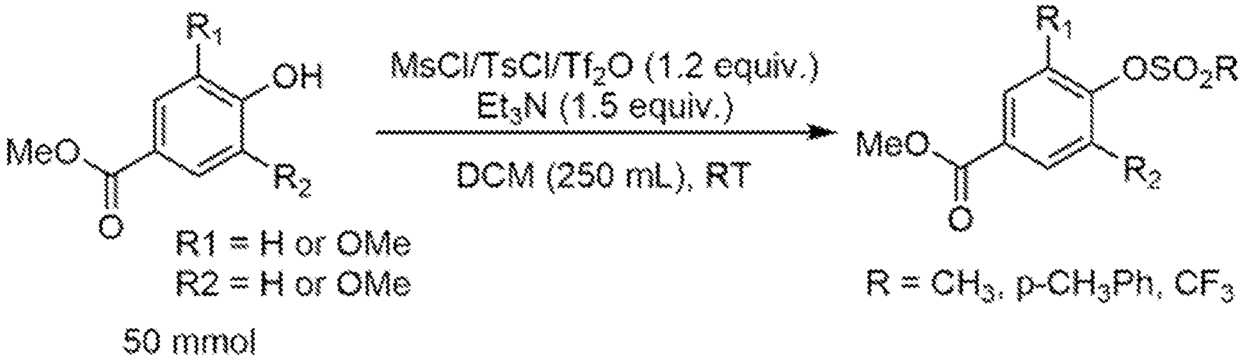
[00144] Characterization of Products

[00145] ^1H and ^{13}C NMR spectra were recorded on Bruker 400 or 600 MHz spectrometers. Chemical shifts are given in parts per million (ppm) relative to residual solvent peaks in the ^1H and ^{13}C NMR spectra or are referenced as noted. The following abbreviations (and their combinations) are used to label the multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). High-resolution mass spectra were obtained using a Thermo Q ExactiveTM Plus by the mass spectrometry facility at the University of Wisconsin. UPLC-MS analysis was conducted on a Waters-Acquity. Chromatographic purification of products was accomplished by chromatography on silica gel 60 M (particle size 40-63 μm, 230-400 mesh) from MACHEREY-NAGEL Inc. Thin-layer chromatography (TLC) was performed on Silicycle silica gel UV254 pre-coated plates (0.25 mm). Visualization of the developed chromatogram was performed by using UV lamps or $KMnO_4$ stain.

[00146] Electrochemical Experiments

[00147] All cyclic voltammetric (CV) and chronoamperometric (CA) experiments were performed using Nuvant Array PGStats or a Pine WaveNow PGstat or a Bipotentiostat BP-300. The CV experiments were carried out in a three-electrode cell configuration with a glassy carbon (GC) working electrode (3 mm diameter), and a platinum wire counter electrode (~ 1.0 cm, spiral wire). The working electrode potentials were measured versus Ag/$AgNO_3$ reference electrode (internal solution, 0.1 M Bu_4NPF_6 and 0.01 M $AgNO_3$ in DMF). The redox potential of ferrocene/ferrocenium (Fc^+/Fc) was measured (under same experimental conditions) and used to provide an internal reference. The potential values were then adjusted relative to Fc^+/Fc, and electrochemical studies in organic solvents were recorded accordingly. The GC working electrode was polished with alumina powder (5 µm) before each experiment. Bulk electrolysis experiments were performed in custom-built undivided or divided cells, with RVC or Ni foam working electrodes, Mg, Fe or stainless-steel counter electrodes and Ag/AgNO$_3$ (internal solution, 0.1 M Bu$_4$NPF$_6$ and 0.01 M AgNO$_3$ in DMF) for a reference electrode.

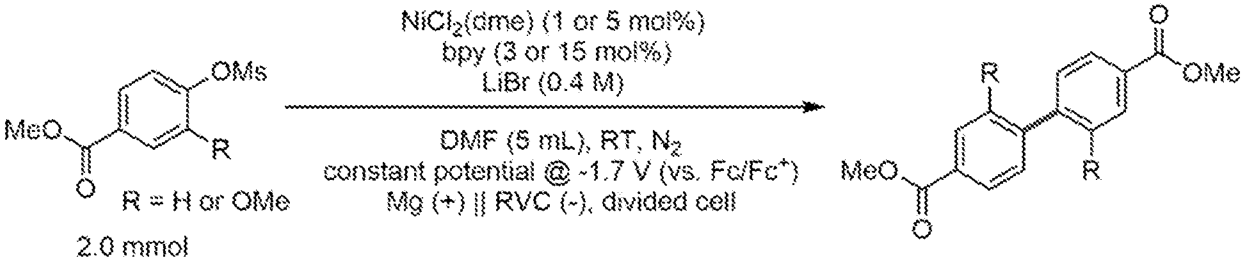
[00148] General Procedures for Aryl Sulfonate Esters Synthesis (GP 1)



[00149] To a 500 mL round-bottom flask was added the substrate (50 mmol) and anhydrous DCM (200 mL). Et$_3$N (10.4 mL, 1.5 equiv.) was then injected to the solution. Another 200 mL round-bottom flask was charged with the sulfonating reagent (60 mmol, 1.2 equiv.) and anhydrous DCM (50 mL), mixed thoroughly, then this solution was added dropwise to the 500 mL flask. The reaction mixture was stirred at room temperature and stopped when full conversion was observed via TLC. The solution was washed with 300 mL water and 300 mL brine sequentially. The aqueous solution was collected and extracted with 200 mL DCM. The organic layers were collected, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography to furnish the desired product (eluent: hexane/ethyl acetate, 2/1).

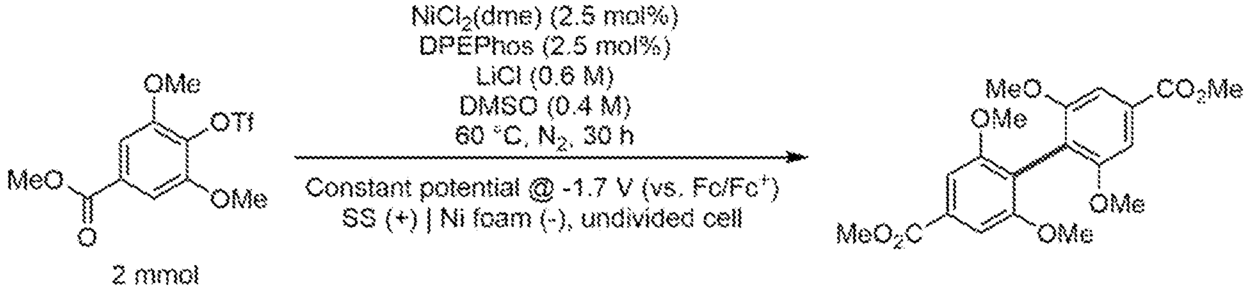
[00150] General Procedures for Bulk Electrolysis

[00151] Electrochemical reductive homo-coupling in a divided cell (**GP 2**)



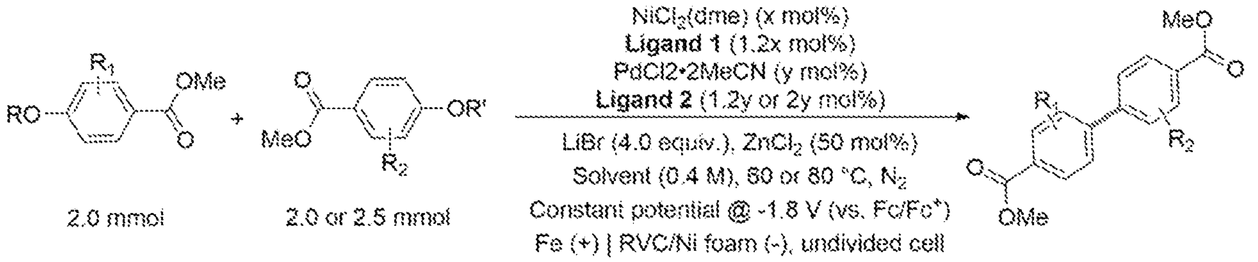
[00152] To the cathodic chamber of the divided cell was added NiCl$_2$(dme) (4.4 or 22 mg, 1 or 5 mol%), LiBr (174 mg, 1.0 equiv.), 2,2'-bipyridyl (9.4 or 47 mg, 3 or 15 mol%), substrate (2 mmol, 1.0 equiv.), and anhydrous DMF (5 mL). Then to the anodic chamber of the divided cell was added LiBr (174 mg, 1.0 equiv.) and anhydrous DMF (5 mL). The cathodic chamber was then installed a RVC cathode and a Ag/AgNO3 reference electrode, and the anodic chamber was installed a Mg anode. The two chambers were sealed with rubber septa, respectively, and each chamber was introduced a thin Teflon tube to allow continuous nitrogen bubbling. The reaction mixture was stirred at 1000 rpm for 30 min to allow full dissolution of LiBr and exclusion of adventitious oxygen. After that, the reaction mixture was electrolyzed under a constant potential of -1.7 V (vs. Fc/Fc^+) for 18 h at room temperature. The resultant solution was directly concentrated *in vacuo*. The crude product was purified by column chromatography to furnish the desired product (eluent: hexane/ethyl acetate, 3/1).

[00153] Electrochemical reductive homo-coupling in an undivided cell (**GP 3**)



[00154] To the undivided cell was added $NiCl_2(dme)$ (11 mg, 2.5 mol%), DPEPhos (32 mg, 2.5 mol%), LiCl (125 mg, 1.5 equiv.), and substrate (2 mmol, 1.0 equiv.). The cell was then introduced in a nitrogen-filled glove box and installed a Ni foam cathode, a Ag/AgNO3 reference electrode, and an iron rod anode. Anhydrous DMSO (5 mL) was injected into the cell with a 5 mL syringe. The cell was sealed with a rubber septum and removed from the glove box. A thin Teflon tube was introduced immediately into the cell to allow continuous nitrogen bubbling. The reaction mixture was stirred at 1000 rpm for 30 min to allow full dissolution of LiCl and exclusion of adventitious oxygen. After that, the reaction mixture was electrolyzed under a constant potential of -1.7 V (vs. Fc/Fc^+) for 30 h at 60 °C. The resultant solution was directly concentrated *in vacuo*. The crude product was purified by column chromatography to furnish the desired product (eluent: hexane/ethyl acetate, 3/1).

[00155] Electrochemical reductive cross-coupling in an undivided cell (**GP 4**)



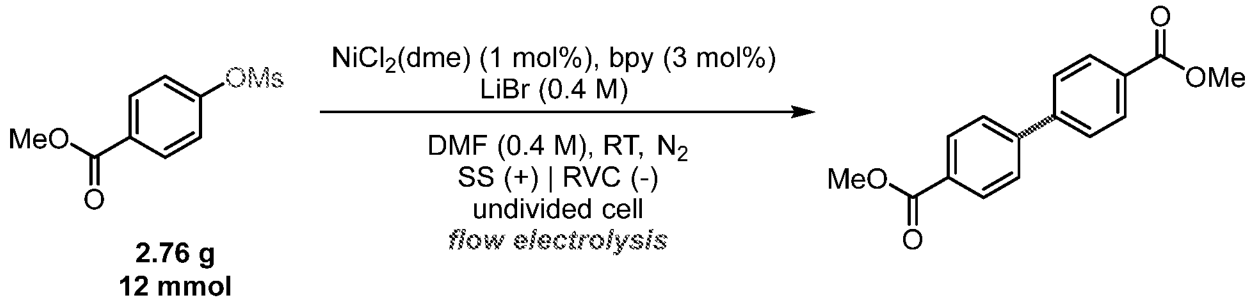
[00156] Under nitrogen atmosphere, NiCl$_2$(dme) (22 or 44 mg, 5 or 10 mol%), Ligand 1 (6 or 12 mol%), and anhydrous solvent (1 mL) was added to a 1.5-dram vial capped with a Teflon septum. Another 1.5-dram vial was charged with PdCl$_2$•2MeCN (10.4 ~ 26 mg, 2 ~ 5 mol%), Ligand 2 (4 ~ 10 mol%), and anhydrous solvent (1 mL) under nitrogen. The two vials were stirred for 30 min so that the ligands are well complexed with the metal.

[00157] To the undivided cell was added the two coupling partners (2 or 2.5 mmol, 1.0 or 1.25 equiv.) and the cell was introduced in a nitrogen-filled glove box and installed a Ni foam or RVC cathode, a Ag/AgNO$_3$ reference electrode, and an iron rod anode. The cell was then charged with LiBr (695 mg, 4.0 equiv.) and anhydrous solvent (5 mL), sealed with rubber septum, and removed from the glove box. A thin Teflon tube was introduced immediately into the cell to allow continuous nitrogen bubbling. The reaction mixture was stirred at 1000 rpm for 30 min to allow full dissolution of LiBr and exclusion of adventitious oxygen. After that, the reaction mixture was electrolyzed under a constant potential of -1.8 V (vs. Fc/Fc$^+$) for 36 or 48 h at 60 or 80 °C. The resultant solution was directly concentrated *in vacuo*. The crude product was purified by column chromatography to furnish the desired product (eluent: hexane/ethyl acetate, 3/1).

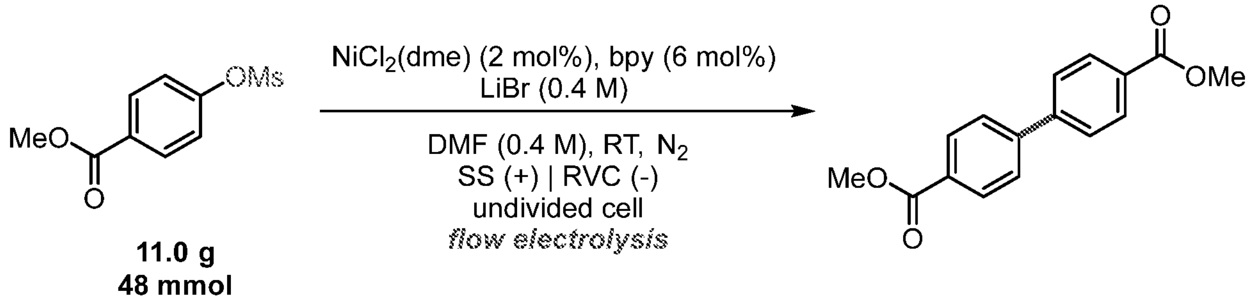
[00158] General Procedures for Flow Electrolysis

[00159] For the electrochemical flow reactions, a commercial Micro Flow Cell (purchased from ElectroCell) with an electrode area of 10 cm^2 was used, the active reactor volume is 5 mL, and a Pine WaveNow PGstat or Bipotentiostat BP-300 was used as power supply. For the divided flow cell, consisting of PTFE end frames, stainless steel plate (316L) as the anode, stainless steel plate and graphite plate overlay together as the cathode, the Nafion™ N324 membrane was used to separate the anode and cathode. The flow cell also contains the flow frames and gaskets. RVC with approx. dimensions = 3.5 × 3.0 × 0.5 cm was used to increase the surface area of electrode and used as turbulence material for diffusion. All electrolysis reactions were performed in DMF solutions. A magnetic stir bar was used in the reservoirs and the reaction mixture was stirred (500 rpm) during flow electrolysis reactions. The reaction mixture is pumped through the system via

peristaltic pump with a flow rate of 40 mL/min. The undivided cell is identical to the divided flow cell, but without the Nafion™ N324 membrane. The components of the electrochemical cell are shown in **Figure S3**.



[00160] To a 100 mL round-bottom flask was injected a solution containing $NiCl_2$(dme) (26.4 mg, 0.12 mmol, 1 mol%), LiBr (1044 mg, 12 mmol, 1.0 equiv.), 2,2'-bipyridyl (56.4 mg, 0.36 mmol, 3 mol%), methyl 4-((methylsulfonyl)oxy)benzoate (2.76 g, 12 mmol, 1.0 equiv.), and anhydrous DMF (30 mL). A thin Teflon tube was introduced immediately into the flask to allow continuous nitrogen bubbling. This solution was pushed via a peristaltic pump to pass through the undivided flow cell, with a flow rate of 40 mL min^{-1} and electrolyzed at a constant current of -100 mA at room temperature until full conversion of the substrate was determined by TLC. The resultant solution was directly concentrated *in vacuo* and analyzed by ^{1}H NMR using mesitylene as an internal standard to give the NMR yield (87%).



[00161] To a 250 mL three-neck round-bottom flask was injected a solution containing $NiCl_2$(dme) (106 mg, 0.48 mmol, 1 mol%), LiBr (4.17 g, 48 mmol, 1.0 equiv.), 2,2'-bipyridyl (226 mg, 1.44 mmol, 3 mol%), methyl 4-((methylsulfonyl)oxy)benzoate (11.0 g, 48 mmol, 1.0 equiv.), and anhydrous DMF (120 mL). A thin Teflon tube was introduced immediately into the flask to allow continuous nitrogen bubbling. This solution was pushed via a peristaltic pump to pass through the undivided flow cells, with a flow rate of 40 mL min^{-1} and electrolyzed at a constant cell potential of -2.1 V at room temperature. Two flow cells were connected in parallel via copper wire to increase the electrode surface area in total. An additional amount of catalyst (1 mol%) (106 mg $NiCl_2$(dme), 226 mg 2,2'-bipyridyl dissolved in 5 mL DMF) was injected into the reaction mixture via a syringe after 24 h of electrolysis without stopping the reaction. Electrolysis was conducted until full conversion of the substrate was determined by TLC. The resultant solution was directly concentrated *in vacuo* and analyzed by ^1H NMR using mesitylene as an internal standard to give the NMR yield (80%).

