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(71) Applicant: **THE UNIVERSITY OF MANCHESTER** [GB/GB]; Oxford Road, Mancheser M13 9PL (GB).

(72) Inventors: **LARROSA, Igor**; 4 Gerrards Gardens, Hyde, Cheshire SK14 5SH (GB). **SIMONETTI, Marco**; Flat 94, 6 Chapeltown Street, Manchester M1 2BQ (GB). **CANNAS, Diego Maria**; 18 Milnrow Close, Manchester M13 9UZ (GB).

(74) Agent: **APPLEYARD LEES IP LLP**; 15 Clare Road, Halifax, Yorkshire HX1 2HY (GB).

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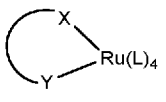
(54) Title: PROCESS FOR FORMING A CARBON-CARBON BOND



(I)

(57) Abstract: A process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an alkyl or cycloalkyl moietyof a second compound, the process comprising reacting the first compound with the second compound in the presence of a catalytically effective amount of a neutral or cationic ruthenium(II) catalyst of formula (I).

PROCESS FOR FORMING A CARBON-CARBON BOND

Technical Field of the Invention

The invention relates to a process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an alkyl or cycloalkyl moiety of a second compound. The process comprises reacting the first compound with the second compound in the presence of a catalytically effective amount of a neutral or cationic ruthenium(II) catalyst.

Background to the Invention

Coupled aryl/alkyl, aryl/cycloalkyl, heteroaryl/cycloalkyl and heteroaryl/alkyl units are common structural motifs in many compounds, such as pharmaceutically active compounds and agrochemicals. Such coupled units are typically incorporated into compounds during their synthesis using cross-coupling reactions (in the presence of metal catalysts) that are well known to persons skilled in the art.

It would be desirable to incorporate coupled aryl/alkyl, aryl/cycloalkyl, heteroaryl/cycloalkyl and heteroaryl/alkyl units into complex compounds via late-stage C-H alkylation reactions, as this would enable the preparation of compounds of diverse structures and potentially novel compounds. However, C-H (cyclo)alkylation reactions are typically conducted under reaction conditions that are too harsh to be applied at late stages in synthesis to already functionalised compounds and functional groups present in such functionalised compounds can interfere with and poison the metal catalyst.

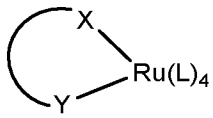
Ru(II)-catalysed C–H alkylation reactions between directing group (DG)-containing arenes and alkyl halides are known (for example see, *Angew. Chem., Int. Ed.* **2009**, *48*, 6045; *Chem. Commun*. **2015**, *51*, 12807; J. *Am. Chem. Soc*. **2015**, *137*, 13894), but it would be desirable to establish more general and efficient reaction conditions. For example, it would be desirable to provide such reactions that do not require the use of high temperatures and/or several fold excess of the (cyclo)alkyl (pseudo)halide. It would also be desirable to provide such reactions that can be used with polar sensitive groups, which are ubiquitous in pharmaceutical and natural products.

Thus, it is an object of the invention to provide a process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an alkyl or cycloalkyl moiety of a second compound, for example to prepare compounds including coupled aryl/alkyl, aryl/cycloalkyl, heteroaryl/cycloalkyl and/or heteroaryl/alkyl units (such as, for example, compounds including such units as part of complex compound, such as a pharmaceutically

active compound or agrochemical) by a late stage formation of a carbon-carbon bond, for example by adding alkyl units to already functionalised complex molecules.

Summary of the Invention

According to a first aspect of the invention, there is provided a process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an alkyl (preferably (4-15C)alkyl) or cycloalkyl (preferably (4-10C)cycloalkyl) moiety of a second compound, the process comprising reacting the first compound with the second compound in the presence of a catalytically effective amount of a neutral or cationic ruthenium(II) catalyst of formula (I):



formula (I)

wherein:

each L is independently selected from neutral and anionic ligands in any combination that balances the bonding and charge requirements of the ruthenium, and wherein any two ligands L can be linked so as to form a bidentate ligand; and

X and Y together form a bidentate cyclometalated ligand for the ruthenium (for example resulting in a five- or six-membered metallacycle), wherein the bidentate cyclometalated ligand comprises an organic group represented by X which is bonded to the ruthenium by a heteroatom selected from N, P or O (preferably N or P) and an organic group represented by Y which is bonded to the ruthenium via an sp2 or an sp3 carbon.

The process of the present invention can be conducted under mild reaction conditions, such as at low temperatures. The ruthenium(II) catalysts used in the process are inexpensive, display extremely high reactivity and are highly robust. The ruthenium(II) catalysts display unprecedented high reactivity under remarkably mild reaction conditions. Thus, the process of the invention may be used for forming carbon-carbon bonds at a late-stage in the preparation of a wide range of complex compounds, wherein the complex compounds may include a range of functional groups previously considered to be incompatible with such coupling reactions.

The ruthenium(II) catalyst of formula (I) may be neutral or it may be cationic, depending on the nature of the ligands bonded to the ruthenium. When the catalyst is charged, it includes an associated counterion, such as for example hexafluorophosphate (PF_6^-), tetrafluoroborate (BF_4^-), trifluoromethanesulfonate (OTf^-), perchlorate (ClO_4^-), tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($BAr^F{}_4^-$), nitrate (NO_3^-), or bis(trifluoromethylsulfonyl)imide (NTf_2^-).

Unless otherwise stated, the following terms used in the specification and claims have the meanings set out below.

The term “alkyl” includes both straight and branched chain alkyl groups. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as “isopropyl” are specific for the branched chain version only. For example, “(1-20C)alkyl” includes (1-10C)alkyl, (1-4C)alkyl, propyl, isopropyl and t-butyl. References to “alkyl” within other functional groups, such as in “alkylamino” and “alkylthio” groups etc, are to be interpreted analogously. For example, “(1-10C)alkylamino” includes (1-4C)alkylamino, methylamino, propylamino, isopropylamino and tert-butylamino.

As would be appreciated by persons skilled in the art, a “moiety” is a group within a molecule/compound. Thus, by the term “alkyl moiety” we mean an alkyl (functional) group that is part of a compound (i.e. part of the second compound). In other words, the second compound includes an alkyl moiety in addition to at least one other (functional group). For example, the second compound may comprise (or consist of) an alkyl moiety and a leaving group (such as when the second compound is n-octyl bromide or tert-butylbromide for example). In addition to the alkyl moiety and the leaving group, the second compound may comprise any additional group(s) required to form the desired final product.

The term “alkenyl” includes both straight and branched chain alkenyl groups. References to individual alkenyl groups such as “propenyl” are specific for the straight chain version only and references to individual branched chain alkenyl groups such as “isopropenyl” are specific for the branched chain version only. For example, “(2-10C)alkenyl” includes (2-6C)alkenyl, propenyl, isopropenyl and t-butenyl.

The term “cycloalkyl” means a saturated hydrocarbon ring. The term “(4-10C)cycloalkyl” means a hydrocarbon ring containing from 4 to 10 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, bicyclo[2.2.2]octyl, bycyclo[2.1.1]hexyl, bicyclo[1.1.1]pentyl and bicyclo[2.2.1]heptyl.

by the term “cycloalkyl moiety” we mean a cycloalkyl (functional) group that is part of a compound (i.e. part of the second compound). In other words, the second compound includes a cycloalkyl moiety in addition to at least one other (functional group). For example, the second compound may comprise (or consist of) a cycloalkyl moiety and a leaving group (such as when the second compound is cyclohexylbromide or cycloheptylbromide for example). In addition to the cycloalkyl moiety and the leaving group, the second compound may comprise any additional group(s) required to form the desired final product.

The term “alkoxy” includes both straight and branched chain alkoxy groups. References to individual alkoxy groups such as “propoxy” are specific for the straight chain version only and references to individual branched chain alkyl groups such as “isopropoxy” are specific for the branched chain version only. For example, “(1-10C)alkoxy” includes (1-6C)alkoxy, (1-4C)alkoxy, propoxy, isopropoxy and t-butoxy.

The term “heterocyclic ring” means a non-aromatic saturated or partially saturated monocyclic or fused, bridged or spiro bicyclic heterocyclic ring system.

The term “aryl” means a cyclic or polycyclic aromatic ring having from 5 to 20 carbon atoms. . Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, pyrenyl and perylenyl. In particular, an aryl is phenyl.

The term “heteroaryl” means an aromatic mono-, bi- or poly-cyclic ring incorporating one or more (for example from 1 to 4, such as 1, 2 or 3) heteroatoms selected from nitrogen, oxygen and sulfur. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from 5 to 12 ring members, typically from 5 to 10 ring members. The heteroaryl group can, for example, be a 5 or 6 membered monocyclic ring or a 9 or 10 membered bicyclic ring, for example a bicyclic structure formed from fused 5 and 6 membered rings or two 6 membered rings. Each ring may contain up to 4 heteroatoms typically selected from nitrogen, oxygen and sulfur. Typically, the heteroaryl ring will contain up to 3 heteroatoms, for example up to 2, such as 1 heteroatom.

The term “halo” includes fluoro, chloro, bromo and iodo.

The term “pseudohalide” means a substituent that behaves like a ‘halo’ in the context of the present invention and includes triflate, tosylate, mesylate.

The term “optionally substituted” is used to indicate optional substitution by the group or groups specified at any suitable position. Examples of suitable optional substituents include halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (4-10C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

Throughout this specification, the term “comprising” or “comprises” means including the component(s) specified but not to the exclusion of the presence of other components. The term “consisting essentially of” or “consists essentially of” means including the components specified but excluding other components except for components added for a purpose other than achieving the technical effect of the invention. The term “consisting of” or “consists of”

means including the components specified but excluding other components. Whenever appropriate, depending upon the context, the use of the term “comprises” or “comprising” may also be taken to include the meaning “consists essentially of” or “consisting essentially of”, and also may also be taken to include the meaning “consists of” or “consisting of”.

In formula (I), each L is independently selected from neutral and anionic ligands in any combination that balances the bonding and charge requirements of the ruthenium, and wherein any two ligands L can be linked so as to form a bidentate ligand. As the skilled person would appreciate, each L may be the same or different.

Examples of suitable neutral ligands L include H_2O, benzonitrile, (1-20C)alkylnitrile, tri-[(2-10C)alkyl]amine, (2-10C)alkenyl and di[(2-10C)alkyl]sulfide, wherein each benzonitrile, (1-20C)alkylnitrile, tri[(2-10C)alkyl]amine, (2-10C)alkenyl or di[(2-10C)alkyl]sulfide group is optionally substituted. For example, each benzonitrile, (1-20C)alkylnitrile, tri[(2-10C)alkyl]amine, (2-10C)alkenyl or di[(2-10C)alkyl]sulfide group may be optionally substituted by one or more substituents independently selected from (1-10C)alkyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, (1-10C)alkoxy, trifluoromethyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl and (1-10C)alkylthio. Examples of suitable anionic ligands L include halides such as chloride, bromide and iodide, (1-20C)alkylcarboxylate and aryl carboxylate.

Suitably, L does not represent a tridendate ligand of the η^6-arene type. Examples of unsuitable such η^6-arene ligands are benzene, *o*-, *m*-, *p*-xylene, mesitylene, *p*-cymene, and hexamethylbenzene.

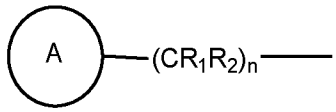
Suitably, the ligand L represents (1-20C)alkylnitrile, such as (1-5C)alkylnitrile, for example methylnitrile (i.e. acetonitrile). Suitably, all four ligands L represent acetonitrile.

X and Y together form a bidentate cyclometalated ligand for the ruthenium, wherein the bidentate cyclometalated ligand comprises an organic group represented by X which is bonded to the ruthenium by a heteroatom selected from N, P or O (preferably N or P, more preferably N) and an organic group represented by Y which is bonded to the ruthenium via an sp2 or an sp3 carbon. The organic group represented by X may be any group provided it is bonded to the ruthenium by a heteroatom selected from N, P or O. The organic group represented by Y may be any group provided that it is bonded to the ruthenium via an sp2 or sp3 carbon atom.

The bidentate cyclometalated ligand may form a 5- or 6-membered ruthenacycle with the ruthenium.

The organic group represented by Y may comprise an aryl or heteroaryl group bonded to the ruthenium via an sp2 or an sp3 carbon atom.

For example, the organic group represented by Y may comprise a group of formula (II) bonded to the ruthenium via an sp2 or an sp3 carbon atom:



formula (II)

wherein

A represents an optionally substituted aryl or heteroaryl group;

n is 0 or 1; and

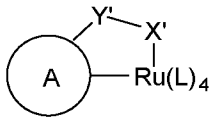
R_1 and R_2 are each independently selected from H or (1-4C)alkyl.

The group of formula (II) is bonded to the ruthenium either via the sp3 carbon of the CR_1R_2 group (when n is 1) or via an sp2 ring carbon of the group A.

In formula (II) n represents 0 or 1, particularly 0. Suitably, when n represents 1, R_1 and R_2 are each independently selected from H or (1-2C)alkyl and in particular R_1 and R_2 may both represent H.

The group A in the formula (II) may be optionally substituted by any suitable substituent, for example by one or more (suitably 0, 1, 2, 3 or 4) substituents independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl. For example, suitable substituents may be selected from fluoro, methyl, butyl (such as *tert*-butyl), methoxy, phenoxy and trifluoromethyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IA):



formula (IA)

wherein

L is as defined above;

A represents an optionally substituted aryl or heteroaryl group;

X' represents NR_6R_7 and Y' represents NR_{11}, $CR_{12}R_{13}$ or C(O), or X' represents PR_8R_9 and Y' represents $CR_{12}R_{13}$, or X' represents O and Y' represents $CR_{12}R_{13}$ or C(O); wherein R_6,

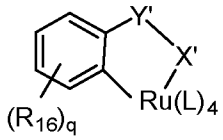
R_7, R_8, R_9, R_{11}, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, or R_6 and R_7, or R_8 and R_9 together with the N or P to which they are attached form a 4 to 6 membered heterocyclyl group and/or R_{12} and R_{13} together with the C to which they are attached form a (4-10C)cycloalkyl group, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted;

or any of the groups R_6, R_7, R_8 or R_9, and any of the groups R_{11}, R_{12} or R_{13} together with the N, C or P to which they are attached may form a cycloalkyl, heterocyclyl, heteroaryl or aryl ring, wherein the cycloalkyl, heterocyclyl, heteroaryl or aryl ring so formed is optionally substituted.

Examples of suitable optional substituents for the aryl or heteroaryl group represented by A in the formula (IA) include halo (for example fluoro), (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl. Any suitable number of optional substituents may be present depending on the particular aryl or heteroaryl group A.

Suitably, in the formula (IA), the group A may represent an optionally substituted aryl group, such as an optionally substituted phenyl or napthyl group, particularly an optionally substituted phenyl group. Examples of suitable optional substituents for the aryl group represented by A include halo (for example fluoro), (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl. Suitably, optional substituents for the aryl group represented by A include halo (for example fluoro), (1-5C)alkyl (for example methyl or tert-butyl), phenoxy and trifluoromethyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IA'):



formula (IA')

wherein:

L is as defined above;

q represents 0, 1, 2, 3 or 4;

X' represents NR_6R_7 and Y' represents $CR_{12}R_{13}$ or C(O), or X' represents PR_8R_9 and Y' represents $CR_{12}R_{13}$, or X' represents O and Y' represents $CR_{12}R_{13}$ or C(O);

wherein R_6, R_7, R_8, R_9, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, or R_6 and R_7, or

R_8 and R_9 together with the N or P to which they are attached form a 4 to 8 membered heterocyclyl group and/or R_{12} and R_{13} together with the C to which they are attached form a (4-10C)cycloalkyl group, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted;

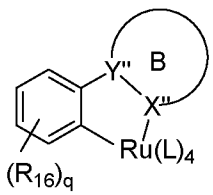
each R_{16} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

In the formulae (IA and IA'), X' may suitably represent NR_6R_7 and Y' may represent $CR_{12}R_{13}$, wherein R_6, R_7, R_{12} and R_{13} are as defined above. For example, R_6 and R_7 may suitably each be independently selected from (1-10C)alkyl, wherein each (1-10C)alkyl is optionally substituted by one or more substituents independently selected from (1-15C)alkoxy, fluoro, trifluoromethyl and (1-15C)alkyl (especially (1-15C)alkoxy), or R_6 and R_7 together with the N to which they are attached may form a 4 to 8 membered heterocyclic ring, wherein the heterocyclic ring is optionally substituted by one or more substituents independently selected from (1-10C)alkyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, (1-10C)alkoxy, trifluoromethyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl and (1-10C)alkylthio. Suitably, R_{12} and R_{13} may each be independently selected from H or (1-4C)alkyl, such as from H, methyl or ethyl.

In the formulae (IA and IA'), X' may suitably represent PR_8R_9 and Y' may represent $CR_{12}R_{13}$, wherein R_8, R_9, R_{12} and R_{13} are as defined above. R_8 and R_9 may for example each independently represent (4-10C)cycloalkyl, such as for example adamantyl. Suitably, R_{12} and R_{13} may each be independently selected from H or (1-4C)alkyl, such as from H, methyl or ethyl.

In the formulae (IA and IA'), X' may suitably represent O and Y' may represent C(O).

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IA''):



formula (IA'')

wherein:

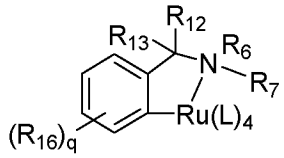
L is as defined above;

q represents 0, 1, 2, 3 or 4;

B represents a heteroaryl or heterocyclyl group containing a heteroatom N or P represented by X'' and an sp2 or sp3 heteroatom N or an sp2 or sp3 C represented by Y'', wherein the heteroaryl or heterocyclyl group is optionally substituted;

each R_{16} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IA'''):



formula (IA''')

wherein:

L is as defined above;

q represents 0, 1, 2, 3 or 4;

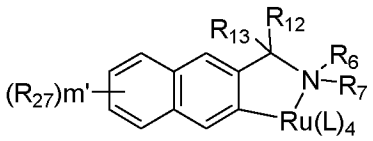
R_6, R_7, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, or R_6 and R_7 together with the N to which they are attached form a 4 to 6 membered heterocyclyl group, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted;

each R_{16} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

In the formulae (IA), (IA'), (IA'') and (IA'''), the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and cycloalkyl groups may be optionally substituted by any suitable substituents. Examples of suitable optional substituents include halo (such as fluoro), (1-15C)alkyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, (1-15C)alkoxy, trifluoromethyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl and (1-10C)alkylthio.

The substituent(s) R_{16} (when present) in the formula (IA'), (IA'') and (IA''') may be located at any suitable position on the phenyl ring.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IA''''):



formula (IA'''')

wherein:

L is as defined above;

m' represents 0, 1, 2, 3, 4, 5 or 6;

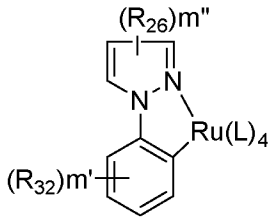
R_6 and R_7 are each independently selected from H, (1-10C)alkyl, phenyl or (4-10C)cycloalkyl, wherein each (1-10C)alkyl, phenyl and (4-10C)cycloalkyl is optionally substituted by one or more substituents independently selected from (1-15C)alkoxy, fluoro, trifluoromethyl and (1-15C)alkyl;

R_{12} and R_{13} are each independently selected from H or (1-10C)alkyl, wherein each (1-10C)alkyl is optionally substituted by one or more substituents independently selected from (1-10C)alkyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, (1-10C)alkoxy, trifluoromethyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl and (1-10C)alkylthio;

each R_{27} (is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

The substituent(s) R_{27} (when present) in the formula (IA'''') may be located on one or both of the rings of the napthyl group and at any suitable position on the rings.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IA''''):



formula (IA'''')

wherein:

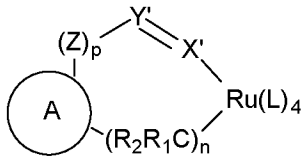
L is as defined above;

m' represents 0, 1, 2, 3 or 4;

m'' represents 0, 1, 2 or 3;

each R_{26} and R_{32} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IB):



formula (IB)

wherein

L is as defined above;

n is 0 or 1;

R_1 and R_2 are each independently selected from H or (1-4C)alkyl;

A represents an optionally substituted aryl or heteroaryl group;

p represents 0 or 1;

Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H or (1-4C)alkyl;

X' represents NR_{14} and Y' represents CR_{15} or N, wherein R_{14} and R_{15} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted

or R_{14} and R_{15} can together with the N or C to which they are attached form a heterocyclyl or heteroaryl ring, wherein the heterocyclyl or heteroaryl ring so formed is optionally substituted.

