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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 November 2019 (14.11.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/215426 A1

(51) International Patent Classification:
C07F 15/00 (2006.01)

(21) International Application Number:
PCT/GB2019/051226

(22) International Filing Date:
02 May 2019 (02.05.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1807672.9 11 May 2018 (11.05.2018) GB

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

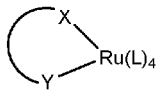
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2019/215426 A1

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

(57) Abstract: A process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an aryl or heteroaryl group 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)

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 aryl or heteroaryl group 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/aryl, aryl/heteroaryl and heteroaryl/heteroaryl 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.

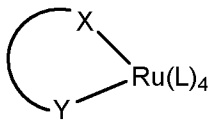
It would be desirable to incorporate coupled aryl/aryl, aryl/heteroaryl and heteroaryl/heteroaryl units into complex compounds via late-stage C-H arylation reactions, as this would enable the preparation of compounds of diverse structures and potentially novel compounds. However, C-H arylation reactions 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.

In the context of *ortho*-directed C–H arylation reactions with aryl (pseudo)halides, palladium-catalysed processes are by far the most studied (see, for example, *Adv. Organomet. Chem.* **2017**, *67*, 299–399). The use of ruthenium however often brings several benefits. In addition to being more than 15 times cheaper than palladium, electrophiles like aryl chlorides, triflates, and bromides can be coupled by ruthenium with similar levels of efficiency (see, for example, *ACS Catal.* **2017**, *7*, 5721–5745; *Adv. Organomet. Chem.* **2017**, *67*, 299–399). Ru(II)-catalysed C–H arylation reactions between directing group (DG)-containing arenes and aryl halides are known, 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 aryl (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 aryl or heteroaryl group of a second compound, for example to prepare compounds including coupled aryl/aryl, aryl/heteroaryl and/or heteroaryl/heteroaryl units (such as, for example, compounds including biaryl 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 aryl or heteroaryl 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 aryl or heteroaryl group 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, resulting in a five- or six-memebered 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.

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 “(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.

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.

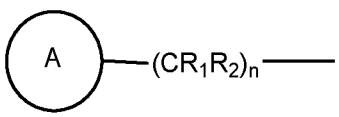
Suitably, the ligand L represents (1-20C)alkylnitrile, such as (1-5C)alkylnitrile, for example methylnitrile (i.e. acetonitrile). Suitably, all four ligands L represent acetonitrile.

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

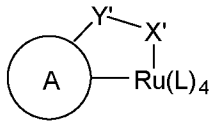
R_1 and R_2 are each independently selected from H or (1-4C)alkyl.

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;

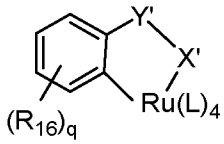
X' represents NR_6R_7 and Y' represents NR_{11}, $CR_{12}R_{13}$ or C(O), or X' represents PR_8R_9 and Y' represents $CR_{12}R_{13}$, or X' represents O and Y' represents $CR_{12}R_{13}$ or C(O); wherein R_6, R_7, R_8, R_9, R_{11}, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (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;

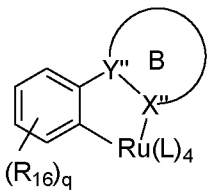
each R_{16} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and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

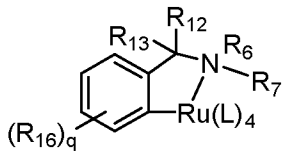
L is as defined above;

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;

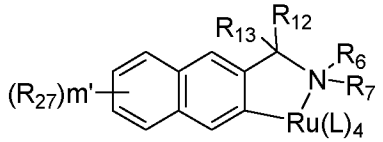
R_6, R_7, R_{12} and R_{13} are each independently selected from H, (1-10C)alkyl, (1-10C)alkoxy, heteroaryl, heterocyclyl, aryl and (4-10C)cycloalkyl, or R_6 and R_7 together with the N to which they are attached form a 4 to 6 membered heterocyclyl group, wherein any of the (1-10C)alkyl, (1-10C)alkoxy,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