[00162] General Procedure for HTE Optimization

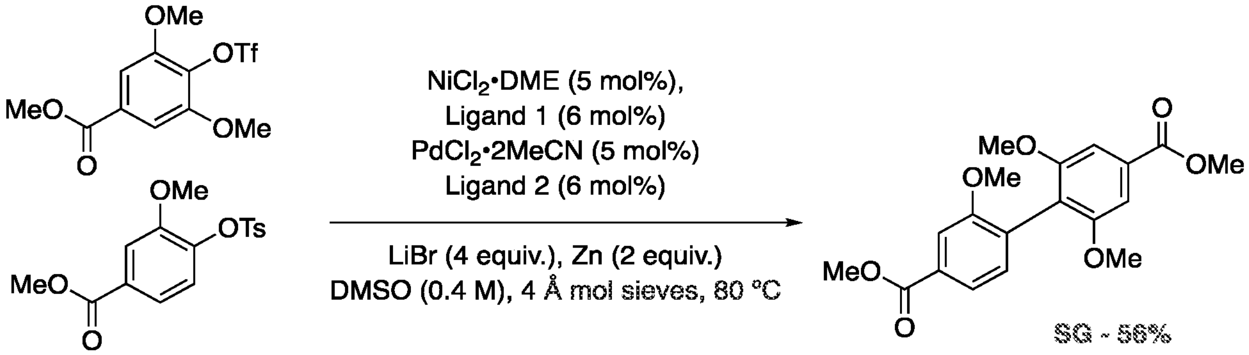
[00163] To a 2-dram vial fitted with cross-shaped stir bar was added $NiBr_2$•glyme and appropriate nitrogen-based ligand. This vial was then transferred into a nitrogen-filled glove box and solvent was added. In a separate 2-dram vial fitted with a cross-shaped stir bar was added $PdCl_2$•2MeCN and appropriate phosphine ligand. This vial was then transferred into a nitrogen-filled glove box and solvent was added. These stock solutions were stirred for 1 h. To a 96-well optimization block (Analytical Sales and Services) with 1-mL glass vial inserts (Analytical Sales and Services) fitted with stainless-steel stir bars (V&P scientific) in a nitrogen-filled glove box, was dispensed appropriate quantities of the stock solutions of the catalysts (concentrations of stock solutions were adjusted so that around 10 μL of each stock solution was dispensed). The blocks were then aged for 15 minutes. To a 2-dram vial fitted with a cross-shaped stir bar was added both aryl sulfonate coupling partners (0.40 M, 1 equiv.), LiBr (1.60 M, 4 equiv.), Zn dust (0.80 M, 2 equiv.), 4 Å mol sieves (5% bv) and solvent. This mixture was then stirred vigorously for 5 minutes. To the aged 96-well optimization block, 50 μl of a suspension containing the two aryl sulfonates (20 mmol, 0.40 M), LiBr (80 mmol, 1.60 M), 4 Å molecular sieves (5% bv) and Zn dust (40 mmol, 0.80 M) in solvent was dispensed to each vial from the rapidly stirred 2-dram vial containing substrate, LiBr, 4 Å molecular sieves and Zn. The plate was then sealed with a screwdriver and placed in a zip lock bag inside the glove box. The plate was then removed from the glove box and agitated on a tumble stirrer (V&P Scientific) at 60 °C for 20 hours. The block was then diluted with a solution of 1,3,5-trimethoxybenzene in 3:1 acetonitrile/DMSO (10 mmol, 0.066 M, 150 mL) and sampled (5 mL) into an HPLC collection block (Analytical Sales and Services) pre-filled with 3:1 acetonitrile/DMSO (200 mL). The HPLC collection block was then analyzed utilizing UPLC-MS (Waters-Acquity) analysis and yields were determined with respect to 1,3,5-trimethoxybenzene utilizing calibration curves. Data was then visualized on Tableu®. Changes were made to this procedure to minimize the number of operations for each variable that was evaluated.

[00164] Optimization of Reaction Conditions

[00165] Optimization of Ni-catalyzed reductive homo-coupling

[00166] Figures 10-16 demonstrate optimizations of Ni-catalyzed reductive homo-coupling.

[00167] Optimization of Ni/Pd-catalyzed reductive cross-coupling (HTE Optimization)

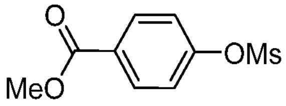


[00168] Separate stock solutions for each ligand were prepared before addition to the 96-well plate to ensure pre-complexation. Ligand structures are shown in Figure 17.

[00169] Compounds Characterization

[00170] methyl 4-((methylsulfonyl)oxy)benzoate (**H-OMs**)

[00171]



[00172] From methyl 4-hydroxybenzoate (7.6 g, 50 mmol) and methanesulfonyl chloride (9.9 mL, 60 mmol), the title compound was prepared following **GP 1** as a pale-yellow powder (11.1 g, 96% yield).

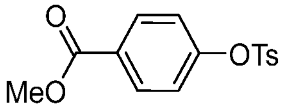
[00173] ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.15 – 8.07 (m, 2H), 7.40 – 7.32 (m, 2H), 3.93 (s, 3H), 3.19 (s, 3H).

[00174] ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 165.86, 152.45, 131.71, 129.23, 121.91, 52.42, 37.85.

[00175] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_9H_{11}O_5S$) 231.0322; measured: 231.0321 = 0.4 ppm difference.

[00176] methyl 4-(tosyloxy)benzoate (**H-OTs**)

[00177]



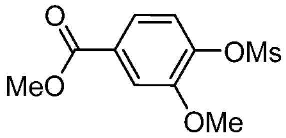
[00178] From methyl 4-hydroxybenzoate (7.6 g, 50 mmol) and *p*-toluenesulfonyl chloride (11.4 g, 60 mmol), the title compound was prepared following **GP 1** as a white powder (14 g, 93% yield).

[00179] ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.74 – 7.67 (m, 2H), 7.35 – 7.28 (m, 2H), 7.10 – 7.02 (m, 2H), 3.90 (s, 3H), 2.45 (s, 3H).

[00180] ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 166.43, 152.96, 145.77, 132.04, 131.30, 129.91, 128.93, 128.49, 122.35, 52.34, 21.74.

[00181] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{15}H_{15}O_5S$) 307.0635; measured: 307.0630 = 1.6 ppm difference.

[00182] methyl 3-methoxy-4-((methylsulfonyl)oxy)benzoate (**G-OMs**)

[00183] 

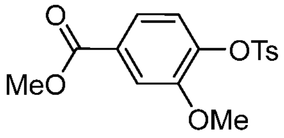
[00184] From methyl 4-hydroxy-3-methoxybenzoate (9.1 g, 50 mmol) and methanesulfonyl chloride (9.9 mL, 60 mmol), the title compound was prepared following **GP 1** as a white powder (12.2 g, 94% yield).

[00185] ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.22 (s, 3H).

[00186] ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 165.97, 151.37, 141.69, 130.06, 124.43, 122.77, 113.96, 56.27, 52.51, 38.69.

[00187] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{10}H_{13}O_6S$) 261.0427; measured: 261.0426 = 0.4 ppm difference.

[00188] methyl 3-methoxy-4-(tosyloxy)benzoate (**G-OTs**)

[00189] 

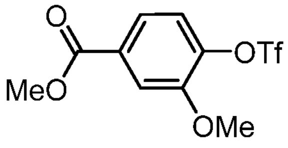
[00190] From methyl 4-hydroxy-3-methoxybenzoate (9.1 g, 50 mmol) and *p*-toluenesulfonyl chloride (11.4 g, 60 mmol), the title compound was prepared following **GP 1** as a white powder (16 g, 95% yield).

[00191] ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 2H), 7.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.62 (s, 3H), 2.45 (s, 3H).

[00192] **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.09, 151.72, 145.34, 141.87, 132.96, 129.75, 129.46, 128.63, 123.90, 122.31, 113.65, 55.77, 52.43, 21.71.

[00193] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{16}H_{17}O_6S$) 337.0740; measured: 337.0736 = 1.2 ppm difference.

[00194] methyl 3-methoxy-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (**G-OTf**)

[00195] 

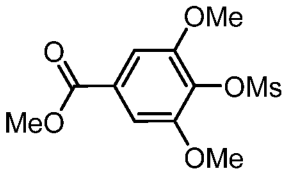
[00196] From methyl 4-hydroxy-3-methoxybenzoate (9.1 g, 50 mmol) and trifluoromethanesulfonic anhydride (10.1 mL, 60 mmol), the title compound was prepared following **GP 1** as a yellow liquid (14.4 g, 92% yield).

[00197] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.9 Hz, 1H), 7.68 (dd, J = 8.4, 1.9 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H).

[00198] **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.58, 151.33, 141.76, 131.11, 122.47, 122.43, 120.28, 117.10, 114.19, 56.42, 52.56.

[00199] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{10}H_{10}F_3O_6S$) 315.0145; measured: 315.0141 = 1.3 ppm difference.

[00200] methyl 3,5-dimethoxy-4-((methylsulfonyl)oxy)benzoate (**S-OMs**)

[00201] 

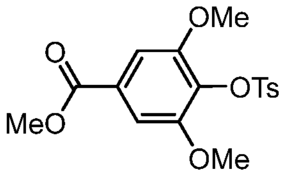
[00202] From methyl 4-hydroxy-3,5-dimethoxybenzoate (10.6 g, 50 mmol) and methanesulfonyl chloride (9.9 mL, 60 mmol), the title compound was prepared following **GP 1** as a white powder (13 g, 89% yield).

[00203] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (s, 2H), 3.95 (s, 6H), 3.93 (s, 3H), 3.33 (s, 3H).

[00204] **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.06, 153.10, 131.58, 129.14, 106.43, 56.54, 52.56, 40.15.

[00205] **HRMS (ESI$^+$)** Calc: $[M+NH_4]^+$ ($C_{11}NH_{18}O_7S$) 308.0799; measured: 308.0796 = 1.0 ppm difference.

[00206] methyl 3,5-dimethoxy-4-(tosyloxy)benzoate (**S-OTs**)

[00207] 

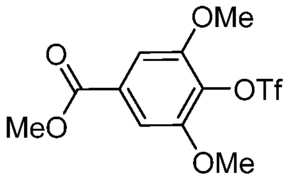
[00208] From methyl 4-hydroxy-3,5-dimethoxybenzoate (10.6 g, 50 mmol) and *p*-toluenesulfonyl chloride (11.4 g, 60 mmol), the title compound was prepared following **GP 1** as a white powder (16.5 g, 90% yield).

[00209] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (s, 2H), 3.91 (s, 3H), 3.73 (s, 6H), 2.46 (s, 3H).

[00210] **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.14, 153.27, 144.79, 134.73, 131.64, 129.25, 129.02, 128.40, 106.31, 56.17, 52.50, 21.69.

[00211] **HRMS (ESI$^+$)** Calc: $[M+NH_4]^+$ ($C_{17}NH_{22}O_7S$) 384.1112; measured: 384.1110 = 0.5 ppm difference.

[00212] methyl 3,5-dimethoxy-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (**S-OTf**)

[00213] 

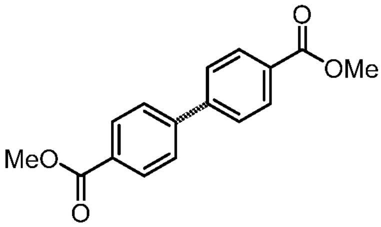
[00214] From methyl 4-hydroxy-3,5-dimethoxybenzoate (10.6 g, 50 mmol) and trifluoromethanesulfonic anhydride (10.1 mL, 60 mmol), the title compound was prepared following **GP 1** as a white powder (16 g, 93% yield).

[00215] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (s, 2H), 3.95 (d, *J* = 2.8 Hz, 9H).

[00216] **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.76, 152.31, 131.03, 130.24, 120.20, 117.02, 106.26, 56.55, 52.66.

[00217] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{11}H_{12}F_3O_7S$) 345.0250; measured: 345.0246 = 1.2 ppm difference.

[00218] dimethyl [1,1'-biphenyl]-4,4'-dicarboxylate (**H-H**)

[00219] 

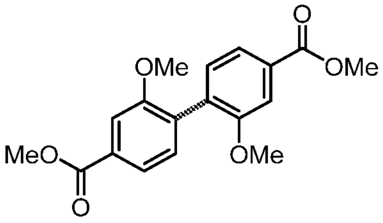
[00220] **GP 2** was followed using H-OMs (460 mg, 2.0 mmol), $NiCl_2$(dme) (4.4 mg, 1 mol%), 2,2'-bipyridyl (9.4 mg, 3 mol%), which furnished the title compound as a white powder (262 mg, 97% yield).

[00221] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, 4H), 7.61 (d, 4H), 3.87 (s, 6H).

[00222] **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.80, 144.37, 130.22, 129.73, 127.26, 52.22.

[00223] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{16}H_{15}O_4$) 271.0965; measured: 271.0973 = 0.7 ppm difference.

[00224] dimethyl 2,2'-dimethoxy-[1,1'-biphenyl]-4,4'-dicarboxylate (**G-G**)

[00225] 

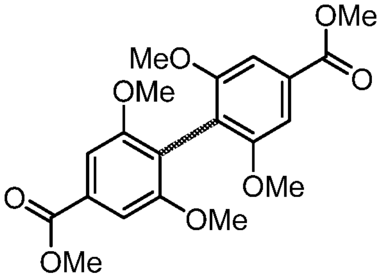
[00226] **GP 2** was followed using G-OMs (520 mg, 2.0 mmol), $NiCl_2$(dme) (22 mg, 5 mol%), 2,2'-bipyridyl (47 mg, 15 mol%), which furnished the title compound as a white powder (297 mg, 90% yield).

[00227] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (dd, $J = 7.8$, 1.6 Hz, 2H), 7.64 (d, $J = 1.5$ Hz, 2H), 7.30 (d, $J = 7.8$ Hz, 2H), 3.94 (s, 6H), 3.83 (s, 6H).

[00228] **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.93, 156.89, 131.78, 131.14, 130.90, 121.79, 111.87, 55.40, 52.23.

[00229] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{18}H_{19}O_6$) 331.1176; measured: 331.1174 = 0.6 ppm difference.

[00230] dimethyl 2,2',6,6'-tetramethoxy-[1,1'-biphenyl]-4,4'-dicarboxylate (**S-S**)

[00231] 

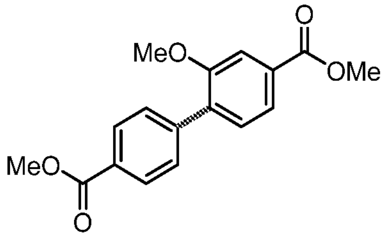
[00232] **GP 3** was followed to furnish the title compound as a pale-yellow powder (293 mg, 75% yield).

[00233] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (s, 4H), 3.94 (s, 6H), 3.77 (s, 12H).

[00234] ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 167.05, 158.46, 130.97, 116.86, 105.55, 56.25, 52.24.

[00235] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{20}H_{23}O_8$) 391.1387; measured: 391.1382 = 1.3 ppm difference.

[00236] dimethyl 2-methoxy-[1,1'-biphenyl]-4,4'-dicarboxylate (**H-G**)

[00237] 

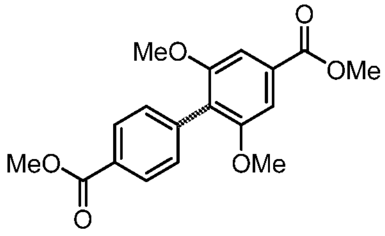
[00238] **GP 4** at 60 °C was followed using H-OMs (460 mg, 2.0 mmol), G-OTs (841 mg, 2.5 mmol), $NiCl_2$(dme) (44 mg, 10 mol%), 4,4'-dPhbpy (74 mg, 12 mol%), $PdCl_2$•2MeCN (15.6 mg, 3 mol%), dppb (30.6 mg, 3.6 mol%), DMA (5 mL), a Ni foam cathode, which furnished the title compound as a white powder (420 mg, 70% yield).

[00239] ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.72 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.66 (d, *J* = 1.5 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.39 (d, *J* = 7.9 Hz, 1H), 3.94 (d, *J* = 5.0 Hz, 6H), 3.88 (s, 3H).

[00240] ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 166.96, 166.78, 156.40, 142.24, 134.12, 131.00, 130.67, 129.51, 129.35, 129.14, 122.26, 112.09, 55.81, 52.32, 52.16.

[00241] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{17}H_{17}O_5$) 301.1071; measured: 301.1071 < 0.1 ppm difference.

[00242] dimethyl 2,6-dimethoxy-[1,1'-biphenyl]-4,4'-dicarboxylate (**H-S**)

[00243] 

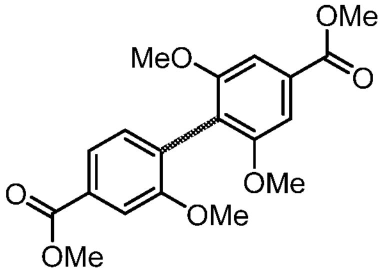
[00244] **GP 4** at 80 °C was followed using H-OTs (612 mg, 2.0 mmol), S-OTf (688 mg, 2.0 mmol), $NiCl_2$(dme) (44 mg, 10 mol%), phen (43 mg, 12 mol%), $PdCl_2$•2MeCN (10.4 mg, 2 mol%), SPhos (33 mg, 4 mol%), DMSO (5 mL), a RVC cathode, which furnished the title compound as a white powder (468 mg, 71% yield).

[00245] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 2H), 7.45 – 7.38 (m, 2H), 7.34 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.79 (s, 6H).

[00246] **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.11, 166.76, 157.33, 138.48, 130.97, 130.79, 129.01, 128.87, 122.96, 105.39, 56.09, 52.40, 52.09.

[00247] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{18}H_{19}O_5$) 331.1176; measured: 331.1172 = 1.2 ppm difference.

[00248] dimethyl 2,2',6-trimethoxy-[1,1'-biphenyl]-4,4'-dicarboxylate (**G-S**)

[00249] 

[00250] **GP 4** at 80 °C was followed using G-OTs (841 mg, 2.5 mmol), S-OTf (688 mg, 2.0 mmol), $NiCl_2$(dme) (44 mg, 10 mol%), phen (43 mg, 12 mol%), $PdCl_2$•2MeCN (15.6 mg, 2 mol%), SPhos (49 mg, 6 mol%), DMSO (5 mL), a Ni foam cathode, which furnished the title compound as a white powder (504 mg, 70% yield).

[00251] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.8, 1.6 Hz, 1H), 7.65 (d, J = 1.6 Hz, 1H), 7.34 (s, 2H), 7.22 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.80 (s, 3H), 3.78 (s, 6H).