Examples of suitable optional substituents for the aryl or heteroaryl group represented by A in the formula (IB) include halo (for example fluoro), (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl. Any suitable number of optional substituents may be present depending on the particular aryl or heteroaryl group A.

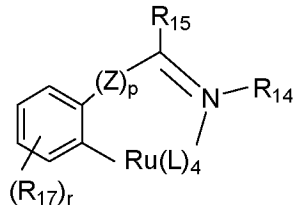
Suitably, in the formula (IB), the group A may represent an optionally substituted aryl group, such as an optionally substituted phenyl or napthyl group, particularly an optionally substituted phenyl group. Examples of suitable optional substituents for the aryl group represented by A include halo (for example fluoro), (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-

10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl. Suitably, optional substituents for the aryl group represented by A include halo (for example fluoro), (1-5C)alkyl (for example methyl or tert-butyl), phenoxy and trifluoromethyl. In particular, the optional substituents may include fluoro and methyl.

Suitably, in the formula (IB), n is 0.

Suitably, in the formula (IB), X' represents NR_{14} and Y' represents CR_{15}, wherein R_{14} and R_{15} are each independently selected from (1-10C)alkyl and aryl, wherein any of the (1-10C)alkyl and aryl groups is optionally substituted, or the group R_{14} and the group R_{15} together with the N and C to which they are attached form a heterocyclyl or heteroaryl ring, wherein the heterocyclyl or heteroaryl ring so formed is optionally substituted.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IB'):



formula (IB')

wherein:

L is as defined as above;

p represents 0 or 1;

r represents 0, 1, 2, 3 or 4;

Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H or (1-4C)alkyl;

wherein R_{14} and R_{15} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, groups is optionally substituted;

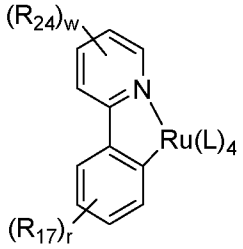
or the group R_{14} and the group R_{15} can together with the N and C to which they are attached form a heterocyclyl or heteroaryl ring, wherein the heterocyclyl or heteroaryl ring so formed is optionally substituted;

each R_{17} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

In the formulae (IB) and (IB'), the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and cycloalkyl groups may be optionally substituted by any suitable substituents. Examples of suitable optional substituents include halo (such as fluoro), (1-15C)alkyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, (1-15C)alkoxy, trifluoromethyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl and (1-10C)alkylthio.

Suitably, in the formulae (IB) and (IB'), Z (when present) represents CH_2, O or NH.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IB''):



formula (IB'')

wherein:

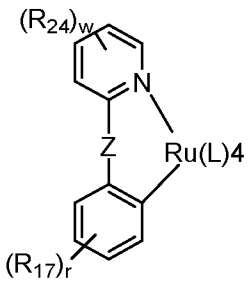
L is as defined above;

w is 0, 1, 2, 3 or 4;

r is 0, 1, 2, 3 or 4; and

each R_{17} and R_{24} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IB'''):



formula (IB''')

wherein:

L is as defined above;

Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H, (1-4C)alkyl or aryl (preferably H or (1-4C)alkyl);

w represents 0, 1, 2, 3 or 4;

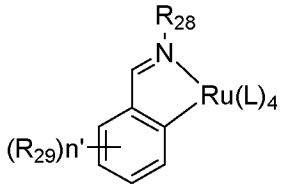
r represents 0, 1, 2, 3 or 4;

each R_{17} and R_{24} (when present) is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

In the formula (IB''), w may represent 0 or 1 (especially 0). In the formula (IB''), r may represent 0 or 1 (especially 0).

Suitably, in the formula (IB''), each R_{17} and R_{24} is independently selected from halo (for example fluoro), (1-5C)alkyl (for example methyl or tert-butyl), phenoxy and trifluoromethyl. In particular, the optional substituents may include fluoro and methyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IB''''):



formula (IB'''')

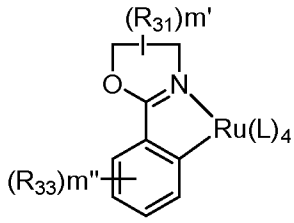
wherein:

L is as defined above;

n' represents 0, 1, 2, 3 or 4;

R_{28} and R_{30} are each independently selected from H, (1-10C)alkyl, phenyl or (4-10C)cycloalkyl, wherein each (1-10C)alkyl, phenyl and (4-10C)cycloalkyl is optionally substituted by one or more substituents independently selected from (1-15C)alkoxy, fluoro, trifluoromethyl and (1-15C)alkyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IB'''''):



formula (IB''''')

wherein:

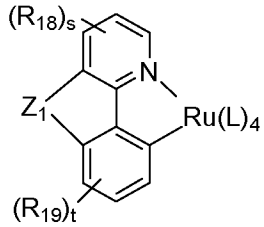
L is as defined above;

m' represents 0, 1 or 2;

m'' represents 0, 1, 2, 3 or 4;

each R_{31} and R_{33} (when present) is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (IC):



formula (IC)

wherein:

L is as defined above;

s represents 0, 1, 2 or 3;

t represents 0, 1, 2 or 3;

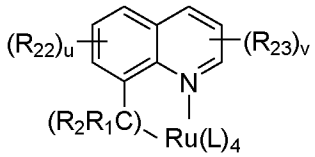
each R_{18} and R_{19} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl;

Z_1 represents –C=C-, -C=N- or -N=C-.

In the formula (IC), s may represent 0 or 1, such as 0. In the formula (IC), t may represent 0 or 1, such as 0.

Suitably, in the formula (IC), each R_{18} and R_{19} (when present) may be independently selected from halo and (1-10C)alkyl (especially (1-4C)alkyl, such as methyl).

Suitably, the neutral or cationic ruthenium(II) catalyst may be represented by the formula (ID):



formula (ID)

wherein:

L is as defined above;

R_1 and R_2 are each independently selected from H or (1-4C)alkyl;

u represents 0, 1, 2 or 3;

v represents 0, 1, 2 or 3;

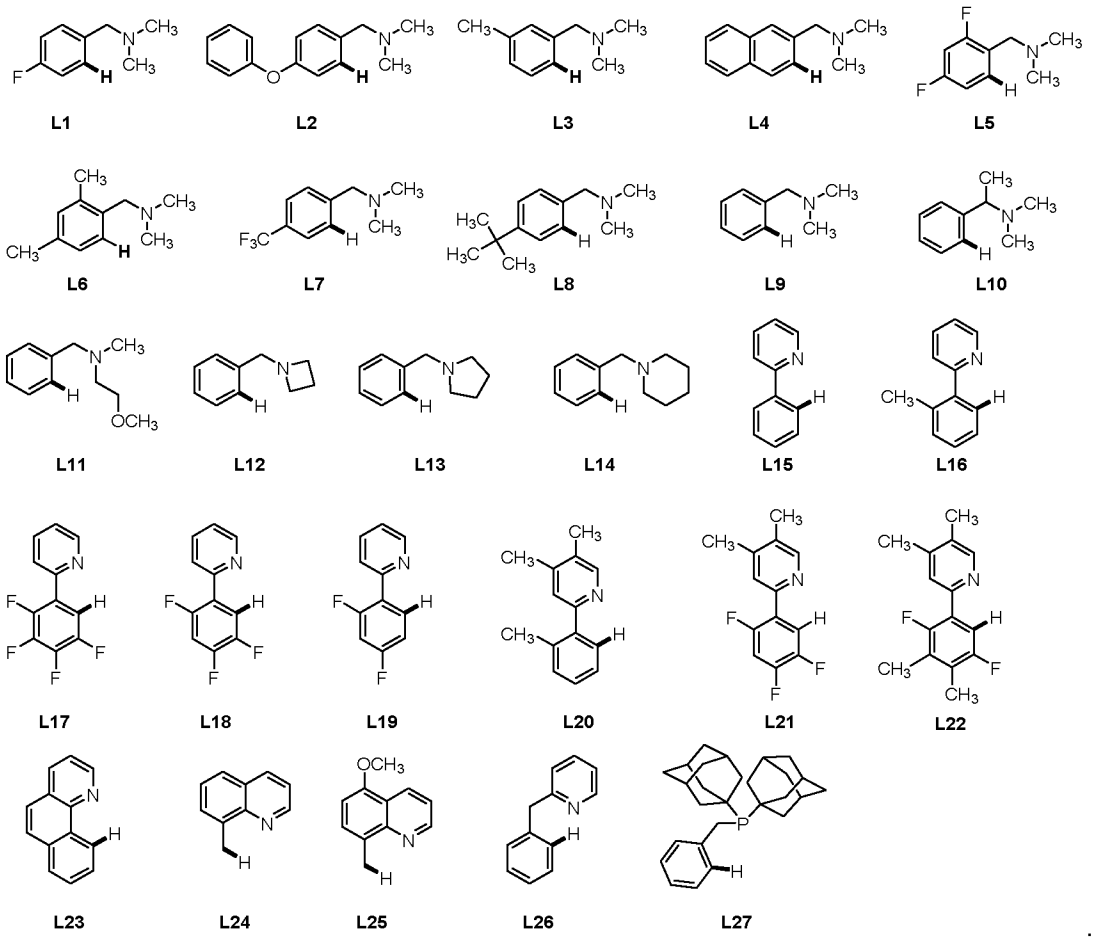
each R_{22} and R_{23} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

In the formula (ID), u may represent 0 or 1. In the formula (ID), v may represent 0 or 1, such as 0.

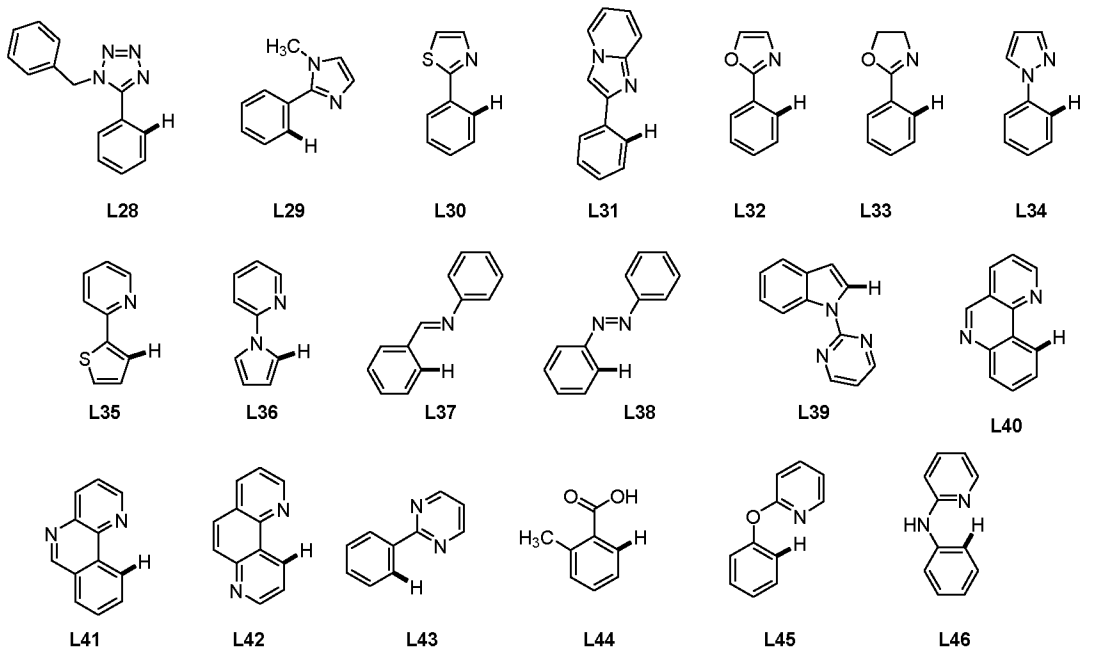
Suitably, in the formula (ID), each R_{22} and R_{23} (when present) may be independently selected from halo, (1-10C)alkyl and (1-10C)alkoxy (especially (1-4C)alkyl, such as methyl, and (1-4C)alkoxy, such as methoxy).

In the formula (ID), suitably R_{22} and R_{23} (when present) may each independently be selected from (1-10C)alkoxy, such as (1-4C)alkoxy, especially methoxy.

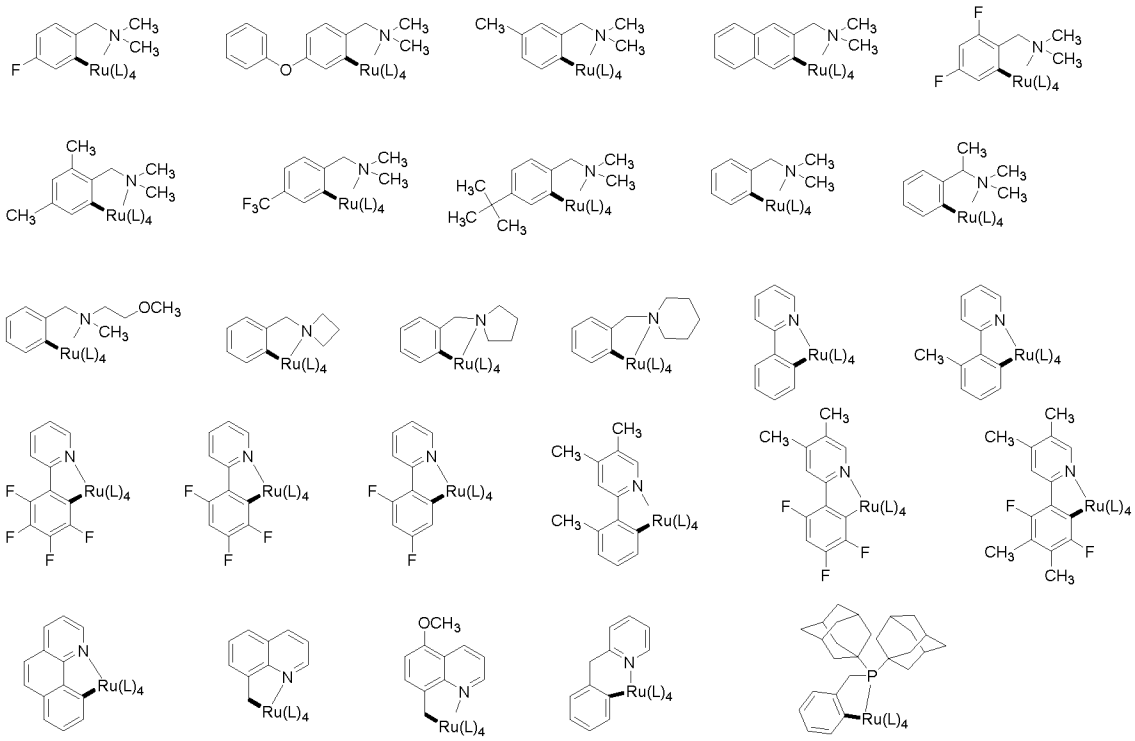
Examples of suitable cyclometalating ligands that may be bonded to the ruthenium to provide a suitable neutral or cationic ruthenium(II) catalyst for use in the process of the invention include (but are not limited to):



Examples of suitable cyclometalating ligands that may be bonded to the ruthenium to provide a suitable neutral or cationic ruthenium(II) catalyst for use in the process of the invention include (but are not limited to):

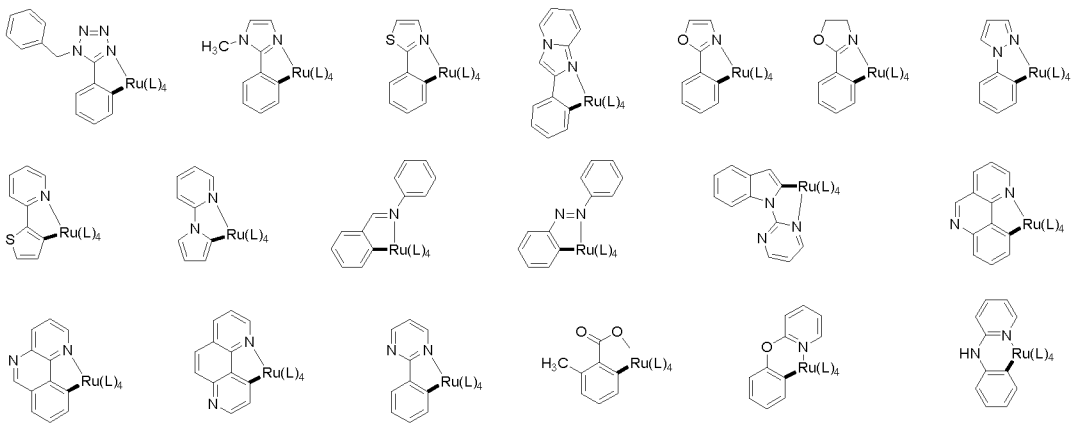


Examples of suitable neutral or cationic ruthenium(II) catalysts for use in the process of the invention include (but are not limited to):



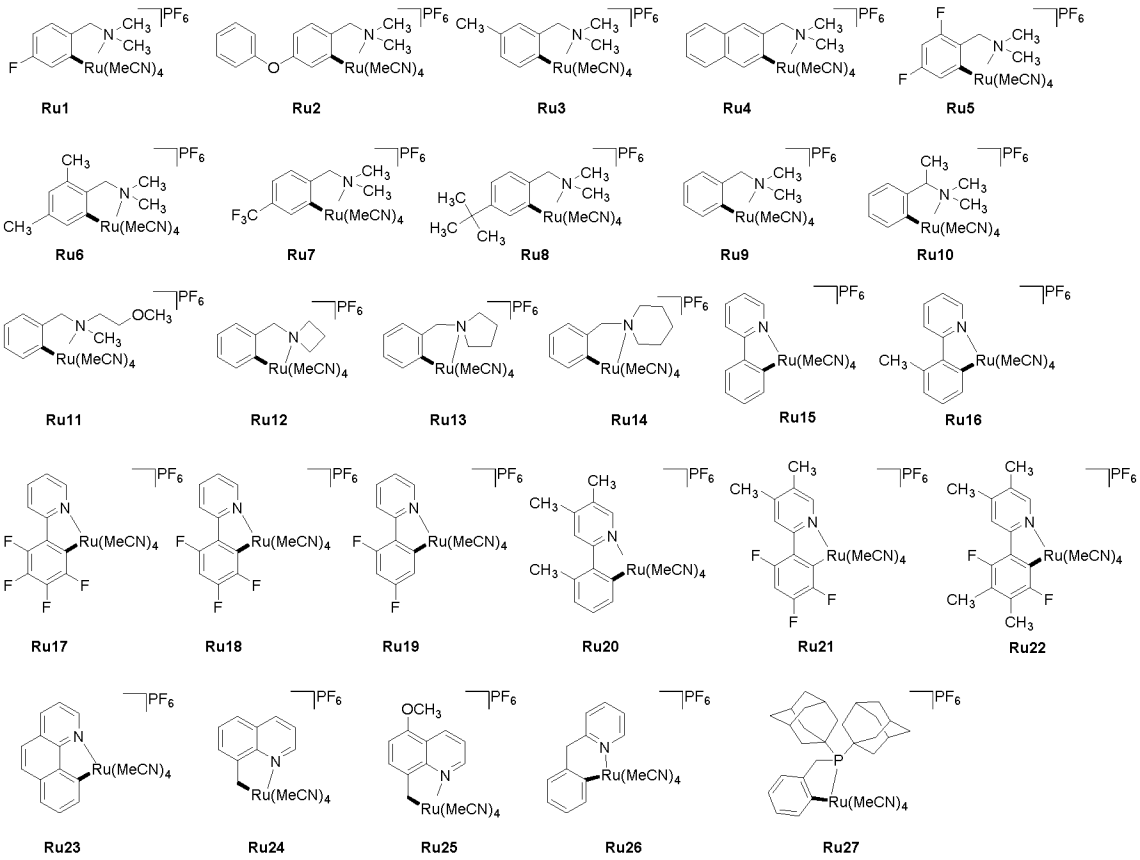
wherein each L is as defined above.

