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(54) Title: C(SP3)-C(SP2) CROSS-COUPLING REACTION OF ORGANOZINC REAGENTS AND HETEROCYCLIC (PSEUDO)HALIDES

(57) Abstract: Provided is a method of synthesizing a $C(sp^3)$-$C(sp^2)$ cross-coupled compound comprising reacting a $C(sp^3)$ coupling partner with a $C(sp^2)$ coupling partner, a catalyst, and a solvent; wherein the $C(sp^3)$ coupling partner comprises an organic zinc reagent; and wherein the $C(sp^2)$ coupling partner comprises a heterocyclic halide or a heterocyclic pseudo halide. The method further comprises synthesis of the organic zinc reagent, wherein the synthesis comprises reacting a zinc powder with an acid, filtering, washing, and drying to obtain an activated zinc powder; and reacting the activated zinc powder with a metal iodide catalyst and a second solvent and heating for a predetermined time to obtain the organic zinc reagent.

C(SP3)-C(SP2) CROSS-COUPLING REACTION OF ORGANOZINC REAGENTS AND HETEROCYCLIC (PSEUDO)HALIDES

RELATED APPLICATIONS

[1] The present patent application claims priority to provisional U.S. Patent Application No. 62/494,142 filed July 29, 2016, which was filed by the inventors hereof and is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[2] The present subject matter relates to the development of a synthetic method involving $C(sp^3)$-$C(sp^2)$ cross-coupling reactions.

BACKGROUND

[3] Alkyl and other sp^3 carbon substitutedheterocycles are important building blocksin natural products, pharmaceuticals, and functional materials. Although tremendous methods have been developed for $C(sp^2)$-$C(sp^2)$ cross-coupling reactions, applying such methods to $C(sp^3)$-$C(sp^2)$ cross-coupling reactions is much more difficult, especially when using heterocyclic (pseudo) halides.

[4] There are a several possible reasons for the difficulty in applying $C(sp^2)$-$C(sp^2)$ cross-coupling reactions methods to $C(sp^3)$-$C(sp^2)$ cross-coupling reactions.On possibility may be because the $C(sp^3)$ based coupling partners easily undergo β-elimination or proto-demetalation in the reaction. Another possibility may be because the $C(sp^3)$ based coupling partners are usually not air-stable, which makes them hard to separate, purify, or store. Another further possibility may be that the key transmetalation step in the $C(sp^3)$-$C(sp^2)$ cross-coupling reaction is usually

very slow when compared to that of the $C(sp^2)$-$C(sp^2)$ cross-coupling reactions. In addition, another possibility may be because the reactions involving $C(sp^3)$ easily undergo undesirable side reactions. As such, an effective $C(sp^3)$-$C(sp^2)$ cross-coupling reaction usually needs the precise control of ligands, metals, and conditions.

[5] To date, several valuable methods are reported for $C(sp^3)$-$C(sp^2)$ cross-coupling reactions using alkenyl or benzyl halides, which benefit both industry and laboratory use. However, the $C(sp^3)$-$C(sp^2)$ cross-coupling reactions involving heterocyclic halides remain rarely investigated, partially because the heterocyclic (pseudo) halides usually have poorer reactivity than alkenyl or benzyl (pseudo) halides and easily undergo side reactions. For example, the alkylation of 3-bromothiophene usually uses a nickel catalyzed Kumada cross-coupling reaction. However, the preparation of the Grignard reagent becomes harder as the number of carbons on the alkyl chain increases. Moreover, for the widely used branched alkyl chains, the Grignard reagent is extremely difficult to prepare and handle. Therefore, the yields of the Kumada cross-coupling reactions using branched alkyl chains are only approximately 50%. What is worse, the numerous side reactions make the separation of the desired product very challenging. In fact, the product has a large and almost identical Rf value on the column compared with the side products (e.g. alkanes and alkenes from homo-coupling and β-elimination, respectively) and a very high boiling point, preventing purification via vacuum distillation.

[6] A recent report of synthesizing 3-(2-decyltetradecyl)thiophene gave up on using the cross-coupling reaction because of the very long 2DT chain, which indicates the difficulties of this type of cross-coupling reactions. However, the reported new synthetic strategy leads to a longer step and modest yield. In another case of synthesizing 4-alkylthiazoles, which are also a common building block in material and biological science, there is virtually no report of any

cross-coupling reactions using 4-halidethiazoles and $C(sp^3)$ coupling partners. Therefore, the synthesis of 4-alkylthiazoles requires multiple steps with a very low yield. As a result, there are merely limited reports of synthesizing linear alkyl chains substituted 4-alkylthiazoles, while there are no reports of derivatives with branched alkyl chains. As such, there is an urgent need, in light of the tremendous application of thiazoles in material and biological science and the recently revealed critical role of the branched alkyl chains in materials, for the development of $C(sp^3)$ cross-coupling reactions with 4-halidethiazoles.

SUMMARY

[7] The present subject matter provides a solution to the aforementioned problems. Namely, the present subject matter is directed to a $C(sp^3)$-$C(sp^2)$ cross-coupling reaction of organozinc reagents and heterocyclic (pseudo)halides.

[8] In an embodiment, the present subject matter is directed to a method of synthesizing a $C(sp^3)$-$C(sp^2)$ cross-coupled compound comprising reacting a $C(sp^3)$ coupling partner with a $C(sp^2)$ coupling partner, a catalyst, and a solvent; wherein the $C(sp^3)$ coupling partner comprises an organic zinc reagent; and wherein the $C(sp^2)$ coupling partner comprises a heterocyclic halide or a heterocyclic pseudo halide.

[9] In an embodiment, the method of the present subject matter further comprises synthesis of the organic zinc reagent, wherein the synthesis comprises reacting a zinc powder with an acid, filtering, washing, and drying to obtain an activated zinc powder; and reacting the activated zinc powder with a metal iodide catalyst and a second solvent and heating for a predetermined time to obtain the organic zinc reagent.

[10] In an embodiment according to the present subject matter, the $C(sp^3)$-$C(sp^2)$ cross-coupled compound is selected from the group consisting of 3-alkylthiophene, 4-alkylthiazole, 3-alkylfuran, 3-alkylselenophene, 3-alkyl-1*H*-pyrrole, bisalkylbithiophene, dialkylthiophene, 2-alkylthiophene, and 3-(substitutedalkyl)thiophene.

DETAILED DESCRIPTION

Definitions

[11] The following definitions are provided for the purpose of understanding the present subject matter and for constructing the appended patent claims.

[12] Where a range of values is provided, for example, concentration ranges, percentage ranges, or ratio ranges, it is understood that each intervening value, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the described subject matter. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and such embodiments are also encompassed within the described subject matter, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the described subject matter.

[13] For purposes of better understanding the present teachings and in no way limiting the scope of the teachings, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached

claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[14] It is noted that, as used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. As such, the use of the singular herein includes the plural (and vice versa) unless specificallystated otherwise. In addition, where the use of the term "about" is before a quantitativevalue, the present teachings also include the specific quantitative value itself, unlessspecifically stated otherwise. As used herein, the term "about" refers to a ±10% variationfrom the nominal value unless otherwise indicated or inferred.

[15] Throughout the application, descriptions of various embodiments use “comprising” language; however, it will be understood by one of skill in the art, that in some specific instances, an embodiment can alternatively be described using the language “consisting essentially of” or “consisting of.”

[16] The use of the terms "include," "includes", "including," "have," "has," or "having"should be generally understood as open-ended and non-limiting unless specifically statedotherwise.

[17] Throughout the application, where compositions are described as having, including,or comprising specific components, or where processes are described as having, including, orcomprising specific process steps, it is contemplated that compositions of the presentteachings also consist essentially of, or consist of, the recited components, and that theprocesses of the present teachings also consist essentially of, or consist of, the recited processsteps.

[18] In the application, where an element or component is said to be included in and/orselected from a list of recited elements or components, it should be understood that theelement or component can be any one of the recited elements or components, or the elementor component can be selected from a group consisting of two or more of the recited elementsor components. Further, it should be understood that elements and/or features of acomposition, an apparatus, or a method described herein can be combined in a variety ofways without departing from the spirit and scope of the present teachings, whether explicit orimplicit herein.

[19] It should be understood that the order of steps or order for performing certainactions is immaterial so long as the present teachings remain operable. Moreover, two ormore steps or actions may be conducted simultaneously.

[20] Unless defined otherwise all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the presently described subject matter pertains.

[21] As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

[22] As used herein, "alkyl" refers to a straight-chain or branched saturated hydrocarbongroup. Examples of alkyl groups include methyl (Me), ethyl (Et), propyl (e.g., n-propyl andi-propyl), butyl (e.g., n-butyl, i-butyl, sec-butyl, tert-butyl), and the like. In various embodiments, an alkyl groupcan have 1 to 40 carbon atoms (i.e., C1-C40 alkyl group). In some embodiments, alkyl groups can be substituted as described herein.

[23] As used herein, "aryl" refers to an aromatic monocyclic hydrocarbon ring system ora polycyclic ring system in which two or more aromatic hydrocarbon rings are fused (i.e.,having a bond in common with) together or at least one aromatic monocyclic hydrocarbonring is fused to one or more cycloalkyl and/or cycloheteroalkyl rings. An aryl group canhave 6 to 24 carbon

atoms in its ring system, which can includemultiple fused rings. In some embodiments, a polycyclic aryl group can have 8 to 24 carbonatoms. Any suitable ring position of the aryl group can be covalently linked to the definedchemical structure. Examples of aryl groups having only aromatic carbocyclic ring(s)include phenyl, 1-naphthyl (bicyclic), 2-naphthyl (bicyclic), anthracenyl (tricyclic),phenanthrenyl (tricyclic), pentacenyl (pentacyclic), and like groups. Examples of polycyclicring systems in which at least one aromatic carbocyclic ring is fused to one or morecycloalkyl and/or cycloheteroalkyl rings include, among others, benzo derivatives ofcyclopentane (i.e., an indanyl group, which is a 5,6-bicyclic cycloalkyl/aromatic ringsystem), cyclohexane (i.e., a tetrahydronaphthyl group, which is a 6,6-bicycliccycloalkyl/aromatic ring system), imidazoline (i.e., a benzimidazolinyl group, which is a 5,6-bicyclic cycloheteroalkyl/aromatic ring system), and pyran (i.e., a chromenyl group, which isa 6,6-bicyclic cycloheteroalkyl/aromatic ring system). Other examples of aryl groups includebenzodioxanyl, benzodioxolyl, chromanyl, indolinyl groups, and the like. In someembodiments, aryl groups can be substituted as described herein. In some embodiments, anaryl group can have one or more halogen substituents, and can be referred to as a "haloaryl"group. Perhaloaryl groups, i.e., aryl groups where all of the hydrogen atoms are replacedwith halogen atoms (e.g.,- C6F5), are included within the definition of "haloaryl." In certainembodiments, an aryl group is substituted with another aryl group and can be referred to as abiaryl group. Each of the aryl groups in the biaryl group can be substituted as disclosedherein.