[00252] **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.08, 166.91, 157.72, 157.28, 131.78, 131.01, 130.72, 128.13, 121.72, 120.14, 111.90, 105.37, 56.15, 55.95, 52.32, 52.17.

[00253] **HRMS (ESI$^+$)** Calc: $[M+H]^+$ ($C_{19}H_{21}O_7$) 361.1282; measured: 361.1278 = 1.1 ppm difference.

References Cited

[00254] 1. Namazi, H. Polymers in our daily life. *BioImpacts* **2017**, *7*, 73.

[00255] 2. Matsuda, T.; Nakamura, T.; Sasakawa, A.; Hayashi, S.; Konai, Y. "Preparation process of biphenyl-4,4'-dicarboxylic acid" US Patent 4,970,338 A; November 13, 1990.

[00256] 3. Matsuda, T.; Nakamura, T.; Sasakawa, A.; Hayashi, S.; Konai, Y. "Preparation process of biphenyl-4,4'-dicarboxylic acid" European Patent 0267774 A1; October 11, 1987.

[00257] 4. Edling, H. E.; Liu, H.; Sun, H.; Mondschein, R. J.; Schiraldi, D. A.; Long, T. E.; Turner, S. R. Copolyesters based on bibenzoic acids. *Polymer* **2018**, *135*, 120.

[00258] 5. Asrar, J. Synthesis and Properties of 4,4'-Biphenyldicarboxylic Acid and 2,6-Naphthalenedicarboxylic Acid. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 3139.

[00259] 6. Bokis, C. P.; Guzman, J.; Lotz, M. D.; Mazoyer, E. "Preparation and purification of biphenyldicarboxylic acids" US Patent 16/753056; September 17, 2020.

[00260] 7. Morris, J. C.; Jackson, W. J. Jr. "Copolyesters from 4,4'-biphenyldicarboxylic acid, 1,6-hexanediol and ethylene glycol" US Patent 5,037,946 A; August 15, 1990.

[00261] 8. Morris, J. C.; Jackson, W. J. Jr. "Copolyesters of 4,4'-biphenyldicarboxylic acid, 1,4-butanediol and ethylene glycol" Canada Patent CA2046634 A1; August 28, 1990.

[00262] 9. Jamarani, R.; Erythopel, H. C.; Nicell, J. A.; Leask, R. L.; Marić, M. How Green is Your Plasticizer? *Polymers* **2018**, *10*, 834.

[00263] 10. For selected reviews on Ni-catalyzed reductive coupling of two electrophiles, see: a). Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767.; b). Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793.; c). Wang, X.; Dai, Y.; Gong, H. Nickel-Catalyzed Reductive Couplings. *Top. Curr. Chem.* **2016**, *374*, 61.

[00264] 11. Ullmann, F., Bielecki, J. Ueber synthesen in der biphenylreihe. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174.

[00265] 12. a). Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl−Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction. *Chem. Rev.* **2002**, *102*, 1359.; b). Nelson, T. D.; Crouch, R. D. Cu, Ni, and Pd Mediated Homocoupling Reactions in Biaryl Syntheses: The Ullmann Reaction. *Org. React.* **2014**, *63*, 265.; c). Vasconcelos, S. N.S.; Reis, J. S.; Oliveira, I. M.; Balfour, M. N.; Stefani, H. A. Synthesis of symmetrical biaryl compounds by homocoupling reaction. *Tetrahedron* **2019**, *75*, 1865.

[00266] 13. For selected examples of Ni-catalyzed reductive homo-coupling of aryl halides, see: a). Jennings, P. W.; Pillsbury, D. G.; Hall, J. L.; Brice, V. T. *J. Org. Chem.* **1976**, *41*, 719.; b). Zembayashi, M.; Tamao, K.; Yoshida, J.; Kumada, M. *Tetrahedron Lett.* **1977**, 4089.; c). Iyoda, M.; Sato, K.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 3829.; d). Qian, Q.; Zang, Z. H.; Wang,

S. L.; Chen, Y.; Lin, K. H.; Gong, H. G. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides. *Synlett* **2013**, *24*, 619.; e). Liao, L. Y.; Kong, X. R.; Duan, X. F. Reductive Couplings of 2-Halopyridines without External Ligand: Phosphine-Free Nickel-Catalyzed Synthesis of Symmetrical and Unsymmetrical 2,2′-Bipyridines. *J. Org. Chem.* **2014**, *79*, 777.; f). Sengmany, S.; Vasseur, S.; Lajnef, A.; Le Gall, E.; Leonel, E. Beneficial Effects of Electrochemistry in Cross-Coupling Reactions: Electroreductive Synthesis of 4-Aryl- or 4-Heteroaryl-6-Pyrrolylpyrimidines. *Eur. J. Org. Chem.* **2016**, *2016*, 4865−4871.; g). Lv, L. Y.; Qiu, Z. H.; Li, J. B.; Liu, M. X.; Li, C. J. N_2H_4 as Traceless Mediator for Homo- and Cross-Aryl Coupling. *Nat. Commun.* **2018**, *9*, 4739.; h). Rahil, R.; Sengmany, S.; Gall, E. L.; Léonel, E. Nickel-Catalyzed Electrochemical Reductive Homocouplings of Aryl and Heteroaryl Halides: A Useful Route to Symmetrical Biaryls. *Synthesis* **2018**, *50*, 146.; i). Qiu, H.; Shuai, B.; Wang, Y.-Z.; Liu, D.; Chen, Y.-G.; Gao, P.-S.; Ma, H.-X.; Chen, S.; Mei, T.-S. Enantioselective Ni-Catalyzed Electrochemical Synthesis of Biaryl Atropisomers.$*J. Am. Chem. Soc.* **2020**, *142*, 9872.

[00267] 14. Besides their use in synthesis, phenolic compounds are found widely in plants, driving recent interest in their conversion to industrially relevant compounds. a). Bravo, L. Polyphenols: Chemistry, Dietary Sources, Metabolism, and Nutritional Significance. *Nutr. Rev.* **1998**, **56**, 317.; b). Stewart, A. J.; Stewart, R. F. Phenols. In Encyclopedia of Ecology; Elsevier Science, 2008; pp 2682−2689.; c). Sun, Z. H.; Fridrich, B.; de Santi, A.; Elangovan, S.; Barta, K. Bright Side of Lignin Depolymerization: Toward New Platform Chemicals. *Chem. Rev.* **2018**, *118*, 614.

[00268] 15. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon−Oxygen Bonds. *Chem. Rev.* **2011**, *111*, 1346.

[00269] 16. Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. Aryl Mesylates in Metal-Catalyzed Homocoupling and Cross-Coupling Reactions. 1. Functional Symmetrical Biaryls from Phenols via Nickel-Catalyzed Homocoupling of Their Mesylates. *J. Org. Chem.* **1995**, *60*, 176.

[00270] 17. Acemoglu, M.; Krell, C. M.; Marterer, W. Experiences with Negishi Couplings on Technical Scale in *Early Development. In Transition Metal-Catalyzed Couplings in Process Chemistry*; Magano, J., Dunetz, J. R., Eds.; Wiley-VCH: Weinheim, Germany, 2013; pp 15−23.

[00271] 18. a). Yin, J.; Maguire, C. K.; Yasuda, N.; Brunskill, A. P. J.; Klapars, A. Impact of Lead Impurities in Zinc Dust on the Selective Reduction of a Dibromoimidazole Derivative. *Org. Process Res. Dev.* **2017**, *21*, 94.; b). Takai, K.; Kataoka, Y.; Miyai, J.; Okazoe, T.; Oshima, K.; Utimoto, K. Alkylidenation of Ester Carbonyl Groups: (Z)-1-Ethoxy-1-Phenyl-1-Hexene. *Org. Synth.* **1996**, *73*, 73.; c). Takai, K.; Kakiuchi, T.; Utimoto, K. A Dramatic Effect of a Catalytic Amount of Lead on the Simmons-Smith Reaction and Formation of Alkylzinc Compounds from Iodoalkanes. Reactivity of Zinc Metal: Activation and Deactivation. *J. Org. Chem.* **1994**, *59*, 2671.

[00272] 19. For selected reviews on organic electrochemistry, see: a). Kingston, C.; Palkowitz, M. D.; Takahira, Y.; Vantourout, J. C.; Peters, B. K.; Kawamata, Y.; Baran, P. S. A Survival Guide for the “Electro-curious”. *Acc. Chem. Res.* **2020**, *53*, 72.; B. Röckl, J. L.; Pollok, D.; Franke, R.; Waldvogel, S. R. A Decade of Electrochemical Dehydrogenative C, C-Coupling of Aryls. *Acc. Chem. Res.* **2020**, *53*, 45.; c). Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230.; d). Yuan, Y.; Lei, A. Electrochemical Oxidative Cross-Coupling with Hydrogen Evolution Reactions. *Acc. Chem. Res.* **2019**, *52*, 3309.; e). Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. Electrochemical Arylation Reaction. *Chem. Rev.* **2018**, *118*, 6706.; f) Xiong, P.; Xu, H.-C. Chemistry with Electrochemically Generated N-Centered Radicals. *Acc. Chem. Res.* **2019**, *52*, 3339.; g). Jiao, K.-J.; Xing, Y.-K.; Yang, Q.-L.; Qiu, H.; Mei, T.-S. Site-Selective C−H Functionalization via Synergistic Use of Electrochemistry and Transition Metal Catalysis. *Acc. Chem. Res.* **2020**, 53, 300.; h). Siu, J. C.; Fu, N.; Lin, S. Catalyzing Electrosynthesis: A Homogeneous Electrocatalytic Approach to Reaction Discovery. *Acc. Chem. Res.* **2020**, *53*, 547.; i). Ackermann, L. Metalla-electrocatalyzed C−H Activation by Earth-Abundant 3d Metals and Beyond. *Acc. Chem. Res.* **2020**, *53*, 84.; j). Wang, F.; Stahl, S. S. Electrochemical Oxidation of Organic Molecules at Lower Overpotential: Accessing Broader Functional Group Compatibility with Electron−Proton Transfer Mediators. *Acc. Chem. Res.* **2020**, *53*, 561.

[00273] 20. Jutand, A.; Mosleh, A. Nickel- and Palladium-Catalyzed Homocoupling of Aryl Triflates. Scope, Limitation, and Mechanistic Aspects. *J. Org. Chem.* **1997**, *62*, 261.

[00274] 21. Kang, K.; Huang, L.; Weix, D. J. Sulfonate Versus Sulfonate: Nickel and Palladium Multimetallic Cross-Electrophile Coupling of Aryl Triflates with Aryl Tosylates. *J. Am. Chem. Soc.* **2020**, *142*, 10634.

[00275] 22. a). Liguori, F.; Moreno-Marrodan, C.; Barbaro, P. Biomass-derived chemical substitutes for bisphenol A: recent advancements in catalytic synthesis. *Chem. Soc. Rev.* **2020**, *49*, 6329.; b). B. Lochab, S. Shukla and I. K. Varma, *RSC Adv.* **2014**, *4*, 21712.; c). W. Schutyser, T. Renders, G. Van den Bossche, S. Van den Bosch, S. F. Koelewijn, T. Ennaert and B. F. Sels, Catalysis in Lignocellulosic Biorefineries: The Case of Lignin Conversion, *Nanotechnology in Catalysis: Applications in the Chemical Industry, Energy Development, and Environment Protection*, Wiley-VCH, 2017, ch. 23.; d). Fache, M.; Darroman, E.; Besse, V.; Auvergne, R.; Caillol, S.; Boutevin, B. Vanillin, a promising biobased building-block for monomer synthesis. *Green Chem.* **2014**, *16*, 1987.; e). Gandini, A.; Belgacem, M. N.; Guo, Z.-X.; Montanari, S. Lignins as Macromonomers for Polyesters and Polyurethanes. In *Chemical Modification, Properties and Usage of Lignin*; Hu, T. Q., Ed.; Kluwer Academic/Plenum: New York, 2002; pp 57−80.

[00276] 23. Upton, B. M.; Kasko, A. M. Strategies for the Conversion of Lignin to High-Value Polymeric Materials: Review and Perspective. *Chem. Rev.* **2016**, *116*, 2275.

[00277] 24. a). Rahimi, A.; Ulbrich, A.; Coon, J. J.; Stahl S. S. Formic-acid-induced depolymerization of oxidized lignin to aromatics. *Nature* **2014**, *515*, 249.; b). Rafiee, M.; Alherech, M.; Karlen, S. D.; Stahl, S. S. Electrochemical Aminoxyl-Mediated Oxidation of Primary Alcohols in Lignin to Carboxylic Acids: Polymer Modification and Depolymerization. *J. Am. Chem. Soc.* **2019**, *141*, 15266.; c). Cui, Y.; Goes, S. L.; Stahl, S. S. Sequential Oxidation-Depolymerization Strategies for Lignin Conversion to Low Molecular Weight Aromatic Chemicals. *Adv. Inorg. Chem.* **2021**, *77*, 99.

[00278] 25. Jose, J. P.; Joesph, K. Advances in Polymer Composites: Macro- and Microcomposites - State of the Art, New Challenges, and Opportunities. In *Polymer Composites: Vol. I*; Thomas, S.; Joseph, K.; Malhotra, S. K.; Goda, K.; Sadasivan, S. M., Eds.; Wiley-VCH Verlag GmbH & Co.: New York, **2012**; pp 1–16.

[00279] 26. For selected examples on cyclic voltemmetric anaylsis for Ni(II)(bpy)X_2, see: a). Urgin, K.; Barhdadi, R.; Condon, S.; Leonel, E.; Pipelier, M.; Blot, V.; Thobie-Gautier, C.; Dubreuil, D. Some mechanistic aspects of a nickel-catalyzed electrochemical cross-coupling between aryl halides and substituted chloropyridazines. *Electrochim. Acta* **2010**, *55*, 4495.; b). Yakhvarov, D. G.; Samieva, E. G.; Tazeev, D. I.; Budnikova, Y. G. The reactivity of 2,2’-bipyridine complexes in the electrochemical reduction of organo-halides. *Russ. Chem. Bull.* **2002**,

51, 796.; c). Budnikova, Y. H.; Perichon, J.; Yakhvarov, D. G.; Kargin, Y. M.; Sinyashin, O. G. Highly reactive organonickel complexes in electrocatalytic process. *J. Organomet. Chem.* **2001**, *630*, 185.; d). Klein, A.; Budnikova, Y. H.; Sinyashin, O. G. Electron transfer in organonickel complexes of c-dimines: Versatile redox catalysts for C−C or C−P coupling reactions-A review. *J. Organomet. Chem.* **2007**, *692*, 3156.

[00280] 27. a). Colon, I.; Kelsey, D. R. Coupling of Aryl Chlorides by Nickel and Reducing Metals. *J. Org. Chem.* **1986**, *51*, 2627.; b). Tsou, T. T.; Kochi, J. K. Mechanism of Biaryl Synthesis with Nickel Complexes. *J. Am. Chem. Soc.* **1979**, *101*, 7547.

[00281] 28. a). Collins, K. D.; Gensch, T.; Glorius, F. Contemporary Screening Approaches to Reaction Discovery and Development. *Nat. Chem.* **2014**, *6*, 859.; b). Preshlock, S. M.; Ghaffari, B.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R. High-Throughput Optimization of Ir-Catalyzed C–H Borylation: A Tutorial for Practical Applications. *J. Am. Chem. Soc.* **2013**, *135*, 7572.

[00282] 29. Aust, N.; Kirste, A.: Paired Electrosynthesis. In *Encyclopedia of Applied Electrochemistry*; Kreysa, G., Ota, K.-i., Savinell, R. F., Eds.; Springer New York: New York, NY, 2014; pp 1505-1510.

[00283] 30. Martín, A. J.; Pérez-Ramírez, J.: Heading to Distributed Electrocatalytic Conversion of Small Abundant Molecules into Fuels, Chemicals, and Fertilizers. *Joule* **2019**, *3*, 2602.

[00284] 31. Wang, F.; Li, W.; Wang, R.; Guo, T.; Sheng, H.; Fu, H.-C.; Stahl, S. S.; Jin, S.: Modular Electrochemical Synthesis Using a Redox Reservoir Paired with Independent Half-Reactions. *Joule* **2021**, *5*, 149.

32. Cardoso, D. S. P.; Šljukić, B.; Santos, D. M. F.; Sequeira, C. A. C.: Organic Electrosynthesis: From Laboratorial Practice to Industrial Applications. *Org. Process Res. Dev.* **2017**, *21*, 1213.

[00285] While a number of embodiments of the present invention have been described above, the present invention is not limited to the disclosed examples.

CLAIMS

We claim:

1. A method of producing one or more desired substituted biaryl products from one or more substituted aryl sulfonate reactants by electrochemical reductive coupling, the method comprising applying an external electromotive force to add electrons to a cathode electrode of an electrosynthetic cell and to simultaneously remove electrons from an anode electrode of the electrosynthetic cell, wherein the cathode electrode is in contact with a liquid phase solution that comprises the one or more substituted aryl sulfonate reactants, whereby the one or more substituted aryl sulfonate reactants are reductively coupled to produce the one or more desired substituted biaryl products.

2. The method of claim 1, wherein the substituted aryl sulfonate reactant is homo-coupled to make the desired substituted biaryl product.

3. The method of claim 2, wherein the liquid phase solution comprises a catalyst that comprises Ni.

4. The method of claim 3, wherein the catalyst is a nickel salt.

5. The method of claim 1, wherein two different substituted aryl sulfonate reactants are cross-coupled to make the desired substituted biaryl product.

6. The method of claim 5, wherein the liquid phase solution comprises a catalyst or a combination of catalysts that together comprise both Ni and Pd.

7. The method of claim 6, wherein the catalyst or the combination of catalysts comprise a nickel salt and/or a palladium salt.

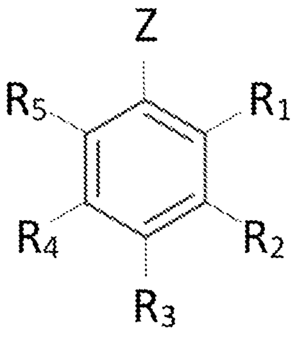
8. The method of any of claims 1-7, wherein the one or more substituted aryl sulfonate reactants are derived from one or more substituted phenols by converting the phenolic –OH to a sulfonate.

