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(54) Title: TRANSITION METAL-CATALYZED ALKYLATION OF C-H BONDS WITH ORGANOBORON REAGENTS

(57) Abstract: One aspect of the present invention relates to methods for functionalization of 2-arylpyridine and arylpyrazoles with organoboron reagents in the presence of a transition metal catalyst to furnish alkylated arylpyridines and arylpyrazoles via regioselective functionalization of sp^2 -hybridized C-H bonds at a position ortho to the point of attachment of the pyridine or pyrazole ring to the aromatic nucleus, hi other embodiments, the present invention provides for alkylation of sp^3 -hybridized C-H bonds in alkylpyridines.



WO 2008/024953 A2

***Transition Metal-Catalyzed Alkylation of C–H
Bonds with Organoboron Reagents***

RELATED APPLICATIONS

5 This application claims the benefit of priority to United States Provisional Patent Application serial number 60/840,078, filed August 25, 2006.

BACKGROUND OF THE INVENTION

10 The controlled functionalization of C–H bonds is one of the most challenging and difficult reactions in organic chemistry, generally requiring either a stoichiometric amount of a heavy-metal salt or a catalyst containing a transition metal (such as Pd, Pt, Rh, Ru, and Cu). New catalytic synthetic methods in chemistry that satisfy increasingly strict environmental constraints are in great demand by the pharmaceutical and chemical industries. In addition, novel catalytic procedures are necessary to produce the new classes of compounds that are becoming the targets of molecular and biomolecular research.

15 Among heterocyclic compounds, functionalized pyridine moieties are used extensively as intermediates in the synthesis of drugs, pharmaceuticals, herbicides, and agrochemicals. Shimizu et al. Jap. Pat. No. JP 01261367A.

 The development of transition metal-mediated C–H activation and C–C bond forming reactions directed by functional groups has witnessed substantial progress in the past three decades. For reviews see Kakiuchi et al. (2003) *Adv. Synth. Catal.*, 345:1077 and

20 *Handbook of C–H Transformations*, Vol. 1-2; Dyker, G. Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005. A wide range of metal catalysts, including Ru, Rh, Pt, Pd, and Cu, have been exploited with varying degrees of success. See Dyker (1999) *Angew. Chem. Int. Ed. Engl.* 38:1698; Pfeffer (2002) *Chem. Rev.* 102:1731; Murai et al. (1999)

25 *Nature* 366:529; Jun et al. (1997) *JOC* 62:1200; Lenges et al. (1999) *JACS* 121:6616; Ellman et al. (2001) *JACS* 123:9692.

 Recently, it has emerged that catalytic activation of sp^3 and sp^2 hybridized C–H bonds in readily available and inexpensive starting materials provides an array of new transformations that are welcome additions to the tool boxes of synthetic organic chemists

30 and the fine-chemicals industry. See Sezen et al. (2002) *JACS* 124:13372; Johnson et al. (2002) *JACS* 124:6900; Dyker (1999) *Angew. Chem. Int. Ed. Engl.* 38:1699; Chen et al. (2000) *Science* 287:1995; Cho et al. (2002) *Science* 295:305. In particular, selective

activation of sp^2 and sp^3 hybridized C–H bonds is a potentially attractive strategy for developing catalytic reactions of broader applications.

A wide range of efficient Ru- and Rh-catalyzed alkylations and arylations of aryl C–H bonds have been achieved with olefins or aryl organometallic reagents. See Murai (ibid.); Oi et al. (1998) *Chem. Commun.* 2439; Lenges (ibid.); Kakiuchi et al. (2003) *JACS* 125:1698; Lim et al. (2004) *Org. Lett.* 6:4687; Thalji et al. (2004) *JACS* 126:7192; Ackermann et al. (2006) *Angew. Chem., Int. Ed.* 45:2619. For Cu-catalyzed cross-dehydrogenation-coupling between sp^3 and sp^3 hybridized C–H bonds, see Li et al. (2005) *JACS* 127:3672. Pd-catalyzed alkenylation of aryl C–H bonds via Pd^{II}/Pd^0 catalysis has been reported. See Jia et al. (2001) *Acc. Chem. Res.* 34:633; Boele et al. (2002) *JACS* 124:1586. Significant results have also been obtained using $Ar_2I^+X^-$ or ArX as the arylating reagents for sp^2 and sp^3 hybridized C–H bonds involving Pd^{II}/Pd^{IV} catalysis. See Kalyani et al. (2005) *JACS* 127:7330; Daugulis and Zaitsev (2005) *Angew. Chem., Int. Ed.* 44:2; Shabashov and Daugulis (2005) *Org. Lett.* 7:3657; Shabashov and Daugulis (2005) *JACS* 127:13154. An alternative strategy involving C–H activation by an intramolecular $ArPdX$ moiety has been developed. See Dyker (1994) *Angew. Chem., Int. Ed.* 33:103; Catellani et al. (1997) *Angew. Chem., Int. Ed.* 36:119; Campo et al. (2003) *JACS* 125:11506; Campeau et al. (2004) *JACS* 126:9186; Bressy et al. (2005) *JACS* 127:13148; Dong and Hu (2006) *Angew. Chem., Int. Ed.* 45:2289. In this context, an impressive example of arylation of sp^3 hybridized C–H bonds via Suzuki-Miyaura coupling has been achieved. Barder et al. (2005) *JACS* 127:4685.

In order to enhance the efficiency and practicality of directed C–H activation reactions, a strategic focus is to develop C–H functionalizations that are directed by synthetically useful groups. Indeed, recent efforts have been directed toward the development of such protocols for with organometallic reagents, which provided the first example for Pd-catalyzed alkylation of sp^2 hybridized C–H bonds. Yu et al. (2006) *JACS* 128:78. In that alkylation reaction, the organotin reagents are added batch-wise to minimize the undesired homo-coupling, which constitutes a practical drawback. The toxicity of organotin reagents also limits the applications. Furthermore, catalytic coupling of sp^3 hybridized C–H bonds with organotin reagents could not be achieved.

Nitrogen-containing heterocycles are profoundly represented among natural products and pharmaceutically relevant small molecules. See Cordell, G.A., *The Alkaloids: Chemistry and Biology*; Elsevier Science: San Diego, CA 2003; Vol. 60; Hesse, M.

Alkaloids: Nature's Curse or Blessing?; Wiley-VCH: Weinheim, Germany, 2003; Southon, I.W.; Buckingham, J. *Dictionary of Alkaloids*; Chapman & Hall: London, UK, 1989.

Methods aimed at achieving such compounds with strict control of regio- and stereochemistry continue to stand as a prominent objective in synthetic organic chemistry.

- 5 An objective of the present invention is to provide a one-pot procedure for the coupling of sp^2 and sp^3 -hybridized C–H bonds with nontoxic and readily available reagents (e.g., organo-boroxines, organo-boronic acids) using a directing group such as pyridyl moiety.

SUMMARY OF THE INVENTION

- One aspect of the present invention relates to methods for direct functionalization of pyridyl- and pyrazole-substituted aromatic compounds. In certain embodiments, a wide range of 2-arylpyridine and arylpyrazole substrates react with various organoboron reagents in the presence of a transition metal catalyst to furnish alkylated arylpyridines and arylpyrazoles via regioselective functionalization of sp^2 -hybridized C–H bonds at a position *ortho* to the point of attachment of the pyridine or pyrazole ring to the aromatic nucleus. In other embodiments, the present invention provides for alkylation of sp^3 -hybridized C–H bonds in alkylpyridines. In certain embodiments, the organoboron reagent is a boroxine, e.g., methylboroxine; in certain embodiments, the organoboron reagents are alkyl-boronic acids. In certain embodiments, the transition metal catalyst is a palladium species. The present invention provides several improvements over known methods, including functional group tolerance, e.g., toward substrates incorporating double bond moieties. Organoboron reagents, such as boronic acids and boroxines, are relatively inexpensive and environmentally friendly coupling partners. In certain embodiments, the use of Cu(II) or Ag_2O and air as oxidant is also practical. The direct coupling of aryl C–H bonds and alkyl C–H bonds with organoboron reagents is a highly efficient process for C–C bond formation. Moreover, said functionalized products are useful building blocks for further synthetic transformations to yield biologically active small molecules.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the structures of substrates 1-22.

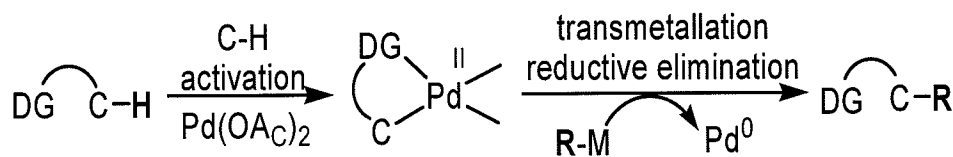
DETAILED DESCRIPTION OF THE INVENTION

30 Overview

The remarkable progress made in Pd-catalyzed alkyl-alkyl Suzuki cross-coupling reactions with boronic acids indicates that a C–H activation/C–C coupling sequence with organoboron reagents, such as that outlined below, is plausible in principle (Scheme 1).

See Kirchoff et al. (2002) *JACS* 124:13662. For a stoichiometric alkylation of sp^3 -hydridized C–H bonds in a single substrate with vinylboronic acid see Dangel et al. (2002) *JACS* 124:11856.

Scheme 1



wherein "DG" is a directing group

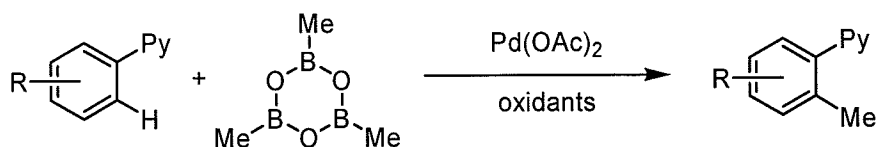
However, the execution of the sequential steps in a catalytic cycle represents a formidable challenge for the following reasons: (1) Pd^{II} -catalyzed homocoupling of organometallic reagents is faster than C–H activation; (2) The palladacycle formed from the C–H activation step catalyzes homocoupling of the organometallic reagents if the subsequent transmetalation and reductive elimination is not sufficiently fast. See Lei and Zhang (2002) *Org. Lett.* 4:2285; Louie and Hartwig (1996) *Angew. Chem., Int. Ed.* 35:2359. A strategy of the present invention is to identify promoters for each step to overcome the undesired homocoupling of the organoboron reagents. In certain embodiments, palladium-catalyzed alkylation of a wide range of aryl- and alkyl-pyridines is achieved using readily available organoboron reagents.

15

In certain embodiments, the invention utilizes a *N*-containing heteroaryl motif to direct transition metal-mediated regioselective functionalization of sp^2 -hydridized aryl C–H bonds using an alkyl-boroxine. In certain embodiments, the present invention relates to the transformation represented by Scheme 2.

20

Scheme 2



wherein Py is an optionally substituted pyridine.

Screening of coupling partners and reaction conditions using 2-phenylpyridine 1 as a model substrate established that the combination of $\text{Pd}(\text{OAc})_2$, methylboroxine, $\text{Cu}(\text{OAc})_2$ and benzoquinone provided a promising solution to this challenging problem (Table 1).

25

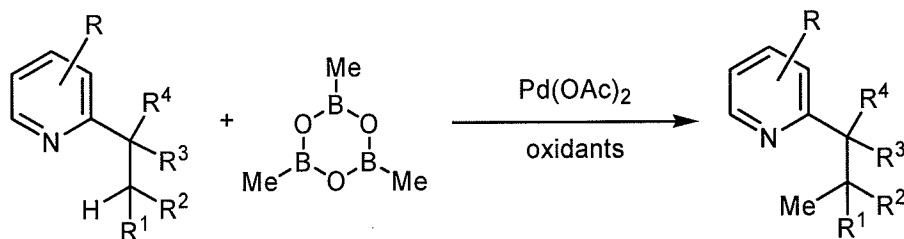
Table 1. Methylation of sp² hybridized C–H Bonds with Methylboroxine^a

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			72 ^b	7			82
2			66	8			65
3			64	9			84
4			62	10			78
5			38	11			93
6			50	12			38

^a10 mol% Pd(OAc)₂, 1 equiv benzoquinone, 1 equiv Cu(OAc)₂, 2 equiv methylboroxine, 100 °C, 24 h, CH₂Cl₂, air. ^b10% dimethylated product (1a') was isolated.

5 Functional groups attached to the aryl rings such as MeO, vinyl, and CF₃ were tolerated (entries 2, 4, 6), while a CHO group decreased the yield (entry 5). Methylated product **12a** was also isolated in 36% yield using pyrazole as a directing group (entry 12).

In certain embodiments, the invention utilizes a *N*-containing heteroaryl motif to direct transition metal-mediated regioselective functionalization of sp³-hybridized alkyl C–H bonds using an alkyl-boroxine. In certain embodiments, the present invention relates to the transformation represented by Scheme 3.

Scheme 3

Importantly, the coupling of sp^3 -hybridized C–H bonds with methylboroxine was also achieved by running the reaction in acetic acid/ O_2 (1 atm), rather than CH_2Cl_2 /air (Table 2).

Table 2. Methylation of sp^3 -hybridized C–H Bonds with Methylboroxine^a

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1		 	79 11	5			60
2		 	50 20	6			50
3			33	7			51
4			70	8			70
				9			22
				10			80

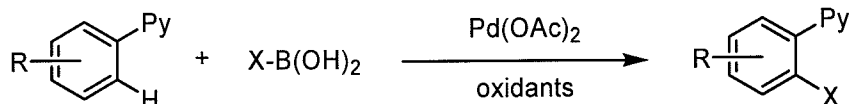
^a10 mol% $Pd(OAc)_2$, 2 equiv benzoquinone, 2 equiv $Cu(OAc)_2$, 2 equiv methylboroxine, 100 °C, 24 h, HOAc, O_2 .

These results establish that ether, alcohol and ester substrates (entries 6, 7, 8) are compatible with the reaction conditions. It is worth noting that alkylation of the methylene group was also possible (entry 9).

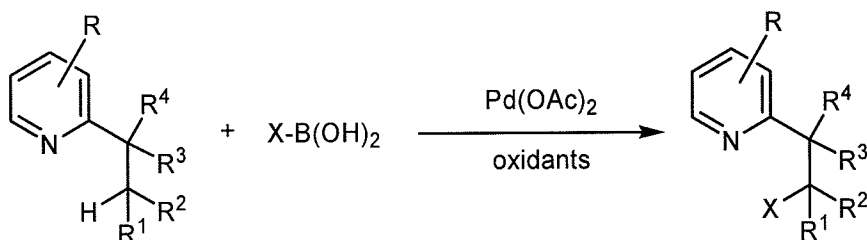
Attention was also devoted to boronic acids. 2-Phenylpyridine **1** was used as a model substrate to screen for the most efficacious protocol in the development of this system. The stoichiometric reaction of the dimeric palladacycle prepared from **1** with ethylboronic acid gives **1b** in less than 5% yield.

In certain embodiments, a subject reaction of the present invention is functionalization with an alkyl-boronic acid, as shown in Schemes 3 and 4:

Scheme 3

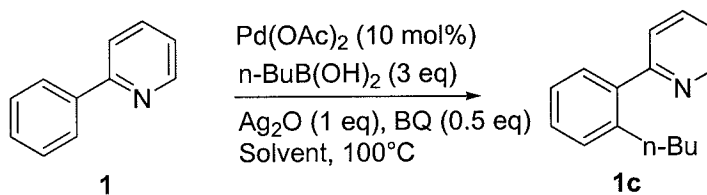


Scheme 4



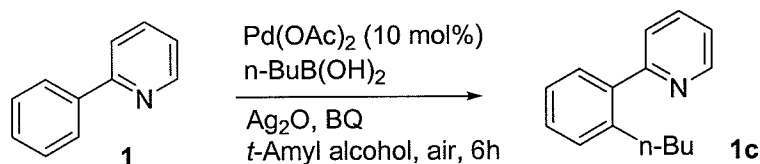
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As detailed in Table 3 and Table 4 below, screening a wide range of solvents, bases, and oxidants established that the alkylation reaction proceeds smoothly in the presence of Ag_2O (or Ag_2CO_3) and benzoquinone ("BQ") using *t*-amyl alcohol as the solvent.

10 **Table 3.** Screening of solvents using substrate **1**

Entry	Solvent	Yield% ^a
1	<i>tert</i>-Amyl alcohol	77
2	<i>tert</i> -butyl alcohol	38
3	DMF	45
4	Dioxane	30
5	Toluene	10
6	HOAc	5

^aYield determined by ^1H NMR.

Table 4. Optimization of various reaction parameters using substrate **1**

Entry	n-BuB(OH) ₂	Ag ₂ O	Additive	benzoquinone	Temp	Yield % ^a
1	3 equiv	1 equiv	--	0.5 equiv	100°	77
2	3 equiv	1 equiv	--	0.5 equiv	120°	72
3	3 equiv	1 equiv	--	0.5 equiv	80°C	64
4	3 equiv	1 equiv	--	2 equiv	100°	41
5	3 equiv	1 equiv	--	1 equiv	100°	65
6	3 equiv	1 equiv	--	0.75 equiv	100°	70
7	3 equiv	1 equiv	--	--	100°	25
8	3 equiv	2 equiv	--	0.5 equiv	100°	76
9	3 equiv	0.5 equiv	--	0.5 equiv	100°	57
10	2 equiv	1 equiv	--	0.5 equiv	100°	60
11	3 equiv	1 equiv	under O ₂	0.5 equiv	100°	78
12	3 equiv	1 equiv	under N ₂	0.5 equiv	100°	75
13	3 equiv	1 equiv	Cu(OAc) ₂ (1 eq)	1 equiv	100°	20
14	3 equiv	--	Cu(OAc) ₂ (1 eq)	1 equiv	100°	15
15	3 equiv	1 equiv	H ₂ O (0.1 mL)	0.5 equiv	100°	26
16	3 equiv	1 equiv	K ₂ CO ₃ (2 eq)	0.5 equiv	100°	17
17	3 equiv	--	KOAc (2 eq)	0.5 equiv	100°	33
18	3 equiv	--	Cu ₂ O (2 eq)	0.5 equiv	100°	19
19	3 equiv	--	MnO ₂ (2 eq)	0.5 equiv	100°	5
20	3 equiv	--	AgOAc (2 eq)	0.5 equiv	100°	10
21	3 equiv	--	Ag₂CO₃ (1 eq)	0.5 equiv	100°	72

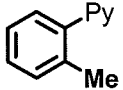
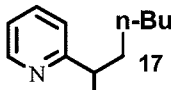
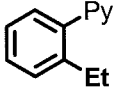
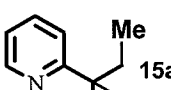
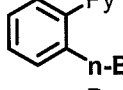
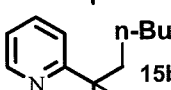
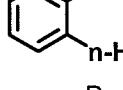
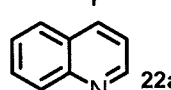
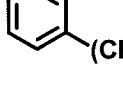
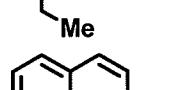
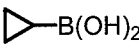
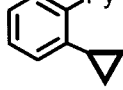
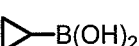
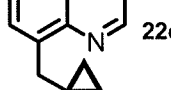
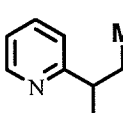
^aYield determined by ¹H NMR.