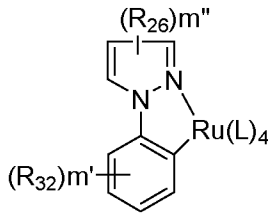
R_6 and R_7 are each independently selected from H, (1-10C)alkyl, phenyl or (4-10C)cycloalkyl, wherein each (1-10C)alkyl, phenyl and (4-10C)cycloalkyl is optionally substituted by one or more substituents independently selected from (1-15C)alkoxy, fluoro, trifluoromethyl and (1-15C)alkyl;

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:

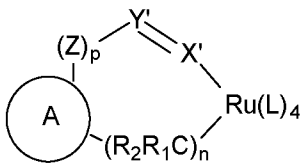
L is as defined above;

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.

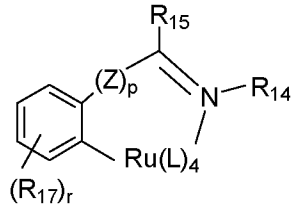
Examples of suitable optional substituents for the aryl or heteroaryl group represented by A in the formula (IB) include halo (for example fluoro), (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (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;

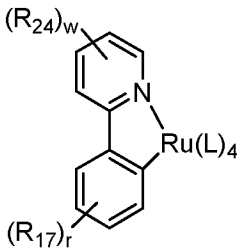
or the group R_{14} and the group R_{15} can together with the N and C to which they are attached form a heterocyclyl or heteroaryl ring, wherein the heterocyclyl or heteroaryl ring so formed is optionally substituted;

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:

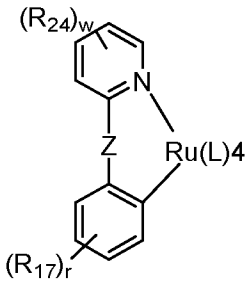
L is as defined above;

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;

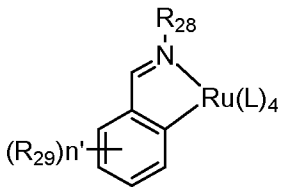
r represents 0, 1, 2, 3 or 4;

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'''')

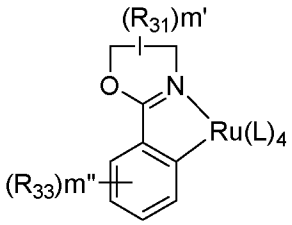
wherein:

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;

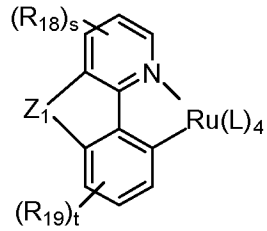
m' represents 0, 1 or 2;

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;

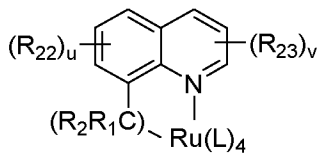
each R_{18} and R_{19} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido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