Examples of neutral or cationic ruthenium(II) catalysts for use in the process of the invention include (but are not limited to):

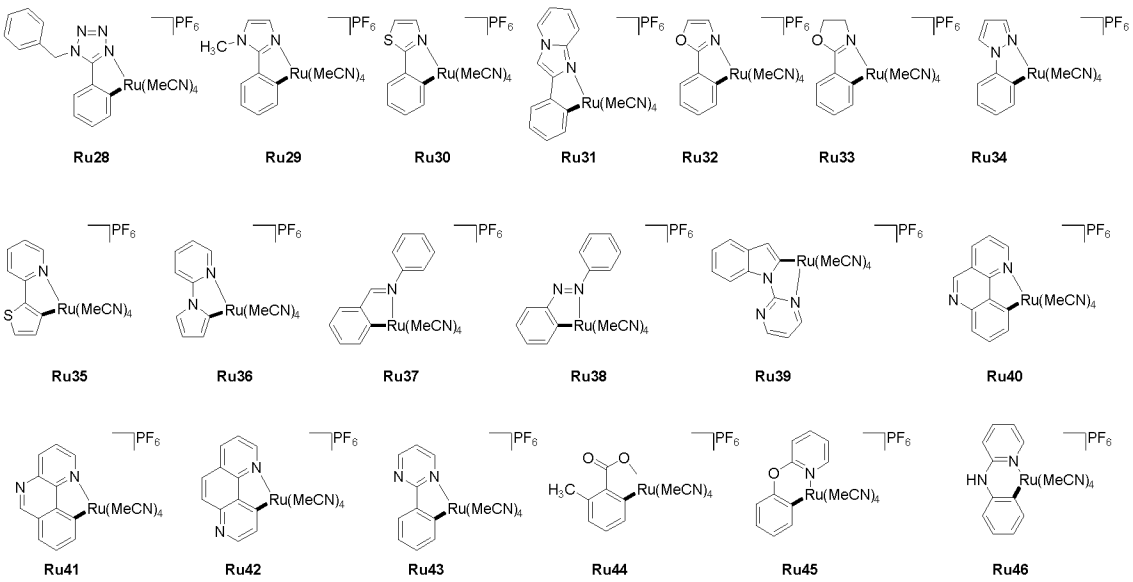


wherein each L is as defined above.

Further examples of suitable cationic ruthenium(II) catalysts for use in the process of the invention include (but are not limited to):



Further examples of cationic ruthenium(II) catalysts for use in the process of the invention include (but are not limited to):



The cyclometalating ligands and ruthenium complexes may be prepared according to standard procedures known to persons skilled in the art (see, for example, *J. Am. Chem. Soc.* **2011**,

133, 10161; *Organometallics*, **1999**, 18, 2390–2394; *Polymer* **2014**, *55,* 1656–1665). For example a suitable ligand precursor may be reacted with a ruthenium complex such as $[Ru(Cl)_2(benzene)]_2$ in the presence of acetonitrile and a suitable base.

The ruthenium catalyst as discussed herein is used in the process of the invention in a catalytically effect amount. As would be appreciated by persons skilled in the art, this amount may vary depending on the exact nature of the process (for example depending on the nature of the first and second compounds, the solvent used and the reaction temperature), but typically the ruthenium catalyst may be used in an amount ranging from a 1 mol % to 10 mol %.

The process of the invention may be conducted with a wide range of first and second compounds so as to prepare a wide range of further compounds. The first compound may comprise a reactive aryl or heteroaryl group, i.e. in addition to other chemical groups. The second compound may comprise a reactive alkyl or cycloalkyl moiety, i.e. in addition to other chemical groups. As the skilled person would appreciate, it is the aryl or heteroaryl group in the first compound that reacts with the alkyl or cycloalkyl moiety in the second compound to form a new carbon-carbon bond.

The first compound may, for example, be any of a wide range of functional aryl and/or heteroaryl containing compounds, including pharmaceuticals, agrochemicals, natural products and organic electronic compounds.

The second compound may, for example, be any of a wide range of functional alkyl and/or cycloalkyl containing compounds, including pharmaceuticals, agrochemicals, natural products and organic electronic compounds.

The first compound comprises an aryl or heteroaryl group and may comprise other organic groups in addition thereto (including further aryl and/or heteroaryl groups).

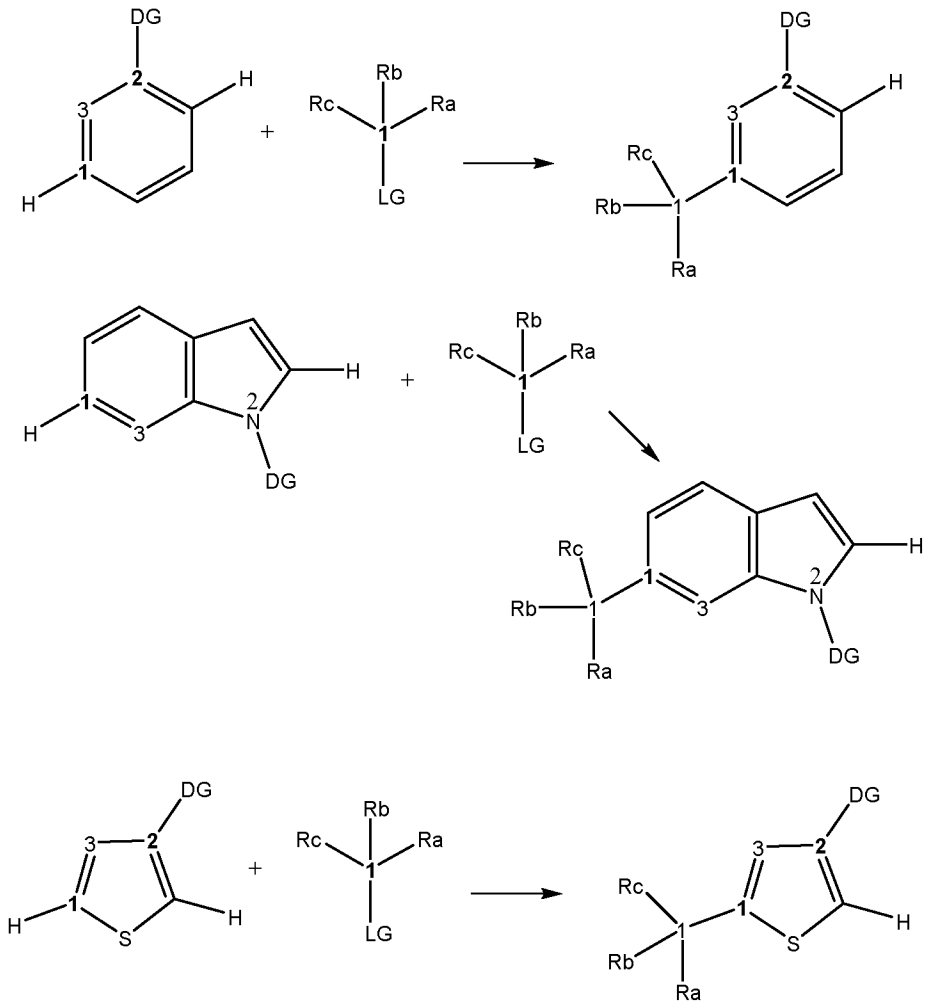
The second compound comprises an alkyl or cycloalkyl moiety and may comprise other organic groups in addition thereto (including further alkyl and/or cycloalkyl groups). As discussed herein, the second compound further comprises a suitable leaving group.

The process may be one in which the first compound comprises an aryl or heteroaryl group having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is adjacent to the first ring atom and which has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto, and wherein the second compound comprises an alkyl or cycloalkyl moiety having a first (sp3) carbon atom

having a leaving group bonded thereto, such that the reaction between the first compound and the second compound results in the formation of a carbon-carbon bond between the first ring atom of the first compound and the first (sp3) carbon atom of the second compound.

The process may be one in which the first compound comprises an aryl or heteroaryl group having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is separated from the first ring atom by one non-bridging third ring atom, wherein the second ring atom has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto and is adjacent to a ring carbon atom having a hydrogen bonded thereto, and wherein the second compound comprises an alkyl or cycloalkyl moiety having a first (sp3) carbon atom having a leaving group bonded thereto, such that the reaction between the first compound and the second compound results in the formation of a carbon-carbon bond between the first ring atom of the first compound and the first (sp3) carbon atom of the second compound.

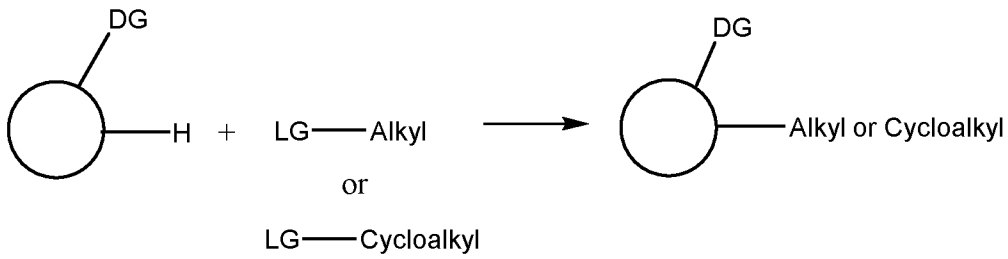
In this case, the second ring atom of the aryl or heteroaryl group may be separated from the first ring atom by one or more (for example 1 or 2) bridging ring atoms in addition to the one non-bridging ring atom. Examples of such processes are as follows:



wherein DG represents a nitrogen containing directing group, LG represents a leaving groupand Ra, Rb and Rc each independently represent H or alkyl, so as to represent the alkyl moiety of the second compound. For example, when LG represents bromo, Ra and Rb represent H and Rc represents $-(CH_2)_6CH_3$, then the second compound is n-octylbromide. In the processes above, the second compound is represented as a compound such as n-octylbromide which comprises an alkyl moiety and a leaving group, but as discussed herein the second compound may comprise additional groups to the alkyl moiety and leaving group.

The first and/or second compound may comprise one or more protecting groups, which protecting groups may be added or removed therefrom by methods well known in the art.

For example, the process may be represented generally as follows:



First aryl or heteroaryl | Second compound | Coupled first and second compounds

wherein LG represents a suitable leaving group, DG represents a nitrogen containing directing group (or a salt or protected derivative thereof) and alkyl and cycloalkyl represent an alkyl and cycloalkyl moiety of a second compound.

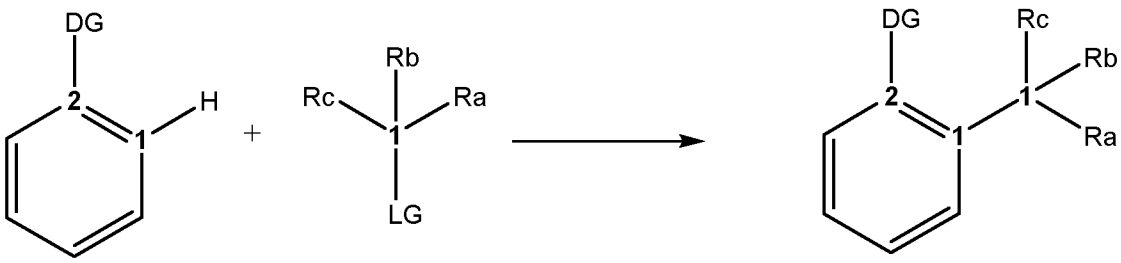
The nitrogen containing directing group may be bonded to a second ring atom of the first compound. The second ring atom may be adjacent (or ortho) to a first ring atom which is a carbon atom having a hydrogen bonded thereto. The directing group is suitably an ortho directing group.

The second ring atom may be separated from the first ring atom of the first compound by one non-bridging third ring atom (and optionally, when present in the first compound, one or more bridging ring atoms). In this case, the second ring atom is adjacent to a ring carbon atom having a hydrogen bonded thereto.

The directing group may be bonded to the second ring atom of the second compound directly or via an intervening linker group.

The leaving group is bonded to a first (sp3) carbon atom of the alkyl or cycloalkyl moiety of the second compound. Upon reaction, a carbon-carbon bond is formed between the first ring atom of the first compound and the first (sp3) carbon atom of the second compound.

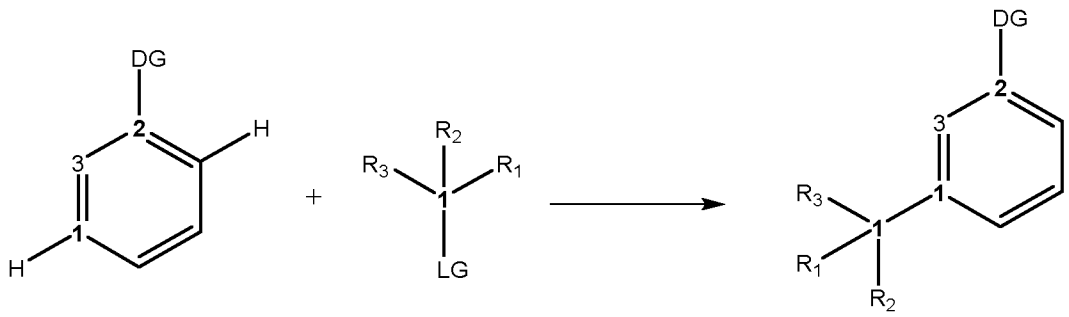
For example, the process may couple a (first) phenyl compound and an alkyl containing (second) compound as follows:



First compound | Second compound | Coupled first and second Compound

In this particular process, where the first compound comprises a phenyl group, it is preferred that the alkyl group of the second compound comprises at least one C-H bond (for example is a primary or secondary halide).

For example, the process may couple a (first) phenyl compound and an alkyl containing (second) compound as follows:



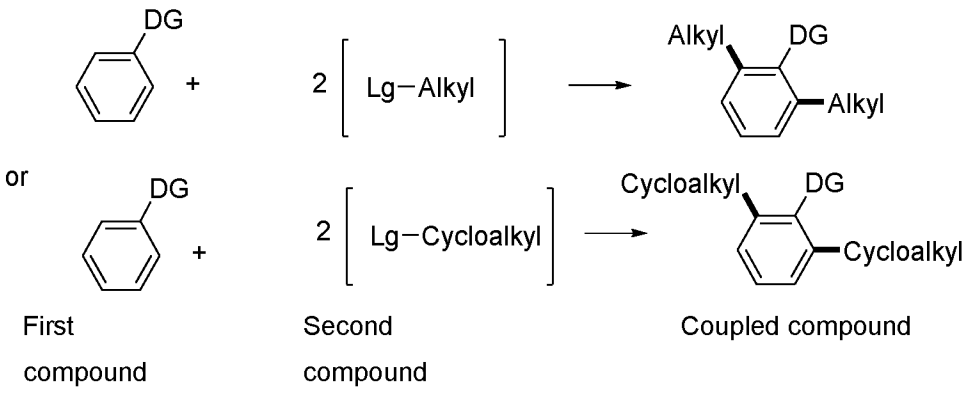
In this particular process, where the first compound comprises a phenyl group, it is preferred that the alkyl group of the second compound comprises at least two C-C bonds (for example is a tertiary or secondary halide).

In the processes shown above, the phenyl and alkyl groups may, of course, be substituted by any suitable substituents, which substituents may be protected by any suitable protecting groups as required and/or may be in the form of suitable salts.

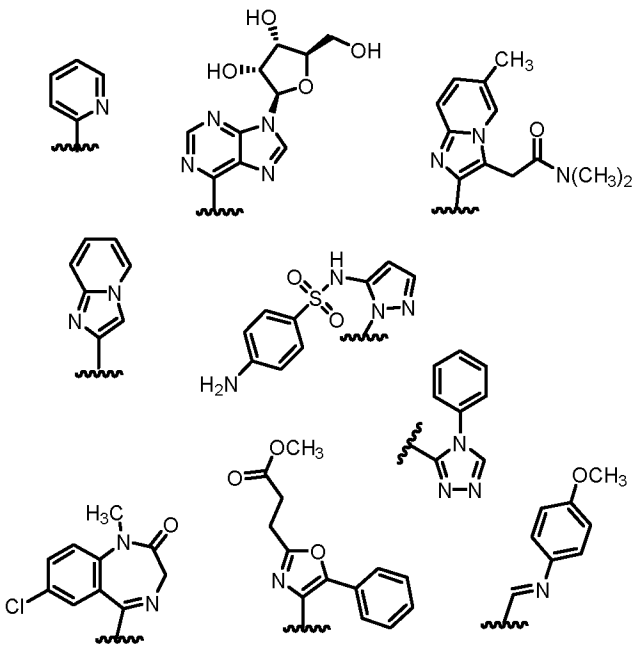
Suitably, the first compound comprises an aryl or heteroaryl group, for example having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is adjacent (for example ortho) to the first ring atom and which has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto.

Suitably, the first compound comprises an aryl or heteroaryl group, for example having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is separated from the first ring atom by one non-bridging third ring atom, wherein the second ring atom has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto and is adjacent to a ring carbon atom having a hydrogen bonded thereto.