Ag₂O appears to play a dual role as an efficient promoter for the transmetallation
 5 and cooxidant with benzoquinone (for an early observation of rate acceleration of Suzuki

coupling by Ag₂O see Uenishi et al. (1987) *JACS* 109:4756). Ag₂O was also shown to be able to replace Cu(OAc)₂ as an oxidant under the conditions indicated in Table 1 above. Benzoquinone is crucial for the reductive elimination step (see Yu et al. (2006) *JACS* 128:78).

5 Pleasingly, the protocol of the present invention allows for the coupling of both sp² and sp³ hydridized C–H bonds with other boronic acids, including cyclopropylboronic acid, thereby substantially expanding the scope of C–H activation/C–C coupling reactions (Table 5).

Table 5. Alkylation of C–H Bonds with Boronic acids^a

entry	RB(OH) ₂	product	yield(%)	entry	RB(OH) ₂	product	yield(%)
1	Me-B(OH) ₂		67	8	n-Bu-B(OH) ₂		55
2	Et-B(OH) ₂		64	9	Me-B(OH) ₂		40
3	n-Bu-B(OH) ₂		75	10	n-Bu-B(OH) ₂		43
4	n-Hex-B(OH) ₂		51	11	Me-B(OH) ₂		48
5	Ph(CH ₂) ₂ B(OH) ₂		53	12	n-Bu-B(OH) ₂		56
6	 -B(OH) ₂		52	13	 -B(OH) ₂		35
7	Me-B(OH) ₂		48				

^a10 mol% Pd(OAc)₂, 1 equiv Ag₂O, 0.5 equiv benzoquinone, 3 equiv boronic acid, 100 °C, 6 h, *tert*-Amyl alcohol, air.

Indeed, model substrate **1** was functionalized with a range of alkyl-boronic acids in good yield to furnish products **1a-1f** (entries 1-6). The boronic acids Me-B(OH)₂ and n-Bu-B(OH)₂ were also successfully coupled to substrate **14** (entries 7 and 8 respectively), substrate **15** (entries 9 and 10 respectively), and substrate **22** (entries 11 and 12 respectively). Further, substrate **22** was functionalized with cyclopropylboronic acid (entry

13). It should be noted that the formation of dialkylated products was not observed in entries 1-10 above.

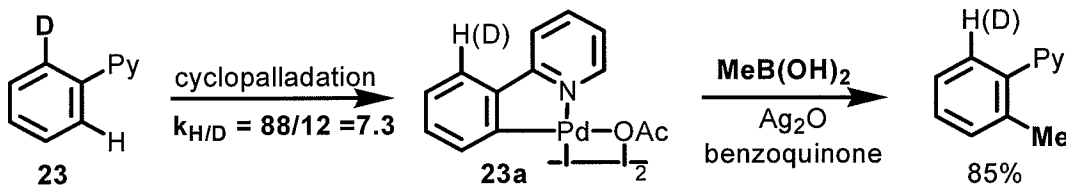
Interestingly, while $\text{Cu}(\text{OAc})_2$ is an efficient oxidant with methylboroxine, the coupling reactions with boronic acids were severely suppressed by $\text{Cu}(\text{OAc})_2$, presumably due to its strong coordination with the pyridine substrate. For coordination of pyridine with $\text{Cu}(\text{OAc})_2$ see Yu et al. (2006) 128:6790. The methylboroxine coordinates with pyridine leading to a different pathway, as described in the speculative mechanistic discussion that follows.

As demonstrated herein, the reactions of the present invention can be catalytic, e.g., utilizing 10-20 mol% transition metal complex.

Mechanistic Speculation

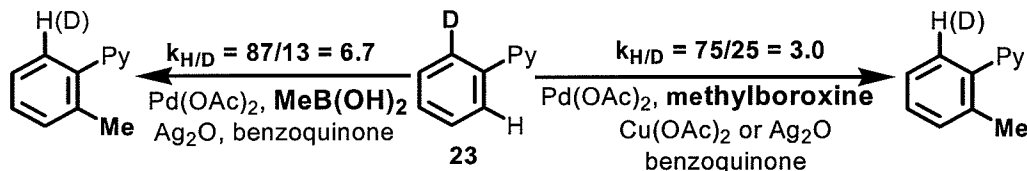
Mechanistic observations were made with methylboroxine and $\text{MeB}(\text{OH})_2$. First, it was determined that the intramolecular kinetic isotope effects ($k_{\text{H/D}}$) in the cyclopalladation of labeled substrate **23** are 7.3 (see Example 40 below). Second, the dimeric palladocycle **23a** reacts with $\text{MeB}(\text{OH})_2$ under the conditions in Table 3 to give the methylated product, but does not react with methylboroxine under the conditions in Table 1 (Scheme 5).

Scheme 5



Third, the intramolecular kinetic isotope effects ($k_{\text{H/D}}$) in the methylation of **23** with $\text{MeB}(\text{OH})_2$ and methylbroxine are 6.7 and 3.0 respectively (Scheme 6), with the former being approximately the same as the isotope effects observed for the cyclopalladation step (within the error of NMR measurement).

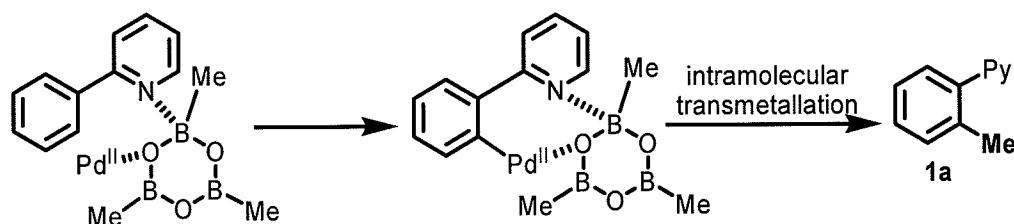
Scheme 6



On the basis of these observations, the coupling reaction with boronic acids most likely involves a conventional cyclopalladation process (i.e., Scheme 5). For the reaction with methylboroxine, it is proposed that the methylboroxine coordinates with the pyridyl

group first, and the chelation of the oxygen atom in the methylboroxine with Pd(OAc)₂ directs the C–H cleavage. The subsequent intramolecular transmetallation is highly efficient, not requiring a promoter (Scheme 7). For a detailed study on chelation of oxygen atom in a B–O bond with Pd^{II} see Sumimoto et al. (2004) *JACS* 126:10457.

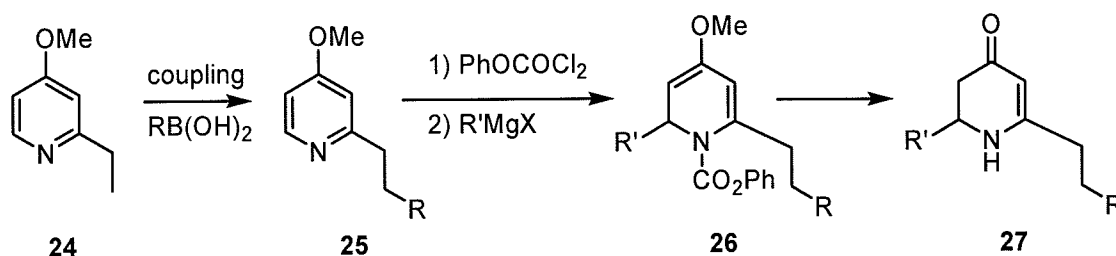
5 Scheme 7



Synthetic Utility

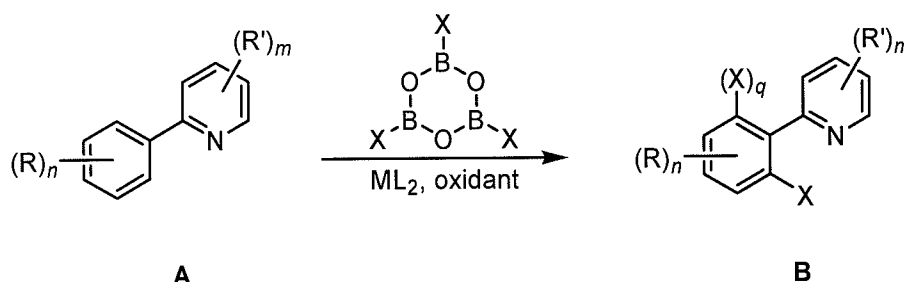
Pyridones can be used towards natural products or novel heterocycles. The 2,3-dihydro-4-pyridone **27** is an important synthetic building block in the synthesis of several classes of azaheterocycles. These dihydropyridones have proficiently served as precursors to piperidine, perhydroquinoline, quinolizidine, and indolizidine skeletons. See Comins and Joseph, In *Advances in Nitrogen Heterocycles*; Moody, C.J., Ed.; JAI Press Inc.: Greenwich, CT 1996; Vol. 2, p 251; Comins and Joseph, In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; McKillop, A., Ed.; Pergamon Press: Oxford, England, 1996; Vol. 5, p 37; Comins (1999) *J. Heterocyclic Chem.* 36:1491; Joseph and Comins (2002) *Curr. Opin. Drug Discovery Dev.* 5:870. To demonstrate the potential utility of the present invention, it is considered that 4-methoxypyridine is a precursor for pyridinone; hence, the alkylated products of the present invention can be converted into pyridinones. Dihydropyridine **26** may be prepared through formation of an *N*-acylpyridinium salt with a chloroformate (e.g., phenyl chloroformate) and a 6-substituted-4-methoxypyridine resulting from the novel coupling methodology provided by certain embodiments the present invention **25**, followed by treatment with a Grignard reagent (e.g., *iso*-butylmagnesium bromide). Further elaboration furnishes the desired pyridone **27** (Scheme 8). See Young and Comins (2005) *Org. Lett.* 7(25):5661. Said compounds containing a pyridyl moiety should be building blocks for pharmaceuticals and other chemical reagent applications.

Scheme 8

*Methods of the Invention*

- In certain embodiments, the present invention relates to a method of functionalizing an aryl C-H bond as represented by Scheme 9, comprising the step of combining an
- 5 an arylpyridine (A), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkylboroxine, thereby producing a functionalized product (B):

Scheme 9



- 10 wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

- 15 (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio,

20 arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

(alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

5 M represents a transition metal;

L independently for each occurrence represents a ligand;

X represents alkyl;

m represents an integer in the range 0 to 4 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

10 q is 0 or 1.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

15 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the arylpyridine.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the arylpyridine.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the arylpyridine.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group

consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method
5 and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method
10 and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

15 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Cu(OAc)₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

In certain embodiments, the present invention relates to the aforementioned method
20 and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Cu(OAc)₂, and air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is methyl.

In certain embodiments, the present invention relates to the aforementioned method
25 and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides,
30 hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected

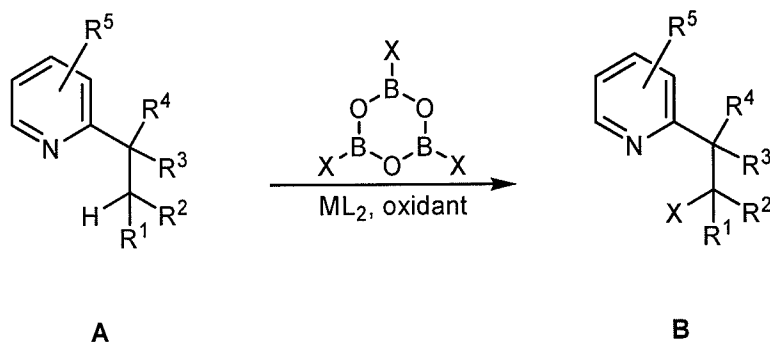
from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a
5 combination of benzoquinone, Cu(OAc)₂, and air; and X is methyl.

In certain embodiments, the present invention relates to the method of any one of the above, wherein m is 0; and n is 0.

In certain embodiments, the present invention relates to a method of functionalizing an alkyl C–H bond as represented by Scheme 10, comprising the step of combining an
10 alkylpyridine (A), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (B):

Scheme 10



wherein

- 15 R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,
20 (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,
25 (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
R³ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 5 R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 10 R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 15 R^3 , R^4 , and R^5 may be bonded together as part of a ring that may be optionally substituted; M represents a transition metal;

L independently for each occurrence represents a ligand; and

- 20 X represents alkyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

- 25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the alkylpyridine.

- 30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyridine.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyridine.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Cu(OAc)₂.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Cu(OAc)₂, and O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is methyl.

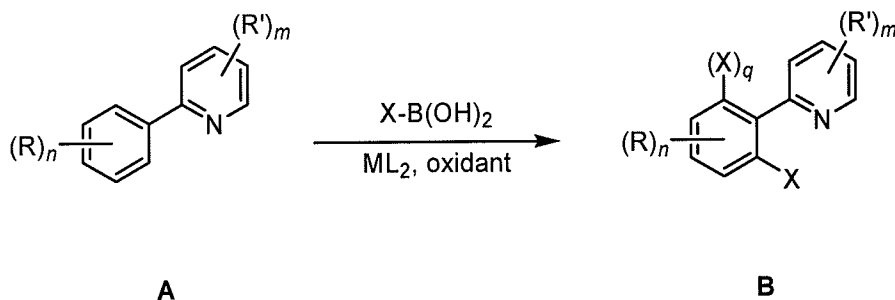
In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Cu(OAc)₂, and O₂; and X is methyl.

In certain embodiments, the present invention relates to a method of functionalizing an aryl C-H bond as represented by Scheme 11, comprising the step of combining an arylpyridine (**A**), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boronic acid, thereby producing a functionalized product (**B**):

Scheme 11



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

(alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl,

cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy,

5 arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio,

arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

(alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl,

(arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally

10 substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

15 M represents a transition metal;

L independently for each occurrence represents a ligand;

X represents alkyl;

m represents an integer in the range 0 to 4 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

20 q is 0 or 1.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the arylpyridine.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the arylpyridine.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the arylpyridine.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

15 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is selected from the group consisting of Me,

Et,

n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Et.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.

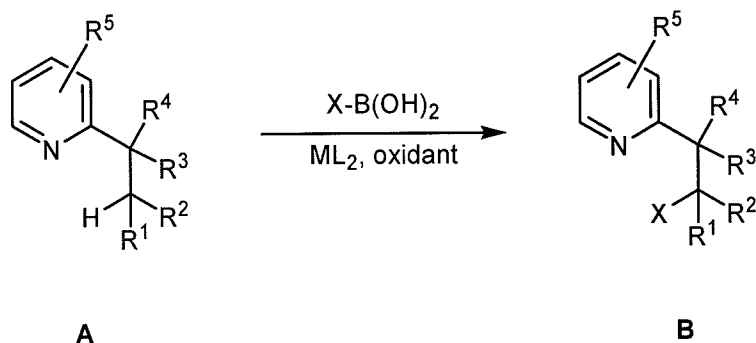
In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

In certain embodiments, the present invention relates to the method of any one of the above, wherein m is 0; and n is 0.

10 In certain embodiments, the present invention relates to a method of functionalizing an alkyl C-H bond as represented by Scheme 12, comprising the step of combining an alkylpyridine (**A**), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (**B**):

Scheme 12



15 wherein

R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^3 , R^4 , and R^5 may be bonded together as part of a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand; and

X represents alkyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the alkylpyridine.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyridine.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyridine.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, 15 benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is selected from the group consisting of Me,

Et,

n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Et.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.

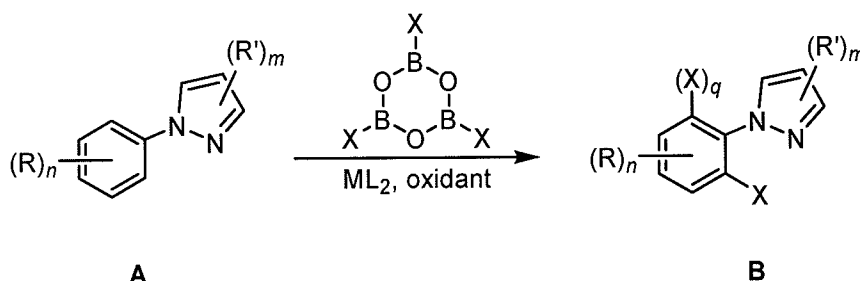
In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

In certain embodiments, the present invention relates to a method of functionalizing an aryl C-H bond as represented by Scheme 13, comprising the step of combining an arylpyrazole (A), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkylboroxine, thereby producing a functionalized product (B):

Scheme 13



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand;

5 X represents alkyl;

m represents an integer in the range 0 to 3 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

q is 0 or 1.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

15 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the arylpyrazole.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the arylpyrazole.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the arylpyrazole.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides,

transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Cu(OAc)₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Cu(OAc)₂, and air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected

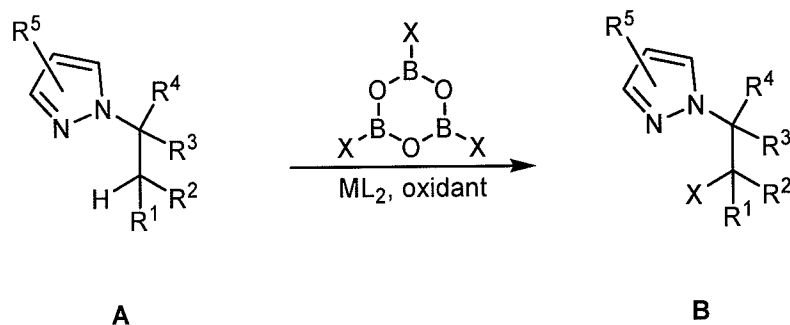
from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Cu(OAc)₂, and air; and X is methyl.