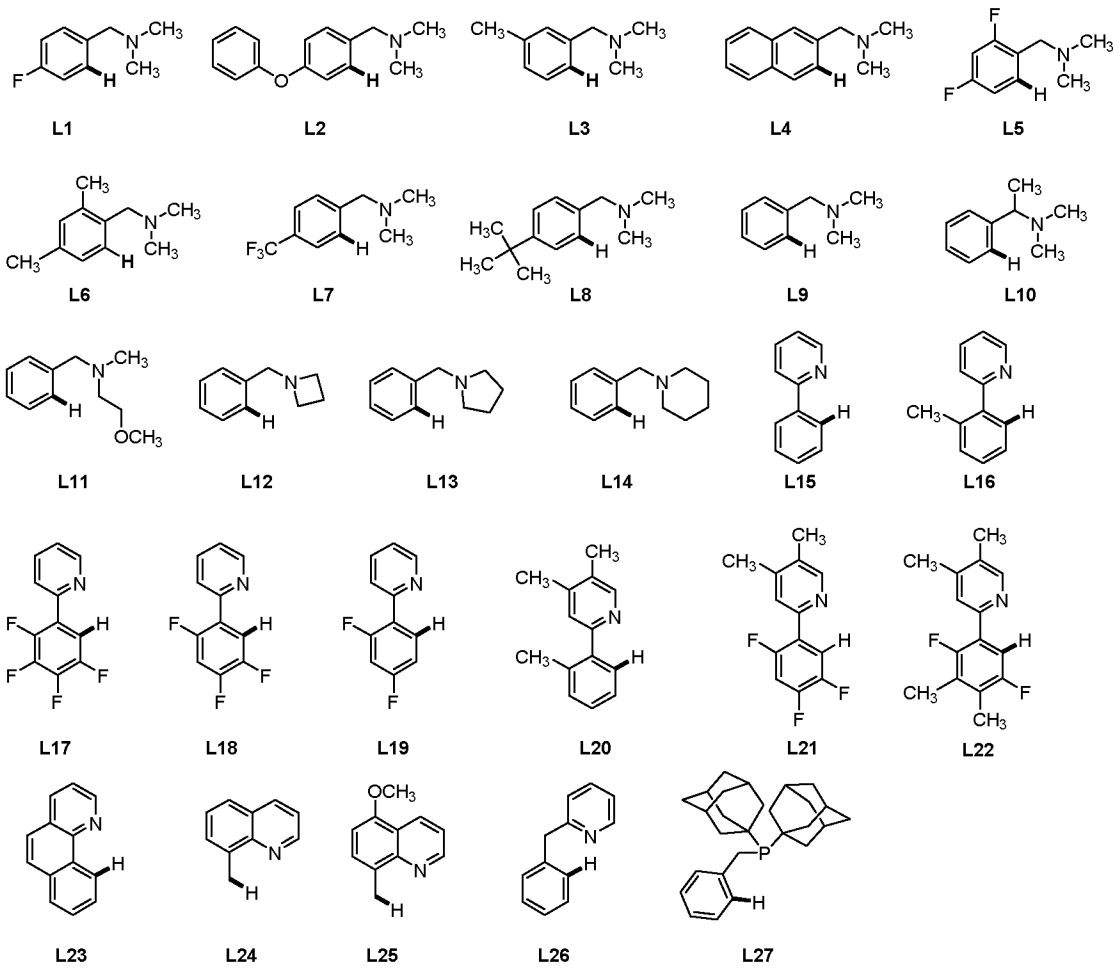
10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido and carboxy(1-10C)alkyl.

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

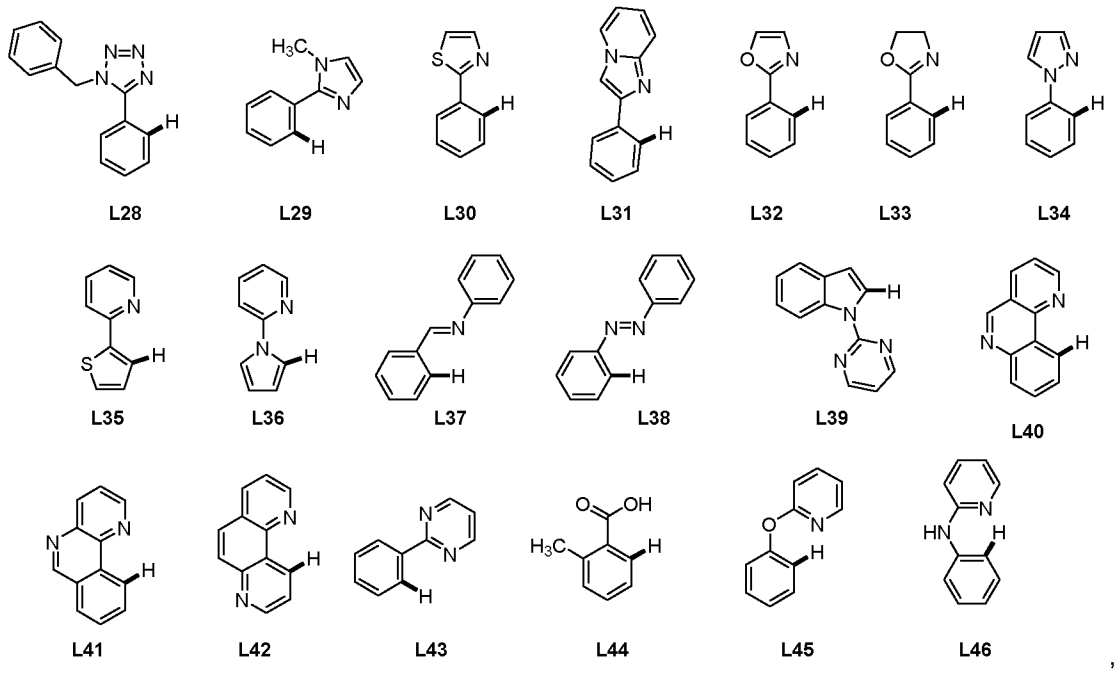
Suitably, in the formula (ID), each R_{22} and R_{23} (when present) may be independently selected from halo, (1-10C)alkyl and (1-10C)alkoxy (especially (1-4C)alkyl, such as methyl, and (1-4C)alkoxy, such as methoxy).