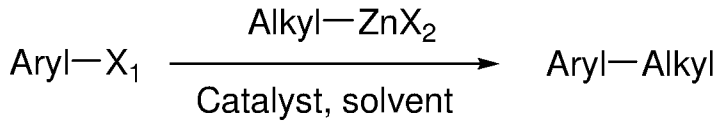
[24] As used herein, "heteroaryl" refers to an aromatic monocyclic ring systemcontaining at least one ring heteroatom selected from oxygen (O), nitrogen (N), sulfur (S),silicon (Si), and selenium (Se) or a polycyclic ring system where at least one of the ringspresent in the ring system is aromatic and contains at least one ring heteroatom. Polycyclicheteroaryl groups

include those having two or more heteroaryl rings fused together, as wellas those having at least one monocyclic heteroaryl ring fused to one or more aromaticcarbocyclic rings, non-aromatic carbocyclic rings, and/or non-aromatic cycloheteroalkylrings. A heteroaryl group, as a whole, can have, for example, 5 to 24 ring atoms and contain1-5 ring heteroatoms (i.e., 5-20 membered heteroaryl group). The heteroaryl group can beattached to the defined chemical structure at any heteroatom or carbon atom that results in astable structure. Generally, heteroaryl rings do not contain O-O, S-S, or S-O bonds.However, one or more N or S atoms in a heteroaryl group can be oxidized (e.g., pyridine Noxidethiophene S-oxide, thiophene S,S-dioxide). Examples of heteroaryl groups include,for example, the 5- or 6-membered monocyclic and 5-6 bicyclic ring systems shown below:where T is O, S, NH, N-alkyl, N-aryl, N-(arylalkyl) (e.g., N-benzyl), SiH2, SiH(alkyl),Si(alkyl)2, SiH(arylalkyl), Si(arylalkyl)2, or Si(alkyl)(arylalkyl). Examples of such heteroarylrings include pyrrolyl, furyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazolyl,tetrazolyl, pyrazolyl, imidazolyl, isothiazolyl, thiazolyl, thiadiazolyl, isoxazolyl, oxazolyl,oxadiazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, quinolyl, 2-methylquinolyl,isoquinolyl, quinoxalyl, quinazolyl, benzotriazolyl, benzimidazolyl, benzothiazolyl,benzisothiazolyl, benzisoxazolyl, benzoxadiazolyl, benzoxazolyl, cinnolinyl, lH-indazolyl,2H-indazolyl, indolizinyl, isobenzofuyl, naphthyridinyl, phthalazinyl, pteridinyl, purinyl,oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl, furopyridinyl, thienopyridinyl,pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, thienothiazolyl, thienoxazolyl,thienoimidazolyl groups, and the like. Further examples of heteroaryl groups include 4,5,6,7-tetrahydroindolyl, tetrahydroquinolinyl, benzothienopyridinyl, benzofuropyridinyl groups,and the like. In some embodiments, heteroaryl groups can be substituted as described herein.

C(sp3)-C(sp2) cross-coupling reactions

[25] In an embodiment, the present subject matter relates to $C(sp^3)$-$C(sp^2)$ cross-coupling reactions using $C(sp^3)$ based organic zinc reagents and $C(sp^2)$ aryl halides or aryl pseudo halides.

[26] The general reaction formula can be described as:



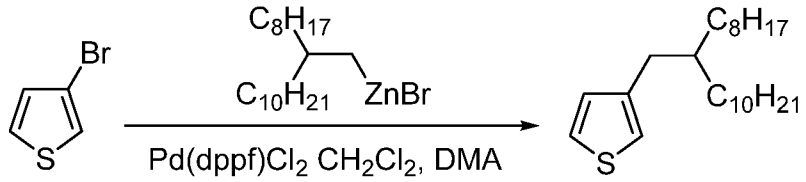
wherein each of Aryl, Alkyl, X_1, X_2, Catalyst, and solvent are set forth further herein.

[27] In the present subject matter, reactions of such a formula surprisingly exhibit very high yields. Additionally, reactionsof such formula surprisingly and beneficially yieldfew side products.As such, working up and purification of the reactions is very easy.As a non-limiting example, this type of reaction can simplify the synthesis of various useful building blocks in natural products, pharmaceuticals, and functional materials.By using this reaction, the number of synthetic steps required can be reduced to improve the overall yield of the synthetic route.

[28] In an embodiment, the present subject matter relates to a synthetic method involving $C(sp^3)$-$C(sp^2)$ cross-coupling reactions, where the $C(sp^3)$ coupling partners are organic zinc reagents, and the $C(sp^2)$ coupling partners are heterocyclic halides or heterocyclic pseudo halides. For instance, non-limiting organic zinc reagents as used herein are compounds containing carbon to zinc chemical bonds.

[29] In an embodiment, the present subject matter further relates to the organic compounds which are synthesized using the present method, the use of the present reaction in synthesizing various organic compounds, and the use of any organic compounds synthesized using the present synthetic method.

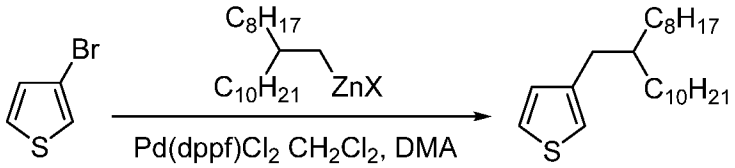
[30] Scheme 1 shown below illustrates a representative cross-coupling reaction between 3-bromothiophene and (2-octyldodecyl)zinc(II) bromide.



Scheme 1

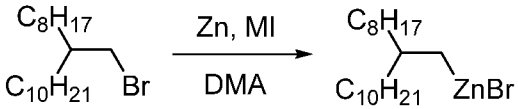
[31] Scheme 2 shown below illustrates preparation of the zinc reagent used in the present subject matter. In particular, **A** illustrates the use of alkyl halides or alkyl pseudo halides in the reaction, **B** illustrates the reaction is catalyzed by a metal iodide, and**C** illustrates the reaction is conducted in various solvents.

A



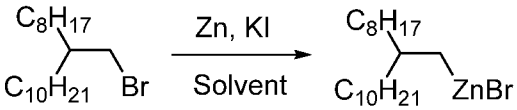
X = Br, I, OTs, OTf, $OPO(OEt)_2$

B



M = Li, Na, K, Rb, Cs, NH_4, Zn

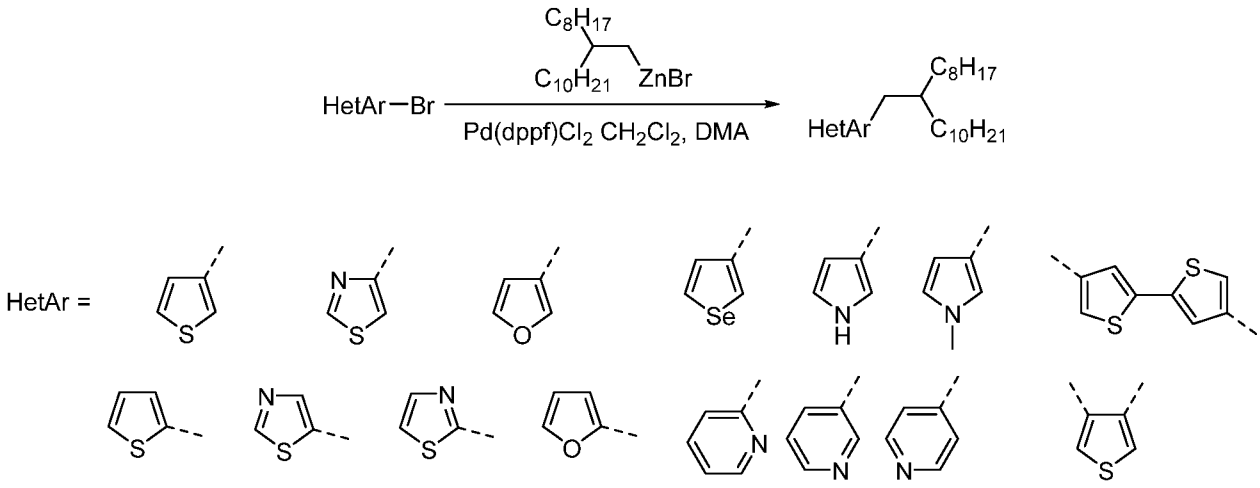
C



Solvent = DMA, DMF, THF, 1,4-dioxane, DMSO, CH_3CN, EA

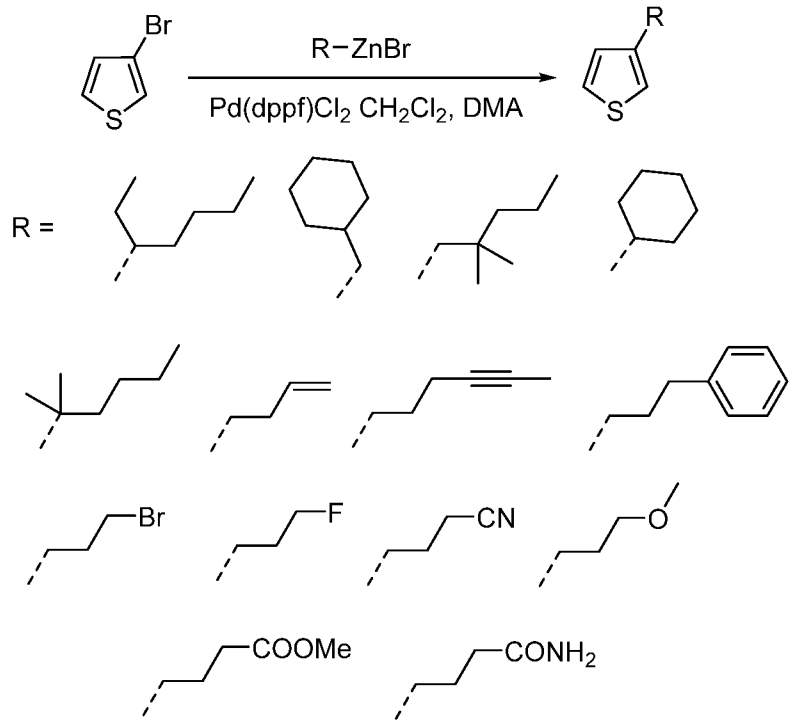
Scheme 2

[32] Scheme 3 shown below illustrates the substrate scope of the heterocyclic halides in the present subject matter.



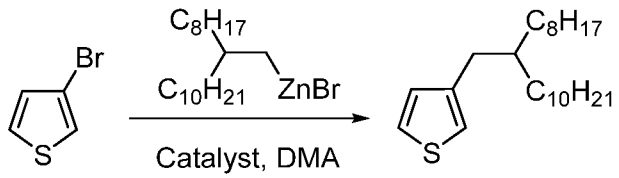
Scheme 3

[33] Scheme 4 shown below illustrates the substrate scope of the substituted alkyl (pseudo)halides in the present subject matter.



Scheme 4

[34] Scheme 5 shown below illustrates the catalyst scope in the present subject matter.



Catalyst = $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, $Pd(dppf)Cl_2$

Scheme 5

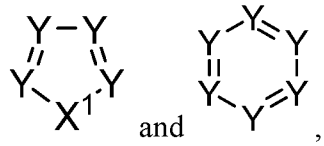
[35] In an embodiment, the present subject matter is directed to a method of synthesizing a $C(sp^3)$-$C(sp^2)$ cross-coupled compound comprising:

reacting a $C(sp^3)$ coupling partner with a $C(sp^2)$ coupling partner, a catalyst, and a solvent;

wherein the $C(sp^3)$ coupling partner comprises an organic zinc reagent; and

wherein the $C(sp^2)$ coupling partner comprises a heterocyclic halide or a heterocyclic pseudo halide.

[36] In an embodiment of the present subject matter, the heterocyclic halide is selected from the group consisting of:

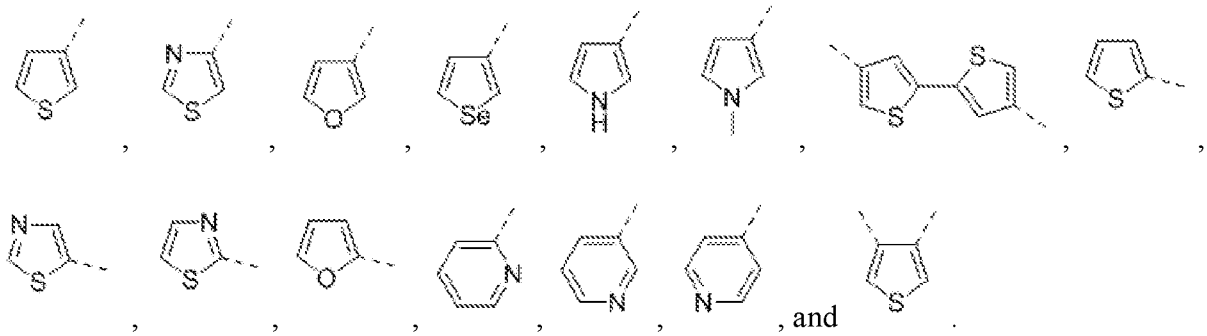


,

wherein each Y is independently selected from the group consisting of N and C-H; and

wherein each X^1 is independently selected from the group consisting of O, S, Se, Te, NH and N-R1, wherein R1 is selected from C1-30 straight-chain or branched alkyl groups.