In certain embodiments, the present invention relates to the method of any one of the above, wherein m is 0; and n is 0.

In certain embodiments, the present invention relates to a method of functionalizing an alkyl C-H bond as represented by Scheme 14, comprising the step of combining an alkylpyrazole (A), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (B):

Scheme 14



wherein

R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R³ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

5 R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

10 R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

15 R^3 , R^4 , and R^5 may be bonded together as part of a ring that may be optionally substituted; M represents a transition metal;

L independently for each occurrence represents a ligand; and

20 X represents alkyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the alkylpyrazole.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyrazole.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyrazole.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, 15 benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Cu(OAc)₂.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Cu(OAc)₂, and O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is methyl.

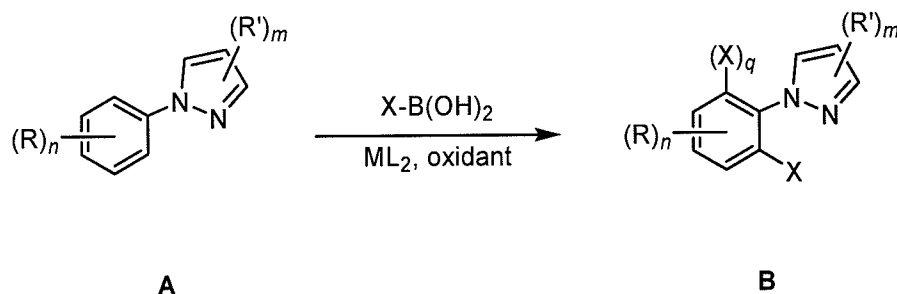
In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Cu(OAc)₂, and O₂; and X is methyl.

In certain embodiments, the present invention relates to a method of functionalizing an aryl C–H bond as represented by Scheme 15, comprising the step of combining an arylpyrazole (A), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boronic acid, thereby producing a functionalized product (B):

Scheme 15



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

(alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, 5 arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
any two instances of R may be bonded together to form a ring that may be optionally substituted;
10 any two instances of R' may be bonded together to form a ring that may be optionally substituted;
an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;
15 M represents a transition metal;
L independently for each occurrence represents a ligand;
X represents alkyl;
m represents an integer in the range 0 to 3 inclusive;
n represents an integer in the range 0 to (4-q) inclusive; and
20 q is 0 or 1.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

In certain embodiments, the present invention relates to the aforementioned method 25 and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the arylpyrazole.

In certain embodiments, the present invention relates to the aforementioned method 30 and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the arylpyrazole.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the arylpyrazole.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, 15 benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is selected from the group consisting of Me,

Et,

n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Et.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.

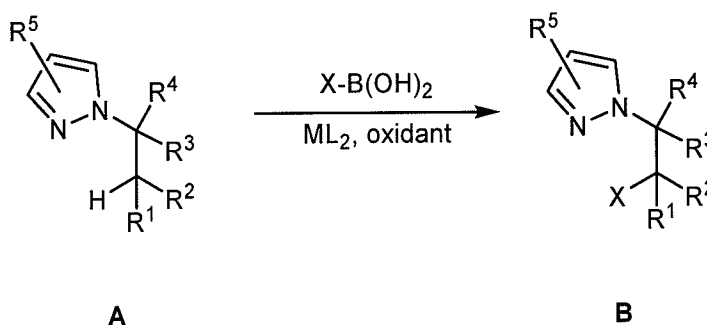
In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

In certain embodiments, the present invention relates to the method of any one of the above, wherein m is 0; and n is 0.

In certain embodiments, the present invention relates to a method of functionalizing an alkyl C-H bond as represented by Scheme 16, comprising the step of combining an alkylpyrazole (A), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (B):

Scheme 16



wherein

R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^3 , R^4 , and R^5 may be bonded together as part of a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand; and

X represents alkyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is Pd.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in a stoichiometric amount relative to the alkylpyrazole.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyrazole.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyrazole.

5 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

10 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein L is acetate.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, 15 benzoquinones, and combinations thereof.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

20 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is O₂.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂O.

25 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is Ag₂CO₃.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is benzoquinone.

30 In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein X is selected from the group consisting of Me,

Et,

n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Et.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.

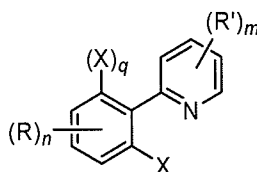
In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

In certain embodiments, the present invention relates to the aforementioned method and any of the attendant definitions, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

Compounds of the Invention

In certain embodiments, the present invention relates to a compound represented by formula I:



I

wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

X represents alkyl;

m represents an integer in the range 0 to 4 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

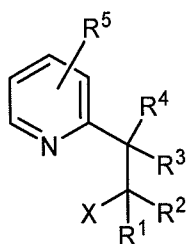
q is 0 or 1.

- 5 In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

- 10 In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is Me.

In certain embodiments, the present invention relates to the aforementioned compounds and any of the attendant definitions, wherein m is 0; and n is 0.

In certain embodiments, the present invention relates to a compound represented by formula II:



15

II

wherein

- R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- 20 R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- 25

R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

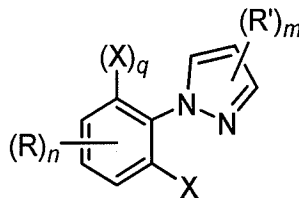
R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl; and

X represents alkyl.

In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is Me.

In certain embodiments, the present invention relates to a compound represented by formula III:



III

wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

- 5 (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio,

- 10 arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

- 15 any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

X represents alkyl;

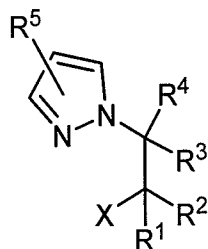
- 20 m represents an integer in the range 0 to 3 inclusive;
n represents an integer in the range 0 to (4-q) inclusive; and
q is 0 or 1.

- In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is selected from the group
25 consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is Me.

- In certain embodiments, the present invention relates to the aforementioned
30 compounds and any of the attendant definitions, wherein m is 0; and n is 0.

In certain embodiments, the present invention relates to a compound represented by formula IV:



IV

wherein

- R^1 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R^2 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,

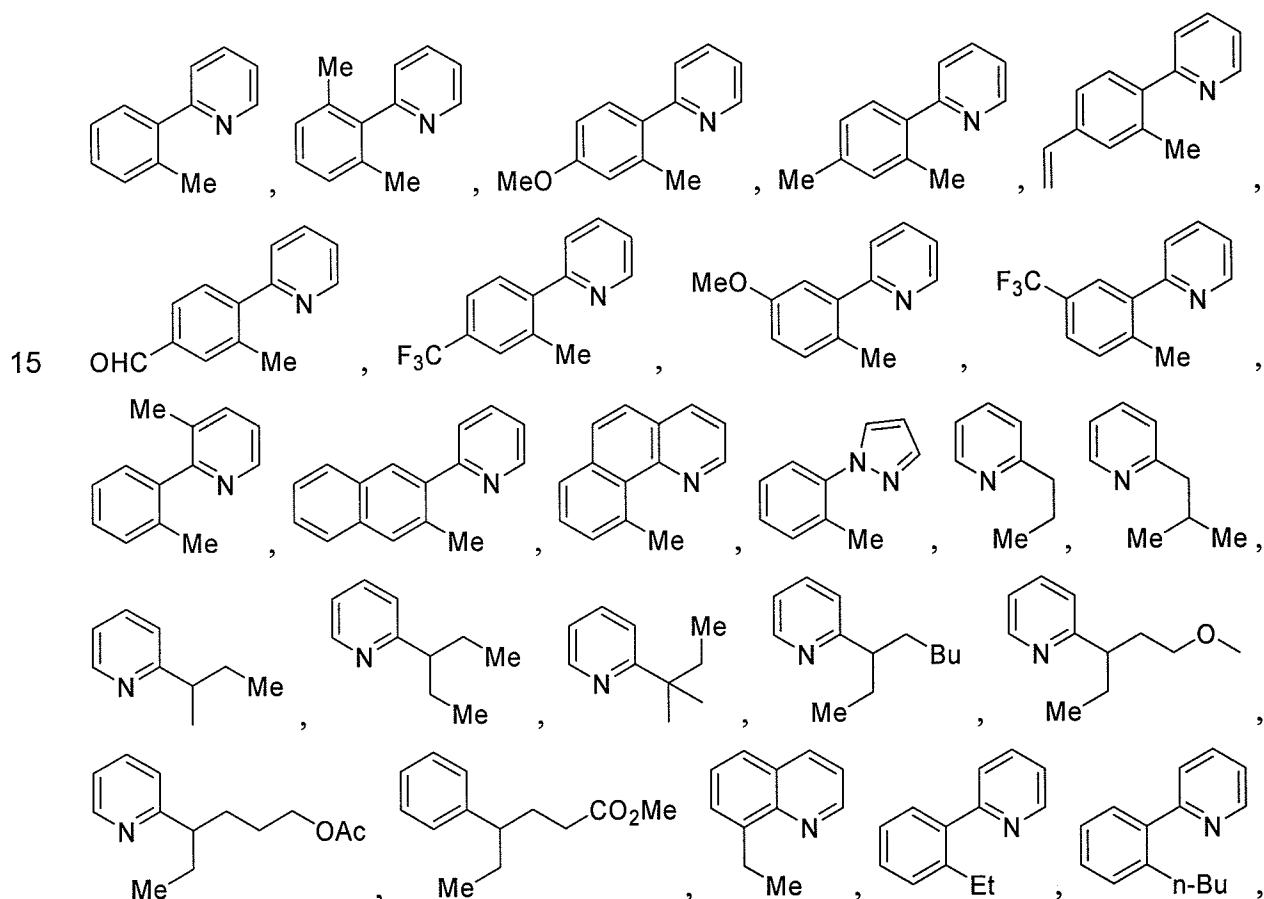
arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl; and

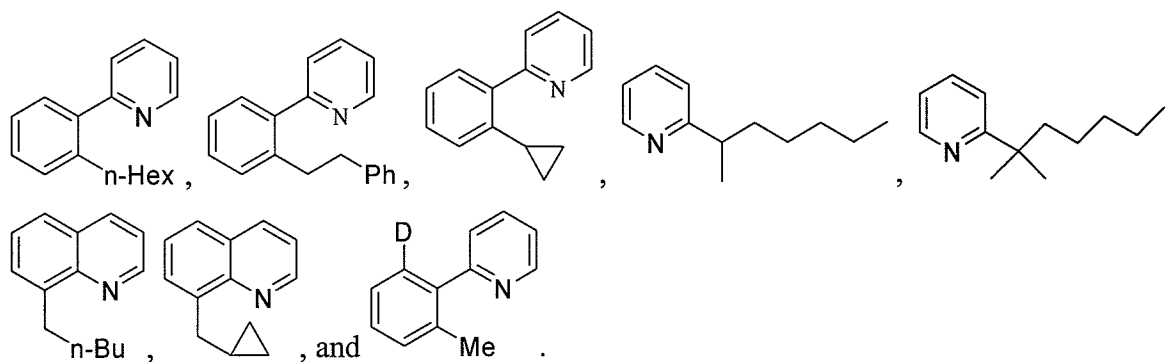
5 X represents alkyl.

In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

10 In certain embodiments, the present invention relates to the aforementioned compound and any of the attendant definitions, wherein X is Me.

In certain embodiments, the present invention relates to a compound selected from the group consisting of:





Definitions

For convenience, certain terms employed in the specification, examples, and
 5 appended claims are collected here.

The term “nucleophile” is recognized in the art, and as used herein means a
 chemical moiety having a reactive pair of electrons. Examples of nucleophiles include
 uncharged compounds, such as water, amines, mercaptans and alcohols; and charged
 moieties, such as alkoxides, thiolates, carbanions, and a variety of organic and inorganic
 10 anions. Illustrative anionic nucleophiles include simple anions such as hydroxide, azide,
 cyanide, thiocyanate, acetate, formate or chloroformate, and bisulfite. Organometallic
 reagents such as organocuprates, organozincs, organolithiums, Grignard reagents, enolates,
 acetylides, and the like may, under appropriate reaction conditions, be suitable
 nucleophiles. Hydride may also be a suitable nucleophile when reduction of the substrate is
 15 desired.

The term “electrophile” is art-recognized and refers to chemical moieties which can
 accept a pair of electrons from a nucleophile as defined above. Electrophiles useful in the
 method of the present invention include cyclic compounds such as epoxides, aziridines,
 episulfides, cyclic sulfates, carbonates, lactones, lactams and the like. Non-cyclic
 20 electrophiles include sulfates, sulfonates (e.g., tosylates), chlorides, bromides, iodides, and
 the like

The terms “electrophilic atom,” “electrophilic center” and “reactive center” as used
 herein refer to the atom of the substrate which is attacked by, and forms a new bond to, the
 nucleophile. In most but not all cases, this atom will also be the one from which the leaving
 25 group departs.

The term “electron-withdrawing group” is recognized in the art, and denotes the
 tendency of a substituent to attract valence electrons from neighboring atoms, *i.e.*, the
 substituent is electronegative with respect to neighboring atoms. A quantification of the

level of electron-withdrawing capability is given by the Hammett sigma (σ) constant. This well known constant is described in many references, for instance, J. March, *Advanced Organic Chemistry*, McGraw Hill Book Company, New York, (1977 edition) pp. 251-259. The Hammett constant values are generally negative for electron donating groups (σ [P] = -0.66 for NH_2) and positive for electron withdrawing groups (σ [P] = 0.78 for a nitro group), σ [P] indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

The terms "Lewis base" and "Lewis basic" are recognized in the art, and refer to a chemical moiety capable of donating a pair of electrons under certain reaction conditions. Examples of Lewis basic moieties include uncharged compounds such as alcohols, thiols, olefins, and amines, and charged moieties such as alkoxides, thiolates, carbanions, and a variety of other organic anions.

The terms "Lewis acid" and "Lewis acidic" are art-recognized and refer to chemical moieties which can accept a pair of electrons from a Lewis base.

The term "regioisomers" refers to compounds which have the same molecular formula but differ in the connectivity of the atoms. Accordingly, a "regioselective process" is one which favors the production of a particular regioisomer over others, e.g., the reaction produces a statistically significant preponderance of a certain regioisomer.

The term "catalytic amount" is recognized in the art and means a substoichiometric amount relative to a reactant. As used herein, a catalytic amount means from 0.0001 to 90 mole percent relative to a reactant, more preferably from 0.001 to 50 mole percent, still more preferably from 0.01 to 10 mole percent, and even more preferably from 0.1 to 5 mole percent relative to a reactant.

As discussed more fully below, reactions contemplated in the present invention may include reactions which are enantioselective, diastereoselective, and/or regioselective.

An enantioselective reaction is a reaction in which an achiral reactant is converted to a chiral product enriched in one enantiomer. Enantioselectivity is generally quantified as "enantiomeric excess" (e.e.) defined as follows:

$$\% \text{ Enantiomeric Excess A (e.e.)} = (\% \text{ Enantiomer A}) - (\% \text{ Enantiomer B})$$

where A and B are the enantiomers formed. Additional terms that are used in conjunction with enantioselectivity include "optical purity" or "optical activity." An enantioselective reaction yields a product with an e.e. greater than zero. Preferred enantioselective reactions

yield a product with an e.e. greater than 20%, more preferably greater than 50%, even more preferably greater than 70%, and most preferably greater than 80%.

A diastereoselective reaction is one in which a chiral reactant (which may be racemic or enantiomerically pure) is converted to a product enriched in one diastereoisomer. If the chiral reactant is racemic, in the presence of a chiral non-racemic reagent or catalyst one reactant enantiomer may react more slowly than the other. This class of reaction is called kinetic resolution, wherein the reactant enantiomers are resolved by differential reaction rate to yield both enantiomerically-enriched product and enantiomerically-enriched unreacted substrate.

A regioselective reaction is a reaction which occurs preferentially at one reactive center rather than another non-identical reactive center. For example, a regioselective reaction of an unsymmetrically substituted epoxide substrate would involve preferential reaction at one of the two epoxide ring carbons.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, compounds of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

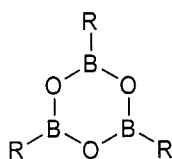
If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

The term "aliphatic" is an art-recognized term and includes linear, branched, and cyclic alkanes, alkenes, or alkynes. In certain embodiments, aliphatic groups in the present invention are linear or branched and have from 1 to about 20 carbon atoms.

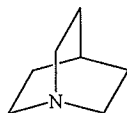
The term “alkyl” is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (*e.g.*, C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, “lower alkyl” refers to an alkyl group, as defined above, but having from one to ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, “lower alkenyl” and “lower alkynyl” have similar chain lengths.

The term “alkyl-boroxine” is art-recognized and as used herein refers to a species such as that shown below, wherein R represents “alkyl” as described above.



The term “bicyclo-ring” as used herein refers to a bridged ring system, such as a quinuclidine (shown below).



The term “aralkyl” is art-recognized, and includes alkyl groups substituted with an aryl group (*e.g.*, an aromatic or heteroaromatic group).

The terms “alkenyl” and “alkynyl” are art-recognized, and include unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term “heteroatom” is art-recognized, and includes an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium, and alternatively oxygen, nitrogen or sulfur.

The term “aryl” is art-recognized, and includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, naphthalene, anthracene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl

groups having heteroatoms in the ring structure may also be referred to as “heteroaryl” or “heteroaromatics.” The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is aromatic, *e.g.*, the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms ortho (o-), meta (m-) and para (p-) are art-recognized and apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene, ortho-dimethylbenzene and o-dimethylbenzene are synonymous.

The terms “heterocyclyl” and “heterocyclic group” are art-recognized, and include 3- to about 10-membered ring structures, such as 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, fluoroalkyl (such as trifluoromethyl), cyano, or the like.

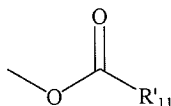
The terms “polycyclyl” and “polycyclic group” are art-recognized, and include structures with two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings,

e.g., the rings are “fused rings”. Rings that are joined through non-adjacent atoms, *e.g.*, three or more atoms are common to both rings, are termed “bridged” rings. Each of the rings of the polycycle may be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, fluoroalkyl (such as trifluoromethyl), cyano, or the like.

The term “carbocycle” is art recognized and includes an aromatic or non-aromatic ring in which each atom of the ring is carbon. The following art-recognized terms have the following meanings: “nitro” means -NO₂; the term “halogen” designates -F, -Cl, -Br or -I; the term “sulfhydryl” means -SH; the term “hydroxyl” means -OH; and the term “sulfonyl” means -SO₂.