9. The method of claim 8, wherein the one or more substituted phenols are derived from lignin.

10. The method of claim 9, wherein the one or more substituted phenols are derived from lignin by depolymerization of the lignin.

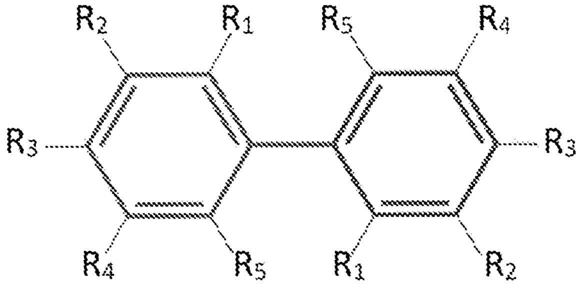
11. The method of claim 10, wherein the lignin is depolymerized by structurally modifying the lignin via selective oxidation, followed by base-promoted depolymerization of the structurally modified lignin.

12. The method of any of claims 1-4 or 8-11, wherein the substituted aryl sulfonate reactant has the chemical formula:



, where Z comprises a sulfonate ester;

and wherein the desired substituted biaryl product has the chemical formula:



;

wherein R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

13. The method of claim 12, wherein Z comprises a sulfonate having the formula -SO_2X, where X is OR_{11}, and where R_{11} is a cation, an alkyl, a haloalkyl, an aryl, or a silyl.

14. The method of claim 12, wherein Z is a mesylate, a tosylate, or a triflate.

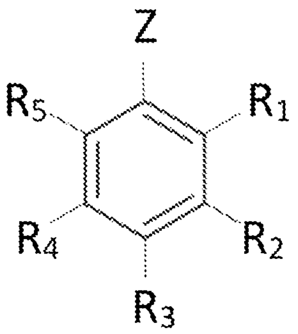
15. The method of any of claims 12-14, wherein R_2 and R_4 are hydrogen.

16. The method of any of claims 12-15, wherein R_1 and R_5 are each independently an alkoxy or hydrogen.

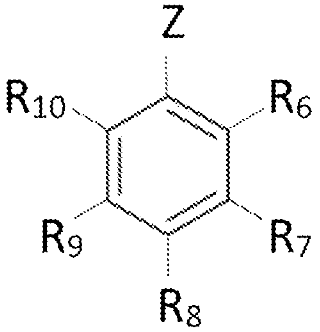
17. The method of claim 16, wherein the alkoxy is methoxy.

18. The method of any of claims 12-17, wherein R_3 is a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

19. The method of any of claims 1 or 5-11, wherein the substituted aryl sulfonate reactants have the chemical formulas:

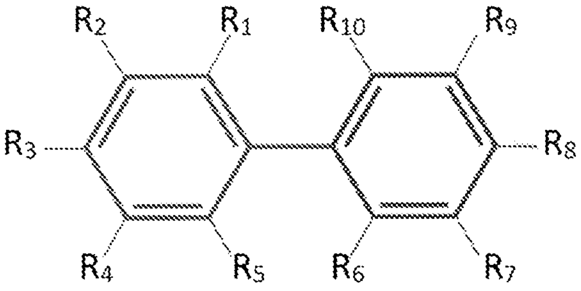


and



, where Z comprises a sulfonate ester;

and wherein the desired substituted biaryl product has the chemical formula:



;

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

20. The method of claim 19, wherein Z comprises a sulfonate having the formula -SO_2X, where X is OR_{11}, and where R_{11} is a cation, an alkyl, an aryl, or a silyl.

21. The method of claim 19, wherein Z is a mesylate, a tosylate or a triflate.

22. The method any of claims 19-21, wherein R_2, R_4, R_7 and R_9 are hydrogen.

23. The method of any of claims 19-22, wherein R_1, R_5, R_6 and R_{10} are each independently an alkoxy or hydrogen.

24. The method of claim 23, wherein the alkoxy is methoxy.

25. The method of any of claims 19-24, wherein R_3 and R_8 are each independently a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

26. The method of any of claims 1-25, wherein the method is performed by batch electrolysis.

27. The method of any of claims 1-25, wherein the method is performed by flow electrolysis.

28. The method of any of claims 1-27, wherein the electrosynthetic cell is a divided cell.

29. The method of any of claims 1-27, wherein the electrosynthetic cell is an undivided cell.

30. The method of any of claims 1-29, wherein the liquid phase further comprises one or more organic solvents.

31. The method of claims 30, wherein the one or more organic solvents are selected from the group consisting of acetone, acetonitrile, benzene, 1-butanol, 2-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethane, dimethyl carbonate, diethyl carbonate, diethylene glycol, diethyl ether, diglyme (diethylene glycol dimethyl ether), 1,2-dimethoxy-ethane (glyme, DME), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-1,3-diazinan-2-one (DMPU), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethanol, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), 1-propanol, 2-propanol, propylene carbonate, pyridine, sulfolane, tetrahydrofuran (THF), 2-methyl tetrahydrofuran toluene, triethyl amine, o-xylene, m-xylene, and p-xylene.

32. An electrosynthetic cell for use in producing one or more desired substituted biaryl products from one or more substituted aryl sulfonate reactants by electrochemical reductive coupling, the electrosynthetic cell comprising a cathode electrode and an anode electrode, wherein the cathode electrode is in contact with a liquid phase solution that comprises the one or more substituted aryl sulfonate reactants.

33. The electrosynthetic cell of claim 32, further comprising a device configured to externally apply an electromotive force to add electrons to the cathode electrode and to simultaneously remove electrons from the anode electrode, whereby when the electromotive force is applied, the one or more substituted aryl sulfonate reactants are reductively coupled to produce the one or more desired substituted biaryl products.

34. The electrosynthetic cell of claim 32 or claim 33, wherein the cell is configured to homo-couple the substituted aryl sulfonate reactant to make the desired substituted biaryl product.

35. The electrosynthetic cell of claim 34, wherein the liquid phase solution comprises a catalyst that comprises Ni.

36. The electrosynthetic cell of claim 35, wherein the catalyst comprises a nickel salt.

37. The electrosynthetic cell of claim 32 or claim 33, wherein the cell is configured to cross-couple two different substituted aryl sulfonate reactants to make the desired substituted biaryl product.

38. The electrosynthetic cell of claim 37, wherein the liquid phase solution comprises a catalyst or a combination of catalysts that together comprise both Ni and Pd.

39. The electrosynthetic cell of claim 38, wherein the catalyst or the combination of catalysts comprise a nickel salt and/or a palladium salt.

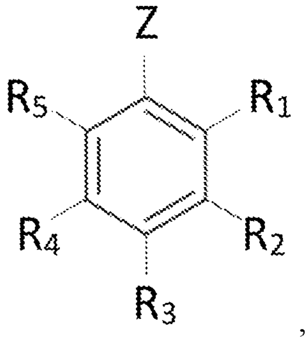
40. The electrosynthetic cell of any of claims 32-39, wherein the one or more substituted aryl sulfonate reactants are derived from one or more substituted phenols by converting the phenolic –OH to a sulfonate.

41. The electrosynthetic cell of claim 40, wherein the one or more substituted phenols are derived from lignin.

42. The electrosynthetic cell of claim 41, wherein the one or more substituted phenols are derived from lignin by depolymerization of the lignin.

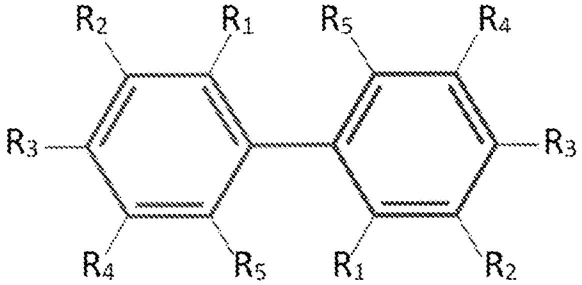
43. The electrosynthetic cell of claim 42, wherein the lignin is depolymerized by structurally modifying the lignin via selective oxidation, followed by base-promoted depolymerization of the structurally modified lignin.

44. The electrosynthetic cell of any of claims 32-36 or 40-43, wherein the substituted aryl sulfonate reactant has the chemical formula:



, where Z comprises a sulfonate ester;

and wherein the desired substituted biaryl product has the chemical formula:



;

wherein R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

45. The electrosynthetic cell of claim 44, wherein Z comprises a sulfonate having the formula $-SO_2X$, where X is OR_{11}, and where R_{11} is a cation, an alkyl, a haloalkyl, an aryl, or a silyl.

46. The electrosynthetic cell of claim 44, wherein Z is a mesylate, a tosylate or a triflate.

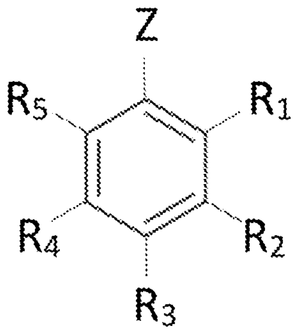
47. The electrosynthetic cell method of any of claims 44-46, wherein R_2 and R_4 are hydrogen.

48. The electrosynthetic cell of any of claims 44-47, wherein R_1 and R_5 are each independently an alkoxy or hydrogen.

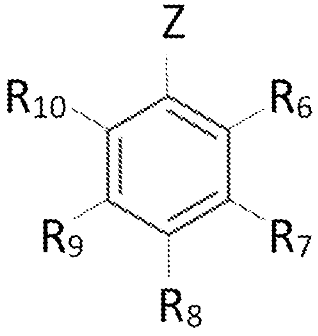
49. The electrosynthetic cell method of claim 48, wherein the alkoxy is methoxy.

50. The electrosynthetic cell of any of claims 44-49, wherein R_3 is a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

51. The electrosynthetic cell of any of claims 32-33 or 37-43, wherein the substituted aryl sulfonate reactants have the chemical formulas:

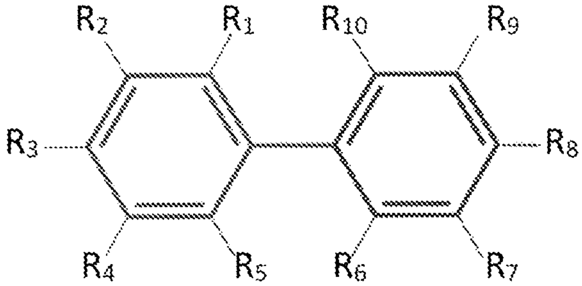


and



, where Z comprises a sulfonate ester;

and wherein the desired substituted biaryl product has the chemical formula:



;

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are independently selected from the group consisting of hydrogen, an alkoxy, a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, and a dione.

52. The electrosynthetic cell of claim 51, wherein Z comprises a sulfonate having the formula $-SO_2X$, where X is OR_{11}, and where R_{11} is a cation, an alkyl, an aryl, or a silyl.

53. The electrosynthetic cell of claim 51, wherein Z is a mesylate, a tosylate or a triflate.

54. The electrosynthetic cell of any of claims 51-53, wherein R_2, R_4, R_7 and R_9 are hydrogen.

55. The electrosynthetic cell of any of claims 51-54, wherein R_1, R_5, R_6 and R_{10} are each independently an alkoxy or hydrogen.

56. The electrosynthetic cell of claim 55, wherein the alkoxy is methoxy.

57. The electrosynthetic cell of any of claims 51-56, wherein R_3 and R_8 are each independently a carboxylic acid, a carboxylate ester, an aldehyde, a ketone, or a dione.

58. The electrosynthetic cell of any of claims 32-57, wherein the cell is configured for batch electrolysis.

59. The electrosynthetic cell of any of claims 33-57, wherein the cell is configured for flow electrolysis.

60. The electrosynthetic cell of any of claims 32-59, wherein the cell is a divided cell.

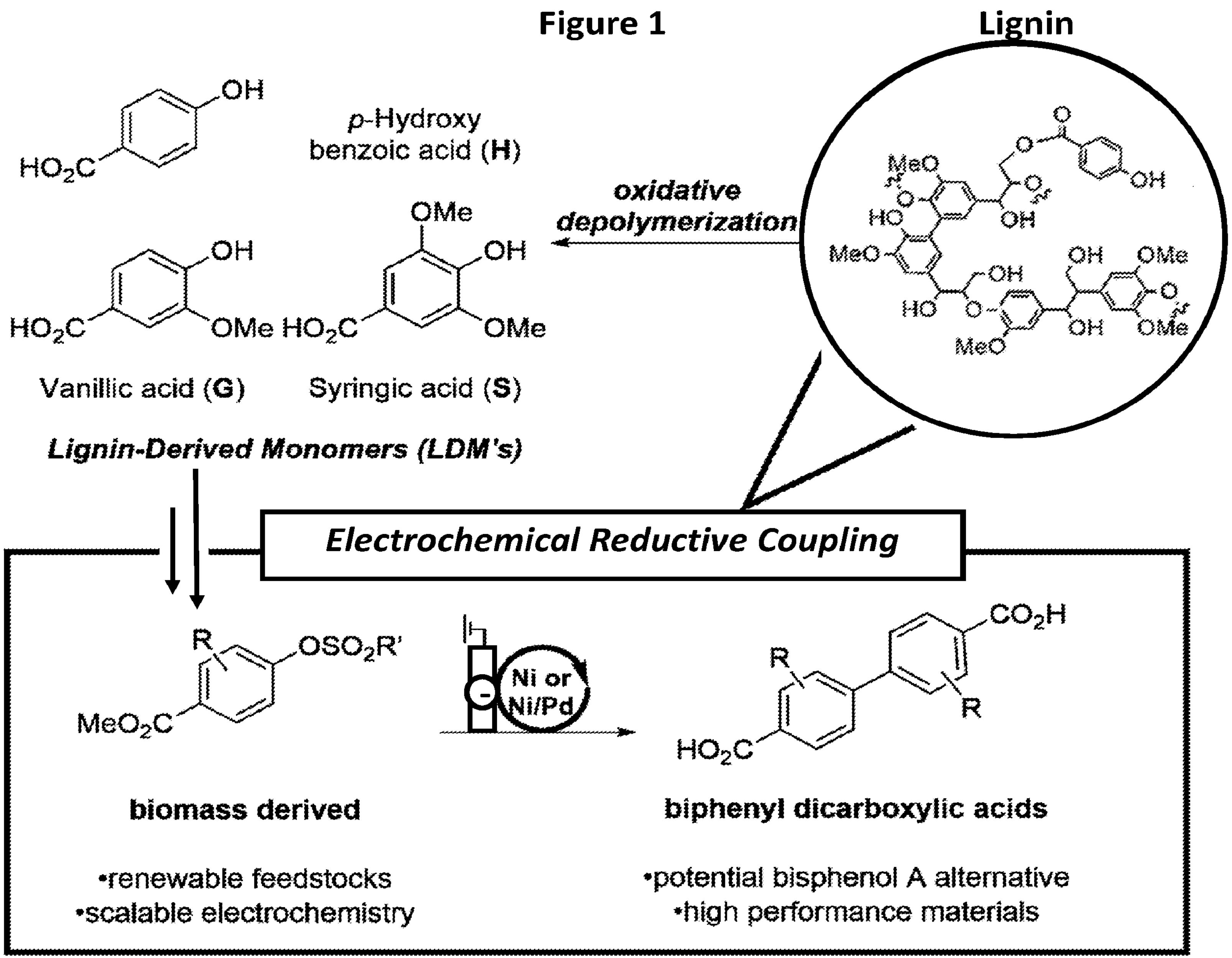
61. The electrosynthetic cell of any of claims 32-59, wherein the cell is an undivided cell.

62. The electrosynthetic cell of any of claims 32-61, wherein the liquid phase further comprises one or more organic solvents.

63. The electrosynthetic cell of claim 62, wherein the one or more organic solvents are selected from the group consisting of acetone, acetonitrile, benzene, 1-butanol, 2-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-

dichloroethane, dimethyl carbonate, diethyl carbonate, diethylene glycol, diethyl ether, diglyme (diethylene glycol dimethyl ether), 1,2-dimethoxy-ethane (glyme, DME), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-1,3-diazinan-2-one (DMPU), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethanol, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), 1-propanol, 2-propanol, propylene carbonate, pyridine, sulfolane, tetrahydrofuran (THF), 2-methyl tetrahydrofuran toluene, triethyl amine, o-xylene, m-xylene, and p-xylene.