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):

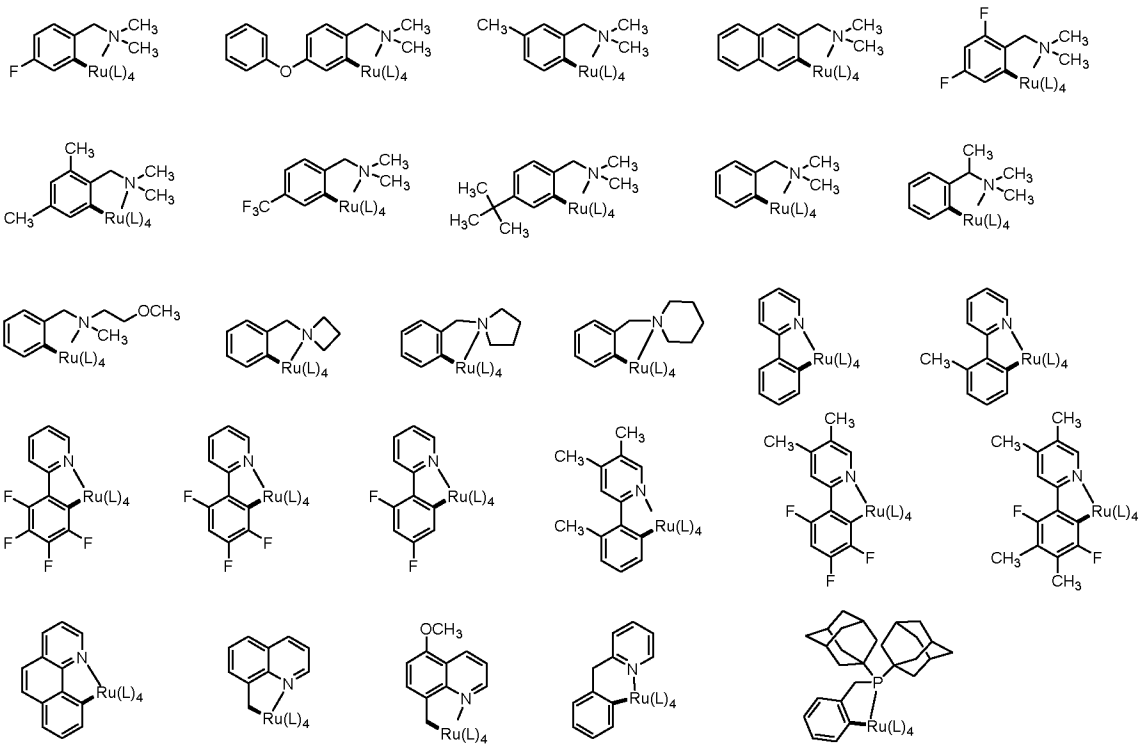


Examples of suitable cyclometalating ligands that may be bonded to the ruthenium to provide a suitable neutral or cationic ruthenium(II) catalyst for use in the process of the invention include (but are not limited to):