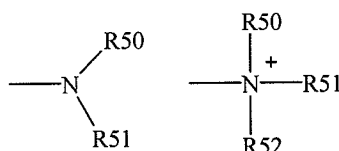
The term “acyl” is art-recognized and refers to any group or radical of the form RCO- where R is any organic group. Representative acyl group include acetyl, benzoyl, and malonyl.

The term “acyloxy” is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R'₁₁ represents a hydrogen, an alkyl, an aryl, an alkenyl, an alkynyl or -(CH₂)_m-R₈, where m is 1-30 and R₈ represents a group permitted by the rules of valence.

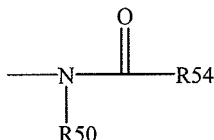
The terms “amine” and “amino” are art-recognized and include both unsubstituted and substituted amines, *e.g.*, a moiety that may be represented by the general formulas:



wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, -(CH₂)_m-R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R50 or R51 may be a carbonyl, *e.g.*, R50, R51 and the nitrogen together do not form an imide. In other embodiments, R50 and R51 (and optionally R52) each independently represent a hydrogen,

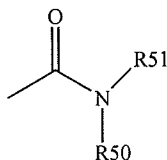
an alkyl, an alkenyl, or $-(CH_2)_m-R61$. Thus, the term “alkylamine” includes an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, *i.e.*, at least one of R50 and R51 is an alkyl group.

The term “acylamino” is art-recognized and includes a moiety that may be
 5 represented by the general formula:



wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R61$, where m and R61 are as defined above.

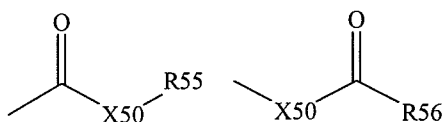
The term “amido” is art recognized as an amino-substituted carbonyl and includes a
 10 moiety that may be represented by the general formula:



wherein R50 and R51 are as defined above. Certain embodiments of the amide in the present invention will not include amides which may be unstable.

The term “alkylthio” is art recognized and includes an alkyl group, as defined
 15 above, having a sulfur radical attached thereto. In certain embodiments, the “alkylthio” moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S- $(CH_2)_m-R61$, wherein m and R61 are defined above. Representative alkylthio groups include methylthio, ethylthio, and the like.

The term “carbonyl” is art recognized and includes such moieties as may be
 20 represented by the general formulas:



wherein X50 is a bond or represents an oxygen or a sulfur, and R55 represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R61$ or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R61$, where m and R61 are defined above. Where
 25 X50 is an oxygen and R55 is not hydrogen, the formula represents an “ester”. Where X50 is an oxygen, and R55 is as first defined above, the moiety is referred to herein as a carboxyl group, and particularly when R55 is a hydrogen, the formula represents a “carboxylic acid”. Where X50 is an oxygen, and R56 is hydrogen, the formula represents a “formate”. In

general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a “thiocarbonyl” group. Where X50 is a sulfur and R55 or R56 is not hydrogen, the formula represents a “thioester.” Where X50 is a sulfur and R55 is hydrogen, the formula represents a “thiocarboxylic acid.” Where X50 is a sulfur and R56 is hydrogen, the formula represents a “thioformate.” On the other hand, where X50 is a bond, and R55 is not hydrogen, the above formula represents a “ketone” group. Where X50 is a bond, and R55 is hydrogen, the above formula represents an “aldehyde” group.

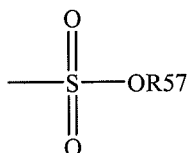
The terms “oxime” and “oxime ether” are art-recognized and refer to moieties that may be represented by the general formula:



wherein R75 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, or $-(\text{CH}_2)_m\text{-R61}$. The moiety is an “oxime” when R is H; and it is an “oxime ether” when R is alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, or $-(\text{CH}_2)_m\text{-R61}$.

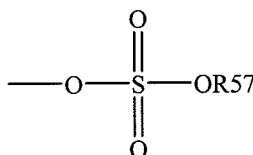
The terms “alkoxyl” or “alkoxy” are art recognized and include an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An “ether” is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of $-\text{O-alkyl}$, $-\text{O-alkenyl}$, $-\text{O-alkynyl}$, $-\text{O}-(\text{CH}_2)_m\text{-R61}$, where m and R61 are described above.

20 The term “sulfonate” is art recognized and includes a moiety that may be represented by the general formula:



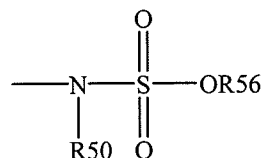
in which R57 is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

25 The term “sulfate” is art recognized and includes a moiety that may be represented by the general formula:



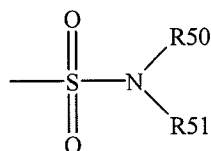
in which R57 is as defined above.

The term “sulfonamido” is art recognized and includes a moiety that may be represented by the general formula:



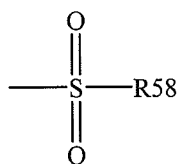
in which R50 and R56 are as defined above.

- 5 The term “sulfamoyl” is art-recognized and includes a moiety that may be represented by the general formula:



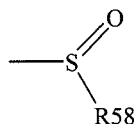
in which R50 and R51 are as defined above.

- 10 The term “sulfonyl” is art recognized and includes a moiety that may be represented by the general formula:



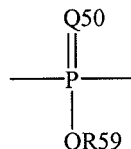
in which R58 is one of the following: hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

- 15 The term “sulfoxido” is art recognized and includes a moiety that may be represented by the general formula:



in which R58 is defined above.

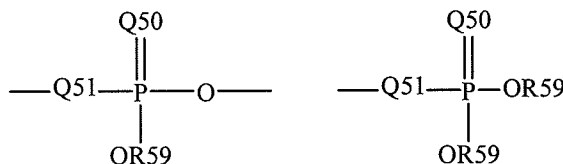
The term “phosphoryl” is art-recognized and may in general be represented by the formula:



20

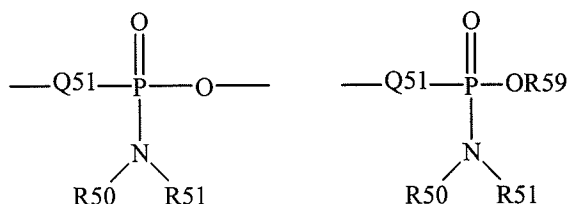
wherein Q50 represents S or O, and R59 represents hydrogen, a lower alkyl or an aryl.

When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



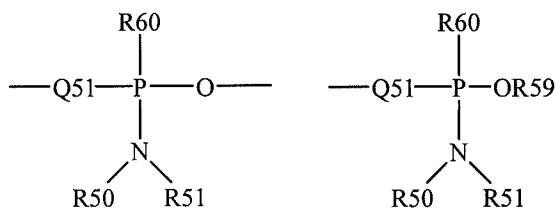
wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N. When Q50 is S, the phosphoryl moiety is a “phosphorothioate”.

5 The term “phosphoramidite” is art recognized and includes moieties represented by the general formulas:



wherein Q51, R50, R51 and R59 are as defined above.

The term “phosphonamidite” is art recognized and includes moieties represented by the general formulas:



10

wherein Q51, R50, R51 and R59 are as defined above, and R60 represents a lower alkyl or an aryl.

The term “selenoalkyl” is art-recognized and refers to an alkyl group having a substituted seleno group attached thereto. Exemplary “selenoethers” which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-(CH₂)_m-R61, m and R61 being defined above.

The terms triflyl, tosyl, mesyl, and nonafllyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms, and Bz represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and benzoyl respectively. A more comprehensive list of the abbreviations

utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby

5 incorporated by reference.

It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization,
10 elimination, or other reaction.

The term “substituted” is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those
15 described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible
20 substituents of organic compounds.

Analogous substitutions may be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

The definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than
25 once in any structure, is intended to be independent of its definition elsewhere in the same structure unless otherwise indicated expressly or by the context.

For purposes of the invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 67th Ed., 1986-87, inside cover.

30 *Catalysts of the Invention*

Transition metal complexes which are useful in the present invention may be determined by the skilled artisan according to several criteria. In general, a suitable transition metal complex will have one or more of the following properties: 1) It will be

capable of reaction with the substrate at the desired site; 2) It will yield a useful product upon reaction with the substrate; 3) It will not react with the substrate at functionalities other than the desired site; 4) It will not substantially undergo further undesired reaction after reacting with the substrate in the desired sense; 5) It will be able to be reoxidized by an oxidant so as to be catalytic. It will be understood that while undesirable side reactions may occur, the rates of such reactions can be rendered slow – through the selection of reactants and conditions – in comparison with the rate of the desired reaction.

Transition metal complexes which satisfy the above criteria can be chosen for each substrate and may vary according to the substrate structure and desired product. Routine experimentation may be necessary to determine the transition metal for a given transformation. In certain embodiments of the present invention, metal salts are used. In certain embodiments of this invention, the metal salts are palladium(II) salts. In certain embodiments of the present invention, transition metal acetates are used. In other embodiments, metal acetate hydrates may be used. In certain embodiments of this invention, the metal acetate is palladium(II) acetate. One of ordinary skill in the art will appreciate that the palladium catalyst may be provided in a lower oxidation state (e.g., Pd(I) or Pd(0)) because the stoichiometric oxidant may be used in sufficient excess to oxidize that palladium to palladium(II), the presumed active form. In certain embodiments, the catalyst may be comprised of a metal complex as described above on solid support. In certain embodiments, the catalyst may be comprised of ligands containing stereogenic centers.

Oxidants of the Invention

Any oxidant capable of oxidizing a relevant metal species can be utilized. In certain embodiments, any oxidant capable of oxidizing Pd(II) to Pd(IV) is acceptable. In one embodiment, the oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides and other acyloxy halides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, and air. The oxidant may be a peroxide or a hydroperoxide. The oxidant may be represented by R–O–O–R' or R–O–O–H, wherein R and R' are, for example, independently for each occurrence, alkyl, aryl, or acyl. Examples of such peroxides and hydroperoxides are MeC(=O)OO*t*Bu, PhC(=O)OO*t*Bu, [PhC(=O)]₂O₂, [CH₃(CH₂)_{*n*}C(=O)]₂O₂ (wherein *n* is an integer ≥ 1 (e.g., *n* = 10)), *t*BuOO*t*Bu, and *t*BuOOH. In certain embodiments, the oxidant may be Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, air, or combinations thereof.

Reaction Conditions

The reactions of the present invention may be performed under a wide range of conditions, though it will be understood that the solvents and temperature ranges recited herein are not limitative and only correspond to particular modes of the processes of the invention.

5 In general, it will be desirable that reactions are run using mild conditions which will not adversely effect the substrate, the catalyst, or the product. For example, the reaction temperature influences the speed of the reaction, as well as the stability of the reactants, products, and catalyst. In certain embodiments of the present invention, the manipulation of reaction temperature determines the level of functionalization observed.

10 In general, the synthetic reactions of the present invention are carried out in a liquid reaction medium. The reactions may be run without addition of solvent. Alternatively, the reactions may be run in an inert solvent, preferably one in which the reaction ingredients, including the catalyst, are substantially soluble. Suitable solvents include ethers such as diethyl ether, 1,2-dimethoxyethane, diglyme, *tert*-butyl methyl ether, tetrahydrofuran and
15 the like; halogenated solvents such as chloroform, dichloromethane, dichloroethane, chlorobenzene, and the like; aliphatic or aromatic hydrocarbon solvents such as benzene, toluene, hexane, pentane and the like; esters and ketones such as ethyl acetate, acetone, and 2-butanone; polar aprotic solvents such as acetonitrile, dimethylsulfoxide, dimethylformamide and the like; or combinations of two or more solvents. Furthermore, in
20 certain embodiments, it may be advantageous to employ a solvent which is not inert to the substrate under the conditions employed, e.g., use of ethanol as a solvent when ethanol is the desired nucleophile. In embodiments where water or hydroxide are not nucleophiles, the reactions can be conducted under anhydrous conditions. In embodiments where water or hydroxide are nucleophiles, the reactions are run in solvent mixtures comprising an
25 appropriate amount of water and/or hydroxide.

The invention also contemplates reaction in a biphasic mixture of solvents, in an emulsion or suspension, or reaction in a lipid vesicle or bilayer. In certain embodiments, it may be to perform the catalyzed reactions in the solid phase.

30 In certain embodiments it is preferable to perform the reactions under an inert atmosphere of a gas such as nitrogen or argon. In many embodiments sealing of the reaction flask is critical to prevent the decomposition on the metal species.

The synthetic processes of the present invention can be conducted in continuous, semi-continuous or batch fashion and may involve a liquid recycle and/or gas recycle

operation as desired. The processes of this invention are preferably conducted in batch fashion. Likewise, the manner or order of addition of the reaction ingredients, catalyst and solvent are also not critical and may be accomplished in any conventional fashion.

The reaction can be conducted in a single reaction zone or in a plurality of reaction
5 zones, in series or in parallel or it may be conducted batchwise or continuously in an elongated tubular zone or series of such zones. The materials of construction employed should be inert to the starting materials during the reaction and the fabrication of the equipment should be able to withstand the reaction temperatures and pressures. Means to introduce and/or adjust the quantity of starting materials or ingredients introduced
10 batchwise or continuously into the reaction zone during the course of the reaction can be conveniently utilized in the processes especially to maintain the desired molar ratio of the starting materials. The reaction steps may be affected by the incremental addition of one of the starting materials to the other. Also, the reaction steps can be combined by the joint addition of the starting materials to the catalyst. When complete conversion is not desired
15 or not obtainable, the starting materials can be separated from the product and then recycled back into the reaction zone.

The processes may be conducted in either glass lined, stainless steel or similar type reaction equipment. The reaction zone may be fitted with one or more internal and/or external heat exchanger(s) in order to control undue temperature fluctuations, or to prevent
20 any possible "runaway" reaction temperatures.

Furthermore, the catalyst can be immobilized or incorporated into a polymer or other insoluble matrix by, for example, covalently linking it to the polymer or solid support through one or more of its substituents. An immobilized catalyst may be easily recovered after the reaction, for instance, by filtration or centrifugation.

25 *Subsequent Transformations*

A product synthesized by a process of the present invention may be either an end-product or an intermediate in a synthesis scheme. In cases where the product synthesized by a process of the present invention is an intermediate, the product may be subjected to one or more additional transformations to yield the desired end-product. The set of
30 additional transformations contemplated comprises isomerizations, hydrolyses, oxidations, reductions, additions, eliminations, olefinations, functional group interconversions, transition metal-mediated reactions, transition metal-catalyzed reactions, bond-forming reactions, cleavage reactions, fragmentation reactions, thermal reactions, photochemical

reactions, cycloadditions, sigmatropic rearrangements, electrocyclic reactions, chemoselective reactions, regioselective reactions, stereoselective reactions, diastereoselective reactions, enantioselective reactions, and kinetic resolutions. The invention expressly comprises use of a process of the present invention as a step – either
5 initial, intermediate or final – in the synthesis of known or new pharmaceuticals, e.g., antivirals, antibiotics, and analgesics, herbicides, and agrochemicals.

Combinatorial Libraries

The subject C–H functionalization reactions readily lend themselves to the creation of combinatorial libraries of compounds for the screening of pharmaceutical, agrochemical,
10 or other biological or medically-related activity or material related qualities. A combinatorial library for the purposes of the present invention is a mixture of chemically related compounds which may be screened together for a desired property; said libraries may be in solution or covalently linked to a solid support. The preparation of many related compounds in a single reaction greatly reduces and simplifies the number of screening
15 processes that need to be conducted. Screening for the appropriate biological, pharmaceutical, agrochemical, or physical property is done by conventional methods. Diversity in the library can be created at a variety of different levels.

A variety of techniques are available in the art for generating combinatorial libraries of small organic molecules. See, for example, Blondelle et al. (1995) Trends Anal. Chem.
20 14:83; the Affymax U.S. Pat. Nos. 5,359,115 and 5,362,899; the Ellman U.S. Pat. No 5,288,514; the Still et al. PCT publication WO 94/08051; Chen et al. (1994) *JACS* 116:2661; Kerr et al. (1993) *JACS* 115:252; PCT publications WO 92/100092, WO 93/09668, and WO 91/07087; and the Lemer et al. PCT publication WO 93/20242. Accordingly, a variety of libraries on the order of about 16 to 1,000,000 or more
25 diversomers of the subject arylpyridines can be synthesized and screened for particular activity or property.

In an exemplary embodiment, a library of substituted diversomers can be synthesized using the subject functionalization reaction adapted to the techniques described in the Still et al. PCT publication WO 94/08051, e.g., being linked to a polymer bead by a
30 hydrolyzable or photolabile group e.g., located at one of the positions of the aryl group or a substituent of the pyridyl or the like. According to the Still et al. technique, the library is synthesized on a set of beads, each bead including a set of tags identifying the particular diversomer on that bead. In one embodiment, which is particularly suitable for discovering

enzyme inhibitors, the beads can be dispersed on the surface of a permeable membrane, and the diversomers released from the beads by lysis of the bead linker. The diversomer from each bead will diffuse across the membrane to an assay zone, where it will interact with an enzyme assay.

5 EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

10 *General Information*

Solvents were obtained from Aldrich, Acros, and Fisher and used directly without further purification. All organoboron reagents are commercially available. Organic solutions were concentrated by rotary evaporation under house vacuum (~25 Torr) at 23-30°C. Analytical thin layer chromatography (TLC) was performed using aluminum plates
15 pre-coated with silica gel (0.25 mm, 60Å pore size, 230-400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to UV light and/or phosphomolydic acid followed by brief heating on a hot plate. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) were recorded with Varian Mercury 400 (400 MHz / 100 MHz)
20 NMR spectrometers. Chemical shifts for protons are reported in parts per million scale (δ scale) and internally referenced to tetramethylsilane signal. Chemical shifts for carbon are reported in parts per million (δ scale) and are referenced to the carbon resonances of the solvent (CDCl₃: δ77.36, the middle peak). Data are represented as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double
25 doublet, dt = double triplet, td = triple doublet), coupling constant in Hz, and integration. High resolution mass spectra (HRMS) were obtained at the Mass Spectrometry Facilities of the University of Illinois at Urbana-Champaign.