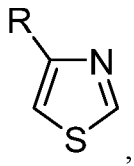
[37] In an embodiment, the heterocyclic halide of the present subject matter is selected from the group consisting of:



[38] In an embodiment, the heterocyclic pseudo halide of the present subject matter has a structure of

wherein R is selected from the group consisting of straight-chain, branched, and cyclic alkyl with 1-40 C atoms, wherein one or more non-adjacent C atoms are optionally replaced by –O–, –S–, –C(O)–, –C(O–)–O–, –O–C(O)–, –O–C(O)–O–, $–CR^0=CR^{00}–$, or –C≡C–, and wherein one or more H atoms are optionally replaced by F, Cl, Br, I, or CN or denote aryl, heteroaryl, aryloxy, heteroaryloxy, arylcarbonyl, heteroarylcarbonyl, arylcarbonyloxy, heteroarylcarbonyloxy, aryloxycarbonyl, or heteroaryloxycarbonyl having 4 to 30 ring atoms unsubstituted or substituted by one or more non-aromatic groups, wherein $R^0$and $R^{00}$are independently a straight-chain, branched, or cyclic alkyl group.

[39] In an embodiment, the heterocyclic pseudo halide has a structure of



wherein R is selected from the group consisting of straight-chain, branched, and cyclic alkyl with 1-40 C atoms, wherein one or more non-adjacent C atoms are optionally replaced by –O–, –S–, –C(O)–, –C(O–)–O–, –O–C(O)–, –O–C(O)–O–, $–CR^0=CR^{00}–$, or –C≡C–, and wherein one or more H atoms are optionally replaced by F, Cl, Br, I, or CN or denote aryl, heteroaryl, aryloxy, heteroaryloxy, arylcarbonyl, heteroarylcarbonyl, arylcarbonyloxy, heteroarylcarbonyloxy, aryloxycarbonyl, or heteroaryloxycarbonyl having 4 to 30 ring atoms unsubstituted or substituted by one or more non-aromatic groups, wherein $R^0$and $R^{00}$are independently a straight-chain, branched, or cyclic alkyl group.

[40] In an embodiment of the present subject matter, the catalyst is selected from the group consisting of a phosphorus-based ligand and any metal-based catalyst. In an embodiment, the catalyst is selected from the group consisting of a palladium-based catalyst and any phosphorus-based ligand. In an embodiment, the catalyst is selected from the group consisting of 1,1'-bis(diphenylphosphino)ferrocene (dppf) and any palladium-based catalyst. In an embodiment, the catalyst is selected from the group consisting of $Pd(dppf)Cl_2·CH_2Cl_2$ and $Pd(dppf)Cl_2$.

[41] In an embodiment, the solvent of the present subject matter is DMA or DMF.

[42] In an embodiment, the present subject matter further comprises synthesis of the organic zinc reagent, wherein the synthesis comprises:

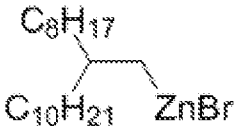
reacting a zinc powder with an acid, filtering, washing, and drying to obtain an activated zinc powder; and

reacting the activated zinc powder with a metal iodide catalyst and a second solvent and heating for a predetermined time to obtain the organic zinc reagent.

[43] In an embodiment, the metal iodide catalyst of the present subject matter is selected from the group consisting of NaI, LiI, NH_4I, RbI, CsI, ZnI_2, and KI.

[44] In an embodiment, the second solvent of the present subject matter is selected from the group consisting of CH_3CN, DMA, DMF, DMSO, Ethyl acetate, THF, and 1,4-dioxane.

[45] In an embodiment, the organic zinc reagent of the present subject matter is selected from the group consisting of:



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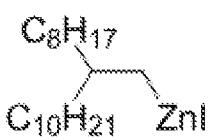

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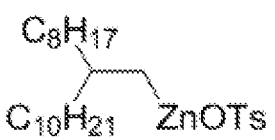

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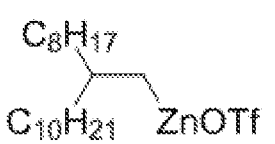
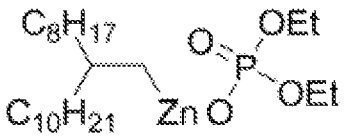
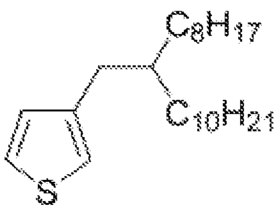
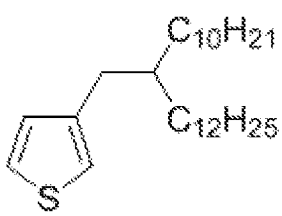
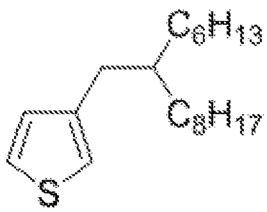
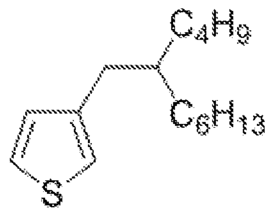


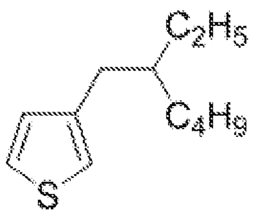
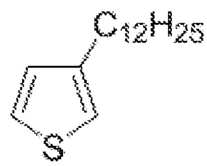
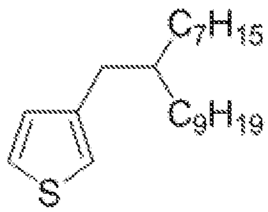
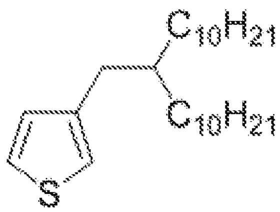
, and


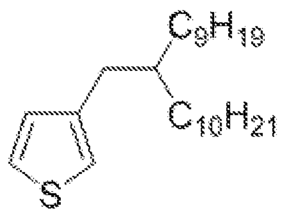
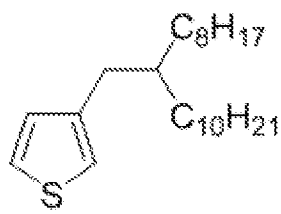
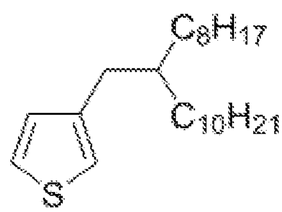
.

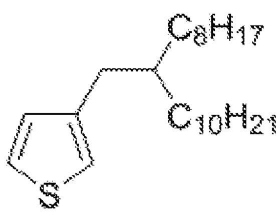
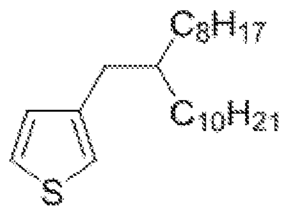
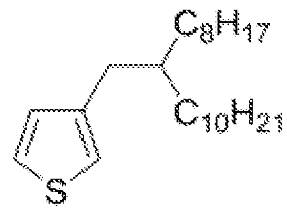
[46] In an embodiment according to the present subject matter, the $C(sp^3)$-$C(sp^2)$ cross-coupled compound is selected from the group consisting of 3-alkylthiophene, 4-alkylthiazole, 3-alkylfuran, 3-alkylselenophene, 3-alkyl-1*H*-pyrrole, bisalkylbithiophene, dialkylthiophene, 2-alkylthiophene, and 3-(substitutedalkyl)thiophene.

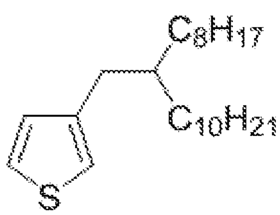
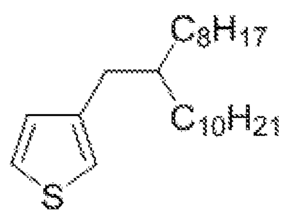
[47] In an embodiment, the 3-alkylthiophene of the present subject matter is selected from the group consisting of:

 ,  ,  ,  ,

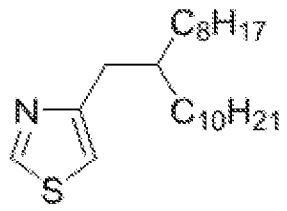
 ,  ,  ,  ,

 ,  ,  ,

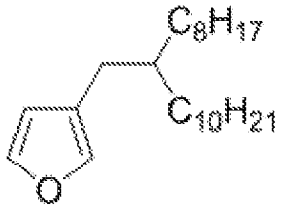
 ,  ,  ,

 , and  .

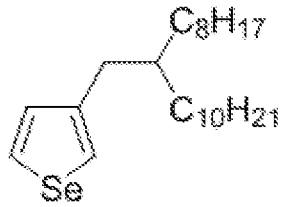
[48] In an embodiment, the 4-alkylthiazole of the present subject matter is



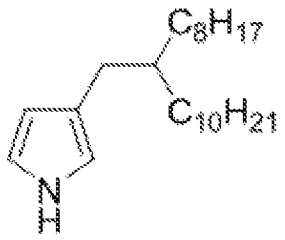
[49] In an embodiment, the 3-alkylfuran of the present subject matter is



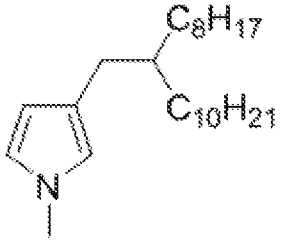
[50] In an embodiment, the 3-alkylselenophene of the present subject matter is



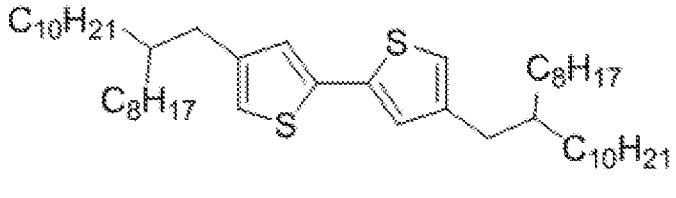
[51] In an embodiment, the 3-alkyl-1*H*-pyrrole of the present subject matter is selected from the group consisting of:



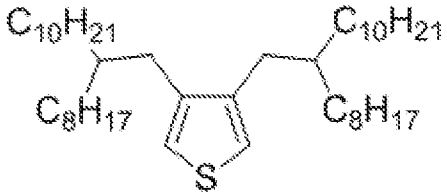
and



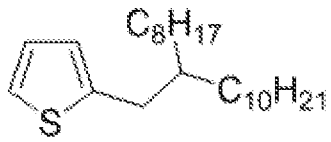
[52] In an embodiment, the bisalkylbithiophene of the present subject matter is



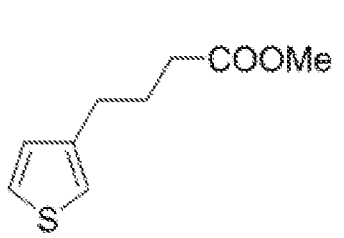
[53] In an embodiment, the dialkylthiophene of the present subject matter is



[54] In an embodiment, the 2-alkylthiophene of the present subject matter is



[55] In an embodiment, the 3-(substitutedalkyl)thiophene of the present subject matter is selected from the group consisting of:



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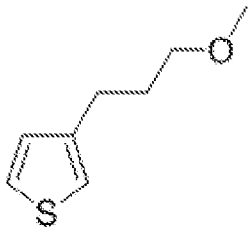