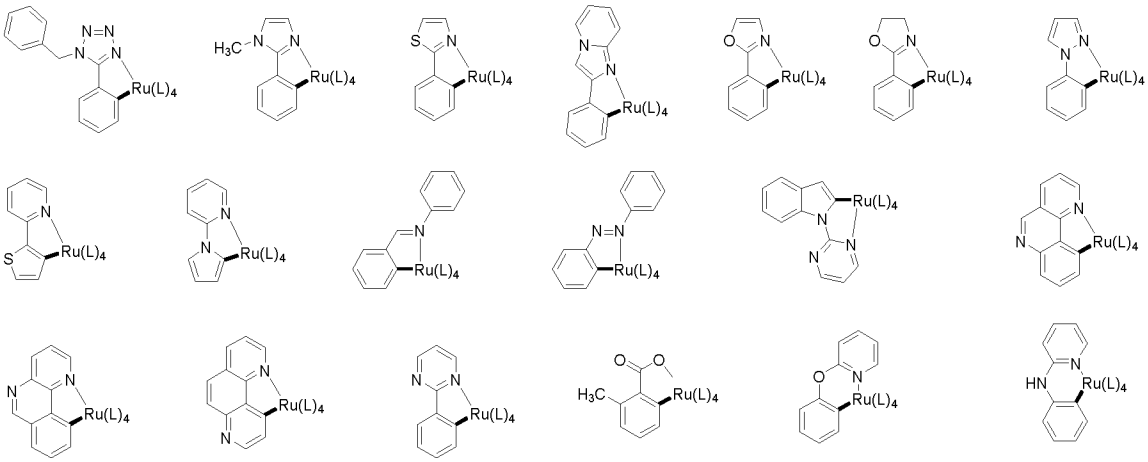
,

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



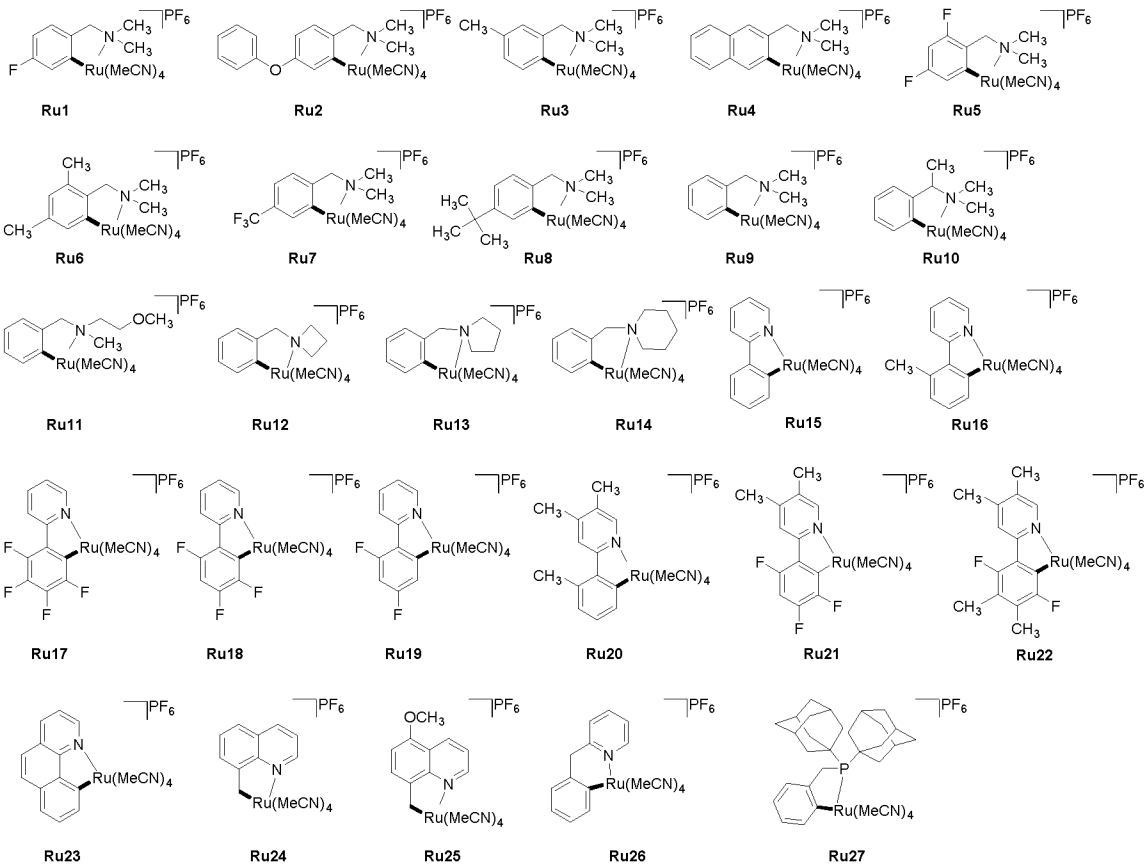
wherein each L is as defined above.