Preparation of Substrates 13-22

Substrates **1**, **3**, **5**, **11** and **12** were purchased from Aldrich. Substrates **2**, **4**, **6**, **7**, **8**, **9**, and
30 **10** were prepared *via* Suzuki coupling of the corresponding boronic acid and 2-bromopyridine using a literature procedure. Littke et al. (2000) *JACS* 122:4020.

Preparation of Substrates 13-22

Substrates **13**, **21**, and **22** are commercially available. Substrates **14**, **16**, **17**, and **18** were prepared from a lithium salt of 2-ethylpyridine reacted with the corresponding alkyl iodide (or bromide). Bohme et al. (2003) *J. Med. Chem.* 46:856. By using 2-(2-bromomethyl)-1,3-dioxolane, the precursor of substrates **19** and **20** was obtained. Further functional transformation gave substrates **19** and **20**. Substrate **15** was synthesized by the coupling of 2-bromopyridine and *tert*-butylmagnesium chloride using a literature procedure. Bell et al. (1987) *J. Org. Chem.* 52:3847.

General Procedure 1: Methylation of sp^2 hybridized C-H Bonds with Methylboroxine

In a 20 mL tube, the substrate (0.2 mmol, 1 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), methylboroxine (55.7 μ L, 0.4 mmol, 2 equiv), Cu(OAc)₂ (36.4 mg, 0.2 mmol, 1 equiv) and benzoquinone (21.6 mg, 0.2 mmol, 1 equiv) were dissolved in 1 mL of CH₂Cl₂ under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was diluted with 20 mL of CH₂Cl₂ and then treated with 10 mL of saturated Na₂S aqueous solution. The mixture was filtered through a pad of Celite, and the filtrate was washed twice with saturated brine. The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the methylated product.

General Procedure 2: Methylation of sp^3 hybridized C-H Bonds with Methylboroxine

In a 40 mL tube, the substrate (0.2 mmol, 1 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), methylboroxine (55.7 μ L, 0.4 mmol, 2 equiv), Cu(OAc)₂ (72.8 mg, 0.4 mmol, 2 equiv) and benzoquinone (43.2 mg, 0.4 mmol, 2 equiv) were dissolved in 1 mL of acetic acid under Oxygen. The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was neutralized by 4N NaOH aqueous solution to pH = 8-9 and then treated with 10 mL of saturated Na₂S aqueous solution. The mixture was filtered through a pad of Celite, and the Celite was washed with 20 mL of CH₂Cl₂. The filtrate was washed twice with saturated brine. The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the methylated product.

General Procedure 3: Alkylation of sp^2 and sp^3 hybridized C-H Bonds with Boronic Acids

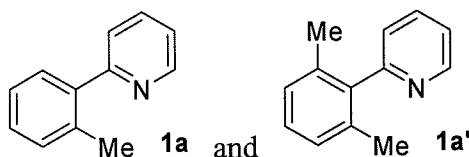
In a 20 mL tube, the substrate (0.2 mmol, 1 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), boronic acid (0.6 mmol, 3 equiv), Ag₂O (46.3 mg, 0.2 mmol, 1 equiv) and

benzoquinone (10.8 mg, 0.1 mmol, 0.5 equiv) were dissolved in 1 mL of *tert*-Amyl alcohol under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 6 hours. The reaction mixture was filtered through a pad of Celite, and the Celite was washed with 20 mL of CH₂Cl₂. The filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the alkylated product.

Methylation of sp^2 hybridized C–H Bonds with Methylboroxine

EXAMPLE 1

Synthesis of 2-*o*-tolylpyridine (**1a**) and 2-(2,6-dimethylphenyl)pyridine (**1a'**)



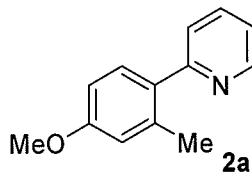
Substrate **1** was methylated following General Procedure 1. After purification by column chromatography, **1a** was obtained as a colorless oil (24.4 mg, 72%), and **1a'** was obtained as a colorless oil (3.7 mg, 10%).

1a: ¹H NMR (400 MHz, CDCl₃) δ 8.70 (d, *J* = 4.4 Hz, 1H), 7.75 (td, *J* = 8.0, 2.0 Hz, 1H), 7.42-7.39 (m, 2H), 7.33-7.23 (m, 4H), 2.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.33, 149.49, 140.70, 136.50, 136.07, 131.06, 129.95, 128.62, 126.20, 124.47, 121.98, 20.60; HRMS (EI) Calcd for C₁₂H₁₁N (M⁺) 169.0891, found 169.0889.

1a': ¹H NMR (400 MHz, CDCl₃) δ 8.72 (dt, *J* = 4.4, 1.6 Hz, 1H), 7.76 (td, *J* = 8.0, 1.6 Hz, 1H), 7.29-7.19 (m, 3H), 7.12-7.09 (m, 2H), 2.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.27, 150.01, 136.64, 136.12, 128.21, 127.86, 124.82, 122.77, 122.00, 20.53; HRMS (EI) Calcd for C₁₃H₁₃N (M⁺) 183.1048, found 183.1045.

EXAMPLE 2

Synthesis of 2-(4-methoxy-2-methylphenyl)pyridine (**2a**)

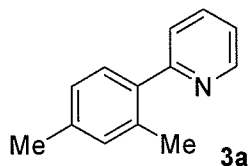


Substrate **2** was methylated following General Procedure 1. Column chromatography gave **2a** as a colorless oil (26.3 mg, 66%). ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, *J* = 4.8 Hz, 1H), 7.71 (td, *J* = 8.0, 1.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 9.2 Hz, 1H), 7.22-7.19 (m, 1H), 6.83 (s, 1H), 6.82 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H), 2.38 (s, 3H); ¹³C NMR

(100 MHz, CDCl₃) δ 160.09, 159.81, 149.51, 137.71, 136.34, 133.62, 131.33, 124.44, 121.57, 116.45, 111.57, 55.61, 21.01; HRMS (EI) Calcd for C₁₃H₁₃NO (M⁺) 199.0997, found 199.1002.

EXAMPLE 3

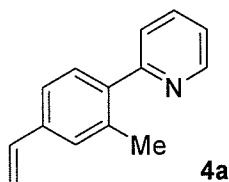
5 Synthesis of 2-(2,4-dimethylphenyl)pyridine (**3a**)



Substrate **3** was methylated following General Procedure 1. Column chromatography gave **3a** as a colorless oil (23.5 mg, 64%). ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, *J* = 4.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.26-7.20 (m, 1H), 7.10 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.40, 149.51, 138.30, 137.98, 136.34, 135.86, 131.84, 129.95, 126.92, 124.43, 121.72, 21.48, 20.57; HRMS (EI) Calcd for C₁₃H₁₃N (M⁺) 183.1048, found 183.1043.

EXAMPLE 4

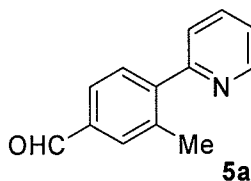
15 Synthesis of 2-(2-methyl-4-vinylphenyl)pyridine (**4a**)



Substrate **4** was methylated following General Procedure 1. Column chromatography gave **4a** as a colorless oil (24.2 mg, 62%). ¹H NMR (400 MHz, CDCl₃) δ 8.70 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 7.6, 1.6 Hz, 1H), 7.41-7.38 (m, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.26-7.23 (m, 1H), 6.74 (dd, *J* = 17.6, 8.4 Hz, 1H), 5.80 (d, *J* = 17.6 Hz, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 2.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.03, 149.61, 137.77, 136.87, 136.43, 130.30, 129.09, 124.41, 124.03, 121.95, 114.47, 20.73; HRMS (EI) Calcd for C₁₄H₁₃N (M⁺) 195.1048, found 195.1047.

EXAMPLE 5

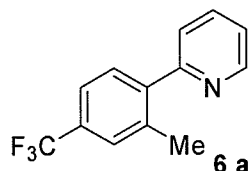
25 Synthesis of 3-methyl-4-(pyridine-2-yl)benzaldehyde (**5a**)



Substrate **5** was methylated following General Procedure 1. Column chromatography gave **5a** as a white solid (15.0 mg, 38%). ¹H NMR (400 MHz, CDCl₃) δ 10.05 (s, 1H), 8.74 (d, *J* = 4.8 Hz, 1H), 7.81-7.79 (m, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.40-7.30 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 192.65, 159.00, 149.82, 146.53, 137.34, 136.74, 136.31, 132.36, 130.76, 127.69, 124.36, 122.74, 20.62; HRMS (EI) Calcd for C₁₃H₁₁NO (M⁺) 197.0841, found 137.0839.

EXAMPLE 6

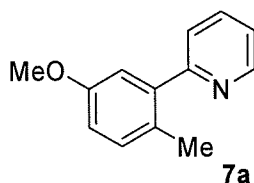
Synthesis of 2-(2-methyl-4-(trifluoromethyl)phenyl)pyridine (**6a**)



Substrate **6** was methylated following General Procedure 1. Column chromatography gave **6a** as a pale yellow liquid (23.7 mg, 50%). ¹H NMR (400 MHz, CDCl₃) δ 8.72 (d, *J* = 4.0 Hz, 1H), 7.79 (td, *J* = 8.0, 1.2 Hz, 1H), 7.55-7.49 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32-7.29 (m, 1H), 2.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.99, 149.81, 144.06, 137.12, 136.75, 130.37, 127.82 (d, *J* = 3.8 Hz), 124.36, 123.05 (d, *J* = 3.8 Hz), 122.64, 115.81, 20.68; HRMS (EI) Calcd for C₁₃H₁₀NF₃ (M⁺) 237.0765, found 237.0765.

EXAMPLE 7

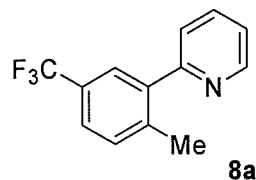
Synthesis of 2-(5-methoxy-2-methylphenyl)pyridine (**7a**)



Substrate **7** was methylated following General Procedure 1. Column chromatography gave **7a** as a colorless oil (32.7 mg, 82%). ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, *J* = 4.0 Hz, 1H), 7.74 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.88-6.86 (m, 1H), 3.82 (s, 3H), 2.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.19, 157.99, 149.60, 141.58, 136.41, 132.02, 128.01, 124.38, 122.04, 114.94, 114.64, 55.73, 19.66; HRMS (EI) Calcd for C₁₃H₁₃NO (M⁺) 199.0997, found 199.1000.

EXAMPLE 8

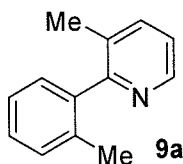
Synthesis of 2-(2-methyl-5-(trifluoromethyl)phenyl)pyridine (**8a**)



Substrate **8** was methylated following General Procedure 1. Column chromatography gave **8a** as a pale yellow liquid (30.8 mg, 65%). ^1H NMR (400 MHz, CDCl_3) δ 8.72 (d, $J = 4.8$ Hz, 1H), 7.79 (td, $J = 8.0, 1.6$ Hz, 1H), 7.66 (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.32-7.29 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.91, 149.83, 141.22, 140.41, 136.78, 131.52, 126.86 (d, $J = 3.8$ Hz), 125.22 (d, $J = 3.8$ Hz), 20.71; HRMS (EI) Calcd for $\text{C}_{13}\text{H}_{10}\text{NF}_3$ (M^+) 237.0765, found 237.0764.

EXAMPLE 9

Synthesis of 3-methyl-2-*o*-tolylpyridine (**9a**)



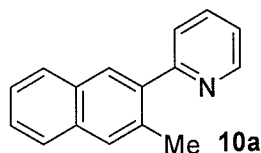
10

Substrate **9** was methylated following General Procedure 1. Column chromatography gave **9a** as a colorless oil (30.8 mg, 84%). ^1H NMR (400 MHz, CDCl_3) δ 8.51 (d, $J = 4.8$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.28-7.20 (m, 3H), 7.19-7.16 (m, 2H), 2.11 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.99, 147.08, 140.60, 138.04, 135.86, 131.81, 130.51, 128.78, 128.24, 126.04, 122.51, 19.70, 19.38; HRMS (EI) Calcd for $\text{C}_{13}\text{H}_{13}\text{N}$ (M^+) 183.1048, found 183.1044.

15

EXAMPLE 10

Synthesis of 2-(3-methylnaphthalen-2-yl)pyridine (**10a**)

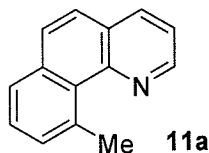


20

Substrate **10** was methylated following General Procedure 1. Column chromatography gave **10a** as a white solid (34.2 mg, 78%). ^1H NMR (400 MHz, CDCl_3) δ 8.73 (d, $J = 4.8$ Hz, 1H), 7.87 (s, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.80-7.76 (td, $J = 7.6, 1.6$ Hz, 2H), 7.73 (s, 1H), 7.50-7.41 (m, 3H), 7.30-7.25 (m, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.36, 149.52, 139.74, 136.57, 134.12, 133.70, 132.22, 129.20, 129.11, 128.23, 127.26, 126.63, 125.73, 124.56, 122.13, 21.19; HRMS (EI) Calcd for $\text{C}_{16}\text{H}_{13}\text{N}$ (M^+) 219.1048, found 219.1043.

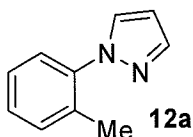
25

EXAMPLE 11

Synthesis of 10-methylbenzo[*h*]quinoline (**11a**)

Substrate **11** was methylated following General Procedure 1. Column chromatography gave **1a** as a white solid (35.9 mg, 93%). ¹H NMR (400 MHz, CDCl₃) δ 9.03 (d, *J* = 4.4 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80-7.77 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59-7.54 (m, 2H), 7.47 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.36 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.32, 147.52, 139.10, 135.64, 135.50, 131.49, 130.26, 129.13, 127.80, 127.61, 127.05, 125.81, 120.87, 27.59; HRMS (EI) Calcd for C₁₄H₁₁N (M⁺) 193.0891, found 193.0895.

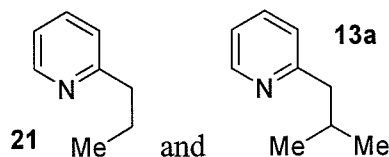
10 EXAMPLE 12

Synthesis of 1-*o*-tolyl-1*H*-pyrazole (**12a**)

Substrate **12** was methylated following General Procedure 1. Column chromatography gave **12a** as a pale yellow liquid (12.0 mg, 38%). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.32-7.29 (m, 4H), 6.44 (s, 1H), 2.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.59, 140.19, 134.09, 131.60, 130.84, 128.70, 126.88, 126.50, 106.50, 18.41; HRMS (EI) Calcd for C₁₀H₁₀N₂ (M⁺) 158.0844, found 158.0844.

Methylation of sp³ hybridized C-H Bonds with Methylboroxine

EXAMPLE 13

20 Synthesis of 2-propylpyridine (**21**) and 2-isobutylpyridine (**13a**)

Substrate **13** was methylated following General Procedure 2. After purification by column chromatography, **21** was obtained as a colorless oil (19.1 mg, 79%), and **13a** was obtained as a colorless oil (3.0 mg, 11%).

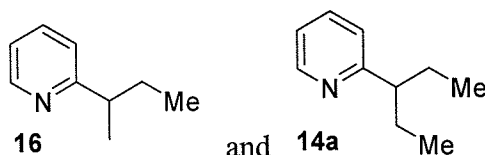
25 **21**: ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.58 (td, *J* = 7.6, 1.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.11-7.08 (m, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.81-1.71 (m, 2H),

0.97 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.35, 149.26, 136.25, 122.83, 120.94, 40.49, 23.19, 13.94; HRMS (EI) Calcd for $\text{C}_8\text{H}_{11}\text{N}$ (M^+) 121.0891, found 121.0893.

- 13a:** ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 4.4$ Hz, 1H), 7.58 (td, $J = 7.6, 1.6$ Hz, 1H), 7.12-7.08 (m, 2H), 2.65 (d, $J = 7.6$ Hz, 2H), 2.15-2.05 (m, 1H), 0.93 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.89, 149.50, 136.34, 123.81, 121.19, 47.93, 29.57, 22.74; HRMS (EI) Calcd for $\text{C}_9\text{H}_{13}\text{N}$ (M^+) 135.1048, found 135.1046.

EXAMPLE 14

Synthesis of 2-*sec*-butylpyridine (**16**) and 2-(pentan-3-yl)pyridine (**14a**)



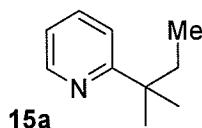
- Substrate **14** was methylated following General Procedure 2. After purification by column chromatography, **16** was obtained as a colorless oil (13.5 mg, 50%), and **14a** was obtained as a colorless oil (6.0 mg, 20%).

- 16:** ^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, $J = 4.8$ Hz, 1H), 7.57 (td, $J = 7.6, 1.6$ Hz, 1H), 7.10 (d, $J = 7.2$ Hz, 1H), 7.08-7.05 (m, 1H), 2.80-2.72 (m, 1H), 1.79-1.68 (m, 1H), 1.65-1.54 (m, 1H), 1.25 (d, $J = 6.8$ Hz, 3H), 0.82 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.84, 149.50, 136.54, 121.92, 121.33, 44.02, 30.34, 20.74, 12.46; HRMS (EI) Calcd for $\text{C}_9\text{H}_{13}\text{N}$ (M^+) 135.1048, found 135.1046.

- 14a:** ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 4.8$ Hz, 1H), 7.59 (td, $J = 7.6, 1.6$ Hz, 1H), 7.10-7.18 (m, 2H), 2.58-2.50 (m, 1H), 1.75-1.67 (m, 4H), 0.78 (t, $J = 7.6$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.60, 149.26, 136.30, 123.12, 121.32, 51.81, 28.58, 12.46; HRMS (EI) Calcd for $\text{C}_{10}\text{H}_{15}\text{N}$ (M^+) 149.1204, found 149.1209.

EXAMPLE 15

Synthesis of 2-*tert*-pentylpyridine (**15a**)

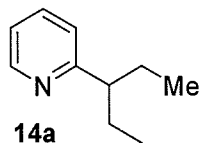


- Substrate **15** was methylated following General Procedure 2. Column chromatography gave **15a** as a pale yellow liquid (9.8 mg, 33%). ^1H NMR (400 MHz, CDCl_3) δ 8.58 (d, $J = 4.8$ Hz, 1H), 7.60 (td, $J = 8.0, 1.6$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.09-7.06 (m, 1H), 1.75 (q, $J = 7.6$ Hz, 2H), 1.3s (s, 6H), 0.68 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ

168.60, 148.99, 136.25, 120.82, 120.41, 36.20, 30.54, 27.74, 9.43; HRMS (EI) Calcd for $C_{10}H_{15}N$ (M^+) 149.2328, found 149.2331.