Figure 1


Lignin
p-Hydroxy benzoic acid (H)
Vanillic acid (G)
Syringic acid (S)
oxidative depolymerization
Lignin-Derived Monomers (LDM's)
Electrochemical Reductive Coupling
Ni or Ni/Pd
biomass derived
•renewable feedstocks
•scalable electrochemistry
biphenyl dicarboxylic acids
•potential bisphenol A alternative
•high performance materials

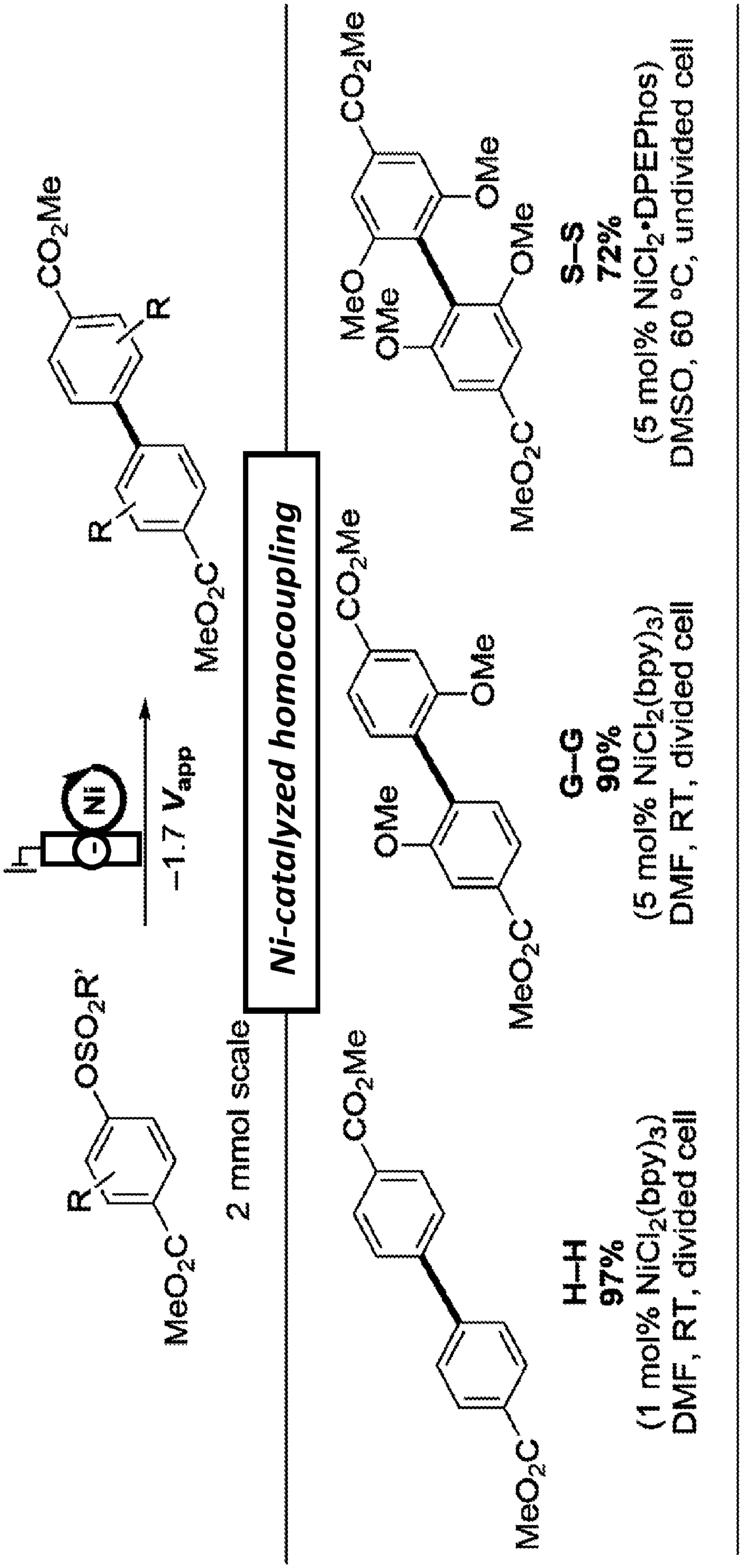

MeO2C
R
OSO2R'
–1.7 Vapp
Ni
MeO2C
R
R
CO2Me
2 mmol scale
Ni-catalyzed homocoupling
MeO2C
CO2Me
H–H
97%
(1 mol% NiCl2(bpy)3)
DMF, RT, divided cell
MeO2C
OMe
OMe
CO2Me
G–G
90%
(5 mol% NiCl2(bpy)3)
DMF, RT, divided cell
MeO2C
OMe
OMe
MeO
OMe
CO2Me
S–S
72%
(5 mol% NiCl2•DPEPhos)
DMSO, 60 °C, undivided cell

Figure 2

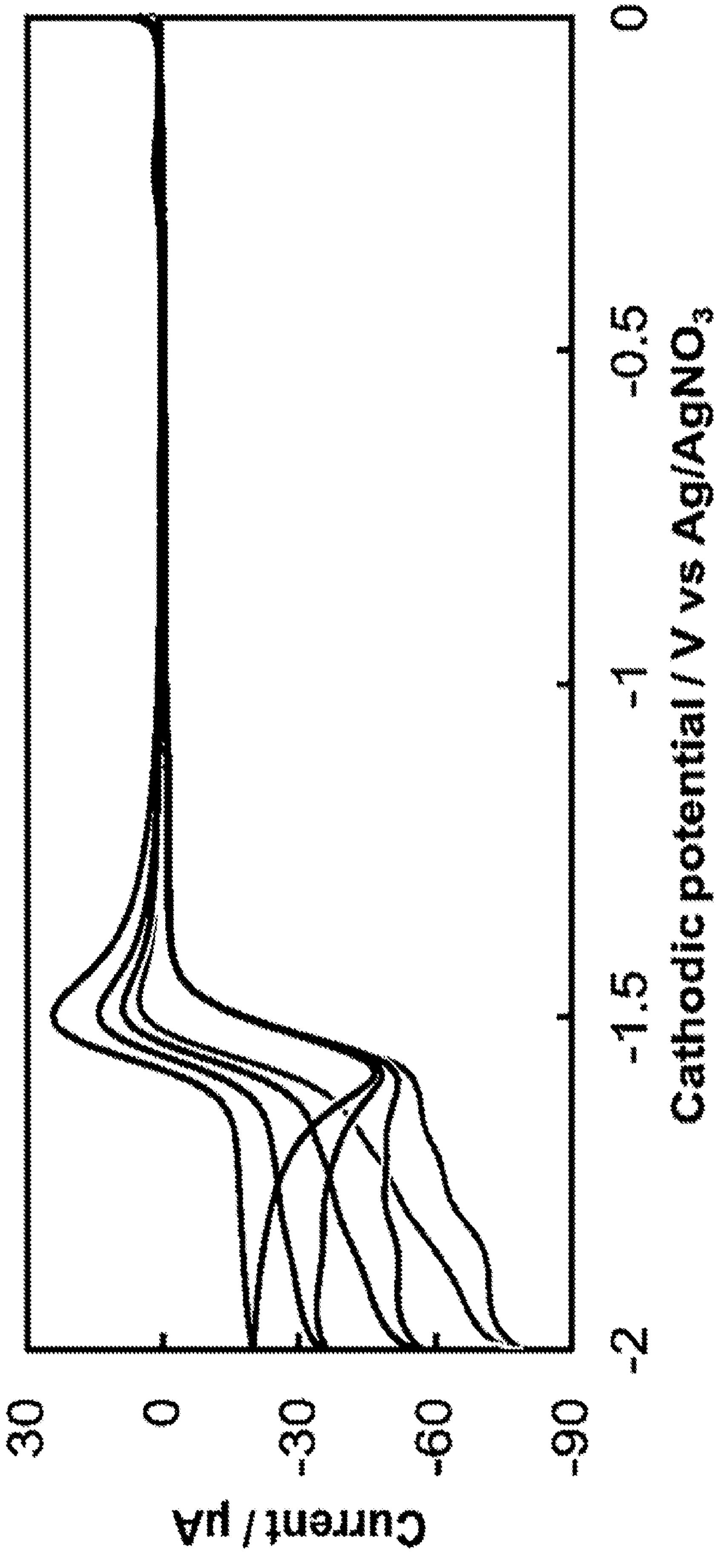

Current / μA
30
0
-30
-60
-90
0
-0.5
-1
-1.5
-2
Cathodic potential / V vs Ag/AgNO$_3$

Figure 3

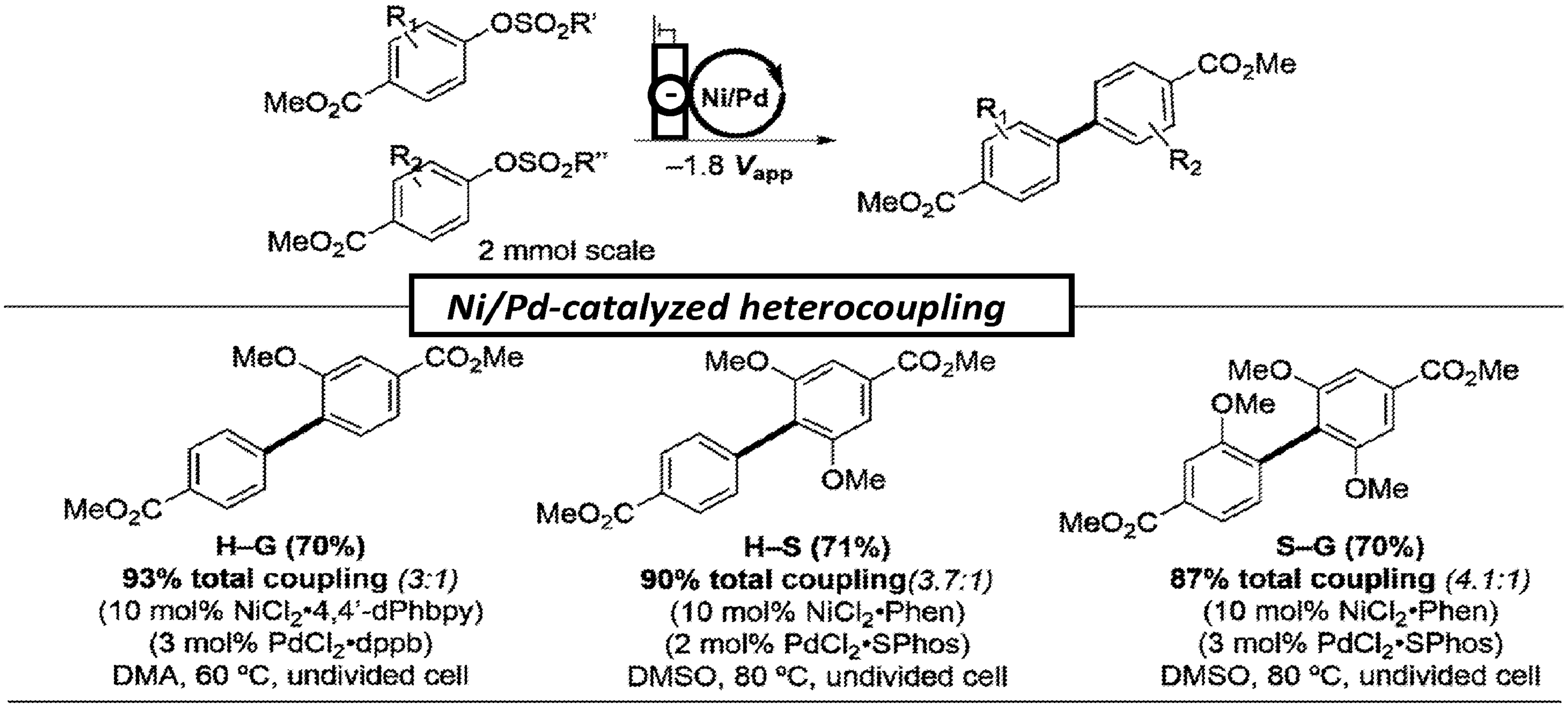

R1
OSO2R'
MeO2C
R2
OSO2R''
MeO2C
2 mmol scale
Ni/Pd
–1.8 Vapp
R1
R2
CO2Me
MeO2C
Ni/Pd-catalyzed heterocoupling
MeO
CO2Me
MeO2C
H–G (70%)
93% total coupling (3:1)
(10 mol% NiCl2•4,4'-dPhbpy)
(3 mol% PdCl2•dppb)
DMA, 60 °C, undivided cell
MeO
CO2Me
OMe
MeO2C
H–S (71%)
90% total coupling(3.7:1)
(10 mol% NiCl2•Phen)
(2 mol% PdCl2•SPhos)
DMSO, 80 °C, undivided cell
MeO
OMe
CO2Me
OMe
MeO2C
S–G (70%)
87% total coupling (4.1:1)
(10 mol% NiCl2•Phen)
(3 mol% PdCl2•SPhos)
DMSO, 80 °C, undivided cell

Figure 4

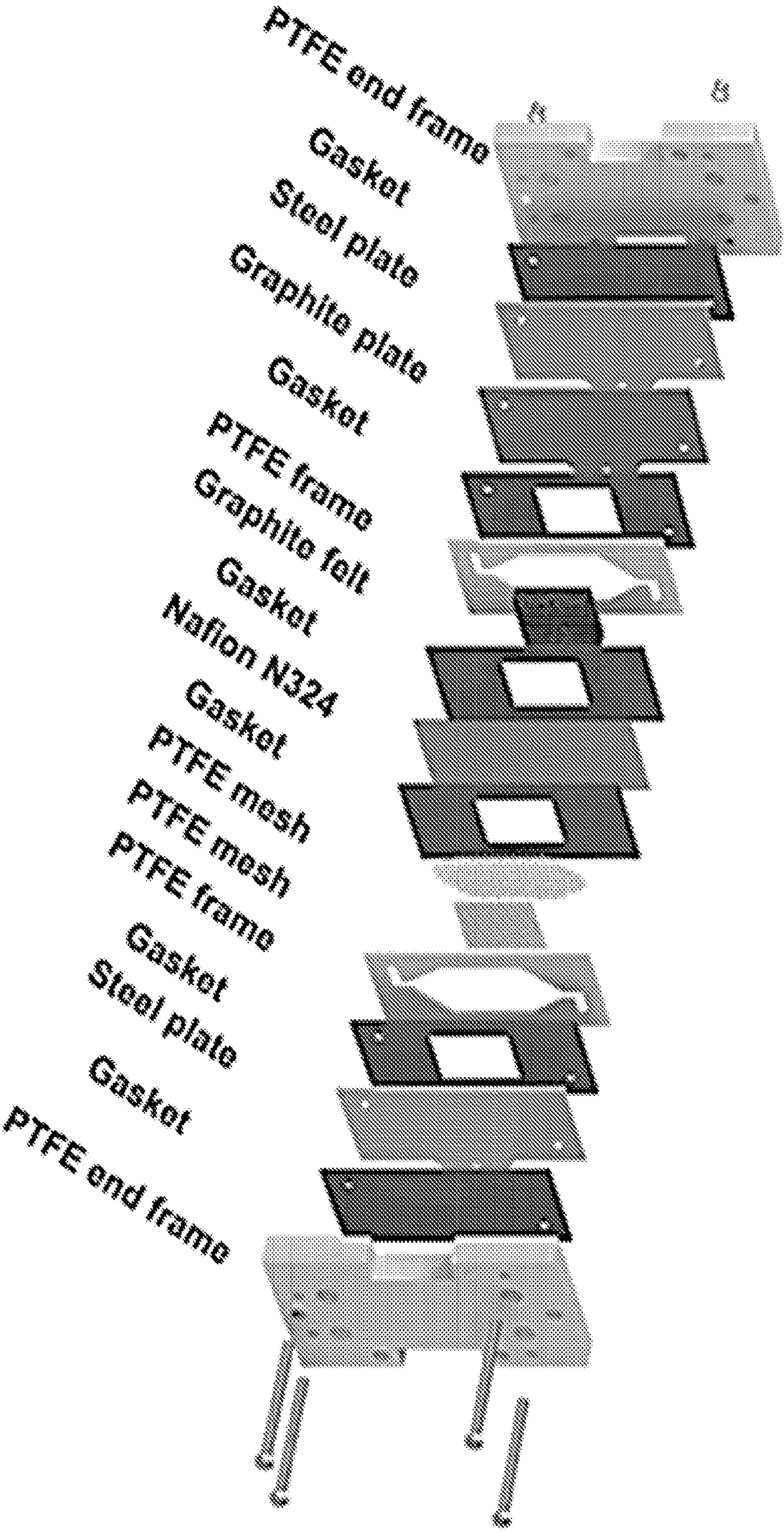
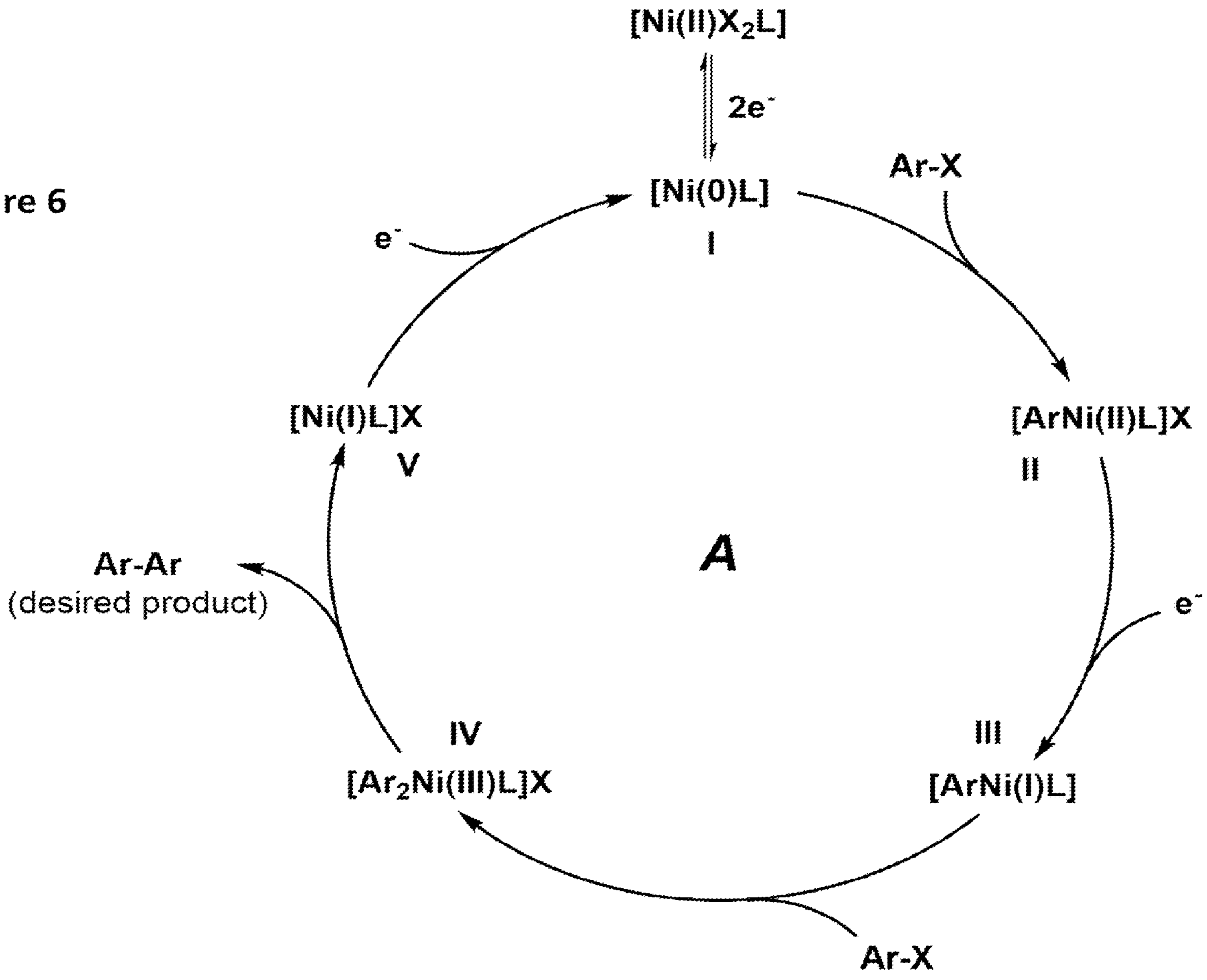