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

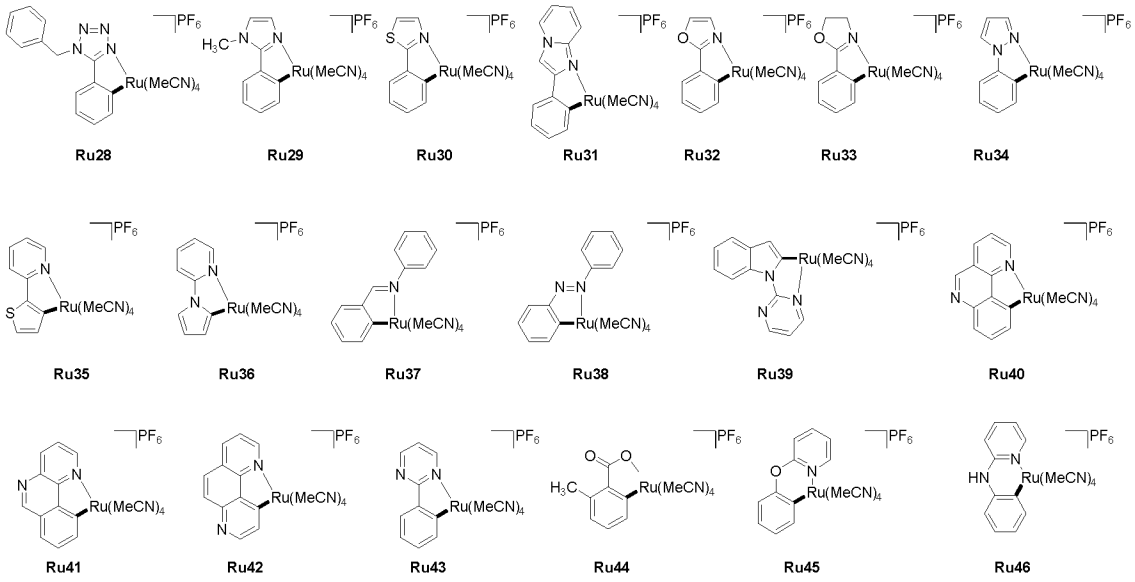


wherein each L is as defined above.

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 3 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 an aryl or heteroaryl group, i.e. in addition to other chemical groups. The second compound may comprise an aryl or heteroaryl group, i.e. in addition to other chemical groups. As the skilled person would appreciate, it is the aryl or heteroaryl groups in the first and second compounds that react and form a new carbon-carbon bond.

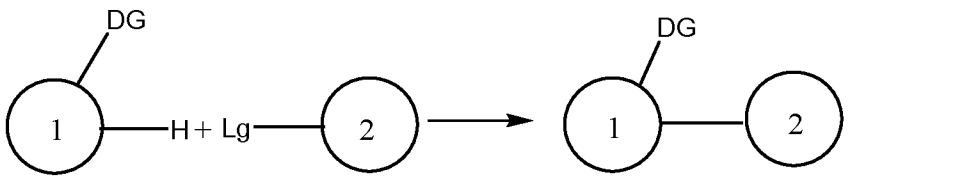
The aryl or heteroaryl groups in the first and second compounds may be the same or different. For example, the first and second compounds may each comprise a phenyl ring, which phenyl rings may be coupled in the process of the invention.

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

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 ortho 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 aryl or heteroaryl group having a first ring atom which is a 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 ring atom of the second compound.