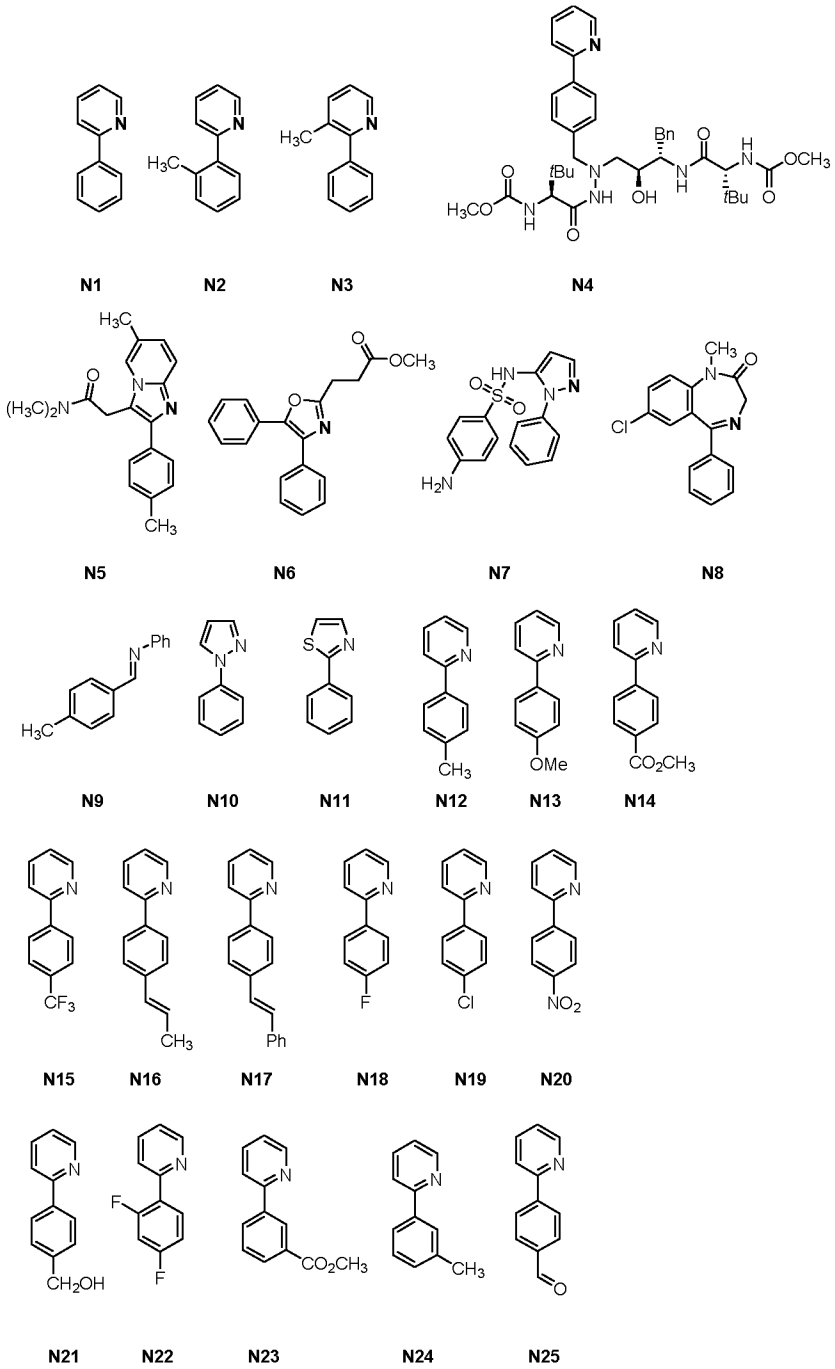
As the skilled person would appreciate, it is possible for more than one carbon-carbon bond to be formed according to the process of the present invention. For example, two second compounds may couple to a single first compound (for example phenyl compound) forming two C-C bonds as follows:



Any suitable nitrogen containing directing group (or a salt or protected derivative thereof) may be used. Examples of suitable nitrogen containing directing groups include (but are not limited to):



Examples of suitable directing group-containing arenes (i.e. first compounds) include (but are not limited to):

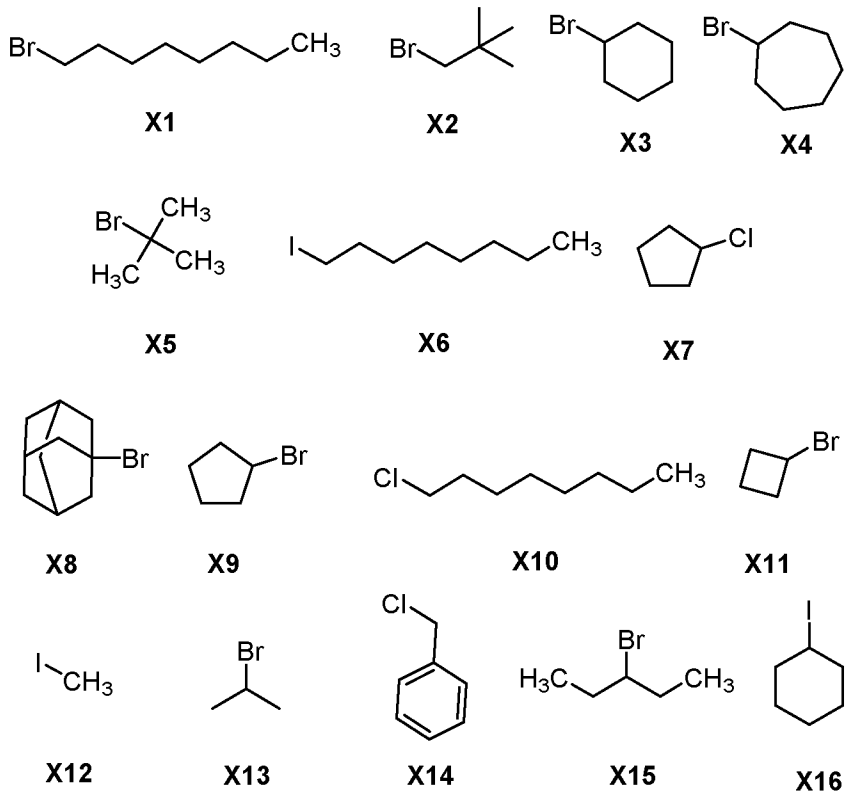


wherein *t*Bu represents *tert*-butyl, and Bn represents benzyl, and Ph represents phenyl.

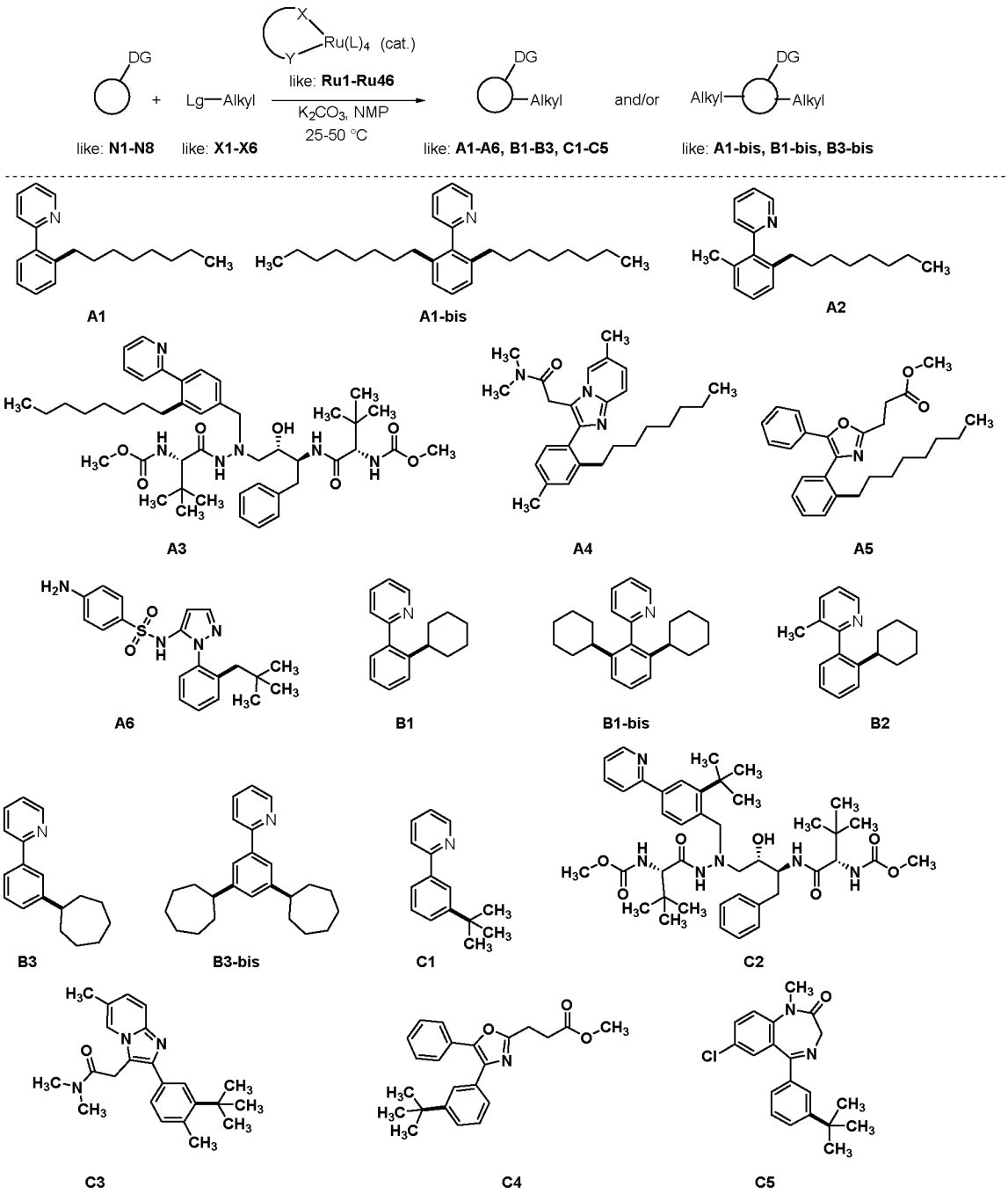
Particularly, an example of a suitable first compound is 2-phenyl pyridine (N1).

The second compound comprises an alkyl or cycloalkyl moiety, for example having a first (sp3) carbon atom having a leaving group bonded thereto. Examples of suitable leaving groups include (but are not limited to) chloro, bromo, iodo, trifluoromethanesulfonate (OTf) *p*-toluenesulfonate (OTs) and methanesulfonate (OMs), N-alkylpyridinium derivatives such as N alkylated derivatives of 2,4,6-triphenylpyridine, suitably bromo and iodo.

The second compound may be any suitable compound comprising an alkyl or cycloalkyl moiety and having a leaving group bonded to a first (sp3) carbon atom. Examples of suitable second compounds include (but are not limited to):



Examples of suitable processes for forming carbon-carbon bonds according to the present invention that can be conducted are (but are not limited to) as follows:



The process may be conducted at any suitable temperature, for example at a temperature from 25 to 50°C.

The process is suitably conducted in the presence of a suitable base, such as potassium carbonate.

The ruthenium(II) catalysts are typically prepared and isolated prior to use in the process of the invention, but may alternatively be prepared in situ.

The process may be conducted in any suitable solvent. Examples of suitable solvents include tetrahydrofuran, toluene, gamma-valerolactone, propylene carbonate, ethylacetate, acetone, gamma-butyrolactone, dioxane and *N*-methyl pyrrolidone.

Cyclometalated ruthenium(II) catalysts are well-known for being oxygen sensitive (see, for example, *Organometallics* **1999**, *18*, 2390–2394) and therefore generally need to be manipulated and stored under inert atmosphere. To overcome this limitation the neutral or cationic ruthenium(II) catalysts discussed herein may be encapsulated in an inert medium such as paraffin to obtain an air stable preparation (for example using the method as discussed in *Org. Lett.* **2016**, *18*, 3934–3936). By using an encapsulated cyclometalated ruthenium(II) catalyst the process can be carried out using standard Schlenk techniques without the need of specialised equipment such as a glove-box.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IA) as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IA') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IA'') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IA''') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IA'''') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IA''''') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB) as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB'') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB''') as defined above.

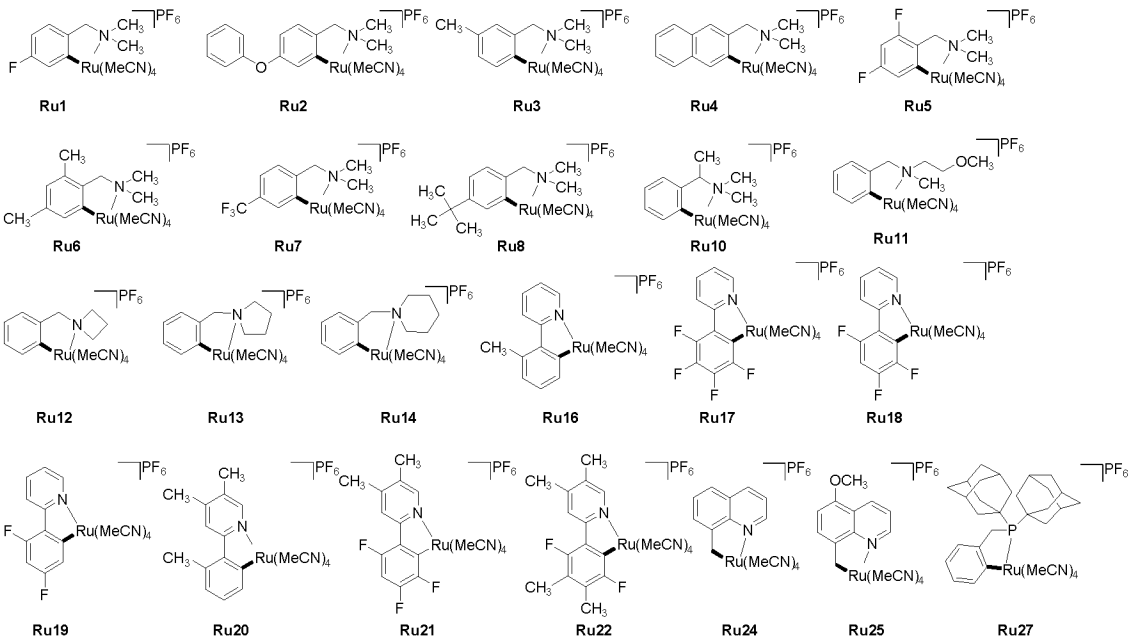
According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB'''') as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB''''') as defined above.

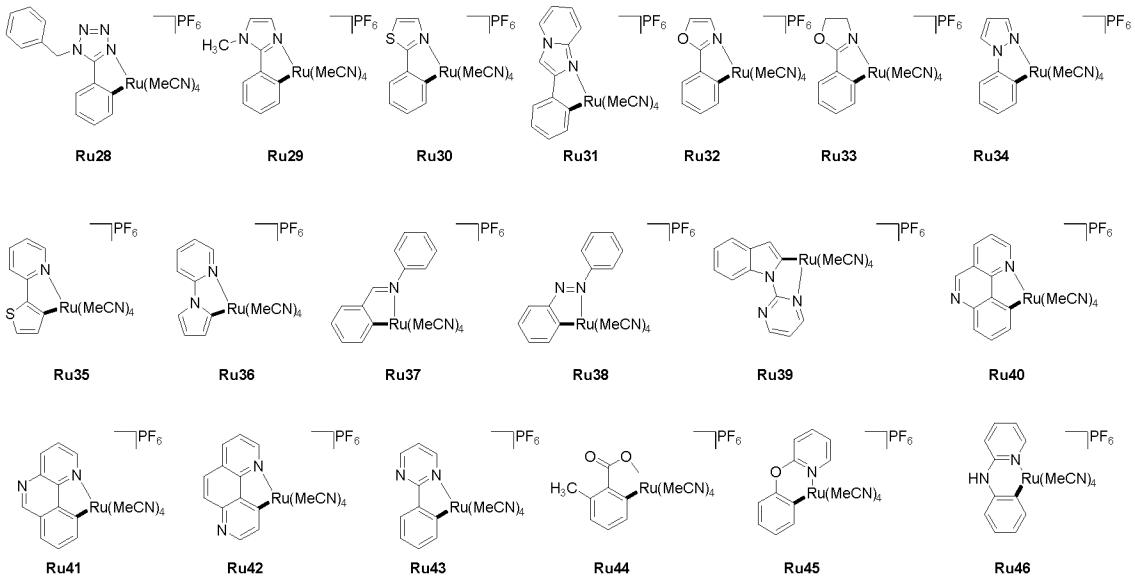
According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IC) as defined above.

According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (ID) as defined above.

For example, according to the second aspect of the present invention, there may be provided a cationic ruthenium(II) catalyst as follows:



For example, according to the second aspect of the present invention, there may be provided a cationic ruthenium(II) catalyst as follows:



According to a third aspect of the invention, there is provided an encapsulated (such as a paraffin encapsulated) cyclometalated ruthenium(II) catalyst of formula (I) (such as of formula (IA), (IB), (1A'), (IA''), (IA'''), (IA''''), (IA'''''), (IB'), (IB''), (IB'''), (IB''''), (IB'''''), (IC) or (ID)).

All of the features disclosed in this specification (including any accompanying claims and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at most some of such features and/or steps are mutually exclusive. Each feature disclosed in this specification (including any accompanying claims, and drawings) may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

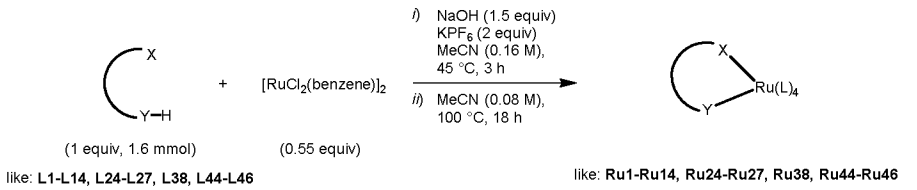
The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

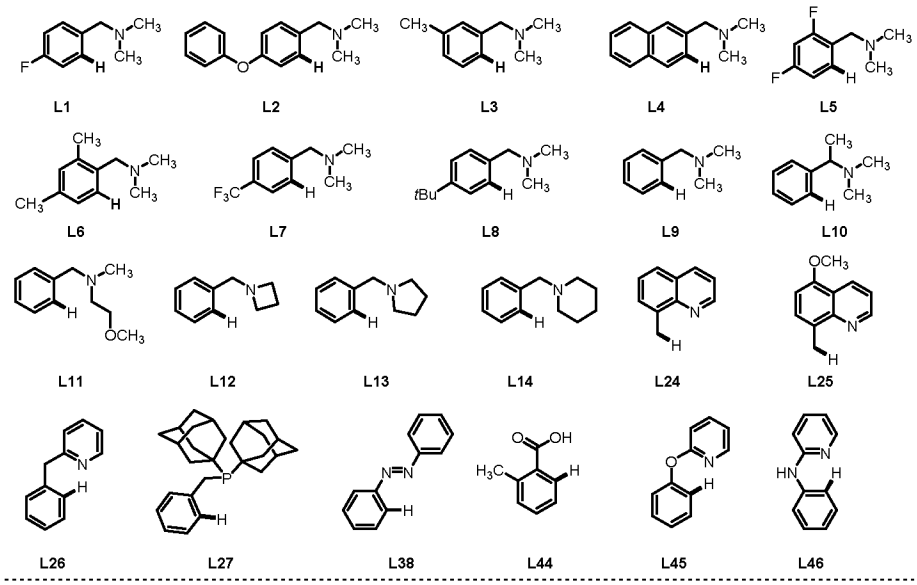
The optional features set out herein may be used either individually or in combination with each other where appropriate and particularly in the combinations as set out in the accompanying claims. The optional features for each exemplary embodiment of the invention, as set out herein are also applicable to any other aspects or exemplary embodiments of the invention, where appropriate. In other words, the skilled person reading this specification should consider the optional features for each aspect or embodiment of the invention as interchangeable and combinable between different aspects of the invention.

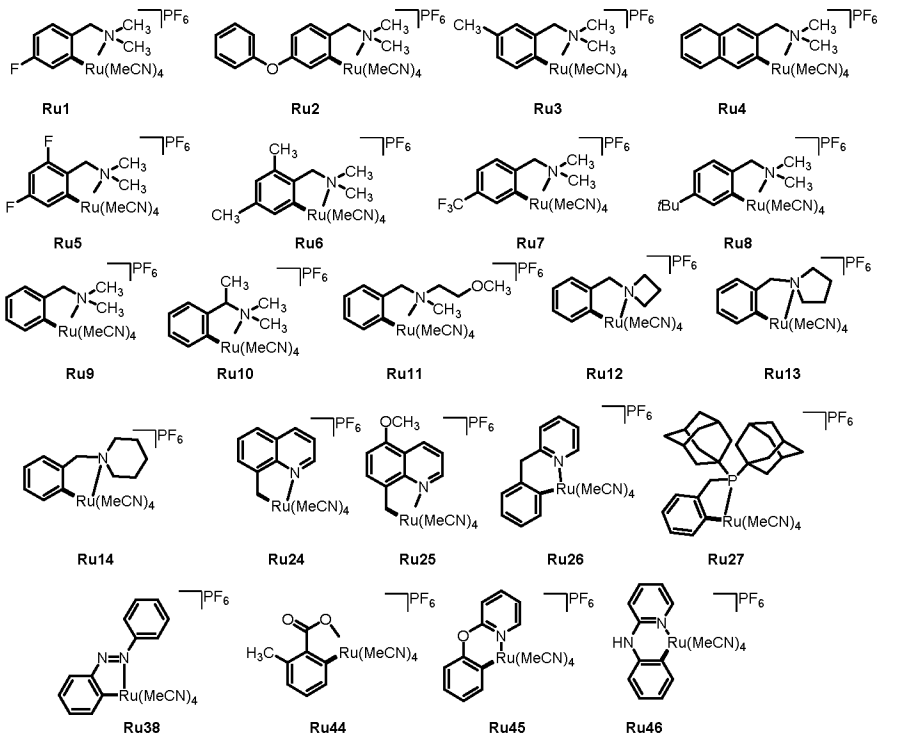
The invention will be further discussed with reference to the following non-limiting Examples.