PTFE end frame
Gasket
Steel plate
Graphite plate
Gasket
PTFE frame
Graphite felt
Gasket
Nafion N324
Gasket
PTFE mesh
PTFE mesh
PTFE frame
Gasket
Steel plate
Gasket
PTFE end frame

Figure 5

Figure 6


[Ni(II)X$_2$L]
2e$^-$
[Ni(0)L]
I
Ar-X
[ArNi(II)L]X
II
e$^-$
III
[ArNi(I)L]
Ar-X
IV
[Ar$_2$Ni(III)L]X
Ar-Ar
(desired product)
[Ni(I)L]X
V
e$^-$
A

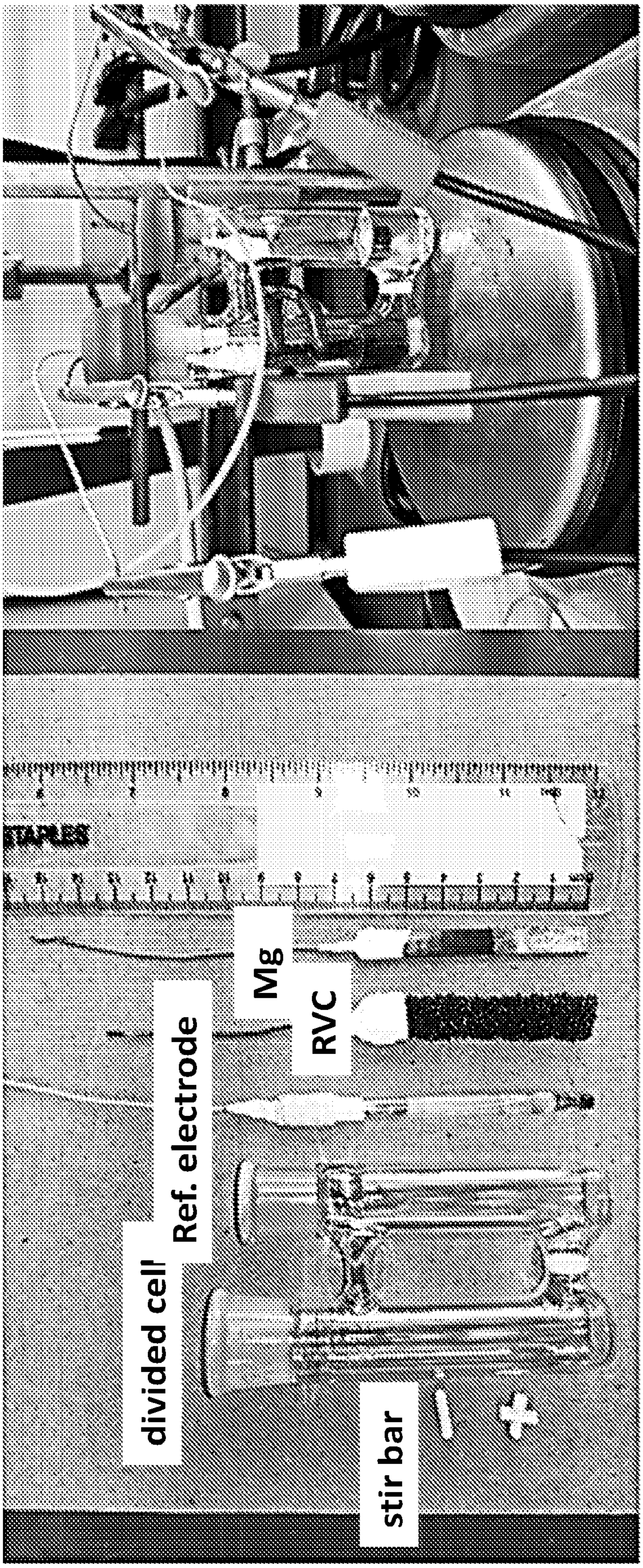


Figure 7

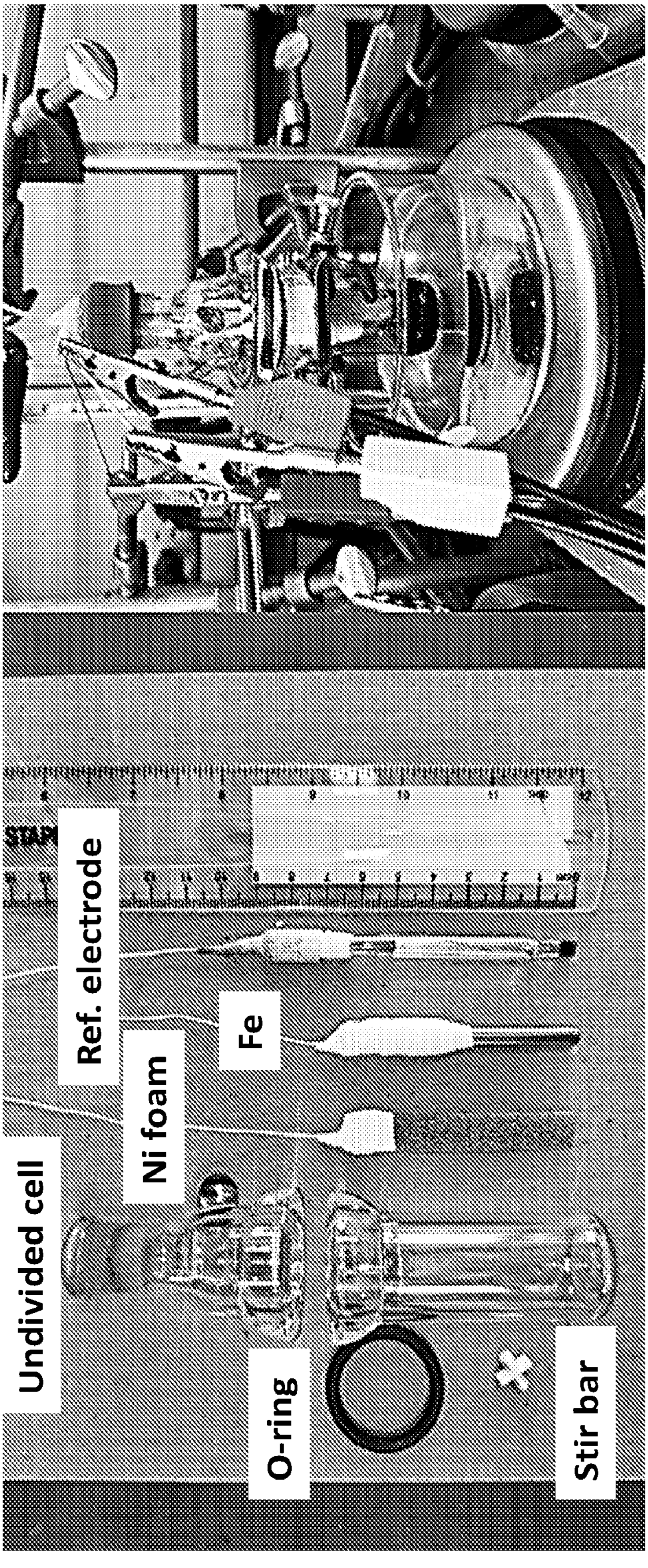


Figure 8

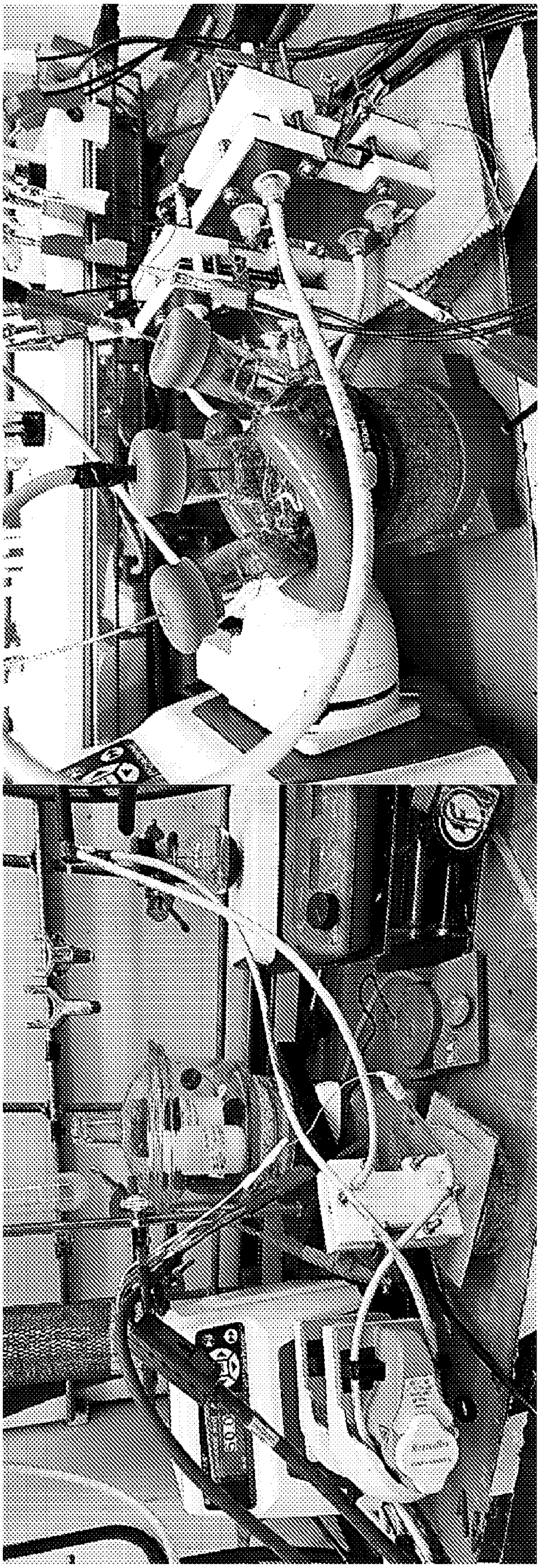
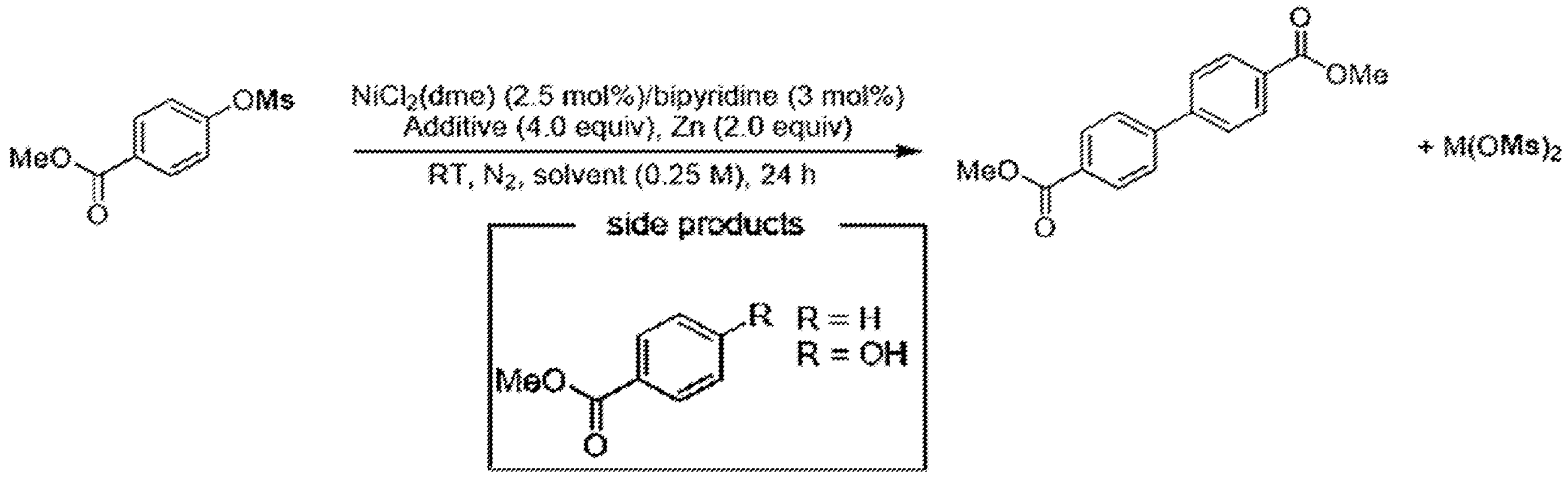


Figure 9

Figure 10



Entry	Additive	Concentration	Mass balance	Conv.	C–H	C–OH	Yield[a]
1	NaBr	0.25 M	95%	100%	86%	3%	6%
2	NaBr	0.50 M	93%	100%	79%	3%	11%
3	NaBr	0.50 M	92%	100%	76%	4%	12%
4[b]	NaBr	0.25 M	98%	48%	27%	16%	3%
5[b,c]	LiBr	0.25 M	94%	33%	7%	18%	2%
6[b]	KBr	0.25 M	97%	100%	38%	n.d.	59%
7[b,d]	LiBr	0.25 M	95%	100%	59%	20%	16%
8[b,e]	LiBr	0.25 M	99%	92%	40%	15%	36%

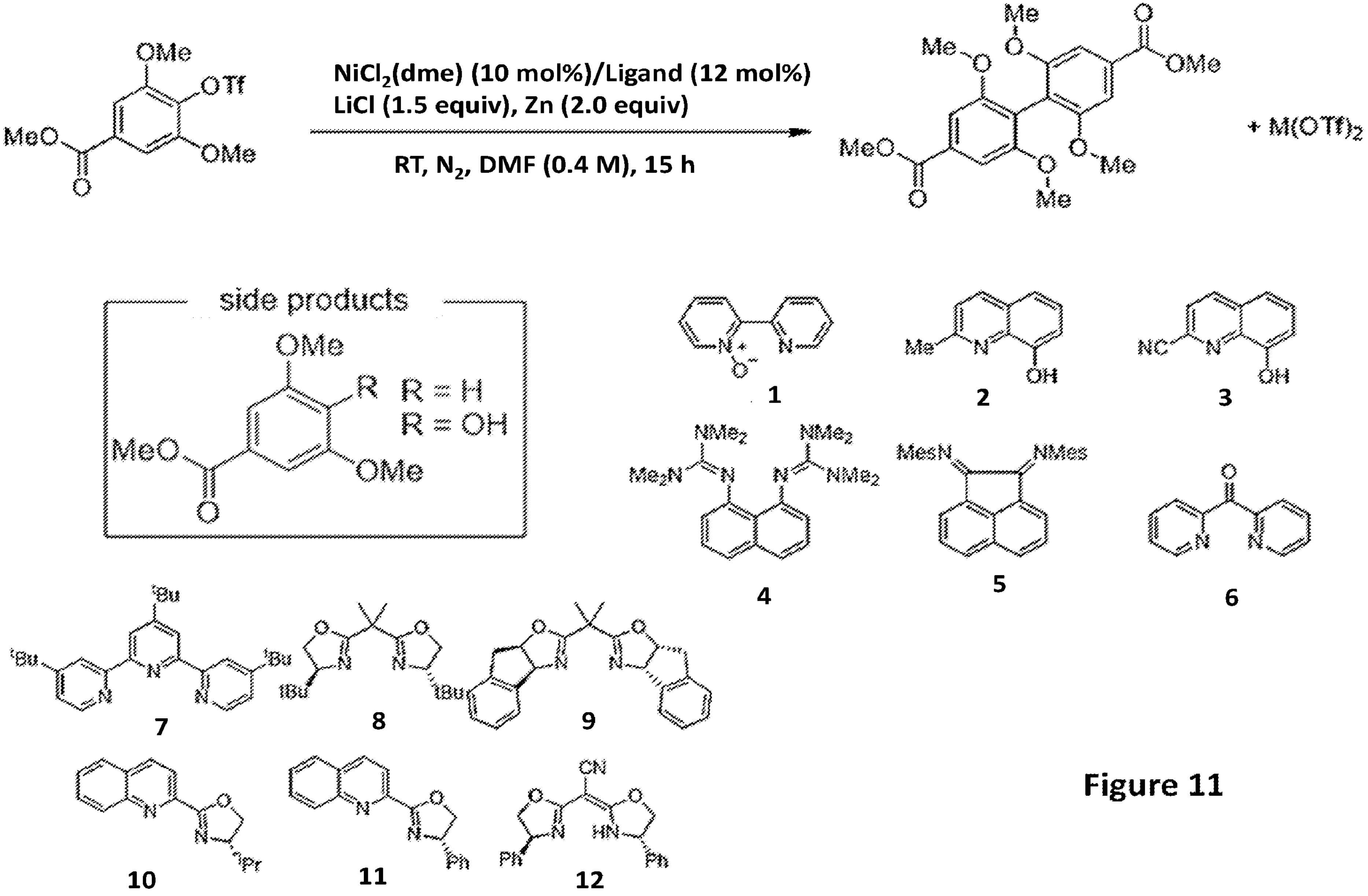

OMe
OTf
MeO
OMe
O
NiCl₂(dme) (10 mol%)/Ligand (12 mol%)
LiCl (1.5 equiv), Zn (2.0 equiv)
RT, N₂, DMF (0.4 M), 15 h
Me
O
OMe
MeO
Me
+ M(OTf)₂
side products
OMe
R
R = H
R = OH
MeO
OMe
N+
O−
N
1
Me
N
OH
2
NC
N
OH
3
NMe₂
Me₂N
N
NMe₂
NMe₂
4
MesN
NMes
5
O
N
6
ᵗBu
N
7
O
N
tBu
8
O
N
9
N
ⁱPr
10
N
Ph
11
CN
HN
Ph
12