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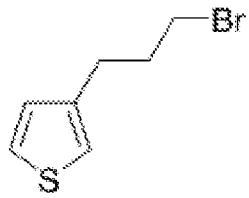

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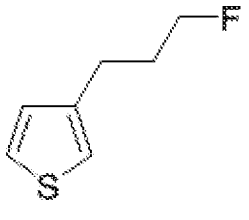

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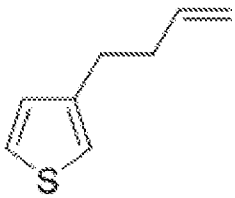

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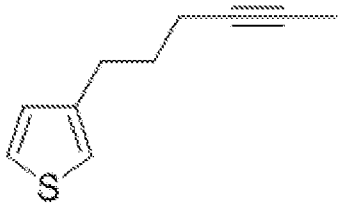

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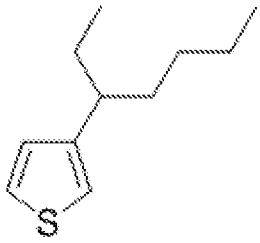

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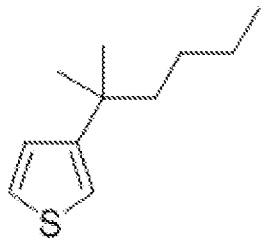

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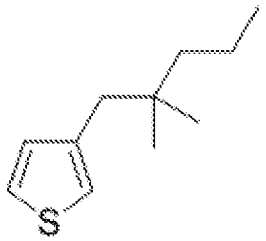

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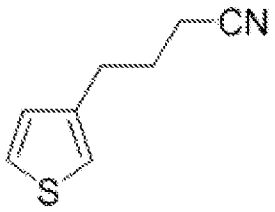

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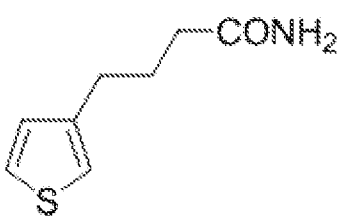

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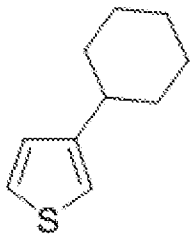

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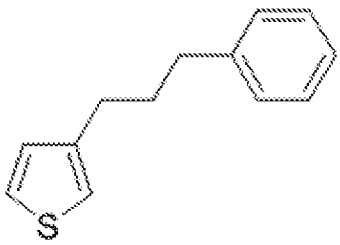


, and .

EXAMPLES

[56] The following examples are illustrative of the presently described subject matter and are not intended to be limitations therein.

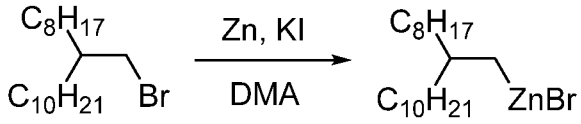
Synthesis of Zinc Reagents

[57] *Activation of zinc powder*

[58] Zinc powder (10 g, 152.9 mmol) was placed in a 100 mL conical flask. Hydrochloric acid (50 mL, 1M, 50 mmol) was added. The mixture was stirred vigorously for 10 minutes and then filtered. The solid was washed with water, acetone and diethyl ether successively. The activated zinc powder was obtained after drying under vacuum, after which it was used immediately in the next step.

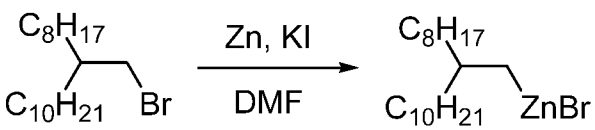
[59] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[60] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL *N*,*N*-dimethylacetamide (DMA) was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



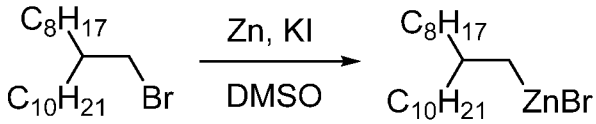
[61] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[62] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL *N*,*N*-dimethylformamide (DMF) was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



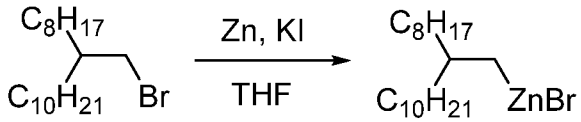
[63] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[64] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL dimethyl sulfoxide (DMSO) was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



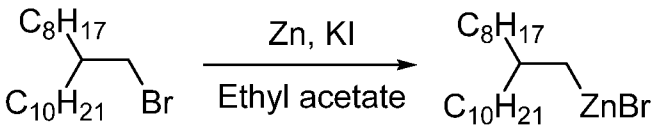
[65] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[66] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL tetrahydrofuran (THF) was heated to reflux. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



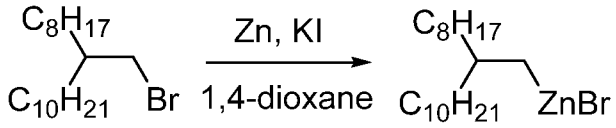
[67] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[68] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL ethyl acetate (EA) was heated to reflux. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



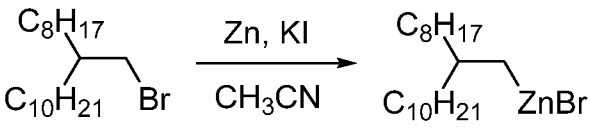
[69] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[70] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL 1,4-dioxane was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



[71] *Preparation of (2-octyldodecyl)zinc(II) bromide*

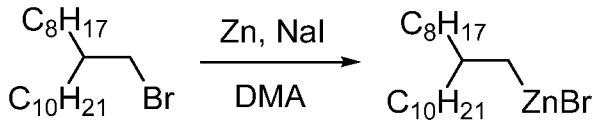
[72] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL acetonitrile (CH_3CN) was heated to reflux. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



[73] *Preparation of (2-octyldodecyl)zinc(II) bromide*

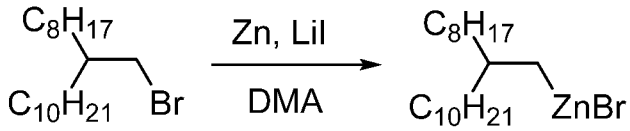
[74] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), sodium iodide (600 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was

completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



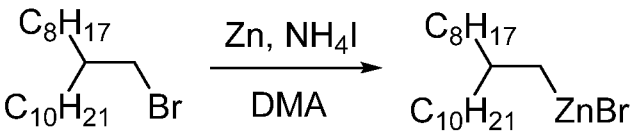
[75] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[76] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), lithium iodide (536 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



[77] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[78] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), ammonium iodide (580 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



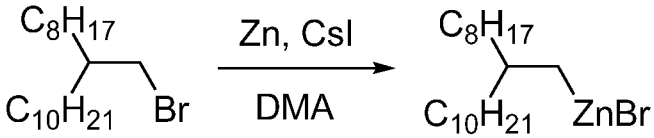
[79] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[80] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), rubidium iodide (850 mg, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL DMA was heated to

80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.

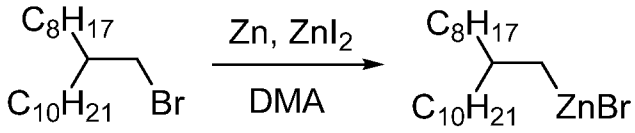
[81] *Preparation of (2-octyldodecyl)zinc(II) bromide*

[82] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), caesium iodide (1.04 g, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



[83] *Preparation of (2-octyldodecyl)zinc(II) bromide*

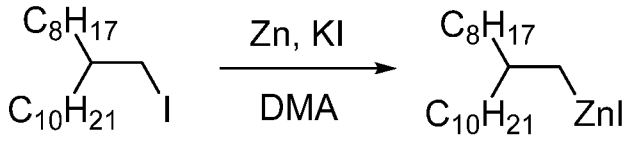
[84] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), zinc iodide (1.28 g, 4 mmol) and 9-(bromomethyl)nonadecane (7.23 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



[85] *Preparation of (2-octyldodecyl)zinc(II) iodide*

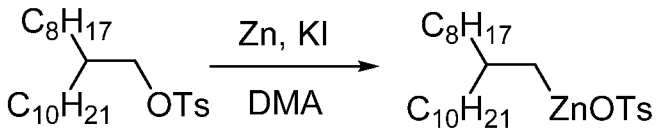
[86] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 9-(iodomethyl)nonadecane (8.17 g, 20 mmol) in 20 mL DMA was heated to

80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction is completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



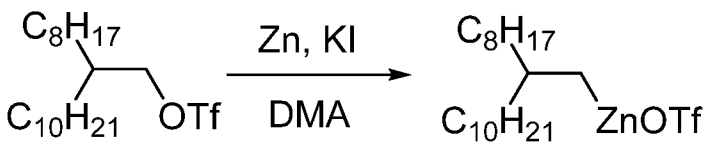
[87] *Preparation of (2-octyldodecyl)(oxo)(tosyl)zinc*

[88] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 2-octyldodecyl 4-methylbenzenesulfonate (9.05 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



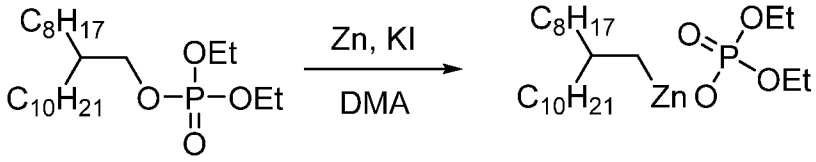
[89] *Preparation of (2-octyldodecyl)(oxo)((trifluoromethyl)sulfonyl)zinc*

[90] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and 2-octyldodecyl trifluoromethanesulfonate (8.61 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



[91] *Preparation of ((diethoxyphosphoryl)oxy)(2-octyldodecyl)zinc*

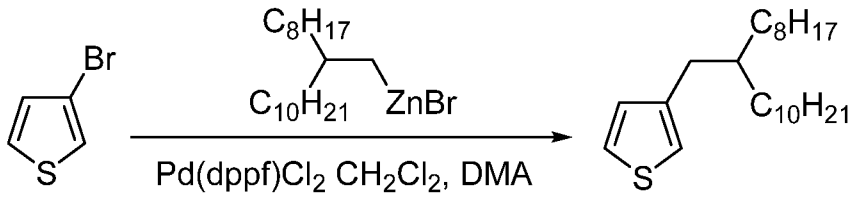
[92] A mixture of freshly activated zinc powder (1.37 g, 21 mmol), potassium iodide (664 mg, 4 mmol) and diethyl (2-octyldodecyl) phosphate (8.69 g, 20 mmol) in 20 mL DMA was heated to 80°C. After ~12 hours, at which the zinc powder was almost disappeared, the reaction was completed. The reaction is shown below. The obtained zinc reagent was directly used in the next step.



Synthesis of Alkylthiophenes

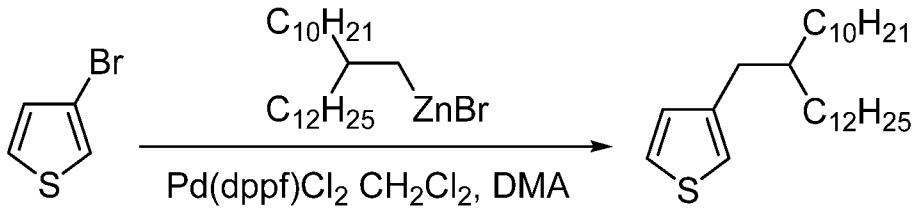
[93] *Synthesis of 3-(2-octyldodecyl)thiophene*

[94] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.21 (m, 1H), 6.90–6.88 (m, 2H), 2.56–2.55 (d, 2H, J = 6.8 Hz), 1.61–1.59 (m, 1H), 1.35–1.22 (m, 32H), 0.90–0.87 (m, 6H). The reaction is shown below.