Examples

General Procedure A: preparation of cyclometalated ruthenium(II) catalysts



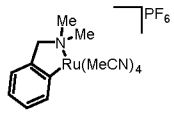




Unless otherwise stated, an oven dried 100 mL Ace pressure tube equipped with a stirring bar was transferred to a glove box, then $[RuCl_2(benzene)]_2$ (440.2 mg, 0.88 mmol, 0.55 equiv.), NaOH (96 mg, 2.4 mmol, 1.5 equiv.), KPF_6 (589.0 mg, 3.2 mmol, 2 equiv.), the appropriate cyclometalating ligand (like **L1-L14**, **L24-L27**, **L38**, **L44-L46**, 1.6 mmol, 1 equiv.) and MeCN (10 mL, 0.16 M) were added. The tube was sealed, transferred out of the box and placed in an oil bath at 45 °C and the reaction was stirred for 3 h. Upon completion, the reaction crude was loaded in an aluminium oxide (Al_2O_3, neutral) column conditioned with CH_2Cl_2, and quickly eluted with MeCN or CH_2Cl_2 using N_2 in replacement of compressed air collecting the yellow/colourless band. The solution was concentrated under reduced pressure and then quickly precipitated with Et_2O affording a yellow solid/orange solid, which was promptly transferred to a glove box as it decomposes turning green/blue if exposed to air. This solid and MeCN (20 mL) were added to an oven dried 100 mL Ace pressure tube equipped with a stirring bar and the reaction was stirred for 24 h at 100 °C. After this time, the reaction mixture was filtered through a short plug of aluminium oxide, eluted with MeCN, concentrated under vacuum and precipitated with Et_2O or pentane affording the corresponding cyclometalated ruthenium(II) catalyst (like **Ru1-Ru14**, **Ru24-Ru27**, **Ru38**, **Ru44-Ru46**) as off-white or yellow/orange solids. These complexes must be kept in a glove box as they quickly decompose turning blue/black if exposed to air.

If not available from commercial source, the cyclometalating ligand was synthesized according to known literature (for example, see *J. Am. Chem. Soc.* **2003**, *125*, 8708-8709). In some cases, known literature procedures were used for synthetizing suitable cyclometalated η^6-arene-conatining Ru(II) complexes, and therefore used in replacement of the first step of this two-step synthetic route (for example, see *Angew. Chem., Int. Ed.* **2015**, *54*, 5513–5517).

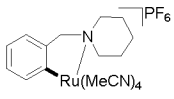
The General Procedure A was applied with *N*,*N*-dimethylbenzylamine **L9** (216.3 mg, 1.6 mmol, 1 equiv.) affording **Ru9** as an off white solid (653.3 mg, 75%).



Ru9

^{1}H-NMR (400 MHz, MeCN-d_3) δ 2.97 (s, 3 H), 2.23 (s, 6 H), 2.42 (s, 3 H), 2.46 (s, 6 H), 3.64 (s, 2 H), 6.76 (t, *J* = 7.4 Hz, 1 H), 6.88-6.95 (m, 2 H), 7.56 (d, *J* = 7.6 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, MeCN-d_3) δ 4.2, 4.4, 53.7, 73.6, 121.2, 121.5, 123.1, 123.3, 125.3, 138.6, 149.6, 175.2 ppm; ^{19}F-NMR (376 MHz, MeCN-d_3) δ –72.9 (d, *J* = 705.4 Hz) ppm; IR ν_{max} (neat/cm^{-1}): 3048, 2977, 2926, 2897, 2855, 2265, 1575, 1472, 1442, 831, 748; HRMS calcd for $C_{15}H_{21}N_4Ru^+$ [M–MeCN–PF_6]$^+$: 359.0804, found 359.0798.

The General Procedure A was applied with 1-benzylpiperidine **L14** (280.4 mg, 1.6 mmol, 1 equiv.) affording **Ru14** as an off white solid (598.5 mg, 64%).

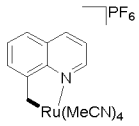


Ru14

^{1}H NMR (500 MHz, CD_3CN) δ 7.55 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.95 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.90 (td, *J* = 7.3, 1.4 Hz, 1H), 6.75 (td, *J* = 7.3, 1.3 Hz, 1H), 3.90

(s, 2H), 2.98 (ddd, *J* = 13.2, 11.5, 3.3 Hz, 2H), 2.75 – 2.65 (m, 2H), 2.42 (s, MeCN), 2.22 (s, 2xMeCN), 1.96 or 2.13 (MeCN), 1.84 – 1.73 (m, 2H), 1.71 – 1.63 (m, 1H), 1.54 – 1.36 (m, 3H) The signals of the coordinated acetonitriles integrate less than expected due to exchange with CD_3CN; ^{13}C NMR (126 MHz, CD_3CN) δ 175.4, 149.4, 138.3, 125.2, 123.2, 123.1, 121.7, 121.1, 59.8, 24.3, 21.9, 4.3, 4.2; ^{19}F NMR (471 MHz, CD_3CN) δ -72.2, -73.7; ESI-MS calcd for $C_{18}H_{25}N_4Ru$ $[M - PF_6 - MeCN]^+$: 399.1, found 399.1.

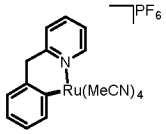
The General Procedure A was applied with 8-methylquinoline **L24** (229.1 mg, 1.6 mmol, 1 equiv.) affording **Ru24** as a red solid (123.9 mg, 14%). However, the reaction time for the first step was extended from 3 to 48 hours.



Ru24

^1H NMR (500 MHz, CD_3CN) δ 9.14 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.74 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.47 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.33 (dd, *J* = 8.3, 5.0 Hz, 1H), 2.79 (t, *J* = 1.2 Hz, 2H), 2.41 (s, MeCN), 2.07 (s, 2xMeCN), 1.96 (s, MeCN) The signals of the coordinated acetonitriles integrate less than expected due to exchange with CD_3CN; ^{13}C NMR (126 MHz, CD_3CN) δ 156.2, 155.7, 153.5, 135.9, 132.0, 129.3, 127.9, 124.3, 123.9, 122.2, 121.7, 17.1, 4.3, 4.0 both carbons of one acetonitrile were not observed. IR ν_{max} (neat/cm^{-1}): 3088, 2845, 2261, 1500, 871; ESI-MS calcd for $C_{17}H_{19}N_4Ru$ $[M - PF_6 - MeCN]^+$: 381.1, found 381.1.

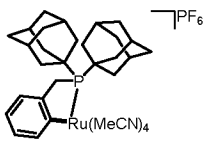
The General Procedure A was applied with 2-benzylpyridine **L26** (270.7 mg, 1.6 mmol, 1 equiv.) affording **Ru26** as a yellow solid (219.1 mg, 22%). However, the reaction time for the first step was extended from 3 to 72 hours. Spectroscopic data matched those previously reported (Organometallics **1999**, *18*, 2390-2394).



Ru26

^1H NMR (500 MHz, CD_3CN) δ 8.83 (dd, *J* = 5.8, 1.6 Hz, 1H), 7.68 (td, *J* = 7.6, 1.7 Hz, 1H), 7.59 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.38 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.14 (ddd, *J* = 7.4, 5.8, 1.6 Hz, 1H), 6.99 (dd, *J* = 7.2, 1.4 Hz, 1H), 6.88 (td, *J* = 7.4, 1.6 Hz, 1H), 6.78 (td, *J* = 7.3, 1.4 Hz, 1H), 4.23 (s, 2H), 2.45 (s, MeCN), 2.22 (s, 2xMeCN), 2.14 (s, MeCN); ^{13}C NMR (126 MHz, CD_3CN) δ 170.5, 165.6, 156.8, 143.0, 141.5, 137.4, 126.0, 125.2, 125.0, 124.0, 122.8, 121.7, 48.5, 4.3, 4.2; ^{19}F NMR (471 MHz, CD_3CN) δ -72.2, -73.7.

The General Procedure A was applied with di(1-adamantyl)benzylphosphine **L27** (628.1 mg, 1.6 mmol, 1 equiv.) affording **Ru27** as a white solid (365.9 mg, 28%). However, the reaction time for the first step was extended from 3 to 24 hours.

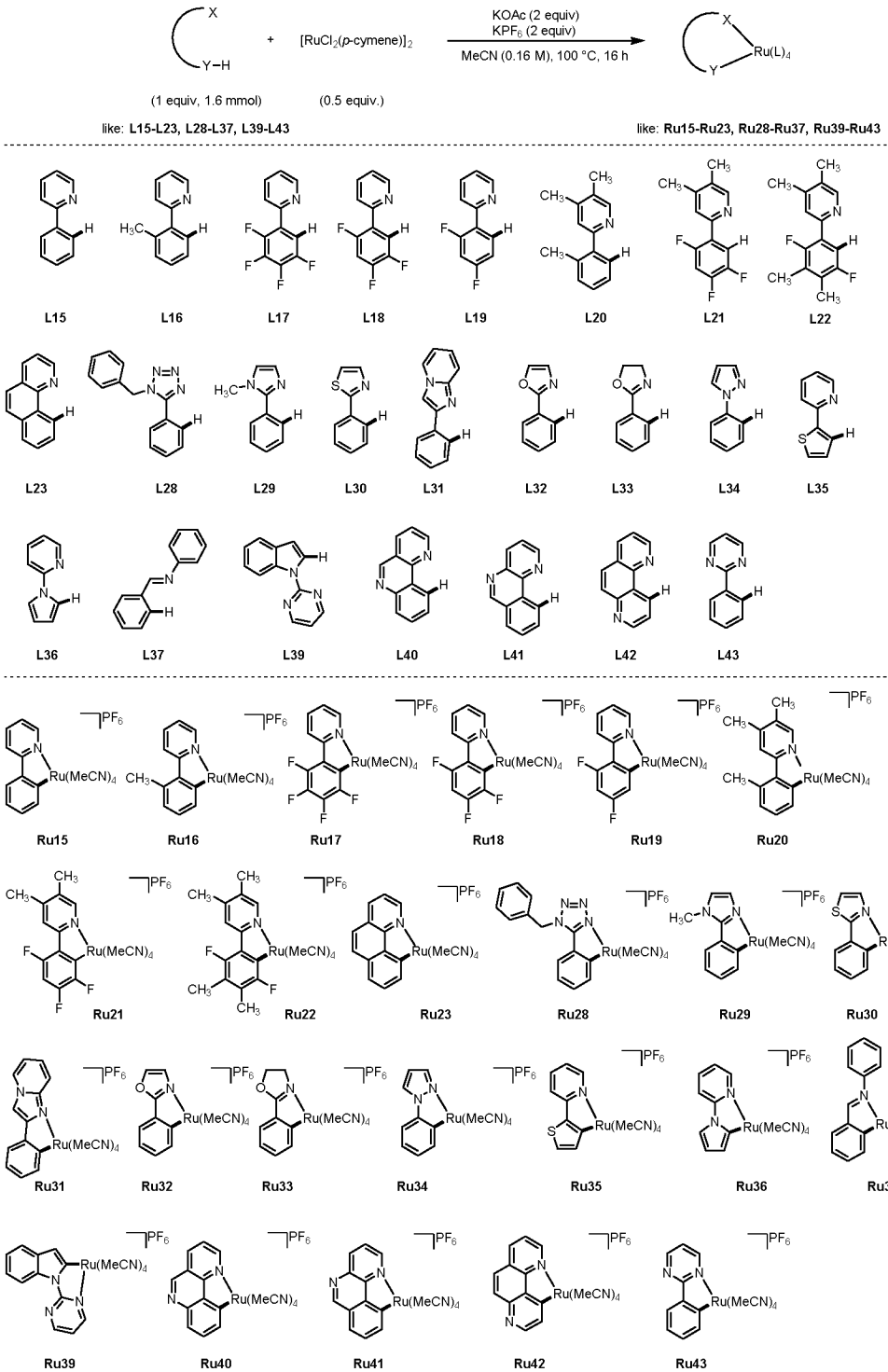


Ru27

^1H NMR (500 MHz, CD_3CN) δ 7.54 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.77 (td, *J* = 7.3, 1.5 Hz, 1H), 6.69 (t, *J* = 7.2 Hz, 1H), 3.11 (d, *J* = 9.4 Hz, 2H), 2.39 (s, MeCN), 2.20 (s, MeCN), 2.13 (s, 2MeCN), 2.05 – 1.99 (m, 12H), 1.91 – 1.88 (m, 6H), 1.74 – 1.61 (m, 12H). The

signals of the coordinated acetonitriles integrate less than expected due to fast exchange with CD_3CN. ^{13}C NMR (126 MHz, CD_3CN) δ 171.9 (d, *J* = 6.7 Hz), 151.8 (d, *J* = 11.7 Hz), 139.3, 125.0 (2C), 124.1, 123.3 (d, *J* = 14.4 Hz), 121.8, 42.3 (d, *J* = 14.2 Hz), 40.2, 37.5, 31.8 (d, *J* = 24.6 Hz), 29.7 (d, *J* = 7.7 Hz), 4.9, 4.6; ^{19}F NMR (471 MHz, CD_3CN) δ -72.2, -73.7; ^{31}P NMR (202 MHz, CD_3CN) δ 89.7; ESI-MS calcd for $C_{33}H_{45}N_3PRu$ $[M - PF_6 - MeCN]^+$: 616.2, found 616.2.

General Procedure B: preparation of cyclometalated ruthenium(II) catalysts

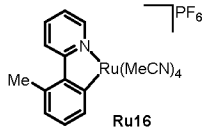


Unless otherwise stated, an oven dried 100 mL Ace pressure tube equipped with a stirring bar was transferred to a glove box, then $[RuCl_2(p\text{-cymene})]_2$ (489.9 mg, 0.8 mmol, 0.5 equiv.), KOAc (235.6 mg, 2.4 mmol, 1.5 equiv.), KPF_6 (589.0 mg, 3.2 mmol, 2 equiv.), the appropriate cyclometalating ligand (like **L15-L23**, **L28-L37**, **L39-L43**, 1.6 mmol, 1 equiv.) and MeCN (10

mL, 0.16 M) were added. The tube was sealed, transferred out of the box, placed in an oil bath at 100 °C and stirred for 16 h. Upon completion, the reaction crude was loaded in an aluminium oxide (Al_2O_3, neutral) column conditioned with CH_2Cl_2, and quickly eluted with MeCN/CH_2Cl_2 (1:1) using N_2 in replacement of compressed air collecting the yellow/orange band. The solution was concentrated under reduced pressure and then quickly precipitated with Et_2O affording the corresponding cyclometalated ruthenium(II) catalyst (like **Ru15-Ru23**, **Ru28-Ru37**, **Ru39-Ru43**) as a yellow/orange solid. These complexes must be kept in a glove box as they quickly decompose turning blue/black if exposed to air.

If not available from commercial source, the cyclometalating ligand was synthesized according to known literature (for example, *Angew. Chem., Int. Ed.* **2015**, *54*, 14103–14107).

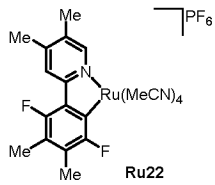
The General Procedure B was applied with 2-(*o*-tolyl)pyridine **L16** (270.8 mg, 1.6 mmol, 1 equiv.) affording **Ru16** as an orange solid (879.3 mg, 95%).



Ru16

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.96 (s, 3 H), 2.00 (s, 6 H), 2.50 (s, 3 H), 2.68 (s, 3 H), 6.74 (d, *J* = 7.5 Hz, 1 H), 6.94 (t, *J* = 7.5 Hz, 1 H), 7.14 (t, *J* = 6.5 Hz, 1 H), 7.75 (t, *J* = 7.5 Hz, 1 H), 7.88 (d, *J* = 7.5 Hz, 1 H), 8.09 (d, *J* = 7.5 Hz, 1 H), 9.05 (d, *J* = 5.5 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 3.8, 4.4, 24.7, 121.4, 121.7, 122.9, 123.7, 126.4, 127.5, 136.1, 136.6, 136.9, 146.4, 153.8, 169.9, 187.7 ppm (signals for both carbons of one of the MeCN ligands were not observed); ^{19}F-NMR (470 MHz, MeCN-d_3) δ –73.0 (d, *J* = 705.9 Hz) ppm; IR ν_{max} (neat/cm^{-1}): 3046, 2274, 1605, 1498, 1269, 1169, 830, 768; HRMS calcd for $C_{18}H_{19}N_4Ru$ [M–MeCN–PF_6]$^+$: 393.0648, found 393.0635.

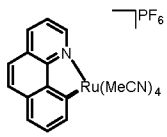
The General Procedure B was applied with 2-(2,5-difluoro-3,4-dimethylphenyl)-4,5-dimethylpyridine **L22** (395.7 mg, 1.6 mmol, 1 equiv.) affording **Ru22** as a yellow solid (924.4 mg, 88%).



Ru22

^{1}H-NMR (500 MHz, MeCN-d_3) δ 1.96 (s, 3 H), 2.05 (s, 6 H), 2.20 (d, *J* = 2.5 Hz, 3 H), 2.22 (d, *J* = 2.5 Hz, 3 H), 2.31 (s, 3 H), 2.39 (s, 3 H), 2.43 (s, 3 H), 8.01 (d, *J* = 1.5 Hz, 1 H), 8.65 (s, 1 H) ppm (exchange with MeCN-d_3 shows a lower integration than expected for the MeCN ligand at 2.43 ppm); ^{13}C-NMR (125 MHz, MeCN-d_3) δ 3.9, 4.0, 11.0 (dd, *J* = 7.3, 2.1 Hz), 11.9 (dd, *J* = 4.9, 1.9 Hz), 16.5, 19.7, 121.9, 122.5, 123.8, 124.0, 124.1, 124.8 (dd, *J* = 25.9, 4.9 Hz), 131.6 (d, *J* = 1.4 Hz), 133.7 (dd, *J* = 19.4, 6.1 Hz), 148.0, 152.6, 156.0 (dd, *J* = 247.8, 1.4 Hz), 160.4 (dd, *J* = 50.9, 2.3 Hz), 164.4 (d, *J* = 7.5 Hz), 167.6 (d, *J* = 223.8 Hz) ppm (signals for both carbons of one of the MeCN ligands were not observed); ^{19}F-NMR (470 MHz, MeCN-d_3) δ –124.4 (d, *J* = 22.9 Hz), –106.7 (d, *J* = 22.9 Hz), –72.9 (d, *J* = 705.8 Hz) ppm; IR ν_{max} (neat/cm^{-1}): 3006, 2927, 2272, 1605, 1484, 1403, 1287, 832; HRMS calcd for $C_{21}H_{23}F_2N_4Ru^+$ [M–MeCN–PF_6]$^+$: 471.0929, found 471.0925.