Figure 11

Entry	Substrate	Conversion	MB	C-H	C-OH	Product
1	15%	85%	82%	29%	35%	3%
2	46%	54%	97%	24%	24%	3%
3	30%	70%	101%	44%	27%	0%
4	61%	39%	98%	14%	22%	1%
5	0%	100%	95%	88%	4%	3%
6	60%	40%	99%	18%	21%	0%
7	0%	100%	78%	38%	40%	0%
8	46%	54%	97%	19%	32%	0%
9	43%	57%	86%	16%	27%	0%
10	7%	93%	70%	36%	27%	0%
11	9%	91%	86%	45%	32%	0%
12	42%	58%	90%	32%	16%	0%

Figure 11 (cont)

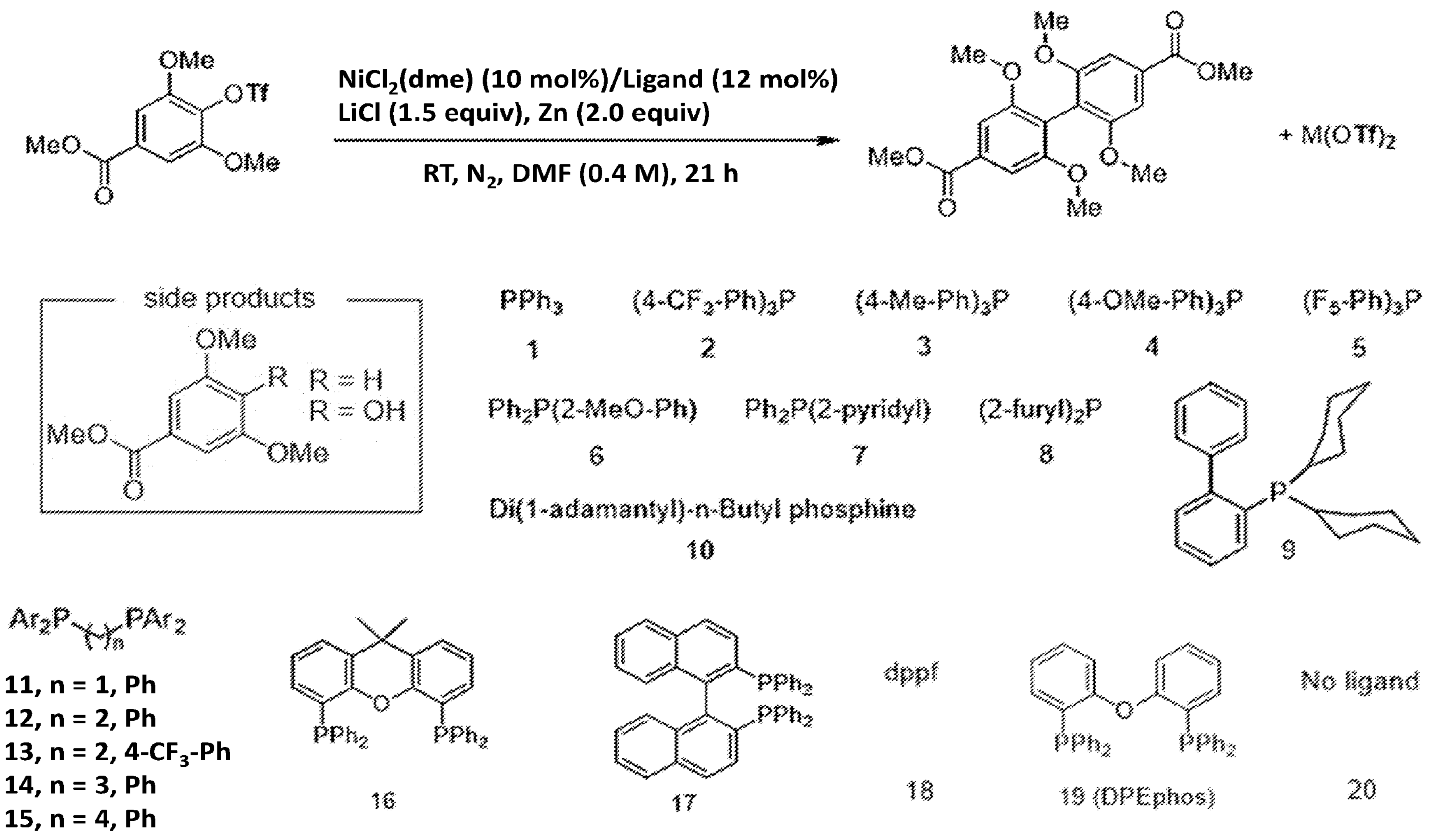
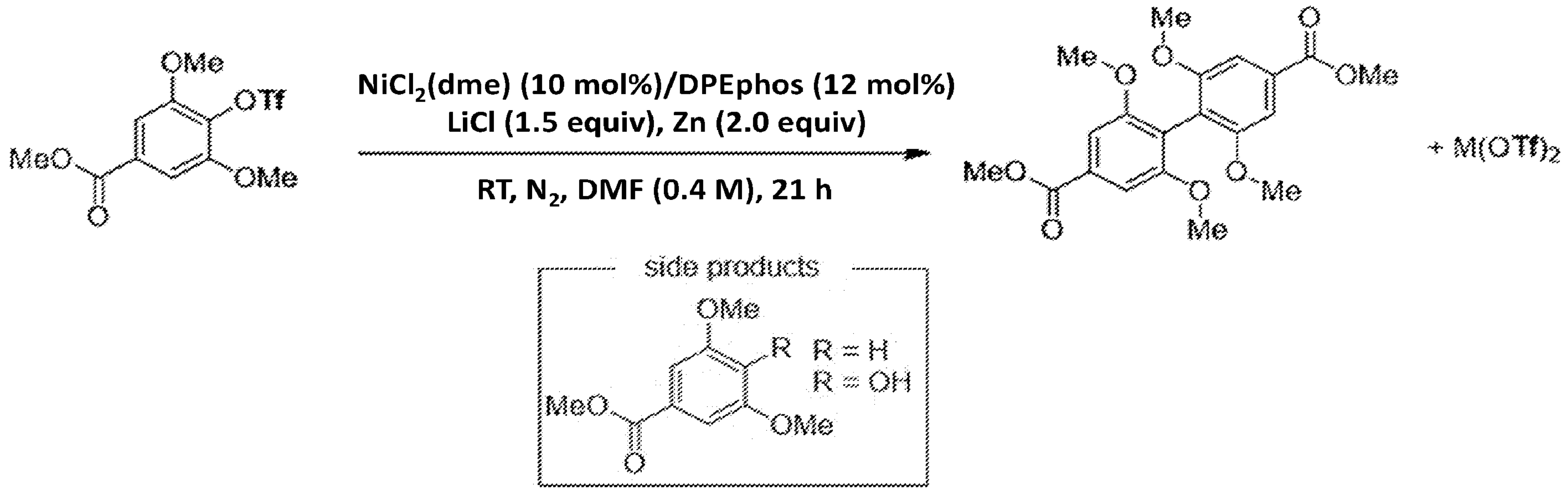

OMe
OTf
MeO
OMe
O
NiCl$_2$(dme) (10 mol%)/Ligand (12 mol%)
LiCl (1.5 equiv), Zn (2.0 equiv)
RT, N$_2$, DMF (0.4 M), 21 h
Me
O
Me
O
OMe
MeO
O
Me
O
Me
+ M(OTf)$_2$
side products
OMe
R
R = H
R = OH
MeO
OMe
O
PPh$_3$
1
(4-CF$_3$-Ph)$_3$P
2
(4-Me-Ph)$_3$P
3
(4-OMe-Ph)$_3$P
4
(F$_5$-Ph)$_3$P
5
Ph$_2$P(2-MeO-Ph)
6
Ph$_2$P(2-pyridyl)
7
(2-furyl)$_2$P
8
P
9
Di(1-adamantyl)-n-Butyl phosphine
10
Ar$_2$P
n
PAr$_2$
11, n = 1, Ph
12, n = 2, Ph
13, n = 2, 4-CF$_3$-Ph
14, n = 3, Ph
15, n = 4, Ph
O
PPh$_2$
PPh$_2$
16
PPh$_2$
PPh$_2$
17
dppf
18
O
PPh$_2$
PPh$_2$
19 (DPEphos)
No ligand
20

Figure 12

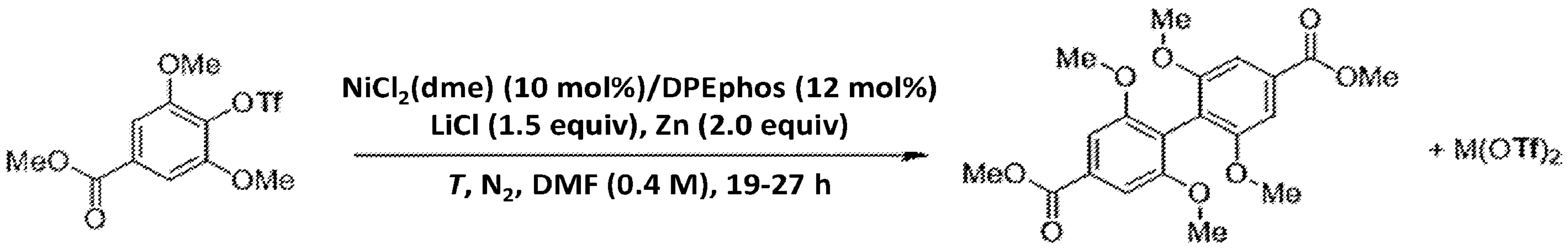
Entry	Substrate	Conversion	MB	C-H	C-OH	Product
1	37%	63%	89%	22%	29%	1%
2	49%	51%	86%	17%	20%	0%
3	42%	58%	91%	20%	29%	0%
4	47%	53%	83%	15%	21%	0%
5	80%	20%	94%	6%	8%	0%
6	44%	56%	93%	20%	29%	0%
7	42%	58%	90%	19%	29%	0%
8	35%	65%	70%	13%	22%	0%
9	31%	69%	80%	21%	28%	0%
10	77%	23%	93%	5%	9%	2%
11	36%	64%	84%	21%	27%	0%
12	57%	43%	97%	14%	26%	0%
13	52%	48%	96%	16%	28%	0%
14	44%	56%	77%	12%	21%	0%
15	43%	57%	82%	17%	22%	0%
16	38%	62%	89%	33%	18%	0%
17	36%	64%	87%	33%	18%	0%
18	32%	68%	94%	48%	9%	5%
19	18%	82%	99%	54%	11%	16%
20	55%	45%	94%	13%	26%	0%

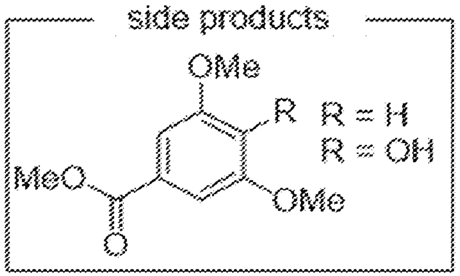
Figure 12 (cont)



Entry	Ligand Loading	Conv.	C–H	C–OH	MB	Yield
1	8 mol%	82%	44%	3%	82%	17%
2	12 mol%	82%	46%	4%	83%	15%
3	15 mol%	75%	46%	8%	92%	13%
4	20 mol%	59%	36%	12%	84%	6%
5[a]	12 mol%	69%	55%	3%	93%	4%
6[b]	12 mol%	77%	54%	2%	82%	3%
7[c]	12 mol%	61%	38%	12%	93%	4%
8[d]	12 mol%	74%	72%	0%	99%	1%

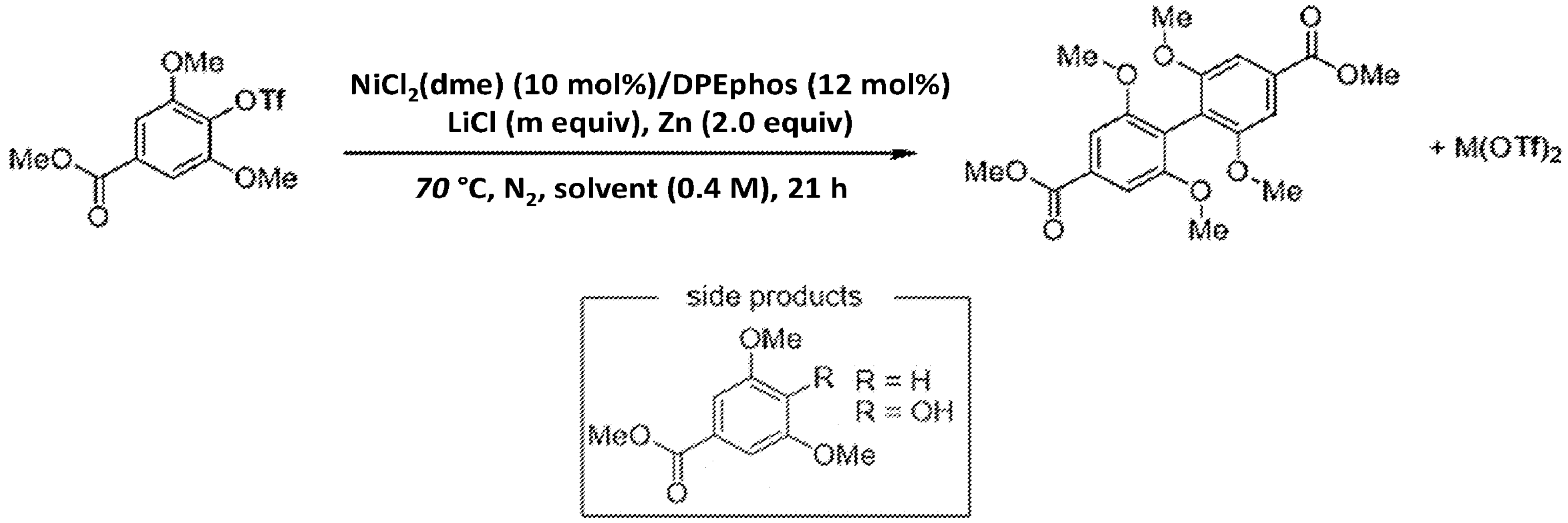
Figure 13





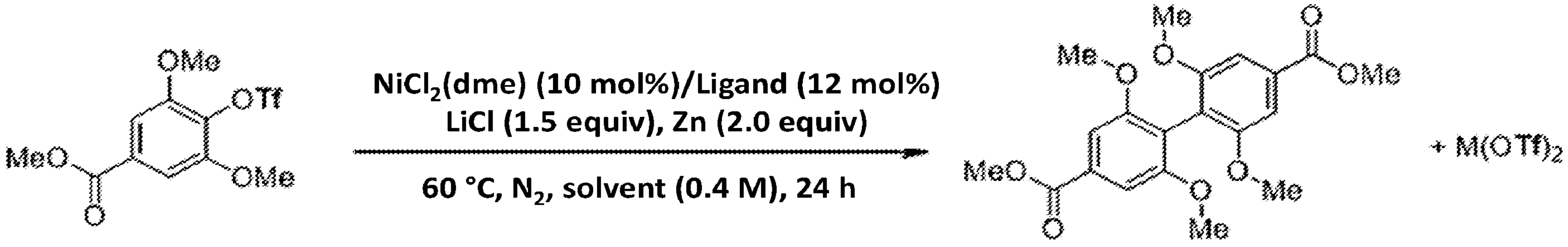
Entry	Temperature	Solvent	Conv.	C–H	C–OH	MB	Yield
1	RT	DMF	82%	46%	4%	83%	15%
2	~ 40 °C	DMF	>99%	58%	<3%	85%	24%
3	~ 50 °C	DMF	>99%	49%	5%	90%	36%
4	~ 60 °C	DMF	98%	37%	8%	85%	38%
5	~ 70 °C	DMF	91%	42%	10%	93%	32%
6	~ 80 °C	DMF	>99%	35%	26%	73%	12%
7	RT	CH_3CN	>99%	72%	0%	76%	4%
8	~ 60 °C	CH_3CN	>99%	73%	0%	87%	10%
9	RT	THF	58%	45%	3%	90%	0%
10	~ 60 °C	THF	98%	66%	1%	76%	7%
11	RT	DMAc	75%	37%	7%	88%	19%
12	~ 60 °C	DMAc	89%	32%	10%	82%	29%

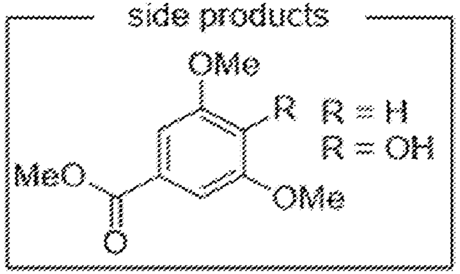
Figure 14



Entry	LiCl (m equiv.)	Conv.	C–H	C–OH	MB	Yield
1	1.0	99%	75%	1%	94%	17%
2	1.5	91%	42%	10%	93%	32%
3	2.5	93%	49%	22%	103%	25%
4	4.0	>99%	36%	36%	81%	9%
5	6.0	>99%	31%	40%	79%	8%

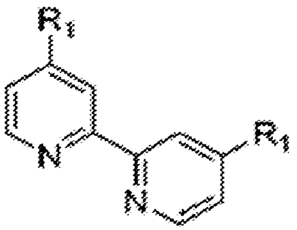
Figure 15



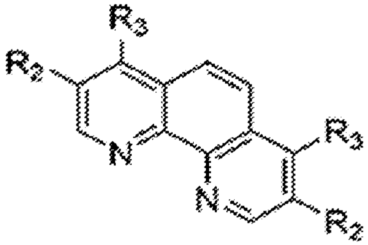


Entry	Ligand	Molecular sieves	Solvent	Conv.	C–H	C–OH	Yield
1	DPEphos	No	DMF	77%	29%	23%	27%
2	DPEphos	No	DMA	74%	29%	7%	33%
3	DPEphos	Yes	DMF	85%	30%	15%	36%
4	DPEphos	Yes	DMA	83%	37%	7%	37%
5	DPEphos	Yes	DMSO	100%	32%	5%	55%
6	DPEphos	Yes	NMP	58%	20%	15%	17%
7	DPEphos	Yes	DMPU	100%	32%	61%	0
8	DCEphos	Yes	DMF	39%	15%	19%	0
9	DCEphos	Yes	DMA	34%	13%	17%	0
10	DCEphos	Yes	DMSO	35%	14%	30%	0
11	DCEphos	Yes	NMP	67%	< 2%	35%	0
12	DCEphos	Yes	DMPU	47%	41%	8%	2%