EXAMPLE 16

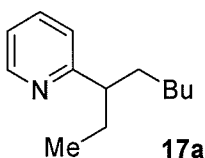
Alternate Synthesis of 2-(pentan-3-yl)pyridine (**14a**)



Substrate **16** was methylated following General Procedure 2. Column chromatography gave **14a** as a white solid (20.9 mg, 70%). The analysis data are supplied in Example 14 above.

EXAMPLE 17

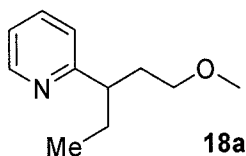
Synthesis of 2-(octan-3-yl)pyridine (**17a**)



Substrate **17** was methylated following General Procedure 2. Column chromatography gave **17a** as a pale yellow liquid (23.0 mg, 60%). 1H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, J = 5.6, 2.0 Hz, 1H), 7.58 (td, J = 7.6, 2.0 Hz, 1H), 7.10-7.08 (m, 2H), 2.65-2.57 (m, 1H), 1.72-1.59 (m, 4H), 1.28-1.18 (m, 6H), 0.83 (t, J = 2.8 Hz, 3H), 0.77 (t, J = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.77, 149.60, 136.29, 123.02, 121.28, 50.11, 35.74, 32.30, 28.94, 27.61, 22.89, 14.39, 12.47, 0.34; HRMS (EI) Calcd for $C_{13}H_{21}N$ (M^+) 191.1674, found 191.1681.

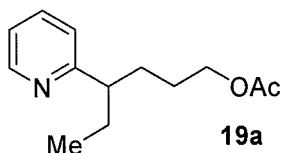
EXAMPLE 18

Synthesis of 2-(1-methoxypentan-3-yl)pyridine (**18a**)



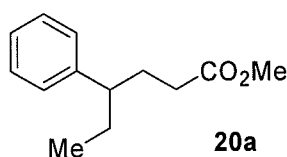
Substrate **18** was methylated following General Procedure 2. Column chromatography gave **18a** as a white solid (17.9 mg, 50%). 1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 1H), 7.59 (td, J = 7.6, 1.6 Hz, 1H), 7.13-7.09 (m, 2H), 3.28-3.23 (m, 1H), 3.25 (s, 3H), 3.19-3.13 (m, 1H), 2.83-2.75 (m, 1H), 1.98 (q, J = 6.8 Hz, 2H), 1.79-1.67 (m, 2H), 0.78 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.79, 149.73, 136.38, 123.53, 121.48, 71.14, 58.84, 46.37, 35.38, 28.92, 12.37; HRMS (EI) Calcd for $C_{11}H_{17}NO$ (M^+) 179.1310, found 179.1309.

EXAMPLE 19

Synthesis of 4-(pyridin-2-yl)hexyl acetate (**19a**)

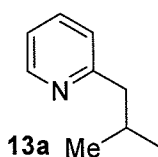
Substrate **19** was methylated following General Procedure 2. Column chromatography gave
5 **19a** as a pale yellow liquid (22.6 mg, 51%). ^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, $J = 4.8$ Hz, 1H), 7.60 (td, $J = 7.6, 1.6$ Hz, 1H), 7.13-7.09 (m, 2H), 4.00 (t, $J = 6.8$ Hz, 3H), 2.67-2.60 (m, 1H), 2.02 (s, 3H), 1.80-1.68 (m, 4H), 1.58-1.50 (m, 1H), 1.48-1.38 (m, 1H), 0.78 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.54, 164.85, 149.76, 136.50, 123.23, 121.57, 64.91, 49.63, 31.82, 28.94, 27.04, 21.35, 12.40; HRMS (EI) Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2$ (M^+) 221.1416, found 221.1414.
10

EXAMPLE 20

Synthesis of Methyl 4-(pyridin-2-yl)hexanoate (**20a**)

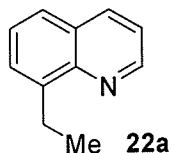
Substrate **20** was methylated following General Procedure 2. Column chromatography gave
15 **20a** as a pale yellow liquid (28.9 mg, 70%). ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 5.2$ Hz, 1H), 7.60 (td, $J = 7.6, 1.6$ Hz, 1H), 7.13-7.09 (m, 2H), 3.62 (s, 3H), 2.68-2.61 (m, 1H), 2.19-2.14 (m, 2H), 2.05 (t, $J = 7.2$ Hz, 2H), 1.79-1.67 (m, 2H), 0.79 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.43, 164.24, 149.83, 136.53, 123.34, 121.68, 51.83, 49.26, 32.48, 30.66, 30.54, 28.88, 12.35; HRMS (EI) Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$ (M^+) 207.1259, found
20 207.1266.

EXAMPLE 21

Alternate Synthesis of 2-isobutylpyridine (**13a**)

Substrate **21** was methylated following General Procedure 2. Column chromatography gave
25 **13a** as a pale yellow liquid (6.0 mg, 22%). The analysis data are supplied in Example 13 above.

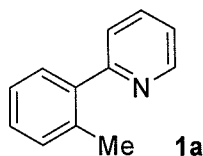
EXAMPLE 22

Synthesis of 8-ethylquinoline (**22a**)

Substrate **22** was methylated following General Procedure 2. Column chromatography gave
5 **22a** as a pale yellow liquid (25.2 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 8.95 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 6.8 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.32 (q, *J* = 7.6 Hz, 2H), 1.40 (t, *J* = 7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 149.59, 147.09, 143.24, 136.72, 128.71, 128.25, 126.77, 126.16, 121.15, 24.93, 15.37; HRMS (EI) Calcd for C₁₁H₁₁N (M⁺) 157.0891, found 157.0887.

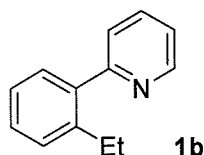
Alkylation of sp² and sp³ hybridized C-H Bonds with Boronic Acids

EXAMPLE 23

Alternate Synthesis of 2-*o*-tolylpyridine (**1a**)

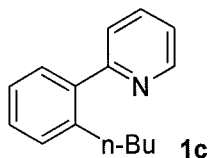
15 Substrate **1** was reacted with methylboronic acid following General Procedure 3. Column chromatography gave **1a** as a colorless oil (22.7 mg, 67%). The analysis data are supplied in Example 1 above.

EXAMPLE 24

Synthesis of 2-(2-ethylphenyl)pyridine (**1b**)

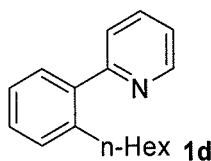
20 Substrate **1** was reacted with ethylboronic acid following General Procedure 3. Column chromatography gave **1b** as a colorless oil (23.5 mg, 64%). ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 7.6, 1.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.35-7.31 (m, 3H), 7.29-7.24 (m, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.57, 149.51, 142.30, 140.50, 136.45, 130.04, 129.32, 128.78,
25 126.08, 124.41, 121.97, 26.38, 15.86; HRMS (EI) Calcd for C₁₃H₁₃N (M⁺) 183.1048, found 183.1049.

EXAMPLE 25

Synthesis of 2-(2-butylphenyl)pyridine (**1c**)

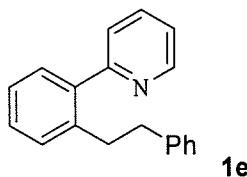
Substrate **1** was reacted with n-butylboronic acid following General Procedure 3. Column chromatography gave **1c** as a colorless oil (31.7 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 7.6, 1.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.34-7.29 (m, 3H), 7.28-7.23 (m, 2H), 2.70 (t, *J* = 8.0 Hz, 2H), 1.47-1.39 (m, 2H), 1.28-1.18 (m, 2H), 0.78 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.66, 149.46, 141.06, 140.68, 136.40, 130.05, 130.03, 128.59, 126.04, 124.45, 121.92, 33.79, 32.91, 22.82, 14.14; HRMS (EI) Calcd for C₁₅H₁₇N (M⁺) 211.1361, found 211.1361.

EXAMPLE 26

Synthesis of 2-(2-hexylphenyl)pyridine (**1d**)

Substrate **1** was reacted with n-hexylboronic acid following General Procedure 3. Column chromatography gave **1d** as a colorless oil (24.4 mg, 51%). ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 7.6, 1.6 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.35-7.29 (m, 3H), 7.28-7.24 (m, 2H), 2.69 (t, *J* = 8.0 Hz, 2H), 1.47-1.40 (m, 2H), 1.22-1.14 (m, 6H), 0.81 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.66, 149.48, 141.13, 140.66, 136.42, 130.06, 130.04, 128.61, 126.06, 124.46, 121.94, 33.25, 31.83, 31.57, 29.45, 22.82, 14.39; HRMS (EI) Calcd for C₁₇H₂₁N (M⁺) 239.1674, found 239.1679.

EXAMPLE 27

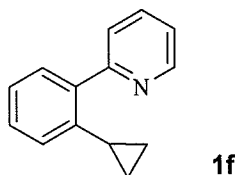
Synthesis of 2-(2-phenethylphenyl)pyridine (**1e**)

Substrate **1** was reacted with phenethylboronic acid following General Procedure 3. Column chromatography gave **1e** as a white solid (27.5 mg, 53%). ¹H NMR (400 MHz, CDCl₃) δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.73 (td, *J* = 7.6, 1.6 Hz, 1H), 7.36-7.26 (m, 6H), 7.21

(d, $J = 8.0$ Hz, 2H), 7.15-7.12 (m, 1H), 7.00 (d, $J = 7.2$ Hz, 2H), 3.03-2.93 (m, 2H), 2.79-2.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.54, 149.43, 142.36, 140.77, 140.10, 136.62, 130.26, 130.13, 128.75, 128.67, 128.57, 126.47, 126.08, 124.41, 122.10, 38.17, 35.72; HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{17}\text{N}$ (M^+) 259.1361, found 259.1365.

5 EXAMPLE 28

Synthesis of 2-(2-cyclopropylphenyl)pyridine (**1f**)

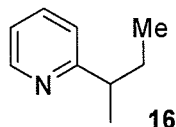


Substrate **1** was reacted with cyclopropylboronic acid following General Procedure 3.

Column chromatography gave **1f** as a colorless oil (20.3 mg, 52%). ^1H NMR (400 MHz, CDCl_3) δ 8.72 (d, $J = 4.8$ Hz, 1H), 7.73 (td, $J = 7.6, 1.6$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 7.2$ Hz, 1H), 7.31 (td, $J = 7.2, 1.6$ Hz, 1H), 7.26-7.23 (m, 2H), 7.01 (d, $J = 7.2$ Hz, 1H), 2.08-2.02 (m, 1H), 0.86-0.81 (m, 2H), 0.69-0.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.22, 149.67, 141.33, 136.14, 129.92, 128.78, 125.79, 125.02, 124.94, 121.96, 121.89, 13.63, 9.69; HRMS (EI) Calcd for $\text{C}_{14}\text{H}_{13}\text{N}$ (M^+) 195.1048, found 195.1050.

15 EXAMPLE 29

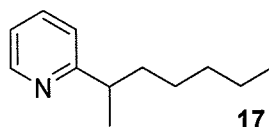
Alternate Synthesis of 2-sec-butylpyridine (**16**)



Substrate **14** was reacted with methylboronic acid following General Procedure 3. Column chromatography gave **16** as a pale yellow liquid (13.0 mg, 48%). The analysis data are supplied in Example 14 above.

EXAMPLE 30

Synthesis of 2-(heptane-2-yl)pyridine (**17**)

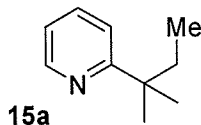


Substrate **14** was reacted with n-butylboronic acid following General Procedure 3. Column chromatography gave **17** as a pale yellow liquid (19.5 mg, 55%). ^1H NMR (400 MHz, CDCl_3) δ 8.54 (d, $J = 4.4$ Hz, 1H), 7.59 (td, $J = 8.0, 1.6$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.10-7.07 (m, 1H), 2.91-2.82 (m, 1H), 1.76-1.68 (m, 1H), 1.61-1.53 (m, 1H), 1.27-1.21 (m,

7H), 1.19-1.11 (m, 1H), 0.84 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.78, 149.22, 136.19, 121.55, 120.98, 42.13, 37.23, 32.02, 27.39, 22.65, 20.88, 14.08; HRMS (EI) Calcd for $\text{C}_{12}\text{H}_{19}\text{N}$ (M^+) 177.1517, found 177.1515.

EXAMPLE 31

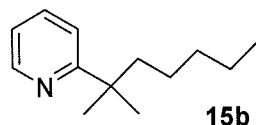
5 Alternate Synthesis of 2-*tert*-pentylpyridine (**15a**)



Substrate **15** was reacted with methylboronic acid following General Procedure 3. Column chromatography gave **15a** as a pale yellow liquid (11.9 mg, 40%). The analysis data are supplied in Example 15 above.

10 EXAMPLE 32

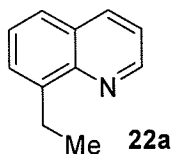
Synthesis of 2-(2-methylheptan-2-yl)pyridine (**15b**)



Substrate **1** was reacted with n-butylboronic acid following General Procedure 3. Column chromatography gave **15b** as a pale yellow liquid (16.4 mg, 43%). ^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, $J = 5.2$ Hz, 1H), 7.59 (td, $J = 8.0, 1.6$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.09-7.06 (m, 1H), 1.68 (t, $J = 8.4$ Hz, 2H), 1.34 (s, 6H), 1.25-1.14 (m, 4H), 1.08-1.00 (m, 1H), 0.81 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.85, 148.96, 136.27, 120.80, 120.25, 43.84, 40.73, 32.84, 28.18, 24.70, 22.90, 14.38; HRMS (EI) Calcd for $\text{C}_{13}\text{H}_{21}\text{N}$ (M^+) 191.1674, found 191.1677.

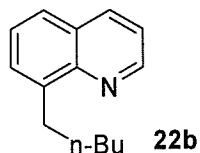
20 EXAMPLE 33

Alternate synthesis of 8-ethylquinoline (**22a**)



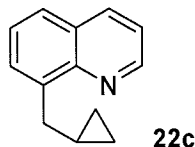
Substrate **22** was reacted with methylboronic acid following General Procedure 3. Column chromatography gave **22a** as a colorless oil (15.1 mg, 48%). The analysis data are supplied in Example 22 above.

EXAMPLE 34

Synthesis of 8-pentylquinoline (**22b**)

Substrate **22** was reacted with n-butylboronic acid following General Procedure 3. Column chromatography gave **22b** as a colorless oil (22.3 mg, 56%). ¹H NMR (400 MHz, CDCl₃) δ 8.94 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.38 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.28 (t, *J* = 7.6 Hz, 2H), 1.83-1.76 (m, 2H), 1.47-1.35 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.58, 147.25, 142.02, 136.68, 128.97, 128.75, 126.61, 126.13, 121.10, 32.30, 31.74, 30.66, 23.04, 14.45; HRMS (EI) Calcd for C₁₄H₁₇N (M⁺) 199.1361, found 199.1364.

EXAMPLE 35

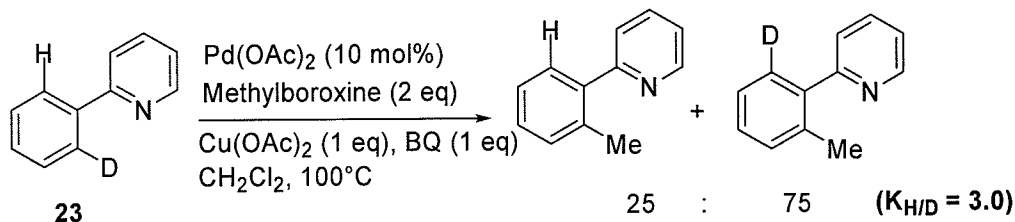
Synthesis of 8-(cyclopropylmethyl)quinoline (**22c**)

Substrate **22** was reacted with ethylboronic acid following General Procedure 3. Column chromatography gave **22c** as a colorless oil (12.8 mg, 35%). ¹H NMR (400 MHz, CDCl₃) δ 8.94 (d, *J* = 4.0, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.21 (t, *J* = 6.8 Hz, 2H), 1.28-1.22 (m, 2H), 0.58-0.54 (m, 2H), 0.32-0.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 149.60, 147.21, 141.17, 136.69, 128.69, 128.62, 126.74, 126.29, 121.16, 36.05, 11.32, 5.27; HRMS (EI) Calcd for C₁₃H₁₃N (M⁺) 183.1048, found 183.1044.

Isotope Effect

EXAMPLE 36

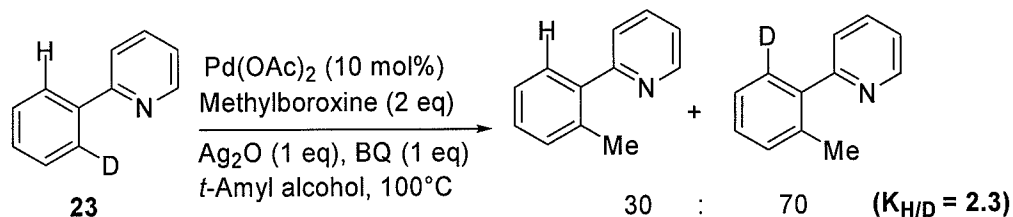
Intramolecular kinetic isotope effect in methylation with boroxine



In a 20 mL tube, substrate **23** (31.2 mg, 0.2 mmol, 1 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), methylboroxine (55.7 μ L, 0.4 mmol, 2 equiv), Cu(OAc)₂ (36.4 mg, 0.2 mmol, 1 equiv) and benzoquinone – “BQ” – (21.6 mg, 0.2 mmol, 1 equiv) were dissolved in 1 mL of CH₂Cl₂ under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was diluted with 20 mL of CH₂Cl₂ and then treated with 10 mL of saturated Na₂S aqueous solution. The mixture was filtered through a pad of Celite, and the filtrate was washed twice with saturated brine. The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the methylated product (78% yield). ¹H NMR analysis showed that the ratio of *ortho*-proton product to *ortho*-deuterium product is 25: 75 (Compared with the standard ¹H NMR spectrum of **1a**, the integration of the peak at 7.53 ppm was 0.25 instead of 1). For the synthesis of substrate **23**, see Yu et al. (2006) *JACS* 128:6790.