[95] *Synthesis of 3-(2-decyltetradecyl)thiophene*

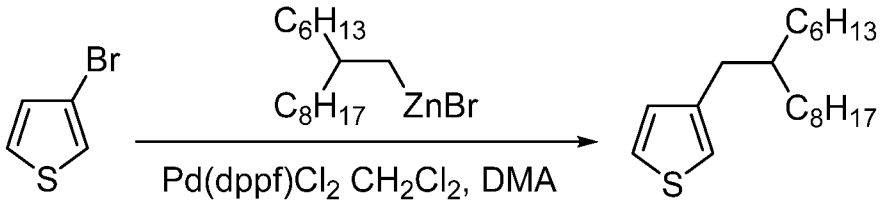
[96] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-decyltetradecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (8.0 g, 95%). The reaction is shown below.



[97] *Synthesis of 3-(2-hexyldecyl)thiophene*

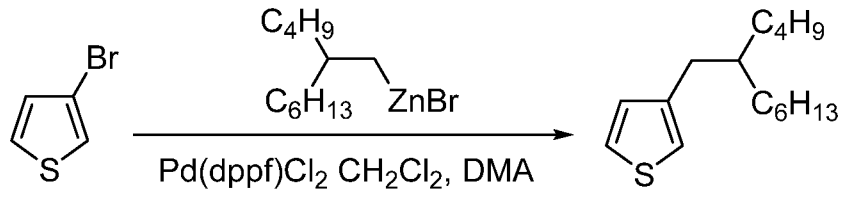
[98] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-hexyldecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The

aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (5.9 g, 95%). The reaction is shown below.



[99] *Synthesis of 3-(2-butyloctyl)thiophene*

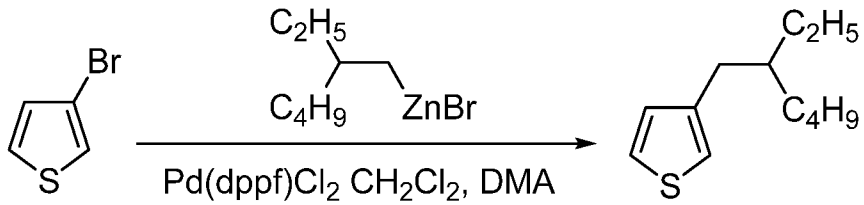
[100] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-butyloctyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (4.8 g, 95%). The reaction is shown below.



[101] *Synthesis of 3-(2-ethylhexyl)thiophene*

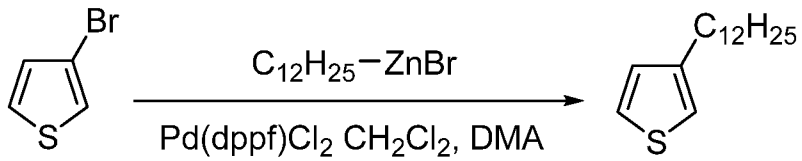
[102] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-ethylhexyl)zinc(II)

bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.7 g, 95%). The reaction is shown below.



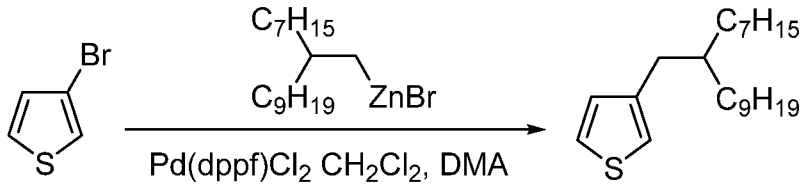
[103] *Synthesis of 3-dodecylthiophene*

[104] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared dodecylzinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (4.8 g, 95%). The reaction is shown below.



[105] *Synthesis of 3-(2-heptylundecyl)thiophene*

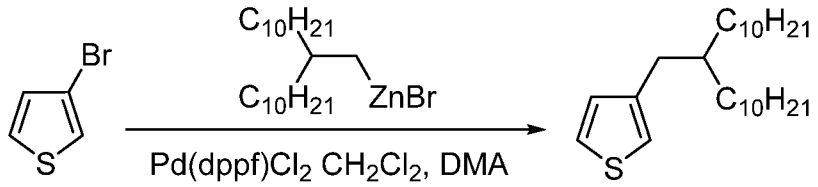
[106] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-heptylundecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.4 g, 95%). The reaction is shown below.



[107] *Synthesis of 3-(2-decyldodecyl)thiophene*

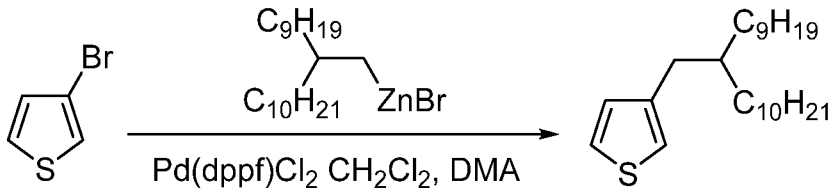
[108] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-decyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced

pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (7.5 g, 95%). The reaction is shown below.



[109] *Synthesis of 3-(2-nonyldodecyl)thiophene*

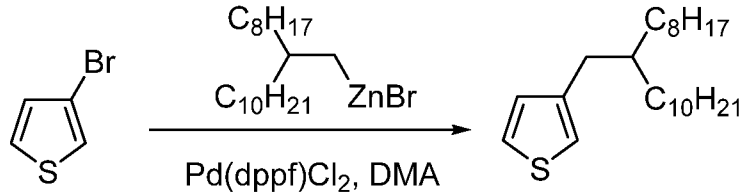
[110] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-nonyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (7.2 g, 95%). The reaction is shown below.



[111] *Synthesis of 3-(2-octyldodecyl)thiophene*

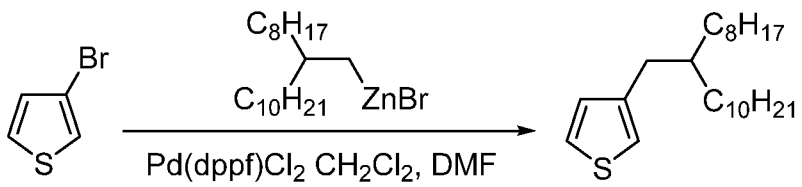
[112] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2$ (146.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL)

were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



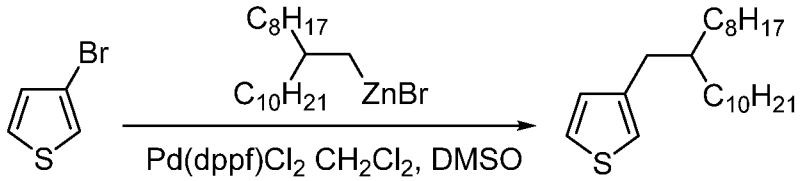
[113] *Synthesis of 3-(2-octyldodecyl)thiophene*

[114] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMF (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



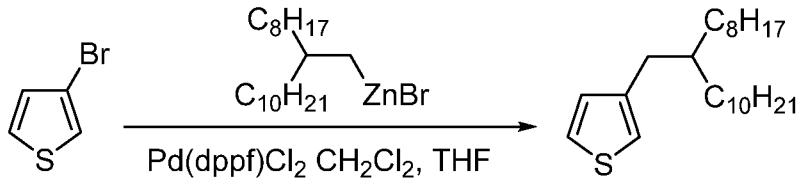
[115] *Synthesis of 3-(2-octyldodecyl)thiophene*

[116] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMSO (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



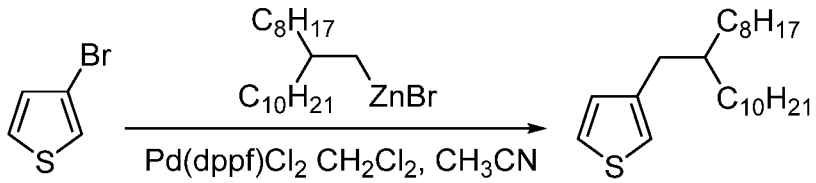
[117] *Synthesis of 3-(2-octyldodecyl)thiophene*

[118] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in THF (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred and refluxed for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



[119] *Synthesis of 3-(2-octyldodecyl)thiophene*

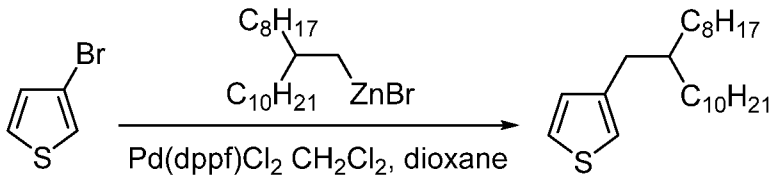
[120] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in CH_3CN (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred and refluxed for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



[121] *Synthesis of 3-(2-octyldodecyl)thiophene*

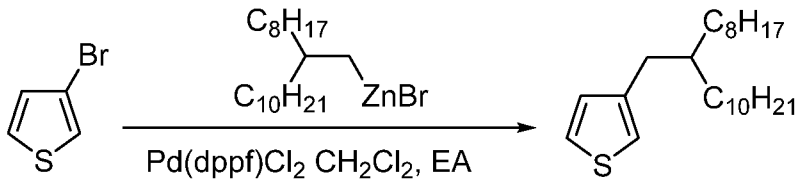
[122] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in 1,4-dioxane (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad

of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



[123] *Synthesis of 3-(2-octyldodecyl)thiophene*

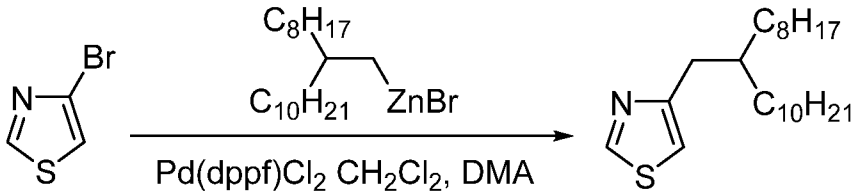
[124] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in EA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred and refluxed for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



Synthesis of Alkylthiazoles

[125] *Synthesis of 4-(2-octyldodecyl)thiazole*

[126] 4-Bromothiazole (3.28 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with water for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.95 g, 95%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 2.75 (d, J = 7.2 Hz, 2H), 2.77 (t, J = 6.7 Hz, 2H), 1.86–1.81 (m, 1H), 1.35–1.22 (m, 32H), 0.90–0.87 (m, 6H). The reaction is shown below.

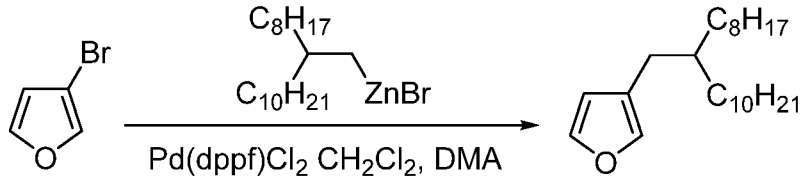


Synthesis of 3-Alkylfurans

[127] *Synthesis of 3-(2-octyldodecyl)furan*

[128] 3-Bromofuran (2.94 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with water

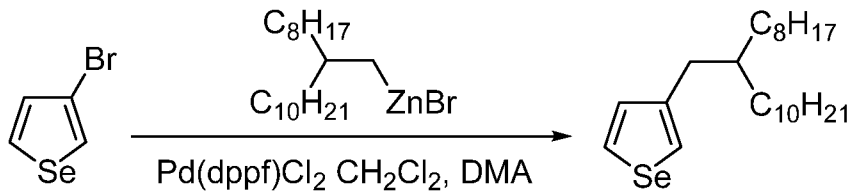
for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (4.2 g, 60%). The reaction is shown below.