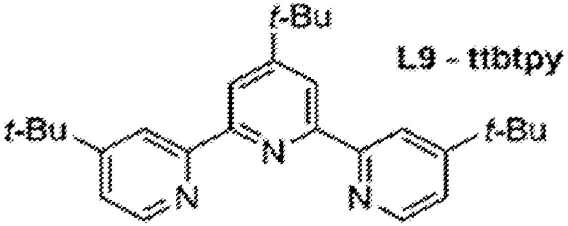
Figure 16



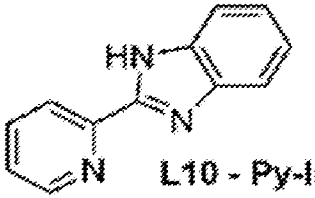
L1 - R_1 = H, bpy
L2 - R_1 = OMe, dOMebpy
L3 - R_1 = *t*-Bu, dtbbpy
L4 - R_1 = *t*-Bu, dtbbpy



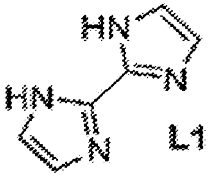
L5 - R_2 = R_3 = H, phen
L6 - R_2 = R_3 = Me, Me$_4$phen
L7 - R_2 = H, R_3 = OMe, dOMephen
L8 - R_2 = H, R_3 = Ph, bathophen



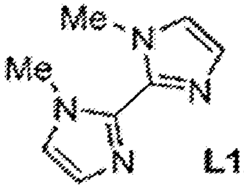
L9 - ttbtpy



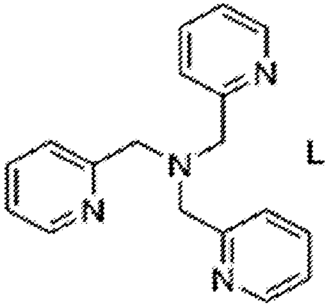
L10 - Py-Imid



L11 - bimid

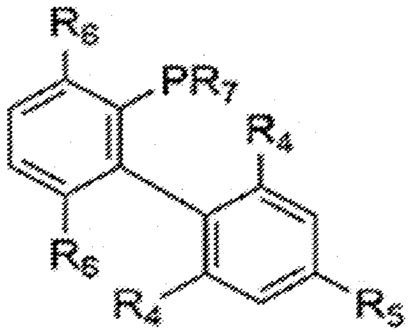


L12 - N,N-dMeb imid

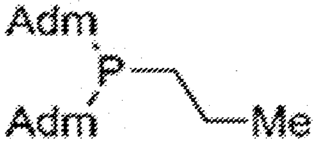


L26 - TPA

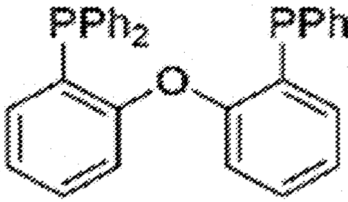
Figure 17



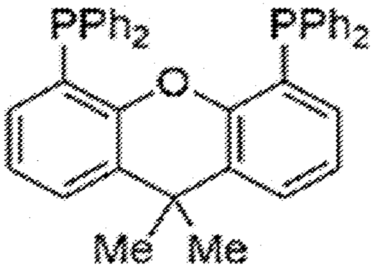
L13 - $R_4 = R_5 = R_6 = H$, $R_7 = Cy$ **CyJohnPhos**
L14 - $R_4 = OMe$, $R_5 = R_6 = H$, $R_7 = Cy$ **SPhos**
L15 - $R_4 = Oi\text{-}Pr$, $R_5 = R_6 = H$, $R_7 = Cy$ **RuPhos**
L16 - $R_4 = R_5 = i\text{-}Pr$, $R_6 = H$, $R_7 = Cy$ **XPhos**
L17 - $R_4 = R_5 = i\text{-}Pr$, $R_6 = H$, $R_7 = t\text{-}Bu$ **tBuXPhos**
L18 - $R_4 = R_5 = i\text{-}Pr$, $R_6 = OMe$, $R_7 = Cy$ **BrettPhos**
L19 - $R_4 = R_5 = i\text{-}Pr$, $R_6 = OMe$, $R_7 = t\text{-}Bu$ **tBuBrettPhos**



L20 - CataCxium A

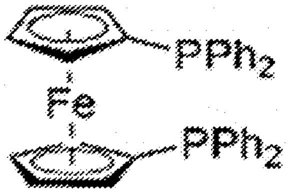


L21 - DPEphos

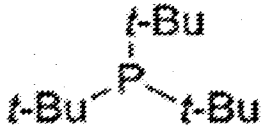


L22 - Xantphos

L23 - dppb



L24 - dppf



L25 - $Pt\text{-}Bu_3$

Figure 17 (cont)

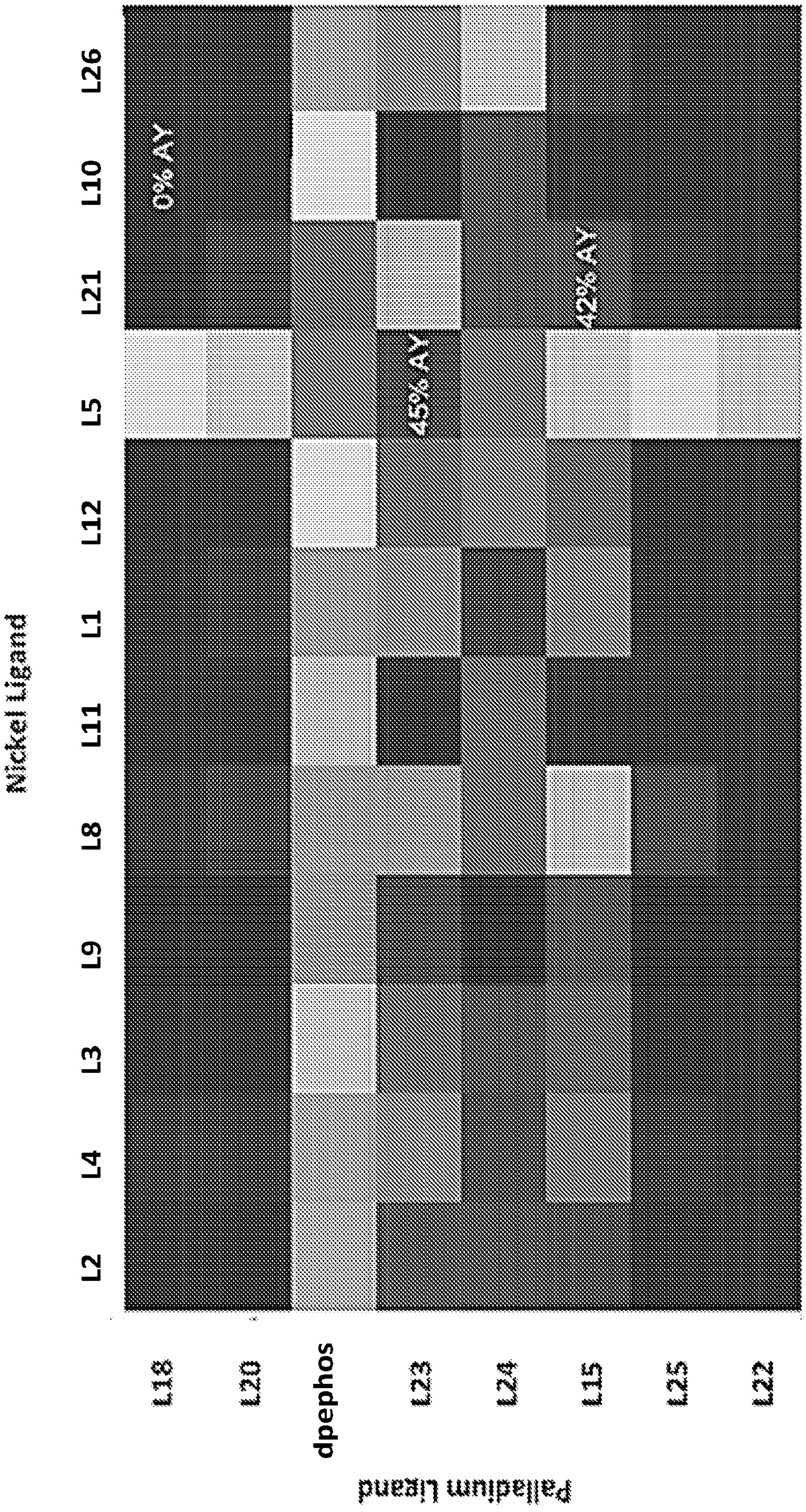

Nickel Ligand
L2
L4
L3
L9
L8
L11
L1
L12
L5
L21
L10
L26
Palladium Ligand
L18
L20
dpephos
L23
L24
L15
L25
L22
0% AY
45% AY
42% AY

Figure 18

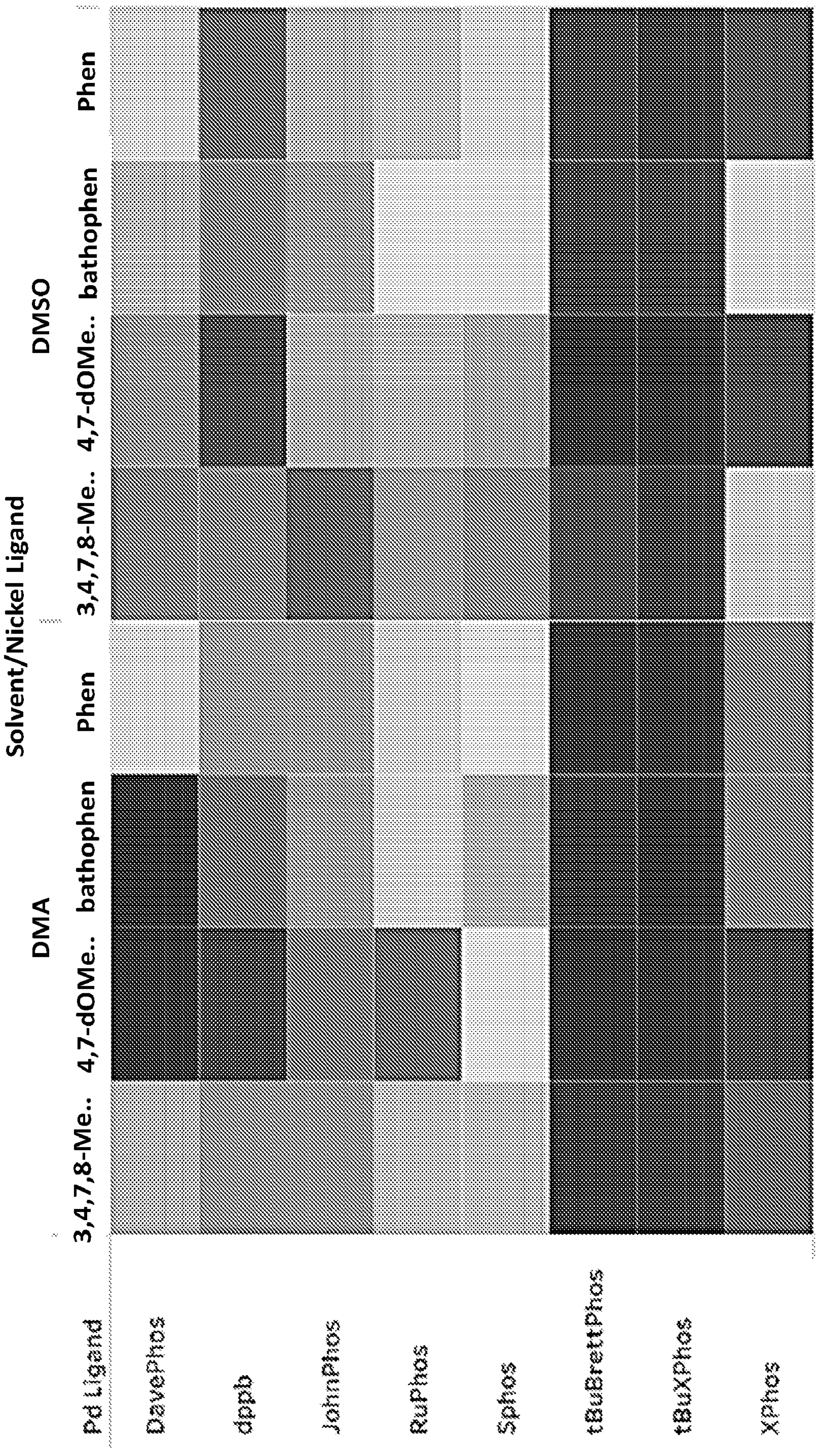

Solvent/Nickel Ligand
DMA
DMSO
3,4,7,8-Me..
4,7-dOMe..
bathophen
Phen
3,4,7,8-Me..
4,7-dOMe..
bathophen
Phen
Pd Ligand
DavePhos
dppb
JohnPhos
RuPhos
Sphos
tBuBrettPhos
tBuXPhos
XPhos

Figure 19

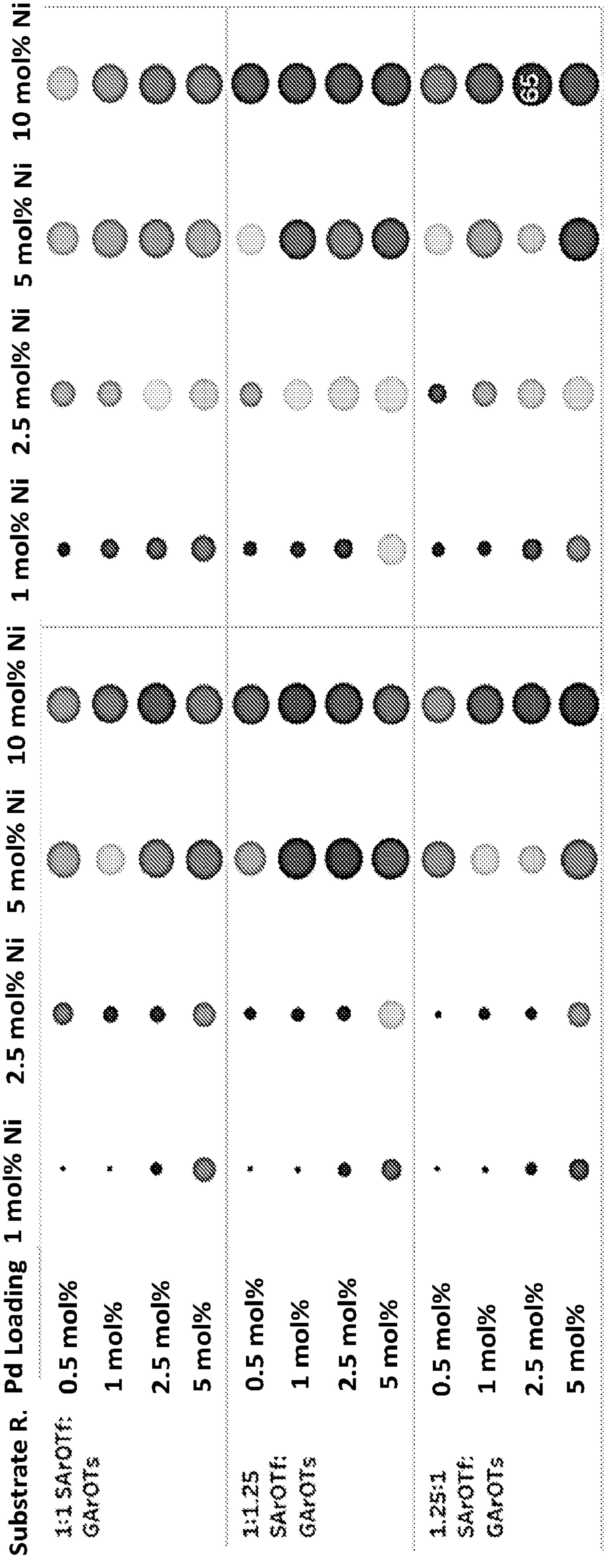

Solvent / Ni Loading
DMA
DMSO
Substrate R.
Pd Loading
1 mol% Ni
2.5 mol% Ni
5 mol% Ni
10 mol% Ni
1 mol% Ni
2.5 mol% Ni
5 mol% Ni
10 mol% Ni
1:1 SArOTf: GArOTs
0.5 mol%
1 mol%
2.5 mol%
5 mol%
1:1.25 SArOTf: GArOTs
0.5 mol%
1 mol%
2.5 mol%
5 mol%
1.25:1 SArOTf: GArOTs
0.5 mol%
1 mol%
2.5 mol%
5 mol%
65

Figure 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/35816

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C25B 3/29, C25B 3/00, C25B 3/20 ; ADD. C07C 51/00 (2022.01)

CPC - INV. C25B 3/29, C25B 3/00, C25B 3/20 ; ADD. C07C 51/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	US 5,602,228 A (Wang et al.) 11 February 1997 (11.02.1997); Abstract col2 col4 col18	1-4, 32-36 5-7, 37-39 8-11
Y A	Kang et al. 'Sulfonate Versus Sulfonate: Nickel and Palladium Multimetallic Cross-Electrophile Coupling of Aryl Triflates with Aryl Tosylates', Journal of the American Chemical Society, 02 June 2020 (02.06.2020), Vol.142, pages10634-10640; p10636	5-7, 37-39 8-11
A	Rao et al. 'Catalytic desulfitative homocoupling of sodium arylsulfinates in water using PdCl2 as the recyclable catalyst and O2 as the terminal oxidant', Green Chemistry, 18 October 2012 (18.10.2012), Vol.14, pages3436-3440; p3437	8-11
A	Zhong et al. 'Palladium-catalyzed reductive homocoupling of aryl sulfonates via cleavage of C-O bond at room temperature', Applied Organometallic Chemistry, 12 January 2017 (12.01.2017), Vol.31, pages1-5; entire document	1-11, 32-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search 09 September 2022	Date of mailing of the international search report OCT 27 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/35816

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 12-31, 40-63
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.