EXAMPLE 37

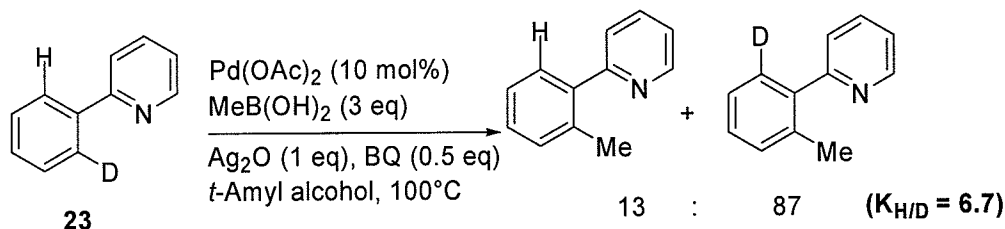
Intramolecular kinetic isotope effect in methylation with boroxine



In a 20 mL tube, substrate **23** (31.2 mg, 0.2 mmol, 1 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), methylboroxine (55.7 μ L, 0.4 mmol, 2 equiv), Ag₂O (46.3 mg, 0.2 mmol, 1 equiv) and benzoquinone – “BQ” – (21.6 mg, 0.2 mmol, 1 equiv) were dissolved in 1 mL of *tert*-Amyl alcohol under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was filtered through a pad of Celite, and the Celite was washed with 20 mL of CH₂Cl₂. The filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the methylated product (50% yield). ¹H NMR analysis showed that the ratio of *ortho*-proton product to *ortho*-deuterium product is 30:70.

EXAMPLE 38

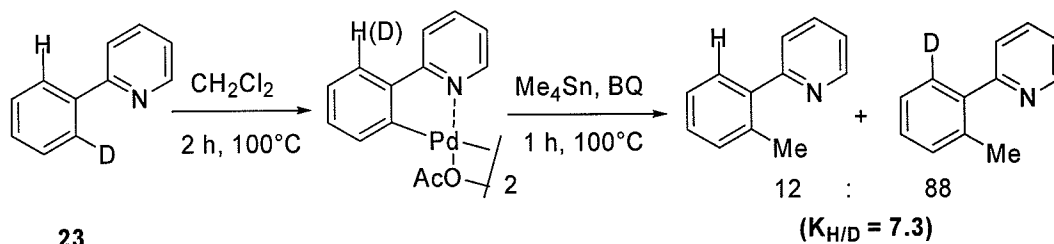
Intramolecular kinetic isotope effect in methylation with boronic acid



In a 20 mL tube, substrate **23** (31.2 mg, 0.2 mmol, 1 equiv), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), methylboronic acid (35.9 mg, 0.6 mmol, 3 equiv), Ag₂O (46.3 mg, 0.2 mmol, 1 equiv) and benzoquinone (10.8 mg, 0.1 mmol, 0.5 equiv) were dissolved in 1 mL of *tert*-Amyl alcohol under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was stirred at 100 °C for 6 hours. The reaction mixture was filtered through a pad of Celite, and the Celite was washed with 20 mL of CH₂Cl₂. The filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the methylated product (65% yield). ¹H NMR analysis showed that the ratio of *ortho*-proton product to *ortho*-deuterium product is 13:87.

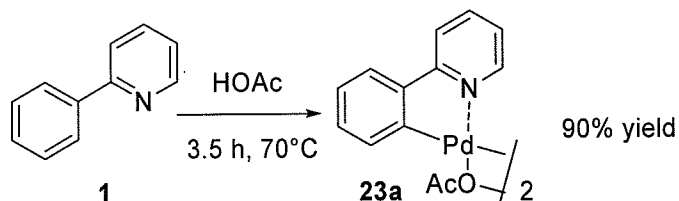
EXAMPLE 39

Intramolecular kinetic isotope effect in cyclopalladation



In a 20 mL tube, substrate **23** (31.2 mg, 0.2 mmol, 1 equiv) and Pd(OAc)₂ (4.5 mg, 0.2 mmol, 1 equiv) were dissolved in 1 mL of CH₂Cl₂ under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was heated at 100 °C for 2 hours. To the reaction mixture, tetramethyltin (35.8 mg, 0.2 mmol, 1 equiv) and benzoquinone (21.6 mg, 0.2 mmol, 1 equiv) were added. The reaction mixture was heated for 1 hour and then filtered through a pad of Celite. The filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane: ether = 10: 1) to give the methylated product (80% yield). ¹H NMR analysis showed that the ratio of *ortho*-proton product to *ortho*-deuterium product is 12:88.

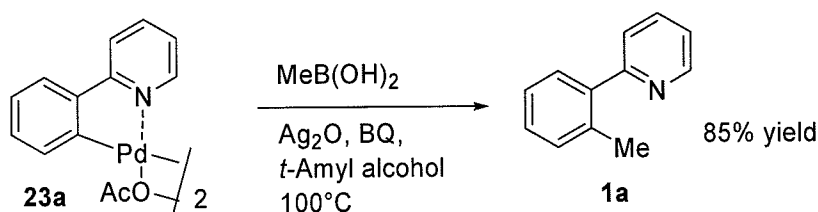
EXAMPLE 40

Synthesis of Palladacycle (**23a**)

To a stirred solution of $\text{Pd}(\text{OAc})_2$ (0.5 g, 2.23 mmol) in 80 mL of acetic acid, the stoichiometric amount of 2-phenylpyridine (0.32 mL, 2.23 mmol) was added and the solution was stirred at 100 °C for 3.5 h. The reaction mixture was filtered through a short Celite column. The solvent was removed under reduced pressure, and the residue was solidified from heptane to give 0.64 g of palladacycle **23a** as a brown solid (90% yield). Aiello et al. (2000) *Inorg. Chim. Acta*. 308:121.

10 EXAMPLE 41

Stoichiometric reaction of the palladacycle with methylboronic acid



In a 20 mL tube, palladacycle **23a** (25.6 mg, 0.04 mmol, 1 equiv), methylboronic acid (14.3 mg, 0.24 mmol, 3 equiv according to Pd), Ag_2O (18.5 mg, 0.08 mmol, 1 equiv according to Pd) and benzoquinone (8.6 mg, 0.08 mmol, 1 equiv according to Pd) were dissolved in 1 mL of *tert*-Amyl alcohol under atmospheric air. The tube was sealed with a Teflon lined cap, and the reaction mixture was heated at 100 °C for 4 hours. The mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The yield of **1a** determined by ^1H NMR analysis was 85%.

INCORPORATION BY REFERENCE

All of the U.S. patents and U.S. patent application publications cited herein are hereby incorporated by reference.

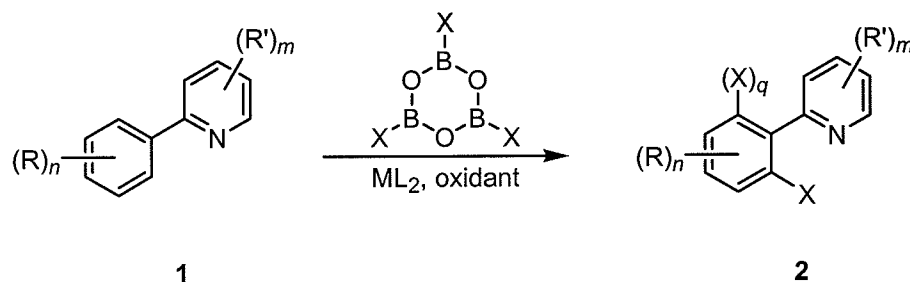
EQUIVALENTS

- 5 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A method of functionalizing an aryl C–H bond as represented by Scheme A, comprising the step of combining an arylpyridine (1), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkylboroxine, thereby producing
5 a functionalized product (2):

Scheme A



wherein

- R represents independently for each occurrence substituted or unsubstituted alkyl,
10 cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- 15 R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- 20 any two instances of R may be bonded together to form a ring that may be optionally substituted;
- any two instances of R' may be bonded together to form a ring that may be optionally substituted;
- 25 an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;
- M represents a transition metal;
- L independently for each occurrence represents a ligand;
- X represents alkyl;

m represents an integer in the range 0 to 4 inclusive;

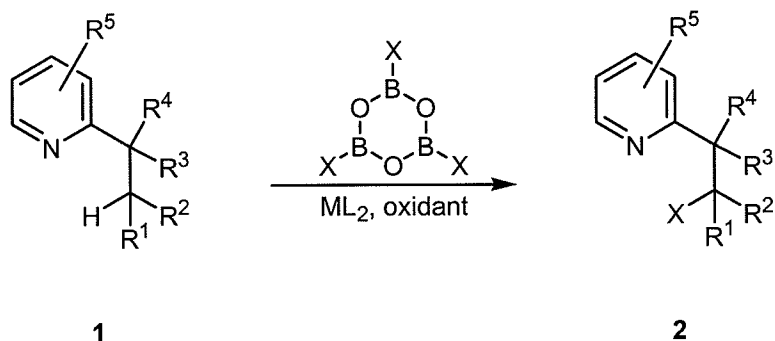
n represents an integer in the range 0 to (4-q) inclusive; and

q is 0 or 1.

2. The method of claim 1, wherein said M is selected from the group consisting of Rh,
5 Ru, Pd, Pt, and Cu.
3. The method of claim 1, wherein said M is Pd.
4. The method of claim 1, wherein said M is present in a stoichiometric amount relative to the arylpyridine.
5. The method of claim 1, wherein said M is present in less than or equal to 20 mol%
10 relative to the arylpyridine.
6. The method of claim 1, wherein said M is present in less than or equal to 10 mol% relative to the arylpyridine.
7. The method of claim 1, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine
15 carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.
8. The method of claim 1, wherein L is acetate.
9. The method of claim 1, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal
20 acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.
10. The method of claim 1, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.
11. The method of claim 1, wherein said oxidant is O₂.
- 25 12. The method of claim 1, wherein said oxidant is air.
13. The method of claim 1, wherein said oxidant is Ag₂O.
14. The method of claim 1, wherein said oxidant is Ag₂CO₃.
15. The method of claim 1, wherein said oxidant is Cu(OAc)₂.
16. The method of claim 1, wherein said oxidant is benzoquinone.
- 30 17. The method of claim 1, wherein said oxidant is a combination of benzoquinone, Cu(OAc)₂, and air.
18. The method of claim 1, wherein X is methyl.

19. The method of claim 1, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.
20. The method of claim 1, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.
21. The method of claim 1, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Cu(OAc)₂, and air; and X is methyl.
22. The method of any one of claims 1-21, wherein m is 0; and n is 0.
23. A method of functionalizing an alkyl C-H bond as represented by Scheme B, comprising the step of combining an alkylpyridine (1), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (2):

Scheme B



- wherein
- R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 5 R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 10 R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 15 R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 20 R^3 , R^4 , and R^5 may be bonded together as part of a ring that may be optionally substituted; M represents a transition metal;

- 25 L independently for each occurrence represents a ligand; and X represents alkyl.

24. The method of claim 23, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

25. The method of claim 23, wherein said M is Pd.

- 30 26. The method of claim 23, wherein said M is present in a stoichiometric amount relative to the alkylpyridine.

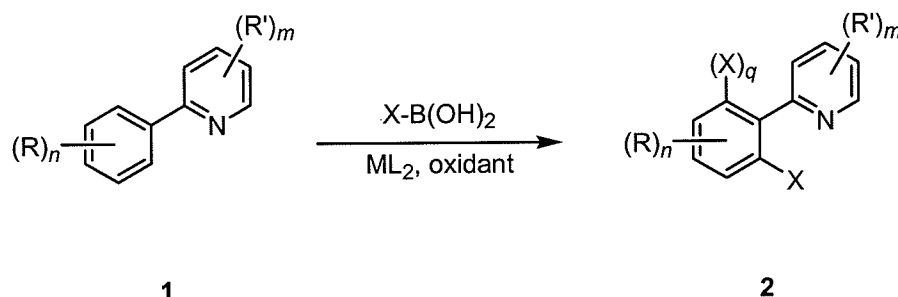
27. The method of claim 23, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyridine.

28. The method of claim 23, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyridine.
29. The method of claim 23, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine
5 carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.
30. The method of claim 23, wherein L is acetate.
31. The method of claim 23, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal
10 acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.
32. The method of claim 23, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.
33. The method of claim 23, wherein said oxidant is O₂.
- 15 34. The method of claim 23, wherein said oxidant is air.
35. The method of claim 23, wherein said oxidant is Ag₂O.
36. The method of claim 23, wherein said oxidant is Ag₂CO₃.
37. The method of claim 23, wherein said oxidant is Cu(OAc)₂.
38. The method of claim 23, wherein said oxidant is benzoquinone.
- 20 39. The method of claim 23, wherein said oxidant is a combination of benzoquinone, Cu(OAc)₂, and O₂.
40. The method of claim 23, wherein X is methyl.
41. The method of claim 23, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate,
25 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.
- 30 42. The method of claim 23, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.

43. The method of claim 23, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, $\text{Cu}(\text{OAc})_2$, and O_2 ; and X is methyl.

44. A method of functionalizing an aryl C–H bond as represented by Scheme C, comprising the step of combining an arylpyridine (**1**), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boronic acid, thereby producing a functionalized product (**2**):

Scheme C



wherein

10 R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

15 R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

20 any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

25 an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand;

X represents alkyl;

m represents an integer in the range 0 to 4 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

5 q is 0 or 1.

45. The method of claim 44, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

46. The method of claim 44, wherein said M is Pd.

47. The method of claim 44, wherein said M is present in a stoichiometric amount
10 relative to the arylpyridine.

48. The method of claim 44, wherein said M is present in less than or equal to 20 mol% relative to the arylpyridine.

49. The method of claim 44, wherein said M is present in less than or equal to 10 mol% relative to the arylpyridine.

15 50. The method of claim 44, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

51. The method of claim 44, wherein L is acetate.

20 52. The method of claim 44, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

53. The method of claim 44, wherein said oxidant is selected from the group consisting
25 of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

54. The method of claim 44, wherein said oxidant is O₂.

55. The method of claim 44, wherein said oxidant is air.

56. The method of claim 44, wherein said oxidant is Ag₂O.

57. The method of claim 44, wherein said oxidant is Ag₂CO₃.

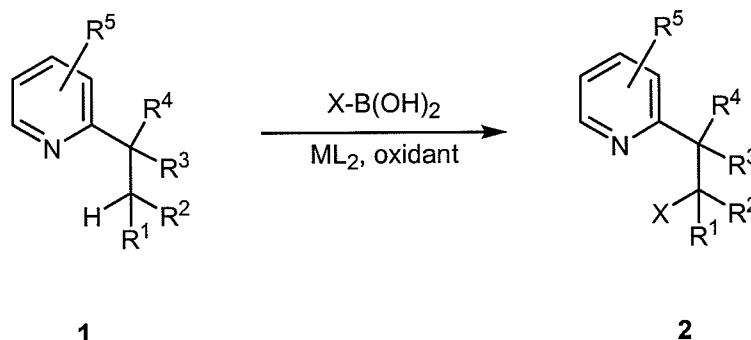
30 58. The method of claim 44, wherein said oxidant is benzoquinone.

59. The method of claim 44, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.

60. The method of claim 44, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
61. The method of claim 44, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
62. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
63. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
64. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.
65. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Et.
66. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.
67. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.
68. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.
69. The method of claim 44, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.
70. The method of any one of claims 44-69, wherein m is 0; and n is 0.
71. A method of functionalizing an alkyl C-H bond as represented by Scheme D, comprising the step of combining an alkylpyridine (1), a complex comprising a transition

metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (2):

Scheme D



5 wherein

R^1 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^2 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

(arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R⁵ represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,

5 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R³, R⁴, and R⁵ may be bonded together as part of a ring that may be optionally substituted;

10 M represents a transition metal;

L independently for each occurrence represents a ligand; and

X represents alkyl.

72. The method of claim 71, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

15 73. The method of claim 71, wherein said M is Pd.

74. The method of claim 71, wherein said M is present in a stoichiometric amount relative to the alkylpyridine.

75. The method of claim 71, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyridine.

20 76. The method of claim 71, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyridine.

77. The method of claim 71, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and
25 acetylacetonate.

78. The method of claim 71, wherein L is acetate.

79. The method of claim 71, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and
30 combinations thereof.

80. The method of claim 71, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

81. The method of claim 71, wherein said oxidant is O₂.

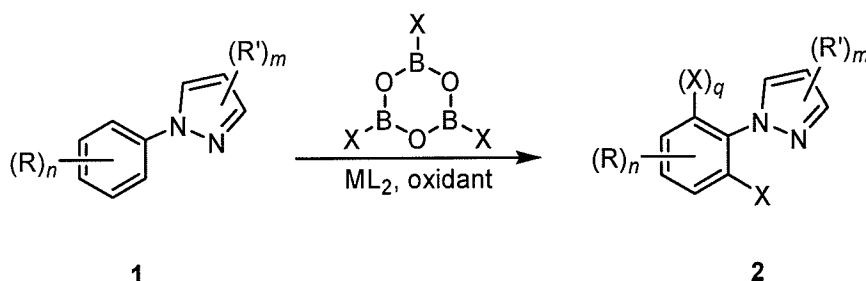
82. The method of claim 71, wherein said oxidant is air.
83. The method of claim 71, wherein said oxidant is Ag_2O .
84. The method of claim 71, wherein said oxidant is Ag_2CO_3 .
85. The method of claim 71, wherein said oxidant is benzoquinone.
- 5 86. The method of claim 71, wherein said oxidant is a combination of benzoquinone, Ag_2O , and air.
87. The method of claim 71, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, $\text{Ph}(\text{CH}_2)_2$ -, and cyclopropyl.
88. The method of claim 71, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, $(\text{OH})\text{PO}_4$, NO_3 , Se, SO_4 , CF_3CO_2 , ClO_4 , 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O_2 , air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, $\text{Ph}(\text{CH}_2)_2$ -, and cyclopropyl.
- 10 15 20 89. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O_2 , Ag_2O , Ag_2CO_3 , benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, $\text{Ph}(\text{CH}_2)_2$ -, and cyclopropyl.
90. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag_2O , and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, $\text{Ph}(\text{CH}_2)_2$ -, and cyclopropyl.
- 25 91. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag_2O , and air; and X is Me.
92. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag_2O , and air; and X is Et.
93. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag_2O , and air; and X is n-Bu.
- 30 94. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag_2O , and air; and X is n-Hex.

95. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

96. The method of claim 71, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

- 5 97. A method of functionalizing an aryl C-H bond as represented by Scheme E, comprising the step of combining an arylpyrazole (1), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkylboroxine, thereby producing a functionalized product (2):

Scheme E



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand;

X represents alkyl;

m represents an integer in the range 0 to 3 inclusive;

5 n represents an integer in the range 0 to (4-q) inclusive; and

q is 0 or 1.

98. The method of claim 97, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

99. The method of claim 97, wherein said M is Pd.

10 100. The method of claim 97, wherein said M is present in a stoichiometric amount relative to the arylpyrazole.

101. The method of claim 97, wherein said M is present in less than or equal to 20 mol% relative to the arylpyrazole.

102. The method of claim 97, wherein said M is present in less than or equal to 10 mol%
15 relative to the arylpyrazole.

103. The method of claim 97, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

20 104. The method of claim 97, wherein L is acetate.

105. The method of claim 97, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

25 106. The method of claim 97, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.

107. The method of claim 97, wherein said oxidant is O₂.

108. The method of claim 97, wherein said oxidant is air.

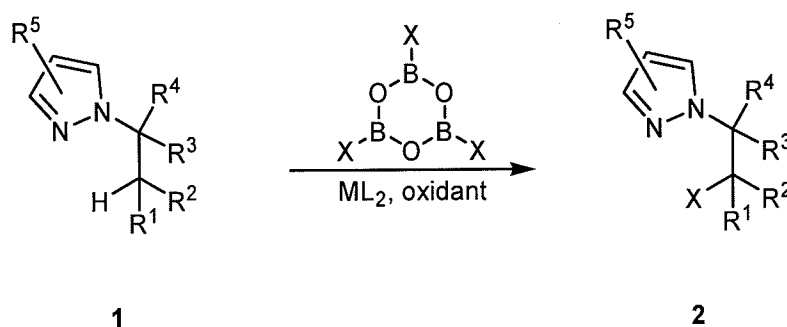
109. The method of claim 97, wherein said oxidant is Ag₂O.

30 110. The method of claim 97, wherein said oxidant is Ag₂CO₃.

111. The method of claim 97, wherein said oxidant is Cu(OAc)₂.

112. The method of claim 97, wherein said oxidant is benzoquinone.

113. The method of claim 97, wherein said oxidant is a combination of benzoquinone, $\text{Cu}(\text{OAc})_2$, and air.
114. The method of claim 97, wherein X is methyl.
115. The method of claim 97, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, $(\text{OH})\text{PO}_4$, NO_3 , Se, SO_4 , CF_3CO_2 , ClO_4 , 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O_2 , air, benzoquinones, and combinations thereof; and X represents methyl.
116. The method of claim 97, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O_2 , Ag_2O , Ag_2CO_3 , $\text{Cu}(\text{OAc})_2$, benzoquinone, and combinations thereof; and X is methyl.
117. The method of claim 97, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, $\text{Cu}(\text{OAc})_2$, and air; and X is methyl.
118. The method of any one of claims 97-117, wherein m is 0; and n is 0.
119. A method of functionalizing an alkyl C-H bond as represented by Scheme F, comprising the step of combining an alkylpyrazole (1), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby producing a functionalized product (2):

Scheme F

wherein

- R^1 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

(arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,

arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino,

5 arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,

alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

(arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R³ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,

10 arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,

alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

(arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

15 R⁴ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,

arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,

alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

(arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

20 (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R⁵ represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,

arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,

alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

25 (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R³, R⁴, and R⁵ may be bonded together as part of a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand; and

30 X represents alkyl.

120. The method of claim 119, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

121. The method of claim 119, wherein said M is Pd.

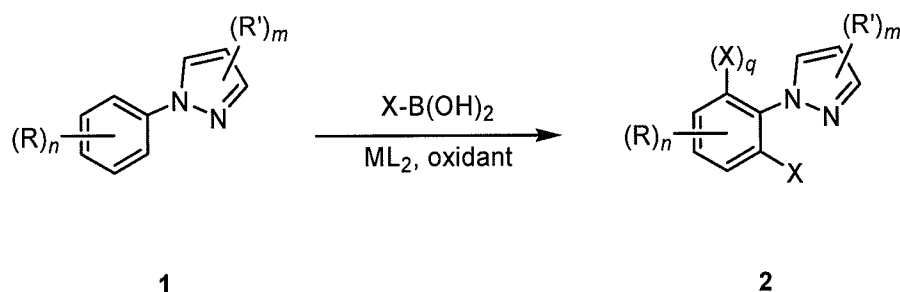
122. The method of claim 119, wherein said M is present in a stoichiometric amount relative to the alkylpyrazole.
123. The method of claim 119, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyrazole.
- 5 124. The method of claim 119, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyrazole.
125. The method of claim 119, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and
10 acetylacetonate.
126. The method of claim 119, wherein L is acetate.
127. The method of claim 119, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and
15 combinations thereof.
128. The method of claim 119, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof.
129. The method of claim 119, wherein said oxidant is O₂.
130. The method of claim 119, wherein said oxidant is air.
- 20 131. The method of claim 119, wherein said oxidant is Ag₂O.
132. The method of claim 119, wherein said oxidant is Ag₂CO₃.
133. The method of claim 119, wherein said oxidant is Cu(OAc)₂.
134. The method of claim 119, wherein said oxidant is benzoquinone.
135. The method of claim 119, wherein said oxidant is a combination of benzoquinone,
25 Cu(OAc)₂, and O₂.
136. The method of claim 119, wherein X is methyl.
137. The method of claim 119, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate,
30 cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X represents methyl.

138. The method of claim 119, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, Cu(OAc)₂, benzoquinone, and combinations thereof; and X is methyl.

139. The method of claim 119, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Cu(OAc)₂, and O₂; and X is methyl.

140. A method of functionalizing an aryl C-H bond as represented by Scheme G, comprising the step of combining an arylpyrazole (1), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boronic acid, thereby producing a functionalized product (2):

10 Scheme G



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

M represents a transition metal;

L independently for each occurrence represents a ligand;

5 X represents alkyl;

m represents an integer in the range 0 to 3 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

q is 0 or 1.

141. The method of claim 140, wherein said M is selected from the group consisting of
10 Rh, Ru, Pd, Pt, and Cu.

142. The method of claim 140, wherein said M is Pd.

143. The method of claim 140, wherein said M is present in a stoichiometric amount relative to the arylpyrazole.

144. The method of claim 140, wherein said M is present in less than or equal to 20
15 mol% relative to the arylpyrazole.

145. The method of claim 140, wherein said M is present in less than or equal to 10 mol% relative to the arylpyrazole.

146. The method of claim 140, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine
20 carboxylate, cyclohexanecarboxylate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate.

147. The method of claim 140, wherein L is acetate.

148. The method of claim 140, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal
25 acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.

149. The method of claim 140, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.

150. The method of claim 140, wherein said oxidant is O₂.

30 151. The method of claim 140, wherein said oxidant is air.

152. The method of claim 140, wherein said oxidant is Ag₂O.

153. The method of claim 140, wherein said oxidant is Ag₂CO₃.

154. The method of claim 140, wherein said oxidant is benzoquinone.

155. The method of claim 140, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.

156. The method of claim 140, wherein X is selected from the group consisting of Me, Et,

5 n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

157. The method of claim 140, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said
10 oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

158. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is selected
15 from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

159. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a
20 combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

160. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.

161. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a
25 combination of benzoquinone, Ag₂O, and air; and X is Et.

162. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.

163. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.

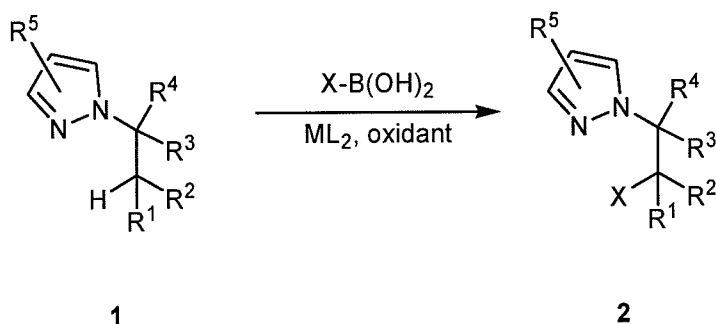
30 164. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

165. The method of claim 140, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

166. The method of any one of claims 140-165, wherein m is 0; and n is 0.

167. A method of functionalizing an alkyl C-H bond as represented by Scheme H, comprising the step of combining an alkylpyrazole (1), a complex comprising a transition metal (M) and at least two ligands (L), an oxidant, and an alkyl-boroxine, thereby
5 producing a functionalized product (2):

Scheme H



wherein

R^1 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,
10 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^2 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,
15 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^3 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,
arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,
25 (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R^4 represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,

arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

- 5 R^5 represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- 10 R^3 , R^4 , and R^5 may be bonded together as part of a ring that may be optionally substituted; M represents a transition metal; L independently for each occurrence represents a ligand; and X represents alkyl.

- 15 168. The method of claim 167, wherein said M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu.

169. The method of claim 167, wherein said M is Pd.

170. The method of claim 167, wherein said M is present in a stoichiometric amount relative to the alkylpyrazole.

- 20 171. The method of claim 167, wherein said M is present in less than or equal to 20 mol% relative to the alkylpyrazole.

172. The method of claim 167, wherein said M is present in less than or equal to 10 mol% relative to the alkylpyrazole.

173. The method of claim 167, wherein L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (HO)PO₃, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetate.
- 25

174. The method of claim 167, wherein L is acetate.

175. The method of claim 167, wherein said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof.
- 30

176. The method of claim 167, wherein said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof.
177. The method of claim 167, wherein said oxidant is O₂.
178. The method of claim 167, wherein said oxidant is air.
- 5 179. The method of claim 167, wherein said oxidant is Ag₂O.
180. The method of claim 167, wherein said oxidant is Ag₂CO₃.
181. The method of claim 167, wherein said oxidant is benzoquinone.
182. The method of claim 167, wherein said oxidant is a combination of benzoquinone, Ag₂O, and air.
- 10 183. The method of claim 167, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
184. The method of claim 167, wherein M is selected from the group consisting of Rh, Ru, Pd, Pt, and Cu; L is independently selected from the group consisting of OAc, Cl, F, OH, Br, (OH)PO₄, NO₃, Se, SO₄, CF₃CO₂, ClO₄, 2-pyrazine carboxylate, cyclohexanebutyrate, 2-ethylhexanoate, 3,5-diisopropylsalicylate, and acetylacetonate; said oxidant is selected from the group consisting of peroxides, hydroperoxides, hyperperoxides, hypervalent acyloxy iodides, transition metal acyloxy complexes, transition metal oxides, dihalogens, O₂, air, benzoquinones, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
- 15 185. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is selected from the group consisting of air, O₂, Ag₂O, Ag₂CO₃, benzoquinone, and combinations thereof; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
- 20 186. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
- 25 187. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Me.
- 30 188. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Et.

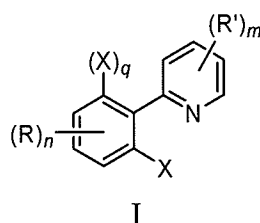
189. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Bu.

190. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is n-Hex.

5 191. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is Ph(CH₂)₂-.

192. The method of claim 167, wherein M is Pd; L is acetate; said oxidant is a combination of benzoquinone, Ag₂O, and air; and X is cyclopropyl.

193. A compound represented by formula I:



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

X represents alkyl;

m represents an integer in the range 0 to 4 inclusive;

n represents an integer in the range 0 to (4-q) inclusive; and

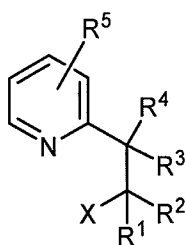
q is 0 or 1.

194. The compound of claim 193, wherein X is selected from the group consisting of Me,
 5 Et,
 n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

195. The compound of claim 193, wherein X is Me.

196. The compound of any one of claims 193-195, wherein m is 0; and n is 0.

197. A compound represented by formula II:



II

wherein

R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,
 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,
 15 arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,
 alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,
 (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,
 (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,
 20 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,
 arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,
 alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,
 (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,
 (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

25 R³ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,
 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,
 arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido,
 alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

(arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl,

(arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R⁴ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino,

5 arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R⁵ represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl,

10 arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl; and

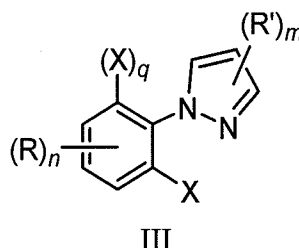
15 X represents alkyl.

198. The compound of claim 197, wherein X is selected from the group consisting of Me, Et,

n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

199. The compound of claim 197, wherein X is Me.

20 200. A compound represented by formula III:



wherein

R represents independently for each occurrence substituted or unsubstituted alkyl,

25 cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxyl, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

R' represents independently for each occurrence, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy,

5 (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;

any two instances of R may be bonded together to form a ring that may be optionally substituted;

any two instances of R' may be bonded together to form a ring that may be optionally substituted;

an instance of R and an instance of R' may be bonded together to form a ring that may be optionally substituted;

X represents alkyl;

m represents an integer in the range 0 to 3 inclusive;

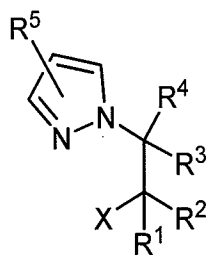
15 n represents an integer in the range 0 to (4-q) inclusive; and
q is 0 or 1.

201. The compound of claim 200, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.

202. The compound of claim 200, wherein X is Me.

203. The compound of any one of claims 200-202, wherein m is 0; and n is 0.

204. A compound represented by formula IV:



IV

25 wherein

R¹ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl,

- (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R² represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R³ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R⁴ represents H, substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl;
- R⁵ represents substituted or unsubstituted alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, arylalkyl, cyano, halogen, hydroxyl, alkoxy, aryloxy, arylalkyloxy, amino, alkylamino, arylamino, arylalkylamino, sulfhydryl, alkylthio, arylthio, arylalkylthio, nitro, azido, alkylseleno, formyl, acyl, carboxy, silyl, silyloxy, (alkyloxy)carbonyl, (aryloxy)carbonyl, (arylalkyloxy)carbonyl, (alkylamino)carbonyl, (arylamino)carbonyl, (arylalkylamino)carbonyl, alkylsulfonyl, or arylsulfonyl; and
- X represents alkyl.
205. The compound of claim 204, wherein X is selected from the group consisting of Me, Et, n-Bu, n-Hex, Ph(CH₂)₂-, and cyclopropyl.
206. The compound of claim 204, wherein X is Me.
207. A compound selected from the group consisting of:

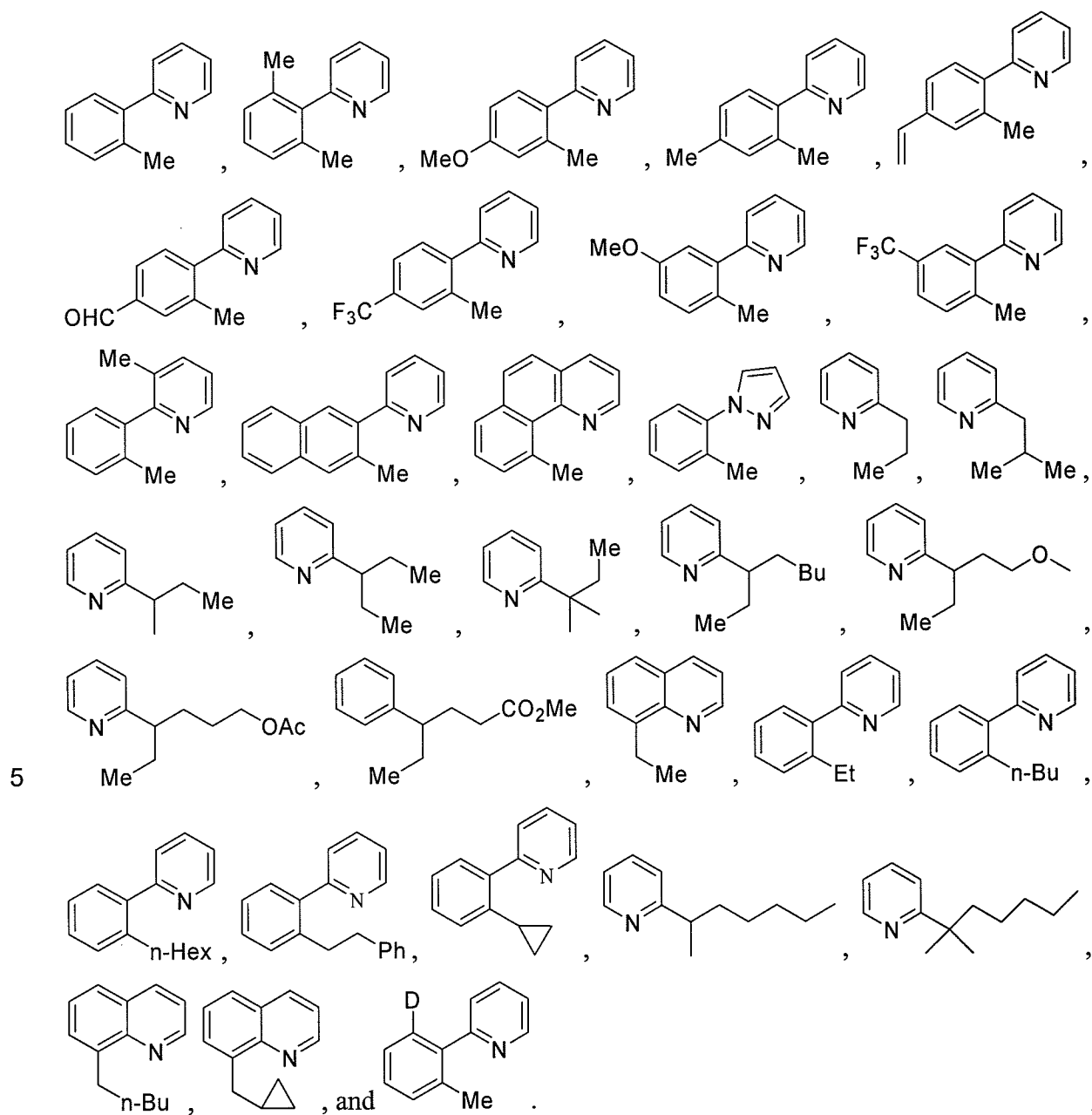


Figure 1