Synthesis of 3-Alkylselenophenes

[129] *Synthesis of 3-(2-octyldodecyl)selenophene*

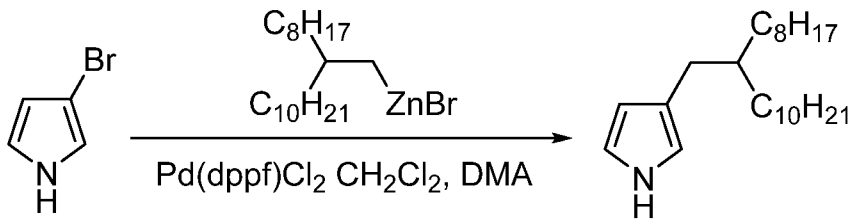
[130] 3-Bromoselenophene (4.20 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with water for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (5.2 g, 63%). The reaction is shown below.



Synthesis of 3-Alkyl-1*H*-pyrroles

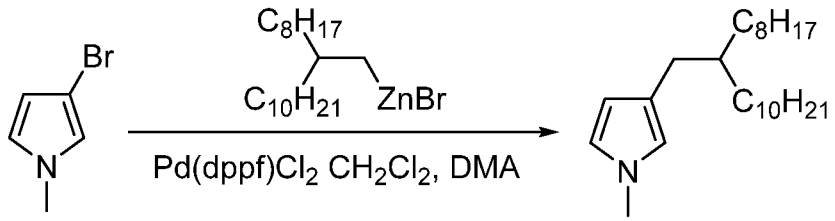
[131] *Synthesis of 3-(2-octyldodecyl)-1H-pyrrole*

[132] 3-Bromo-1*H*-pyrrole (2.92 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with water for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (4.9 g, 71%). The reaction is shown below.



[133] *Synthesis of 1-methyl-3-(2-octyldodecyl)-1H-pyrrole*

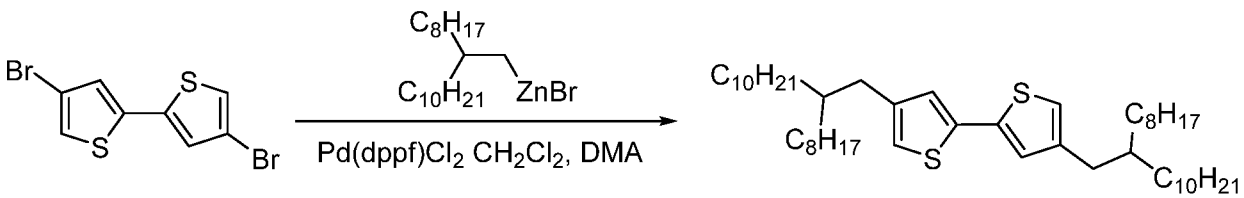
[134] 3-Bromo-1-methyl-1*H*-pyrrole (3.20 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with water for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (5.6 g, 77%). The reaction is shown below.



Synthesis of Bisalkylbithiophenes

[135] *Synthesis of 4,4'-bis(2-octyldodecyl)-2,2'-bithiophene*

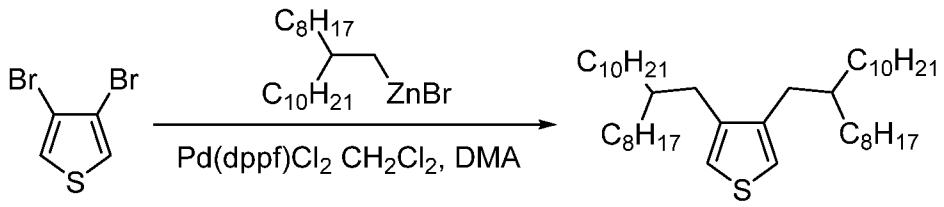
[136] 4,4'-Dibromo-2,2'-bithiophene (3.24 g, 10 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (7.0 g, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 1.2 Hz, 2H), 6.73 (s, 2H), 2.49 (d, J = 6.8 Hz, 4H), 1.61–1.59 (m, 2H), 1.35–1.22 (m, 64H), 0.90–0.87 (m, 12H). The reaction is shown below.



Synthesis of Dialkylthiophenes

[137] *Synthesis of 3,4-bis(2-octyldodecyl)thiophene*

[138] 3,4-dibromothiophene (2.42 g, 10 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.1 g, 95%). The reaction is shown below.

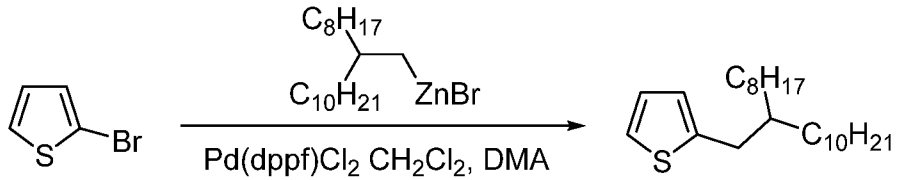


Synthesis of 2-Alkylthiophenes

[139] *Synthesis of 2-(2-octyldodecyl)thiophene*

[140] 2-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-octyldodecyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced

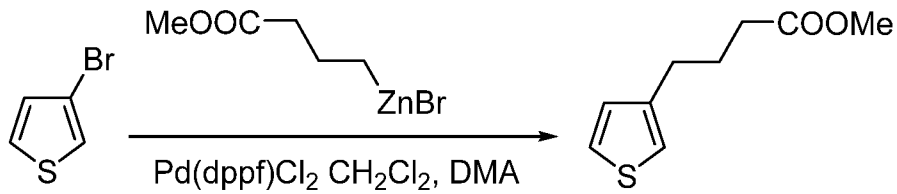
pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (6.93 g, 95%). The reaction is shown below.



Synthesis of 3-(Substitutedalkyl)thiophenes

[141] *Synthesis of methyl 4-(thiophen-3-yl)butanoate*

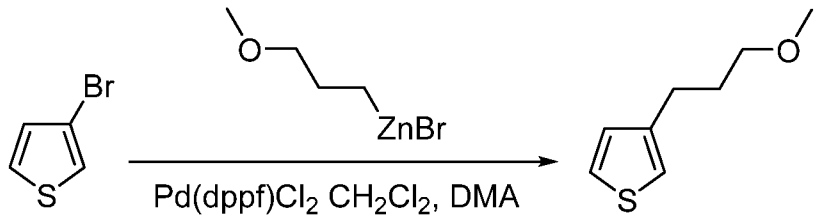
[142] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (4-methoxy-4-oxobutyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 min and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.8 g, 95%). The reaction is shown below.



[143] *Synthesis of 3-(3-methoxypropyl)thiophene*

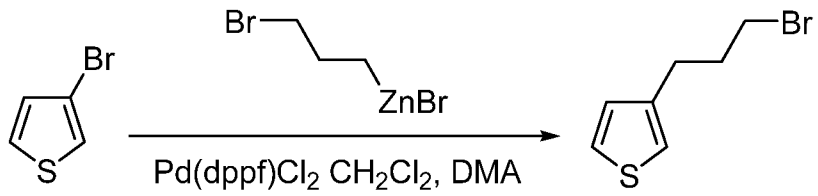
[144] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (3-

methoxypropyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.0 g, 95%). The reaction is shown below.



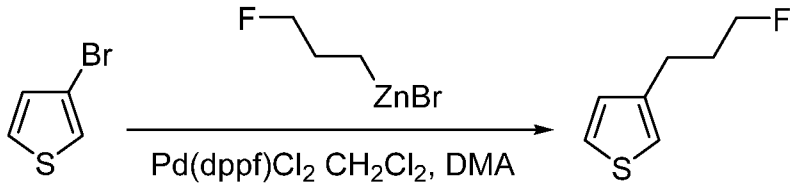
[145] *Synthesis of 3-(3-bromopropyl)thiophene*

[146] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (3-bromopropyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.4 g, 82%). The reaction is shown below.



[147] *Synthesis of 3-(3-fluoropropyl)thiophene*

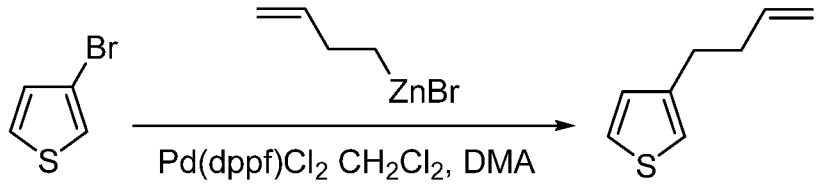
[148] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (3-fluoropropyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (2.7 g, 95%). The reaction is shown below.



[149] *Synthesis of 3-(but-3-en-1-yl)thiophene*

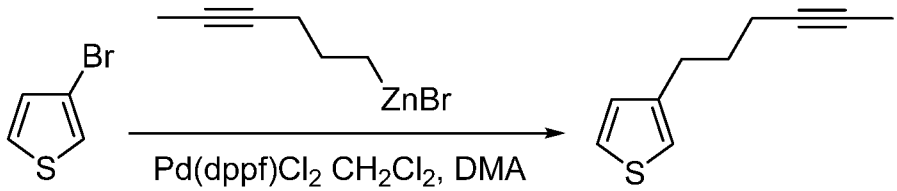
[150] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared but-3-en-1-ylzinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 min and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid

(1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (2.6 g, 95%). The reaction is shown below.



[151] *Synthesis of 3-(hex-4-yn-1-yl)thiophene*

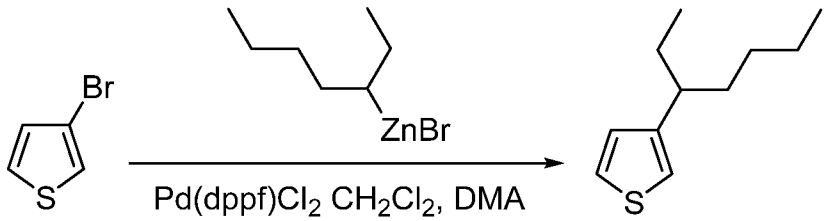
[152] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared hex-4-yn-1-ylzinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.1 g, 95%). The reaction is shown below.



[153] *Synthesis of 3-(heptan-3-yl)thiophene*

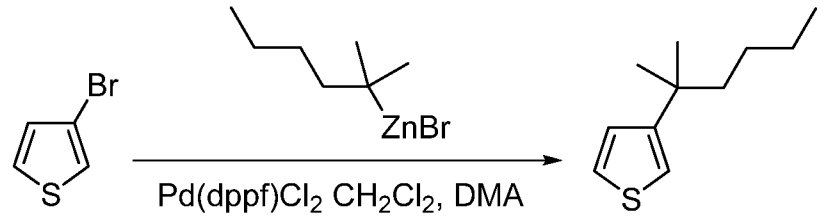
[154] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared heptan-3-ylzinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before

cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.5 g, 95%). The reaction is shown below.



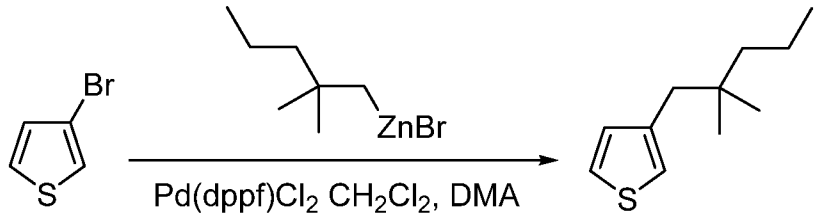
[155] *Synthesis of 3-(2-methylhexan-2-yl)thiophene*

[156] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (2-methylhexan-2-yl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.5 g, 95%). The reaction is shown below.



[157] *Synthesis of 3-(2,2-dimethylpentyl)thiophene*

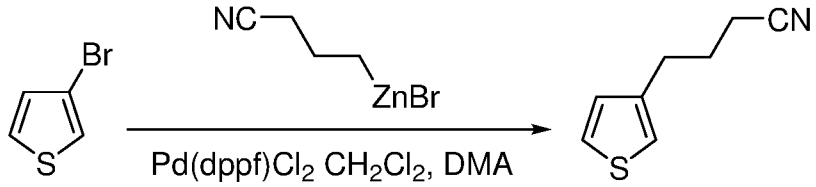
[158] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80 °C. The freshly prepared (2,2-dimethylpentyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80 °C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.5 g, 95%). The reaction is shown below.