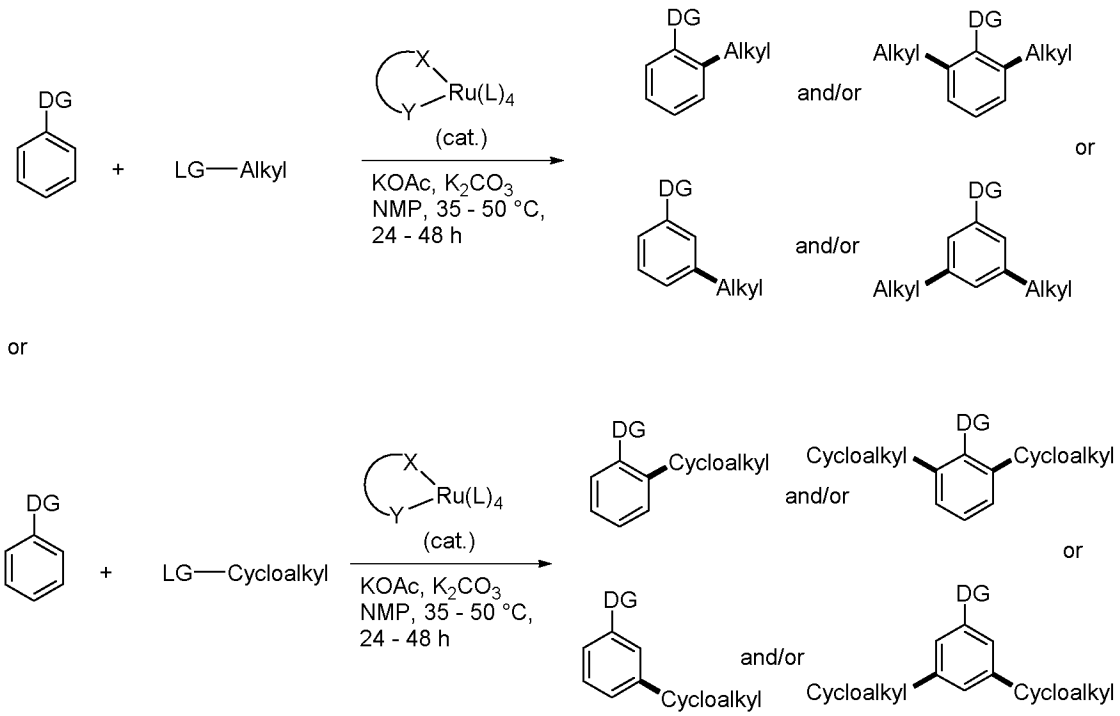
The General Procedure B was applied with benzo[*h*]quinoline **L23** (286.7 mg, 1.6 mmol, 1 equiv.) affording **Ru23** as a light orange solid (782.1 mg, 81%). Spectroscopic data matched those previously reported (*Inorganica Chim. Acta* **2010**, *363*, 567–573).



Ru23

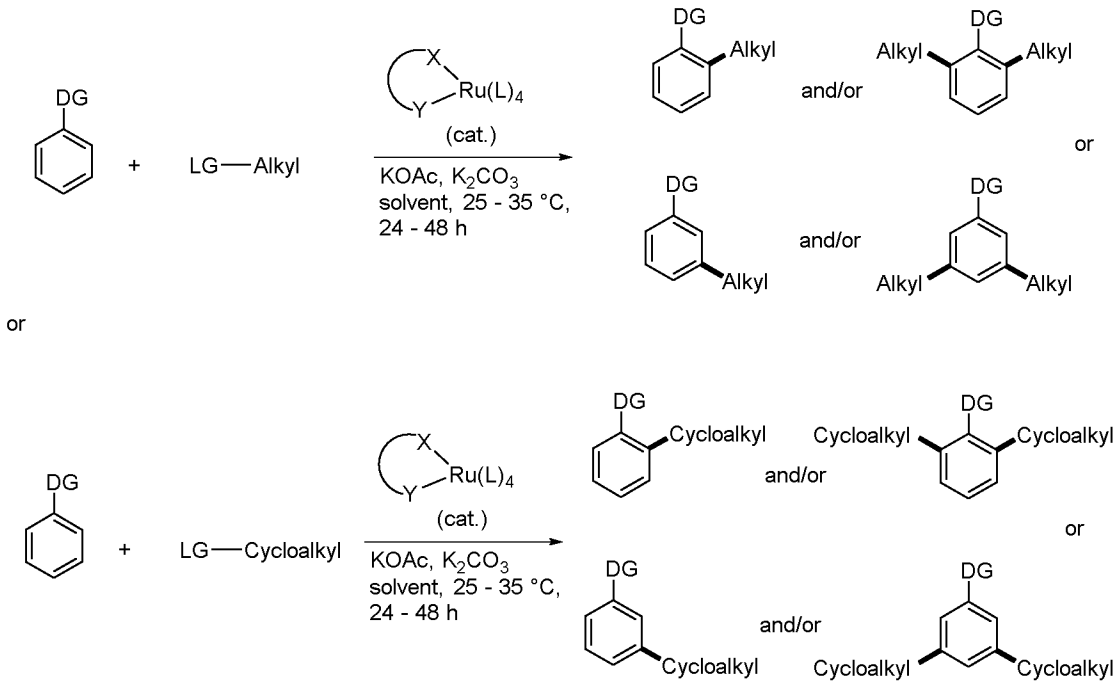
^{1}H NMR (500 MHz, CD_3CN) δ 9.18 (dd, *J* = 5.3, 1.4 Hz, 1H), 8.27 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.17 (dd, *J* = 6.4, 1.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.57 – 7.44 (m, 3H), 2.58 (s, MeCN), 2.14 (s, MeCN) 1.91 (s, 2xMeCN) The signals of the coordinated acetonitriles integrate less than expected due to fast exchange with CD_3CN; ^{13}C NMR (126 MHz, CD_3CN) δ 181.9, 158.5, 152.4, 144.1, 136.6, 135.7, 134.1, 129.9, 128.5, 126.7, 124.4, 124.0, 122.1, 121.6, 119.6, 4.4, 3.8 both carbon of one acetonitrile ligand were not observed; ^{19}F NMR (471 MHz, CD_3CN) δ -72.2, -73.7.

General Procedure C: alkylation of DG-containing (hetero)arenes with alkyl (pseudo)halides using cyclometalated ruthenium(II) catalysts



In an Argon filled glove-box a crimp-cap microwave vial equipped with a magnetic stirring bar was charged with the appropriate cyclometalated Ru(II)-catalyst (like **Ru1-Ru46**, from 1 mol % to 10 mol %), KOAc (5.9 mg, 0.06 mmol, 30 mol %), K_2CO_3 (0.60 mmol, 3.0 equiv.), the appropriate DG-containing arene (like **N1-N20**, 0.20 mmol, 1.0 equiv.), the appropriate alkyl (pseudo)halide (like **X1-X16**, 1.0 – 3.0 equiv.) and *N*-methyl-2-pyrrolidone (NMP) (0.2 M – 1 M). The vial was capped and stirred at 35 °C for 24 hours. Upon completion, the crude mixture was loaded on a silica gel column and purified by flash chromatography.

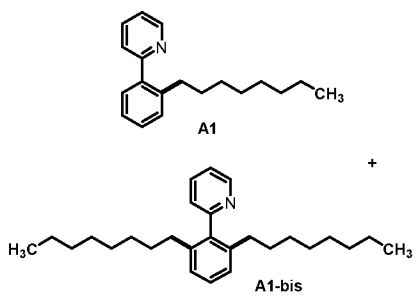
General Procedure D: glove-box free alkylation of DG-containing (hetero)arenes with alkyl (pseudo)halides using cyclometalated ruthenium(II) catalysts



Non-anhydrous solvents degassed by bubbling with nitrogen for 5-10 minutes were used. All other reagents were used as received. The paraffin encapsulated cyclometalated Ru(II)-catalyst was prepared according to known literature (for example, see *Org. Lett.* **2016**, *18* , 3934–3936). A screw-cap schlenk tube equipped with a magnetic stirring bar was charged under air with the appropriate paraffin-encapsulated cyclometalated Ru(II)-catalyst (like **Ru1-Ru46**, from 5 mol % to 10 mol %), K_2CO_3 (0.60 mmol, 3.0 equiv.) and KOAc (5.9 mg, 0.06 mmol, 30 mol %). The tube was evacuated and back-filled with nitrogen three times, then the appropriate DG-containing arene (like **N1-N20**, 0.20 mmol, 1.0 equiv.), the appropriate alkyl halide (like **X1-X16** 1.0 – 3.0 equiv.) and the appropriate solvent(s) (from 0.2 M to 1 M) were added under a flow of nitrogen. The tube was sealed and stirred at 35 °C for 24 hours. Upon completion, the crude mixture was loaded on a silica gel column and purified by flash chromatography.

Characterization data for arylated compounds

The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv.) and NMP (1 mL, 0.2 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **A1** (46.0 mg, 86%) and **A1-bis** (9.9 mg, 13%) both as colourless oils.



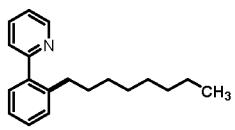
The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *n*-octyl bromide **X1** (35 µL, 0.20 mmol, 1.0 equiv.) and NMP (1 mL, 0.2 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **A1** (35.8 mg, 67%) and **A1-bis** (3.8 mg, 5%).both as colourless oils.

The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *n*-octyl iodide **X6** (108 µL, 0.20 mmol, 3.0 equiv.) and NMP (1 mL, 0.2 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **A1** (42.8 mg, 80%) and **A1-bis** (6.8 mg, 9%) both as colourless oils.

The General Procedure D was applied with encapsulated **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv.), *N,N'*-dicyclohexylcetimidamide (13.3 mg, 0.06 mmol, 30 mol %; synthesised as previously reported US5834058,1998,A) in replacement of KOAc, and dioxane (1 mL, 0.2 M) at 25 °C for 48 hours. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **A1** (44.9 mg, 84%) and **A1-bis** (6.8 mg, 9%) both as colourless oils.

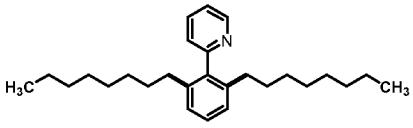
Spectroscopic data matched those previously reported (Synthesis, **2014**, *46*, 2024-2039).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.71 (td, *J* = 7.7, 1.9 Hz, 1H), 7.36 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.27 – 7.20 (m, 2H), 2.78 – 2.59 (m, 2H), 1.44 (ddd, *J* = 12.0, 9.9, 6.6 Hz, 2H), 1.29 – 1.05 (m, 10H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 149.2, 140.9, 140.4, 136.1, 129.8 (2C), 128.3, 125.8, 124.2, 121.7, 33.0, 31.9, 31.4, 29.5, 29.3, 29.2, 22.8, 14.2.



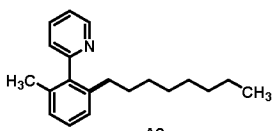
A1

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.7 Hz, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.27 – 7.21 (m, 3H), 7.11 (d, *J* = 7.6 Hz, 2H), 2.50 (dt, *J* = 14.1, 7.5 Hz, 4H), 2.28 (td, *J* = 8.1, 4.1 Hz, 4H), 1.36 – 1.04 (m, 20H), 0.87 (dt, *J* = 14.4, 7.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 149.4, 140.9, 140.0, 135.8, 128.1, 126.6, 125.1, 121.7, 33.7, 32.0, 31.2, 29.7, 29.3, 29.3, 22.8, 14.3.



A1-bis

The General Procedure C was applied with **Ru9** (1.1 mg, 0.002 mmol, 1 mol %), 2-(*o*-tolyl)pyridine **N2** (33.9 mg, 0.20 mmol, 1 equiv.), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv.), and NMP (1 mL, 0.2 M). Column chromatography (hexane/EtOAc 85:15) afforded **A2** as a colourless oil (23.1 mg, 41%).

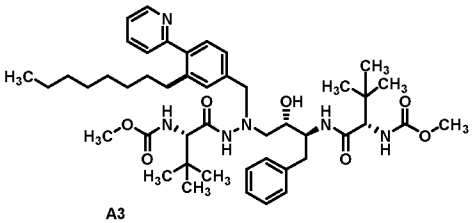


A2

The General Procedure D was applied with encapsulated **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-(*o*-tolyl)pyridine **N2** (33.9 mg, 0.20 mmol, 1 equiv.), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv.), and dioxane (1 mL, 0.2 M). Column chromatography (hexane/EtOAc 85:15) afforded **A2** as a colourless oil (31.0 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 – 8.67 (m, 1H), 7.75 (td, *J* = 7.7, 1.9 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.16 – 7.06 (m, 2H), 2.31 (t, *J* = 8.0 Hz, 2H), 2.02 (s, 3H), 1.43 – 1.39 (m, 2H), 1.25 – 1.02 (m, 10H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 149.6, 140.8, 140.3, 136.1, 136.0, 128.0, 127.6, 126.8, 124.8, 121.7, 33.6, 32.0, 31.3, 29.6, 29.4, 29.3, 22.8, 20.5, 14.3.; EI-MS calcd for $C_{20}H_{26}N$ $[M-H]^+$: 280.2, found 280.2.0

The purity of the Atazanavir purchased from Molekula was assessed to be 92% by quantitative ^{1}H-NMR with an internal standard. The impurity was not NMR-active.

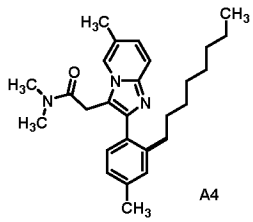


A3

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Atazanavir **N4** (152.3 mg, 0.2 mmol, 1.0 equiv), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv) and NMP (1 mL, 0.2 M) for 48 hours. Column chromatography (hexane/EtOAc 1:1 to EtOAc) afforded **A3** as a yellow wax (58.2 mg, 35%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.67 (td, *J* = 7.7, 1.9 Hz, 1H), 7.23 (dd, *J* = 13.4, 7.7 Hz, 2H), 7.18 – 7.10 (m, 7H), 7.08 (td, *J* = 6.3, 2.5 Hz, 1H), 6.50 (s, 1H), 6.38 (s, 1H), 5.29 (d, *J* = 9.3 Hz, 1H), 5.18 (d, *J* = 8.6 Hz, 1H), 4.80 (s, 1H), 3.97 (d, *J* = 11.7 Hz, 2H), 3.83 (d, *J* = 13.9 Hz, 1H), 3.74 (d, *J* = 8.6 Hz, 1H), 3.63 – 3.48 (m, 9H), 2.87 (d, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 11.5 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.47 (d, *J* = 12.2 Hz, 1H), 1.33 (p, *J* = 7.3 Hz, 2H), 1.18 – 1.02 (m, 10H), 0.83 (s, 9H), 0.79 (t, *J* = 7.1 Hz, 3H), 0.74 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.8, 160.0, 157.1, 157.0, 149.3, 141.4, 140.2, 138.2, 136.2, 135.3, 130.4, 130.3, 129.5, 128.4, 126.4, 124.1, 121.8, 67.3, 63.7, 62.8, 61.6, 61.3, 52.6, 52.5, 52.3, 38.8, 34.4, 34.1, 33.1, 32.0, 31.5, 29.7, 29.3, 29.3, 26.7, 26.4, 22.8, 14.3, One carbon was not observed; ESI-MS calcd for $C_{46}H_{69}N_6O_7$ $[M+H]^+$: 817.5, found 817.5.

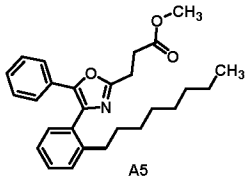
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Zolpidem **N5** (61.5.0 mg, 0.2 mmol, 1.0 equiv), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv) and NMP (1 mL, 0.2 M) at 50 °C. Column chromatography (EtOAc/MeOH 100:0 to 98:2) afforded **A4** product as a light orange wax (18.5 mg, 22%).



A4

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.07 – 6.99 (m, 2H), 3.85 (s, 2H), 2.89 (s, 3H), 2.77 (s, 3H), 2.62 – 2.50 (m, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.17 (s, 2H), 1.41 (q, *J* = 7.7, 7.3 Hz, 2H), 1.21 – 1.06 (m, 10H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 143.5, 142.7, 138.2, 130.9, 130.2, 127.9, 126.5, 122.9, 122.1, 116.2, 115.2, 37.6, 35.9, 33.1, 32.0, 31.3, 29.7, 29.6, 29.3, 22.8, 21.5, 18.6, 14.3; EI-MS calcd for $C_{27}H_{36}N_3O$ $[M-H]^+$: 418.3, found 418.3.

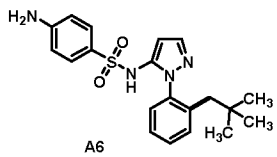
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Oxaprozin **N6** (61.5.0 mg, 0.2 mmol, 1.0 equiv),), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv) and NMP (1 mL, 0.2 M) at 50 °C. Column chromatography (hexane/DCM/Et_2O 7:3.5:0.5) afforded **A5** as a colourless oil (18.5 mg, 22%).



A5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.06 (m, 9H), 3.71 (s, 3H), 3.19 (dd, *J* = 8.4, 6.7 Hz, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.52 (dd, *J* = 9.1, 6.6 Hz, 2H), 1.41 (dd, *J* = 9.2, 5.9 Hz, 2H), 1.27 – 1.04 (m, 10H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 161.3, 145.8, 142.6, 135.2, 132.1, 130.7, 129.9, 128.9, 128.8, 128.7, 127.9, 126.2, 125.0, 52.0, 33.4, 32.0, 31.0, 30.9, 29.5, 29.4, 29.3, 23.7, 22.8, 14.2; EI-MS calcd for $C_{27}H_{32}NO_3$ $[M-H]^+$: 418.3, found 418.3.

The purity of the Sulfaphenazole purchased from Fluorochem was assessed to be 86% by quantitative ^{1}H-NMR with an internal standard. The impurity was not NMR-active.

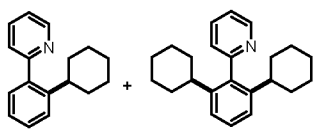


A6

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Sulfaphenazole **N7** (71.7 mg, 0.2 mmol, 1.0 equiv), neopentyl bromide **X2** (77 µL, 0.60 mmol, 3.0 equiv) and NMP (1 mL, 0.2 M) at 50 °C for 48 hours. Column chromatography (DCM/MeOH 99:1 to 97:3) afforded **A6** as a white wax (20.8 mg, 27%).

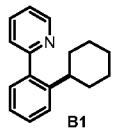
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.19 (td, *J* = 7.5, 1.6 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 2H), 6.30 (d, *J* = 2.1 Hz, 1H), 4.21 (s, 2H), 0.67 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.5, 139.7, 137.8, 136.1 (2C), 133.2, 129.8, 129.1, 128.2, 127.4, 126.5, 114.0, 97.3, 43.9, 32.3, 29.7; EI-MS calcd for $C_{20}H_{23}N_4O_2S$ $[M-H]^+$: 383.2, found 383.2.

The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), cyclohexyl bromide **X3** (74 µL, 0.60 mmol, 3.0 equiv.) and NMP (1 mL, 0.2 M) without KOAc. Column chromatography

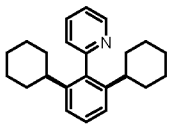


B1 B1-bis

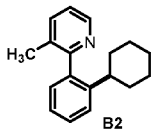
(hexane/DCM/EtOAc 8:1:1) afforded **B1** (20.4 mg, 43%) as colourless oil and **B1-bis** (27.5 mg, 43%) as a white solid.


B1

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (dt, *J* = 4.9, 1.2 Hz, 1H), 7.70 (td, *J* = 7.7, 1.9 Hz, 1H), 7.44 – 7.27 (m, 4H), 7.27 – 7.17 (m, 2H), 2.74 (tt, *J* = 11.9, 3.3 Hz, 1H), 1.85 – 1.76 (m, 3H), 1.75 – 1.70 (m, 2H), 1.68 – 1.61 (m, 1H), 1.43 (qd, *J* = 12.2, 3.2 Hz, 2H), 1.27 – 1.11 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 149.3, 145.6, 140.1, 136.0, 129.8, 128.5, 126.4, 125.5, 124.3, 121.6, 40.0, 34.5, 26.9, 26.3;EI-MS calcd for $C_{17}H_{18}N$ $[M-H]^+$: 236.1, found 236.2.

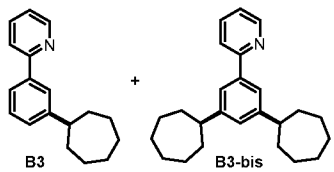

B1-bis

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 – 8.68 (m, 1H), 7.71 (td, *J* = 7.6, 1.9 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.26 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 2.02 (td, *J* = 12.0, 6.0 Hz, 2H), 1.83 – 1.78 (m, 2H), 1.70 – 1.63 (m, 6H), 1.60 – 1.54 (m, 2H), 1.36 (qdd, *J* = 12.0, 8.4, 3.7 Hz, 4H), 1.16 (qt, *J* = 13.0, 3.4 Hz, 2H), 1.06 – 0.92 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 149.3, 145.6, 139.2, 135.6, 128.3, 124.9, 123.4, 121.6, 41.3, 34.6, 34.1, 27.0, 26.9, 26.2; EI-MS calcd for $C_{23}H_{29}N$ $[M-H]^+$: 318.2, found 318.2.


B2

The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 23-methyl-2-phenylpyridine **N2** (33.9 mg, 0.20 mmol, 1 equiv.), cyclohexyl bromide **X3** (74 µL, 0.60 mmol, 3.0 equiv.) and NMP (1 mL, 0.2 M) at 50 °C without KOAc. Column chromatography (hexane/EtOAc/DCM 8:1:1) afforded **B2** as a colourless oil (44.7 mg, 89%).

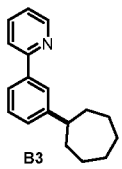
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.63 – 7.51 (m, 1H), 7.41 – 7.31 (m, 2H), 7.26 – 7.16 (m, 2H), 7.10 (dd, *J* = 7.5, 1.3 Hz, 1H), 2.21 (tt, *J* = 12.0, 3.3 Hz, 1H), 2.09 (s, 3H), 1.90 – 1.80 (m, 1H), 1.76 – 1.56 (m, 4H), 1.55 – 1f.44 (m, 1H), 1.37 – 0.97 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 146.6, 145.4, 139.6, 137.6, 131.7, 128.7, 128.2, 126.2, 125.6, 122.2, 40.8, 34.7, 33.6, 27.0, 27.0, 26.3, 19.5; EI-MS calcd for $C_{18}H_{20}N$ $[M-H]^+$: 251.2, found 251.1.


B3 B3-bis

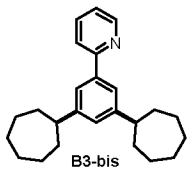
The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), cycloheptyl bromide **X4** (83 µL, 0.60 mmol, 3.0 equiv.) and NMP (200 µL, 1 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **B3** (31.7 mg, 63%) and **B3-bis** (12.5 mg, 18%) both as colourless oils.

Spectroscopic data for **B3** matched those previously reported (*J. Am. Chem. Soc.* **2013**, *135*, 5877−5884).

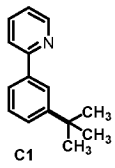
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 – 8.66 (m, 1H), 7.84 (s, 1H), 7.79 – 7.69 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.21 (ddd, *J* = 7.3, 5.4, 2.3 Hz, 1H), 2.76 (tt, *J* = 10.7, 3.6 Hz, 1H), 1.96 (ddt, *J* = 13.4, 6.3, 3.2 Hz, 2H), 1.81 (ddq, *J* = 13.4, 6.6, 3.3 Hz, 2H), 1.77 – 1.67 (m, 4H), 1.65 – 1.51 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 150.7, 149.8, 139.5, 136.8, 128.8, 127.5, 125.6, 124.3, 122.1, 120.8, 47.4, 37.0, 28.1, 27.5.


B3

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.8 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.60 (s, 1H), 7.20 (td, *J* = 5.2, 3.1 Hz, 1H), 7.08 (s, 1H), 2.73 (tt, *J* = 10.7, 3.6 Hz, 2H), 2.08 – 1.91 (m, 4H), 1.81 (ddq, *J* = 12.9, 6.1, 3.3 Hz, 4H), 1.77 – 1.50 (m, 16H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 150.6, 149.7, 139.4, 136.7, 126.1, 122.8, 121.9, 120.9, 47.5, 37.1, 28.1, 27.5; EI-MS calcd for $C_{25}H_{33}N$ $[M]^+$: 347.3, found 347.3.


B3-bis

The General Procedure C was applied with **Ru9** (10.9 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv.) and NMP (200 µL, 1 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **C1** as a colourless oil (23.2 mg, 55%).

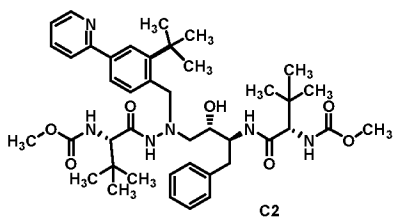

C1

The General Procedure D was applied with encapsulated **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv.), KTFA (9.1 mg, 0.06 mmol, 30 mol %) in replacement of KOAc, and dioxane (200 µL, 1 M) for 48 hours. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **C1** as a colourless oil (23.2 mg, 80%).

Spectroscopic data matched those previously reported (*Chem. Commun.* **2015**, *51*, 12807-12810)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.71 (dt, *J* = 4.9, 1.3 Hz, 1H), 8.05 (t, *J* = 1.9 Hz, 1H), 7.79 – 7.69 (m, 4H), 7.47 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.22 (ddd, *J* = 6.6, 4.8, 2.0 Hz, 1H), 1.40 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.21, 151.75, 149.76, 139.35, 136.76, 128.57, 126.19, 124.31, 124.10, 122.04, 120.90, 35.01, 31.55.

The purity of the Atazanavir purchased from Molekula was assessed to be 92% by quantitative ^{1}H-NMR with an internal standard. The impurity was not NMR-active.

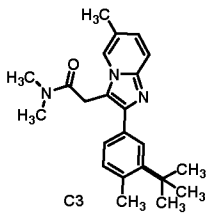

C2

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Atazanavir **N4** (152.3 mg, 0.2 mmol,

1.0 equiv), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv) and NMP (200 µL, 1 M). Column chromatography (hexane/EtOAc 1:1 to EtOAc) afforded the desired product as an off-white solid (62.4 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 – 8.63 (m, 1H), 8.06 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.17 (m, 5H), 7.17 – 7.11 (m, 1H), 6.58 (s, 1H), 6.37 (s, 1H), 5.33 (d, *J* = 9.4 Hz, 1H), 5.20 (d, *J* = 8.7 Hz, 1H), 4.92 (s, 1H), 4.32 – 4.20 (m, 2H), 4.03 (q, *J* = 8.1 Hz, 1H), 3.73 (d, *J* = 8.7 Hz, 1H), 3.64 (s, 8H), 2.91 (dd, *J* = 15.2, 9.2 Hz, 3H), 2.57 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 9H), 0.79 (s, 9H), 0.70 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 170.8, 157.7, 157.1, 156.9, 149.8, 148.3, 138.5, 138.2, 136.8, 135.5, 131.4, 129.5, 128.4, 126.4, 125.3, 124.7, 122.1, 120.7, 67.3, 63.6, 61.6, 61.0, 52.6, 52.4, 52.3, 39.0, 36.0, 34.4, 34.0, 31.8, 29.8, 26.6, 26.2; ESI-MS calcd for $C_{42}H_{61}N_6O_7$ $[M+H]^+$: 761.5, found 761.5

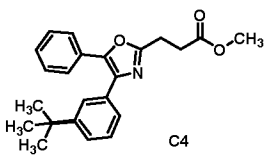
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Zolpidem **N5** (61.5 mg, 0.2 mmol, 1.0 equiv), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv) and NMP (200 µL, 1 M) for 48 hours. Column chromatography (EtOAc/MeOH 100:0 to 98:2) afforded **C3** product as an off-white solid (49.4 mg, 68%).



C3

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.03 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.08 (s, 2H), 2.95 (s, 3H), 2.91 (s, 3H), 2.58 (s, 3H), 2.34 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 148.2, 144.5, 144.2, 135.9, 133.2, 132.1, 127.5, 126.6, 126.0, 122.2, 121.8, 116.7, 113.8, 37.6, 36.1, 35.9, 30.9, 30.5, 23.3, 18.6; ESI-MS calcd for $C_{23}H_{29}N_3O$ $[M+H]^+$: 364.2, found 364.2.

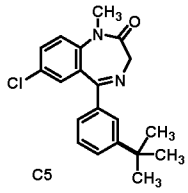
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Oxaprozin methyl ester **N6** (61.5 mg, 0.2 mmol, 1.0 equiv), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv) and NMP (200 µL, 1 M) at 50 °C. Column chromatography (hexane/DCM/Et_2O 7:3.5:0.5) afforded **C4** product as a colourless oil (48.0 mg, 66%).



C4

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, *J* = 1.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.45 (dt, *J* = 7.3, 1.6 Hz, 1H), 7.38 – 7.28 (m, 5H), 3.74 (s, 3H), 3.20 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.92 (dd, *J* = 8.3, 6.8 Hz, 2H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 161.7, 151.3, 145.4, 135.8, 132.1, 129.2, 128.7, 128.5, 128.4, 126.6, 125.3, 125.2, 125.1, 52.1, 34.9, 31.4, 31.1, 23.7; EI-MS calcd for $C_{23}H_{25}NO_3$ $[M]^+$: 363.2, found 363.2.

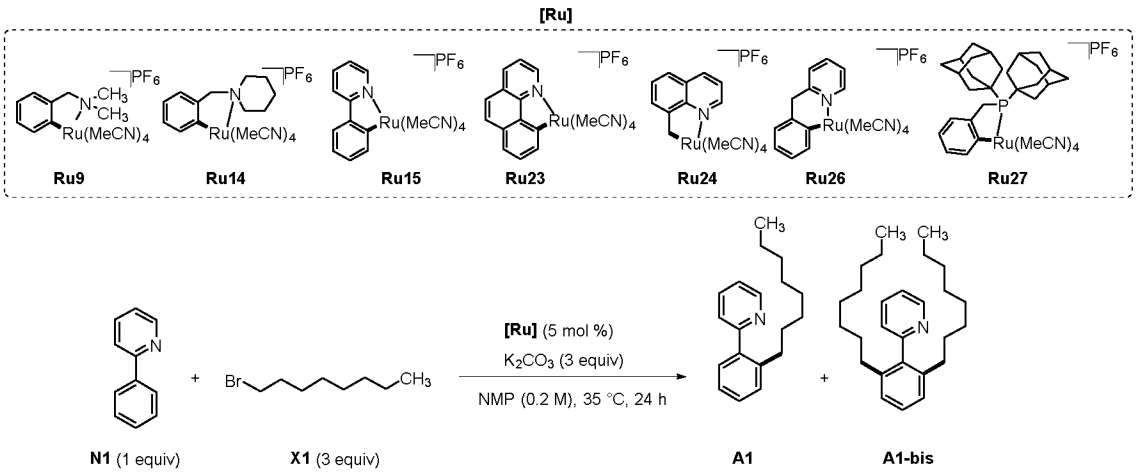
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Diazepam **N8** (57.0 mg, 0.2 mmol, 1.0 equiv), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv) and NMP (200 µL, 1 M). Column chromatography (hexane/EtOAc 7:3) afforded the desired product as a white solid (16.4 mg, 24%).



C5

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, *J* = 1.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.45 (dt, *J* = 7.3, 1.6 Hz, 1H), 7.38 – 7.28 (m, 5H), 3.74 (s, 3H), 3.20 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.92 (dd, *J* = 8.3, 6.8 Hz, 2H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 161.7, 151.3, 145.4, 135.8, 132.1, 129.2, 128.7, 128.5, 128.4, 126.6, 125.3, 125.2, 125.1, 52.1, 34.9, 31.4, 31.1, 23.7; EI-MS calcd for $C_{20}H_{21}ClN_2O$ $[M]^+$: 340.1, found 340.2.

Cyclometalated ruthenium(II) catalysts screening for the alkylation reaction of 2-phenylpyridine (N1) with *n*-octyl bromide (X1)



The General Procedure C was applied with the appropriate cyclometalated ruthenium(II) catalyst (0.01 mmol, 5 mol %; see Table 2 below, denoted as **[Ru]**: **Ru9**, 5.6 mg; **Ru14**, 5.8 mg; **Ru15**, 5.6 mg; **Ru23**, 6.0 mg; **Ru24**, 5.5 mg; **Ru26**, 5.8 mg; or **Ru27**, 8.2 mg), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *n*-octyl bromide **X1** (104 µL, 0.60 mmol, 3.0 equiv.) and NMP (1 mL, 0.2 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **A1** and **A1-bis** both as colourless oils (yield, see Table 1 below).

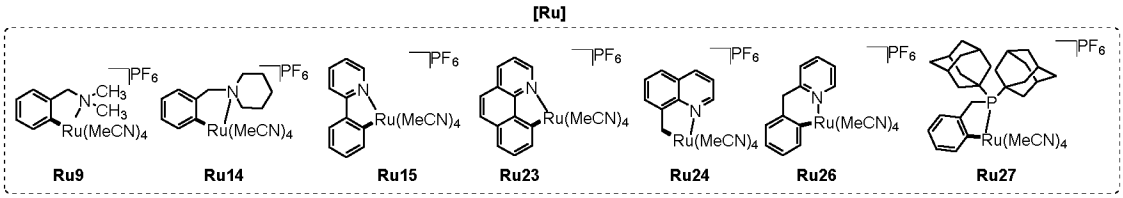
. entry	[Ru]	A1 (%)	A1-bis (%)
1	**Ru9**	86	13
2	**Ru14**	86	11
3	**Ru15**	91	11
4	**Ru23**	88	11
5	**Ru24**	85	13
6	**Ru26**	87	12

7	**Ru27**	87	13

Table 1

The results in Table 1 show that the ruthenium(II) catalysts of formula (I) all display a unique efficacy towards the C–H arylation of DG-containing (hetero)arenes with primary alkyl halides.

Cyclometalated ruthenium(II) catalysts screening for the alkylation reaction of 2-phenylpyridine (N1) with cyclohexyl bromide (X3)



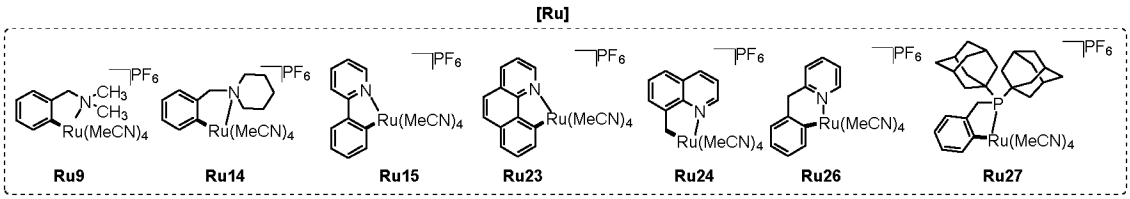
The General Procedure C was applied with the appropriate cyclometalated ruthenium(II) catalyst (0.01 mmol, 5 mol %; see Table 2 below, denoted as **[Ru]**: **Ru9**, 5.6 mg; **Ru14**, 5.8 mg; **Ru15**, 5.6 mg; **Ru23**, 6.0 mg; **Ru24**, 5.5 mg; **Ru26**, 5.8 mg; or **Ru27**, 8.2 mg), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), cyclohexyl bromide **X3** (74 µL, 0.60 mmol, 3.0 equiv.) and NMP (1 mL, 0.2 M) at 50 °C without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **B1** as colourless oil and **B1-bis** as a white solid (yield, see Table 2 below).

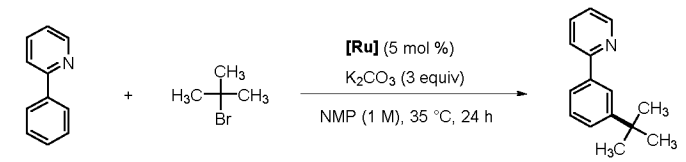
. entry	[Ru]	B1 (%)	B1-bis (%)
1	**Ru9**	43	43
2	**Ru14**	63	28
3	**Ru15**	72	31
4	**Ru23**	59	32
5	**Ru24**	56	34
6	**Ru26**	70	22
7	**Ru27**	85	15

Table 2

The results in Table 2 show that the ruthenium(II) catalysts of formula (I) all display a unique efficacy towards the C–H arylation of DG-containing (hetero)arenes with secondary alkyl halides.

Cyclometalated ruthenium(II) catalysts screening for the alkylation reaction of 2-phenylpyridine (N1) with *tert*-butyl bromide (X5)





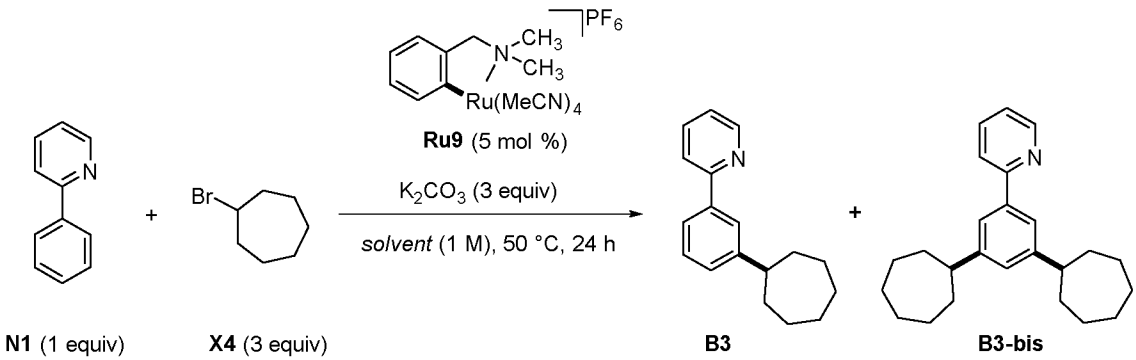
The General Procedure C was applied with the appropriate cyclometalated ruthenium(II) catalyst (0.01 mmol, 5 mol %; see Table 3 below, denoted as **[Ru]**: **Ru9**, 5.6 mg; **Ru14**, 5.8 mg; **Ru15**, 5.6 mg; **Ru23**, 6.0 mg; **Ru24**, 5.5 mg; **Ru26**, 5.8 mg; or **Ru27**, 8.2 mg), 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv.) and NMP (200 µL, 1 M) without KOAc. Column chromatography (hexane/DCM/EtOAc 8:1:1) afforded **C1** as a colourless oil (yield, see Table 3 below).

. entry	[Ru]	C1 (%)
1	**Ru9**	55
2	**Ru14**	62
3	**Ru15**	70
4	**Ru23**	10
5	**Ru24**	63
6	**Ru26**	59
7	**Ru27**	32

Table 3

The results in Table 3 show that the ruthenium(II) catalysts of formula (I) all display a unique efficacy towards the C–H arylation of DG-containing (hetero)arenes with tertiary alkyl halides.