[159] *Synthesis of 4-(thiophen-3-yl)butanenitrile*

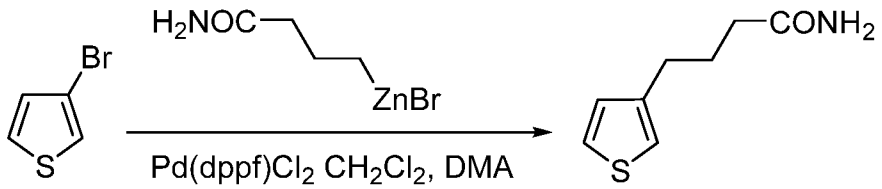
[160] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (3-cyanopropyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced

pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (2.9 g, 95%). The reaction is shown below.



[161] *Synthesis of 4-(thiophen-3-yl)butanamide*

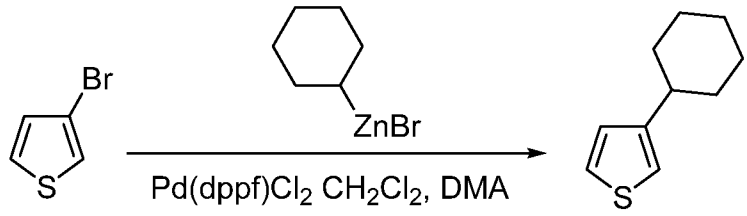
[162] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (4-amino-4-oxobutyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.2 g, 95%). The reaction is shown below.



[163] *Synthesis of 3-cyclohexylthiophene*

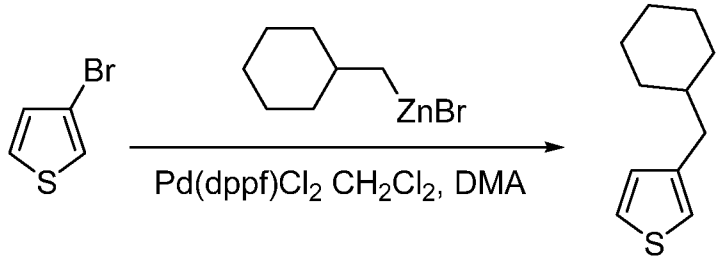
[164] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared cyclohexylzinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL)

were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.2 g, 95%). The reaction is shown below.



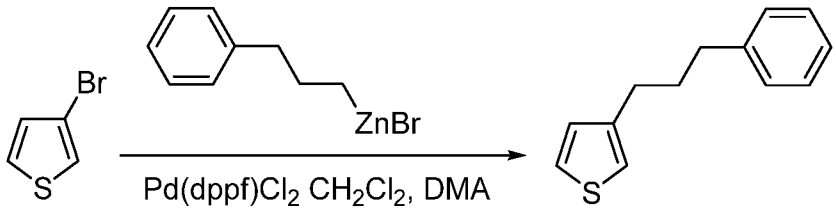
[165] *Synthesis of 3-(cyclohexylmethyl)thiophene*

[166] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (cyclohexylmethyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.4 g, 95%). The reaction is shown below.



[167] *Synthesis of 3-(3-phenylpropyl)thiophene*

[168] 3-Bromothiophene (3.26 g, 20 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (163.3 mg, 0.2 mmol) were dissolved in DMA (40 mL) and stirred at 80°C. The freshly prepared (3-phenylpropyl)zinc(II) bromide was added dropwise. The reaction mixture was stirred at 80°C for 12 hours before cooled to room temperature. Hexane (50 mL) and saturated ammonium chloride solution (50 mL) were added. The mixture was stirred for 30 minutes and passed through a pad of Celite. The aqueous layer was extracted with hexane. The combined organic layer was washed with hydrochloric acid (1M) for three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent: *n*-hexane). The product was obtained as colorless oil (3.8 g, 95%). The reaction is shown below.



[169] With the information contained herein, various departures from precise descriptions of the present subject matter will be readily apparent to those skilled in the art to which the present subject matter pertains, without departing from the spirit and the scope of the below claims. The present subject matter is not considered limited in scope to the procedures, properties, or components defined, since the preferred embodiments and other descriptions are intended only to be illustrative of particular aspects of the presently provided subject matter. Indeed, various modifications of the described modes for carrying out the present subject matter which are obvious to those skilled in chemistry, biochemistry, or related fields are intended to be within the scope of the following claims.

We claim:

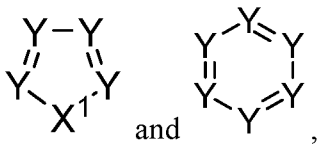
1. A method of synthesizing a $C(sp^3)$-$C(sp^2)$ cross-coupled compound comprising:

reacting a $C(sp^3)$ coupling partner witha $C(sp^2)$ coupling partner, a catalyst, and a solvent;

wherein the $C(sp^3)$ coupling partner comprises an organic zinc reagent; and

wherein the $C(sp^2)$ coupling partner comprises a heterocyclic halide or a heterocyclic pseudo halide.

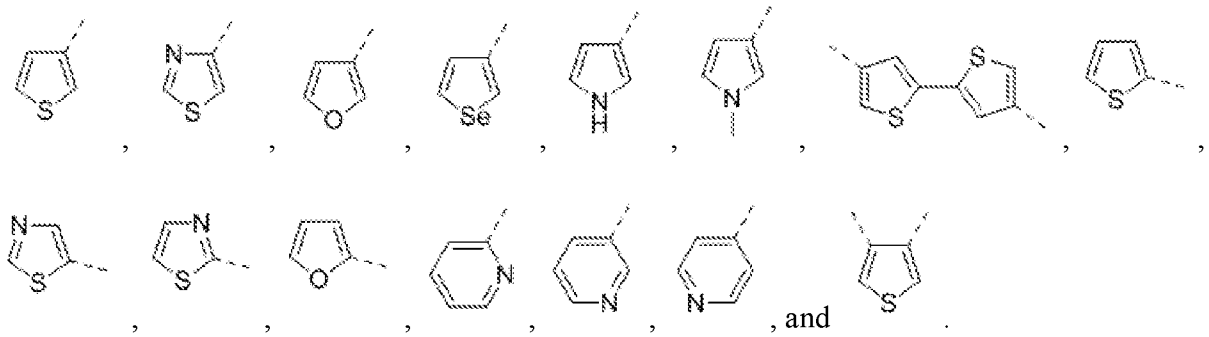
2. The method of claim 1, wherein the heterocyclic halide is selected from the group consisting of:



wherein each Y is independently selected from the group consisting of N and C-H; and

wherein each X^1 is independently selected from the group consisting of O, S, Se, Te, NH and N-R1, wherein R1 is selected from C1-30 straight-chain or branched alkyl groups.

3. The method of claim 2, wherein the heterocyclic halide is selected from the group consisting of:

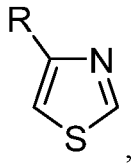


4. The method of claim 1, wherein the heterocyclic pseudo halide has a structure of

,

wherein R is selected from the group consisting of straight-chain, branched, and cyclic alkyl with 1-40 C atoms, wherein one or more non-adjacent C atoms are optionally replaced by –O–, –S–, –C(O)–, –C(O–)–O–, –O–C(O)–, –O–C(O)–O–, $–CR^0=CR^{00}–$, or –C≡C–, and wherein one or more H atoms are optionally replaced by F, Cl, Br, I, or CN or denote aryl, heteroaryl, aryloxy, heteroaryloxy, arylcarbonyl, heteroarylcarbonyl, arylcarbonyloxy, heteroarylcarbonyloxy, aryloxycarbonyl, or heteroaryloxycarbonyl having 4 to 30 ring atoms unsubstituted or substituted by one or more non-aromatic groups, wherein $R^0$and $R^{00}$are independently a straight-chain, branched, or cyclic alkyl group.

5. The method of claim 1, wherein the heterocyclic pseudo halide has a structure of



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wherein R is selected from the group consisting of straight-chain, branched, and cyclic alkyl with 1-40 C atoms, wherein one or more non-adjacent C atoms are optionally replaced by –O–, –S–, –C(O)–, –C(O–)–O–, –O–C(O)–, –O–C(O)–O–, $–CR^0=CR^{00}–$, or –C≡C–, and wherein one or more H atoms are optionally replaced by F, Cl, Br, I, or CN or denote aryl, heteroaryl, aryloxy, heteroaryloxy, arylcarbonyl, heteroarylcarbonyl, arylcarbonyloxy, heteroarylcarbonyloxy, aryloxycarbonyl, or heteroaryloxycarbonyl having 4 to 30 ring atoms unsubstituted or substituted

by one or more non-aromatic groups, wherein $R^0$and $R^{00}$are independently a straight-chain, branched, or cyclic alkyl group.

6. The method of claim 1, wherein the catalyst is selected from the group consisting of a phosphorus-based ligand and any metal-based catalyst.

7. The method of claim 6, wherein the catalyst is selected from the group consisting of a palladium-based catalyst and any phosphorus-based ligand.

8. The method of claim 7, wherein the catalyst is selected from the group consisting of 1,1'-bis(diphenylphosphino)ferrocene (dppf) and any palladium-based catalyst.

9. The method of claim 8, wherein the catalyst is selected from the group consisting of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$and $Pd(dppf)Cl_2$.

10. The method of claim 1, wherein the solvent is DMA or DMF.

11. The method of claim 1, further comprising synthesis of the organic zinc reagent, wherein the synthesis comprises:

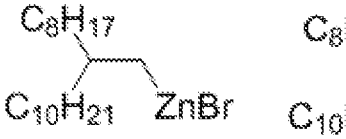
reactinga zinc powder with an acid, filtering, washing, and drying to obtain an activated zinc powder; and

reacting the activated zinc powder with a metal iodide catalyst and a second solvent and heating for a predetermined time to obtain the organic zinc reagent.

12. The method of claim 11, wherein the metal iodide catalyst is selected from the group consisting of NaI, LiI, NH_4I, RbI, CsI, ZnI_2, and KI.

13. The method of claim 11, wherein the second solvent is selected from the group consisting of CH_3CN, DMA, DMF, DMSO, Ethyl acetate, THF, and 1,4-dioxane.