Solvent screening for the alkylation reaction of 2-phenylpyridine (N1) with cycloheptyl bromide (X4)



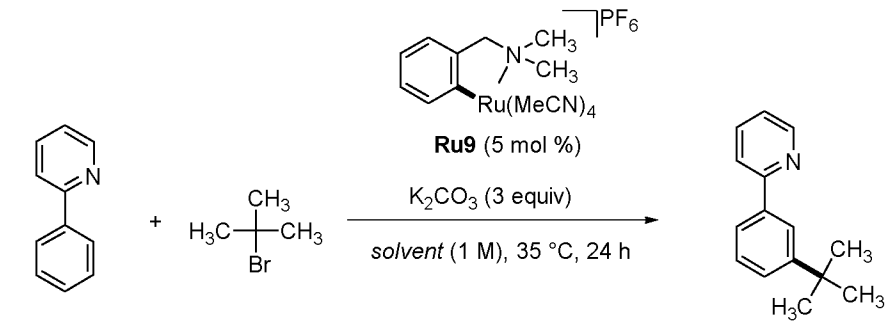
The General Procedure C was applied with **Ru9** (5.6 mg, 0.01 mmol, 5 mol %) 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), cycloheptyl bromide **X4** (83 µL, 0.60 mmol, 3.0 equiv.) and the appropriate solvent (see Table 4 below, 200 µL, 1 M) at 50 °C without KOAc. Column chromatography hexane/DCM/EtOAc 8:1:1) afforded **B3** and **B3-bis** both as colourless oils (yield, see Table 4 below).

entry	*solvent*	**B3**	**B3-bis**
1	NMP	63	18
2	dioxane	61	15
3	gamma-butyrolactone	53	9
4	ethyl acetate	55	-
5	acetone	66	4
6	propylene carbonate	56	12

Table 4

The results from Table 4 indicate that cycloruthenated catalysts of formula (I) retain their exceptional catalytic activity in a wide range of organic solvents in the coupling with secondary alkyl halides.

Solvent screening for the alkylation reaction of 2-phenylpyridine (N1) with *tert*-butyl bromide (X5)



N1 (1 equiv) **X5** (3 equiv) **C1**

The General Procedure C was applied with **Ru9** (5.6 mg, 0.01 mmol, 5 mol %) 2-phenylpyridine **N1** (28.6 µL, 0.20 mmol, 1 equiv.), *tert*-butyl bromide **X5** (68 µL, 0.60 mmol, 3.0 equiv.) and the appropriate solvent (see Table 5 below, 200 µL, 1 M) without KOAc. Column chromatography hexane/DCM/EtOAc 8:1:1) afforded **C1** as a colourless oil (yield, see Table 4 below).

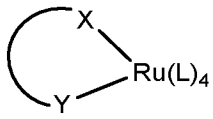
entry	*solvent*	**C1**
1	dioxane	51
2	gamma-butyrolactone	37
3	ethyl acetate	22
4	acetone	46
5	propylene carbonate	32

Table 5

The results from Table 5 indicate that cycloruthenated catalysts of formula (I) retain their exceptional catalytic activity in a wide range of organic solvents in the coupling with tertiary alkyl halides.

Claims

1. A process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an alkyl or cycloalkyl moiety of a second compound, the process comprising reacting the first compound with the second compound in the presence of a catalytically effective amount of a neutral or cationic ruthenium(II) catalyst of formula (I):



formula (I)

wherein:

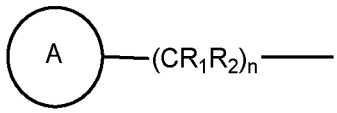
each L is independently selected from neutral and anionic ligands in any combination that balances the bonding and charge requirements of the ruthenium, and wherein any two ligands L can be linked so as to form a bidentate ligand; and

X and Y together form a bidentate cyclometalated ligand for the ruthenium, wherein the bidentate cyclometalated ligand comprises an organic group represented by X which is bonded to the ruthenium by a heteroatom selected from N, P or O (preferably N or P) and an organic group represented by Y which is bonded to the ruthenium via an sp2 or an sp3 carbon.

2. A process according to claim 1, wherein the organic group represented by Y comprises an aryl or heteroaryl group bonded to the ruthenium via an sp2 or an sp3 carbon atom.

3. A process according to a claim 1 or 2, wherein the bidentate cyclometalated ligand forms a 5- or 6-membered ruthenacycle with the ruthenium.

4. A process according to any preceding claim, wherein the organic group represented by Y comprises a group of formula (II) bonded to the ruthenium via an sp2 or an sp3 carbon atom:



formula (II)

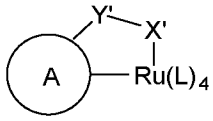
wherein

A represents an optionally substituted aryl or heteroaryl group;

n is 0 or 1; and

R_1 and R_2 are each independently selected from H or (1-4C)alkyl.

5. A process according to any preceding claim, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (IA):



formula (IA)

wherein

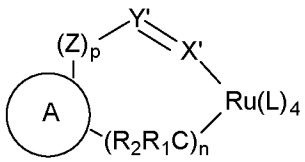
L is as defined in claim 1;

A represents an optionally substituted aryl or heteroaryl group;

X' represents NR_6R_7 and Y' represents NR_{11}, $CR_{12}R_{13}$ or C(O), or X' represents PR_8R_9 and Y' represents $CR_{12}R_{13}$, or X' represents O and Y' represents $CR_{12}R_{13}$ or C(O); wherein R_6, R_7, R_8, R_9, R_{11}, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, or R_6 and R_7, or R_8 and R_9 together with the N or P to which they are attached form a 4 to 8 membered heterocyclyl group and/or R_{12} and R_{13} together with the C to which they are attached form a (4-10C)cycloalkyl group, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted;

or any of the groups R_6, R_7, R_8 or R_9, and any of the groups R_{11}, R_{12} or R_{13} together with the N, C or P to which they are attached may form a cycloalkyl, heterocyclyl, heteroaryl or aryl ring, wherein the cycloalkyl, heterocyclyl, heteroaryl or aryl ring so formed is optionally substituted.

6. A process according to any of claims 1 to 4, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (IB):



formula (IB)

wherein

L is as defined in claim 1;

n is 0 or 1;

R_1 and R_2 are each independently selected from H or (1-4C)alkyl;

A represents an optionally substituted aryl or heteroaryl group;

p represents 0 or 1;

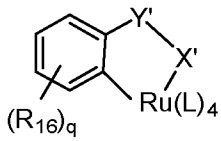
Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H or (1-4C)alkyl;

X' represents NR_{14} and Y' represents CR_{15} or N, wherein R_{14} and R_{15} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted;

or the group R_{14} and the group R_{15} can together with the N or C to which they are attached form a heterocyclyl or heteroaryl ring, wherein the heterocyclyl or heteroaryl ring so formed is optionally substituted.

7. A process according to any of claims 4 to 6, wherein A represents an optionally substituted phenyl group.

8. A process according to claim 5 or 7, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (IA'):



formula (IA')

wherein:

L is as defined in claim 1;

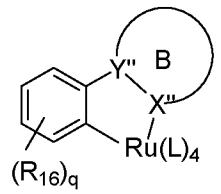
q represents 0, 1, 2, 3 or 4;

X' represents NR_6R_7 and Y' represents $CR_{12}R_{13}$ or C(O), or X' represents PR_8R_9 and Y' represents $CR_{12}R_{13}$, X' represents O and Y' represents $CR_{12}R_{13}$ or C(O);

wherein R_6, R_7, R_8, R_9, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, or R_6 and R_7, or R_8 and R_9 together with the N or P to which they are attached form a 4 to 8 membered heterocyclyl group and/or R_{12} and R_{13} together with the C to which they are attached form a (4-10C)cycloalkyl group, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl groups is optionally substituted;

each R_{16} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

9. A process according to claim 5 or 7, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (IA''):



formula (IA'')

wherein:

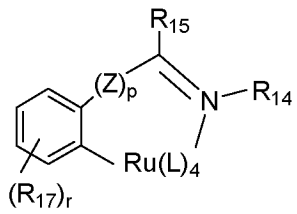
L is as defined in claim 1;

q represents 0, 1, 2, 3 or 4;

B represents a heteroaryl or heterocyclyl group containing a heteroatom N or P represented by X'' and a heteroatom N or an sp2 or sp3 C represented by Y'', wherein the heteroaryl or heterocyclyl group is optionally substituted;

each R_{16} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

10. A process according to claim 6 or 7, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (IB'):



formula (IB')

wherein:

L is as defined in claim 1;

p represents 0 or 1;

r represents 0, 1, 2, 3 or 4;

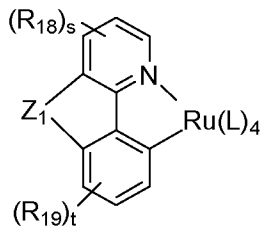
Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H or (1-4C)alkyl;

wherein R_{14} and R_{15} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, wherein any of the (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, groups is optionally substituted;

or the group R_{14} and the group R_{15} can together with the N and C to which they are attached form a heterocyclyl or heteroaryl ring, wherein the heterocyclyl or heteroaryl ring so formed is optionally substituted;

each R_{17} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

11. A process according to any of claims 1 to 4, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (IC):



formula (IC)

wherein:

L is as defined in claim 1;

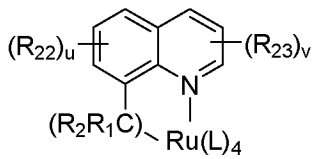
s represents 0, 1, 2 or 3;

t represents 0, 1, 2 or 3;

each R_{18} and R_{19} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl;

Z_1 represents –C=C-, -C=N- or -N=C-.

12. A process according to any of claims 1 to 4, wherein the neutral or cationic ruthenium(II) catalyst is represented by the formula (ID):



formula (ID)

wherein:

L is as defined in claim 1;

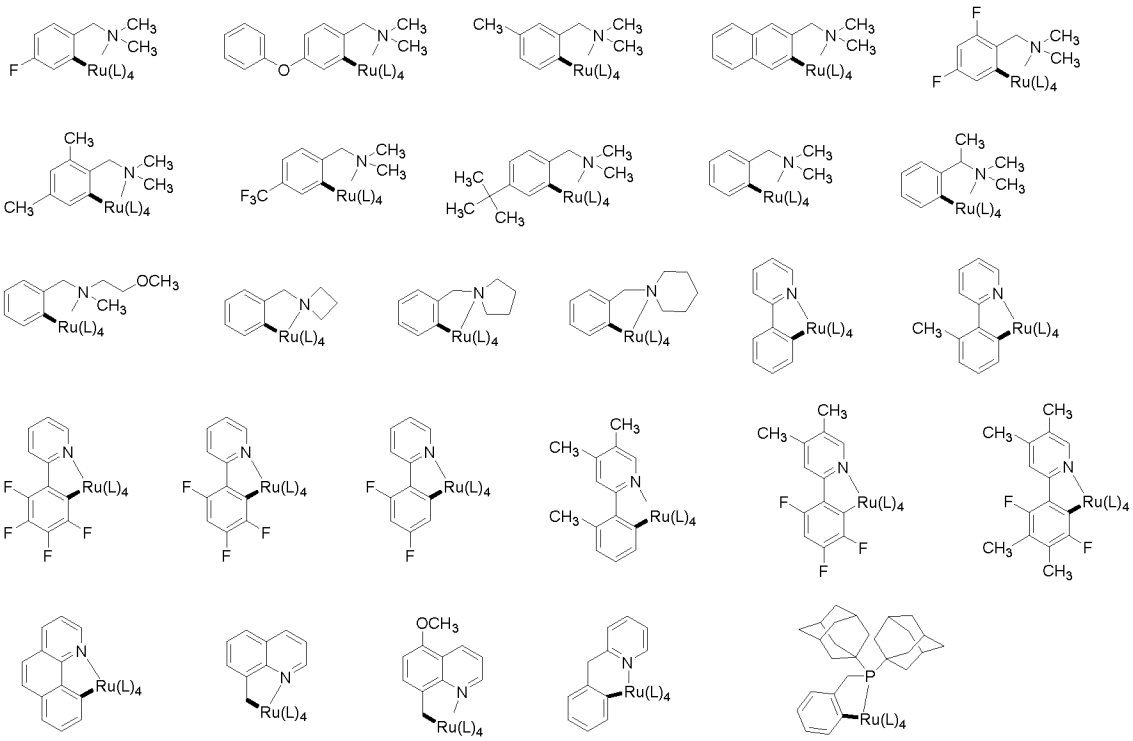
R_1 and R_2 are each independently selected from H or (1-4C)alkyl;

u represents 0, 1, 2 or 3;

v represents 0, 1, 2 or 3;

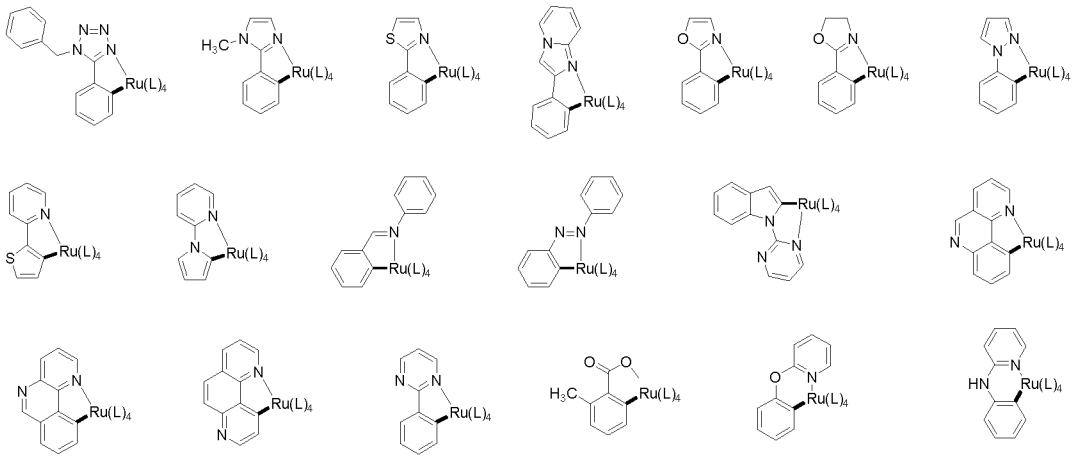
each R_{22} and R_{23} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

13. A process according to any preceding claim, wherein the neutral or cationic ruthenium(II) catalyst is selected from any one of the following:



wherein L is as defined in claim 1.

14. A process according to claims 1 to 10, wherein the neutral or cationic ruthenium(II) catalyst is selected from any one of the following:

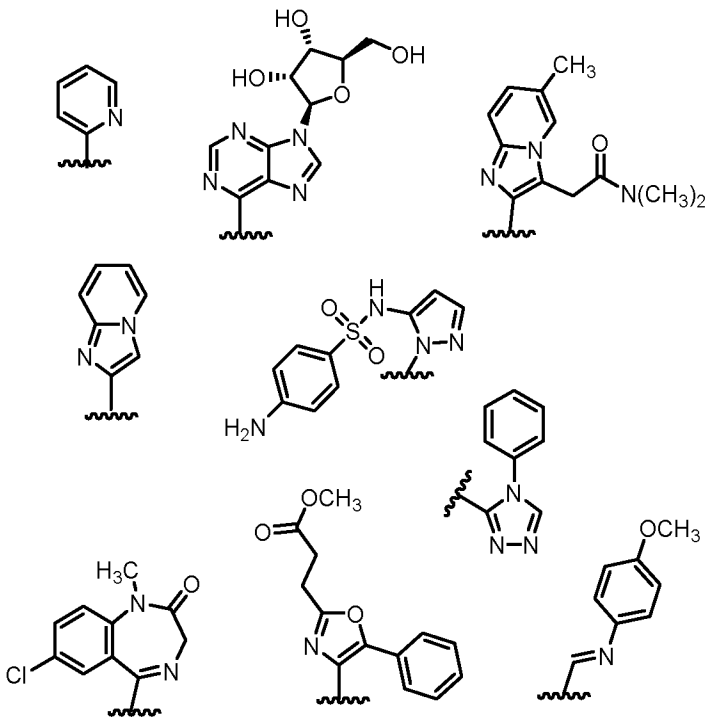


wherein L is as defined in claim 1.

15. A process according to any preceding claim wherein the first compound comprises an aryl or heteroaryl group having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is adjacent to the first ring atom and which has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto, and wherein the second compound comprises a compound containing an alkyl or cycloalkyl moiety having a first sp3 carbon having a leaving group bonded thereto, such that the reaction between the first compound and the second compound results in the formation of a carbon-carbon bond between the first ring atom of the first compound and the first sp3 carbon of the second compound.

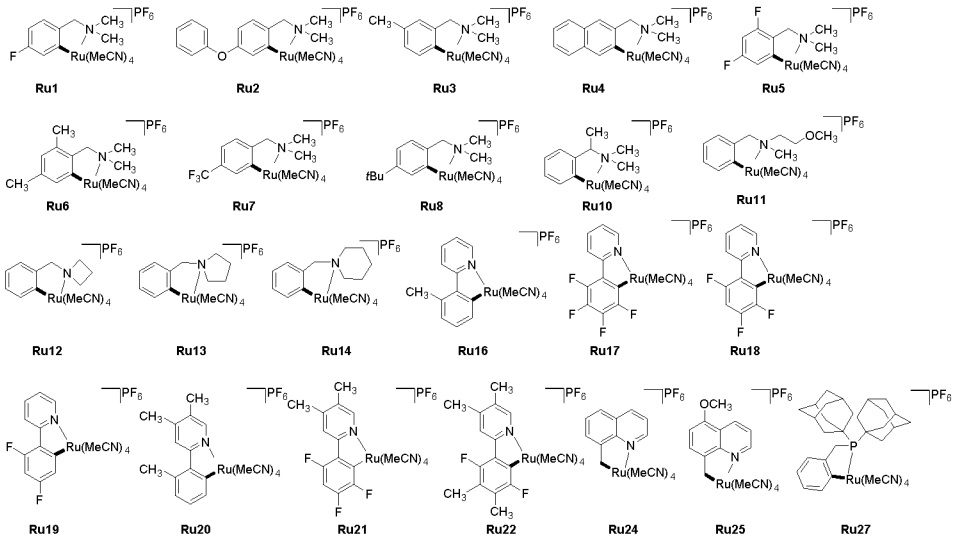
16. A process according to any preceding claim wherein the first compound comprises an aryl or heteroaryl group having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is separated from the first ring atom by one non-bridging third ring atom, wherein the second ring atom has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto and is adjacent to a ring carbon atom having a hydrogen bonded thereto, and wherein the second compound comprises a compound containing an alkyl or cycloalkyl moiety having a first sp3 carbon having a leaving group bonded thereto, such that the reaction between the first compound and the second compound results in the formation of a carbon-carbon bond between the first ring atom of the first compound and the first sp3 carbon of the second compound.

17. A process according to claim 15 or 16, wherein the directing group is selected from any one of the following:



18. A process according to any preceding claim which is conducted at a temperature from 25 to 50°C.

19. A cationic ruthenium(II) catalyst selected from any one of the following:



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/051228

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/54 C07F15/00 C07D243/24 C07D243/30 C07D261/08
C07D211/08 C07D211/10
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LARRY N. LEWIS: "Catalytic C-C Bond Formation via Ortho-Metalated Complexes", J. AM. CHEM. SOC, vol. 108, 1 May 1986 (1986-05-01), pages 2728-2735, XP002791894, page 2730	1-18

Y	LUTZ ACKERMANN ET AL.: "Ruthenium Catalyzed Regioselective Direct Alkylation of Arenes with Unactivated Alkyl Halides through C-H Bond Cleavage", ANGEW. CHEM. IN. ED., vol. 48, 29 July 2009 (2009-07-29), pages 6045-6048, XP002791895, page 6045; table 1	1-18

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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2019	28/06/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bourghida, E

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOTLEY, TYLER C.; TROIAN-GAUTIER, LUDOVIC; BRENNAMAN, M. KYLE; MEYER, GERALD J.: "Excited-State Decay Pathways of Tris(bidentate) Cyclometalated Ruthenium(II) Compounds", INORGANIC CHEMISTRY, vol. 56, no. 21, 25 October 2017 (2017-10-25), pages 13579-13592, XP002791896, ISSN: 0020-1669 page 13581	19
A	LEYVA, LIDA ET AL.: "Synthesis of cycloruthenated compounds as potential anticancer agents", EUROPEAN JOURNAL OF INORGANIC CHEMISTRY, vol. 19, 21 June 2007 (2007-06-21), pages 3055-3066, XP002791897, ISSN: 1434-1948 page 3057; compound 13	19