14. The method of claim 1, wherein the organic zinc reagent is selected from the group consisting of:



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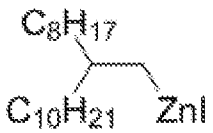

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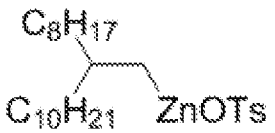

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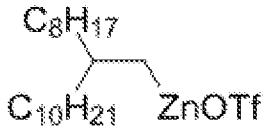
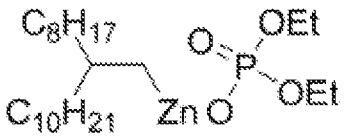


, and


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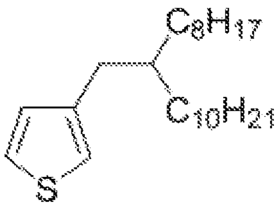
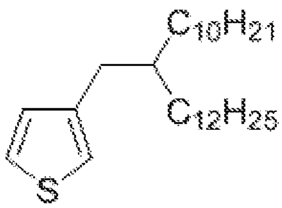
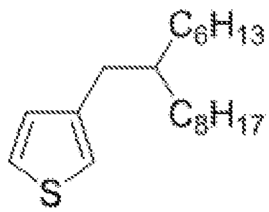
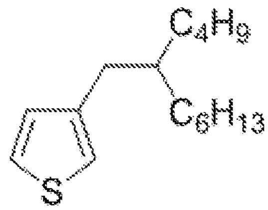
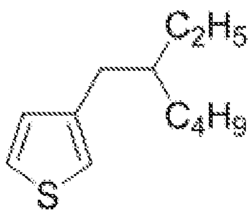
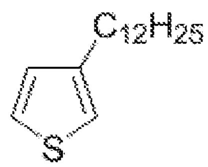
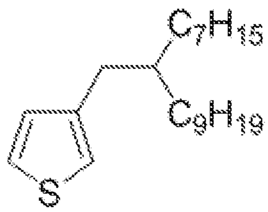
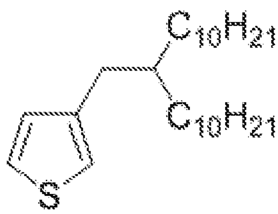
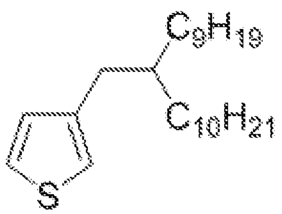
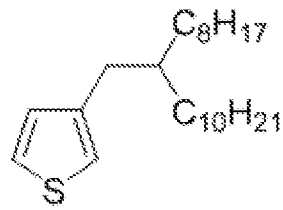
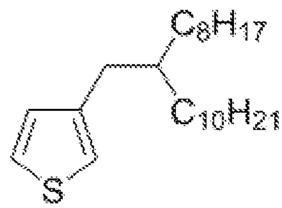
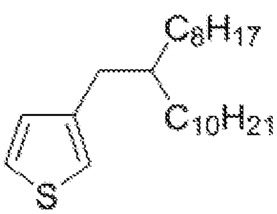
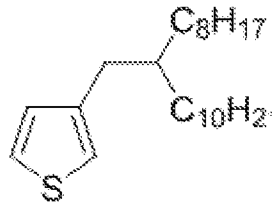
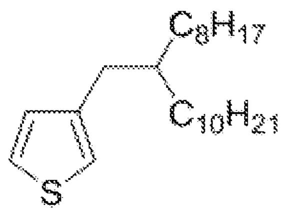
15. The method of claim 1, wherein the $C(sp^3)$-$C(sp^2)$ cross-coupled compound is selected from the group consisting of 3-alkylthiophene, 4-alkylthiazole, 3-alkylfuran, 3-alkylselenophene, 3-alkyl-1*H*-pyrrole, bisalkylbithiophene, dialkylthiophene, 2-alkylthiophene, and 3-(substitutedalkyl)thiophene.

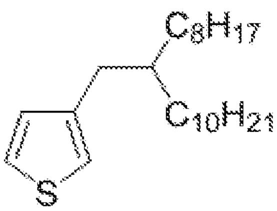
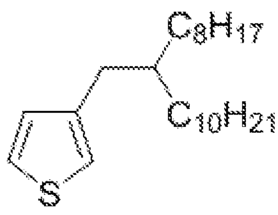
16. The method of claim 15, wherein the 3-alkylthiopheneis selected from the group consisting of:

 ,  ,  ,  ,

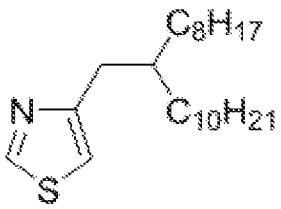
 ,  ,  ,  ,

 ,  ,  ,

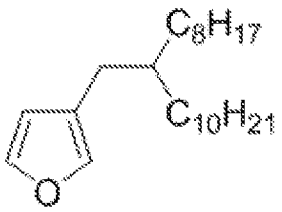
 ,  ,  ,

 , and  .

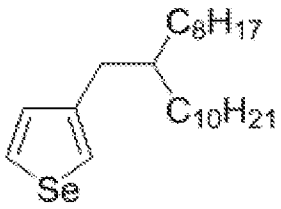
17. The method of claim 15, wherein the 4-alkylthiazoleis



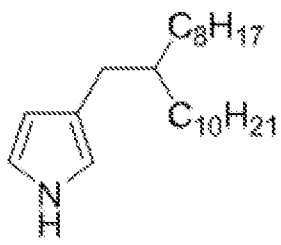
18. The method of claim 15, wherein the 3-alkylfuran is



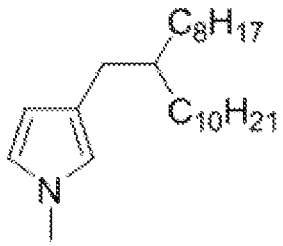
19. The method of claim 15, wherein the 3-alkylselenophene is



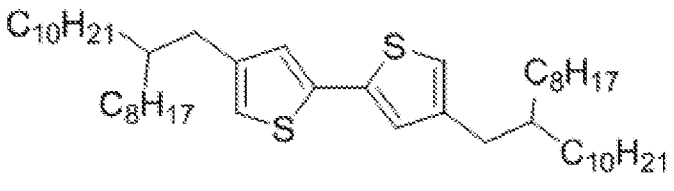
20. The method of claim 15, wherein the 3-alkyl-1*H*-pyrrole is selected from the group consisting of:



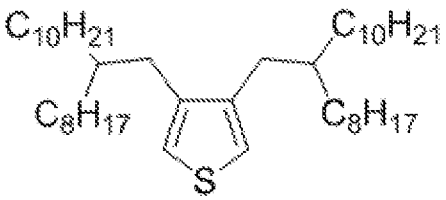
and



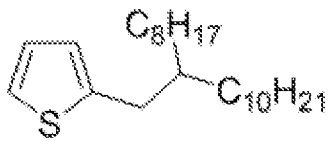
21. The method of claim 15, wherein the bisalkylbithiophene is



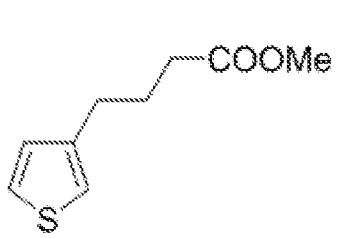
22. The method of claim 15, wherein thedialkylthiophene is



23. The method of claim 15, wherein the 2-alkylthiophene is



24. The method of claim 15, wherein the 3-(substitutedalkyl)thiophene is selected from the group consisting of:



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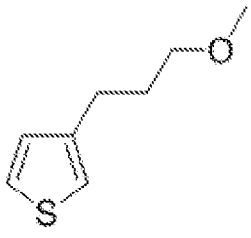

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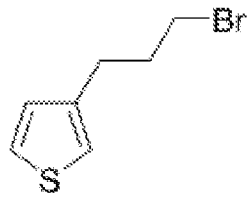

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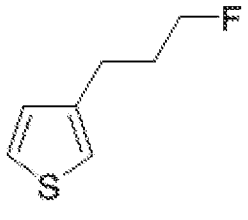

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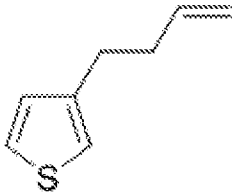

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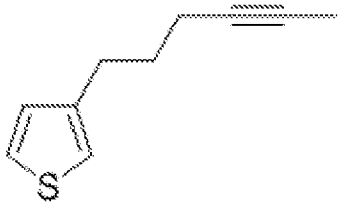

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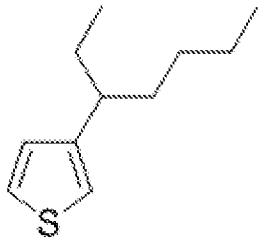

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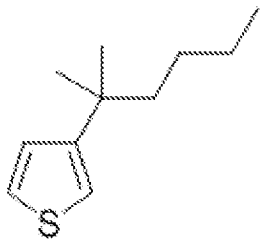

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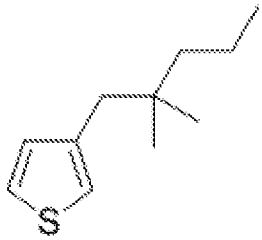

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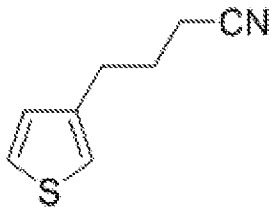

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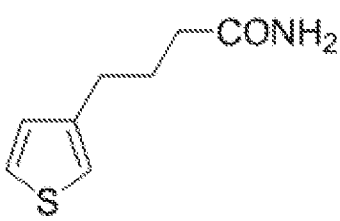

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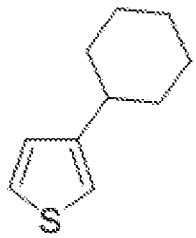

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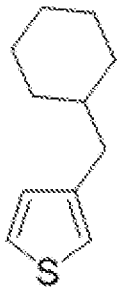

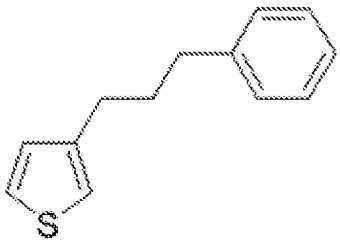

, and .

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/094898

A. CLASSIFICATION OF SUBJECT MATTER

C07B 37/04(2006.01)i; C07D 207/32(2006.01)i; C07D 213/04(2006.01)i; C07D 277/22(2006.01)i; C07D 307/38(2006.01)i; C07D 333/06(2006.01)i; C07D 345/00(2006.01)i

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)

C07B37/-, C07D207/-, C07D213/-, C07D277/-, C07D307/-, C07D333/-, C07D345/-

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

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

CNPAT, CNKI, WPI, EPODOC, ISI Web of Knowledge, Registry, Caplus: HONG KONG UNIWERSITY OF SCIENCE AND THCHNOLOGY, cross w coupl+, organic w zinc, metal w iodide, heterocyclic w halide, pseudo w halide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE LANG, R. -J. et al. "The nickel and palladium catalyzed stereoselective cross coupling of cyclopropyl nucleophiles with aryl halides" *Synthetic Communications*, Vol. 28, No. 2, 31 December 1998 (1998-12-31), ISSN: 0039-7911, pp. 225-232	1-8, 14-24
Y	DE LANG, R. -J. et al. "The nickel and palladium catalyzed stereoselective cross coupling of cyclopropyl nucleophiles with aryl halides" *Synthetic Communications*, Vol. 28, No. 2, 31 December 1998 (1998-12-31), ISSN: 0039-7911, pp. 225-232	11-13
X	KUMADA, Tatsuya et al. "Direct arylation polycondensation of thienothiophenes with various dibromoarylenes" *Bulletin of the Chemical Society of Japan*, Vol. 88, No. 11, 12 August 2015 (2015-08-12), ISSN: 1348-0634, pp. 1530–1535	1, 6-8

☑ 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

"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	Date of mailing of the international search report
06 October 2017	**27 October 2017**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**LI,Bing**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)010-82246673**

INTERNATIONAL SEARCH REPORT

International application No.
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THAPA, Surendra et al. "Ligand-Free Copper-Catalyzed Negishi Coupling of Alkyl-, Aryl-, and Alkynylzinc Reagents with Heteroaryl Iodides" *Angewandte Chemie, International Edition*, Vol. 54, No. 28, 28 May 2015 (2015-05-28), ISSN: 1433-7851, pp. 8236-8240	1-3, 6-8, 10
X	US 2006014737 A1 (JOHN VARGHESE ET AL.) 19 January 2006 (2006-01-19) example 24	1-3, 6-9
X	WO 2005070407 A1 (ELAN PHARMA CEUTICALS, INC. ET AL.) 04 August 2005 (2005-08-04) example 12	1-3, 6-9
X	CN 1694870 A (ELAN PHARMA CEUTICALS, INC. ET AL.) 09 November 2005 (2005-11-09) example 105	1-3, 6-9
X	CN 103347882 A (ARRAY BIOPHARMA, INC.) 09 October 2013 (2013-10-09) example 32 step A and example 33 step A	1-3, 6-9
Y	CN 1861609 A (DALIAN JINGYUAN CLECTRONIC GASEOUS RESEARCH CENTER CO., LTD.) 15 November 2006 (2006-11-15) abstract	11-13

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Information on patent family members

International application No.
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