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.

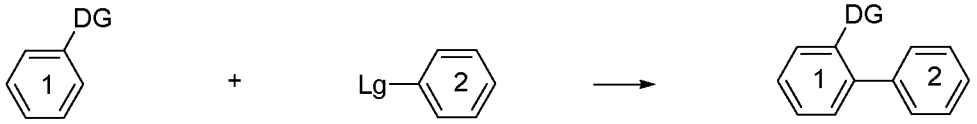
For example, the process may be represented as follows:



First compound | Second compound | Coupled first and second compounds

wherein Lg represents a suitable leaving group and DG represents a nitrogen containing directing group (or a salt or protected derivative thereof). The nitrogen containing directing group is bonded to a second ring atom of the first compound, which second ring atom is 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 directing group may be bonded to the second ring atom of the first compound directly or via an intervening linker group. The leaving group is bonded to a first ring atom of the second compound. Upon reaction, a carbon-carbon bond is formed between the first ring atom of the first compound and the first ring atom of the second compound.

For example, the process may comprise the preparation of a biphenyl compound from a first phenyl compound and a second phenyl compound as follows:

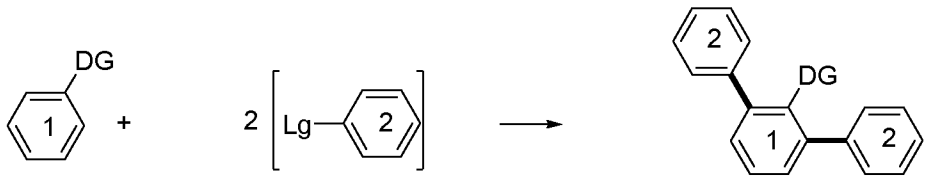


First aryl (phenyl) containing compound | Second aryl (phenyl) containing compound | Biaryl (biphenyl) compound

In the above process, the phenyl 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.

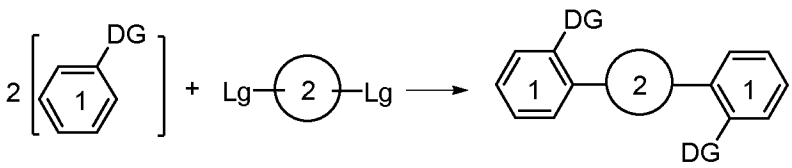
The first compound comprises an aryl or heteroaryl group having a first ring atom which is a carbon atom having a hydrogen bonded thereto and a second ring atom which is ortho to the first ring atom and which has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded 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 (for example phenyl compounds) may couple to single first compound (for example phenyl compound) forming two C-C bonds as follows:



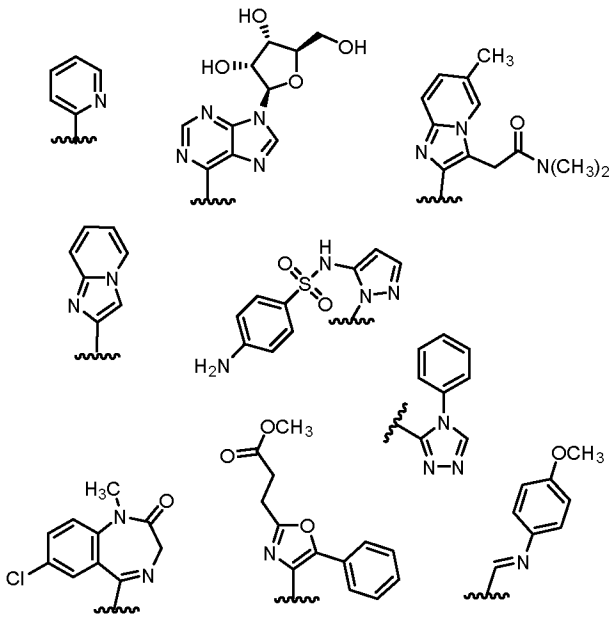
First compound | Second compound | Coupled compound

Alternatively, two first compounds (for example phenyl compounds) may couple to different locations on a single second compound forming two C-C bonds as follows:

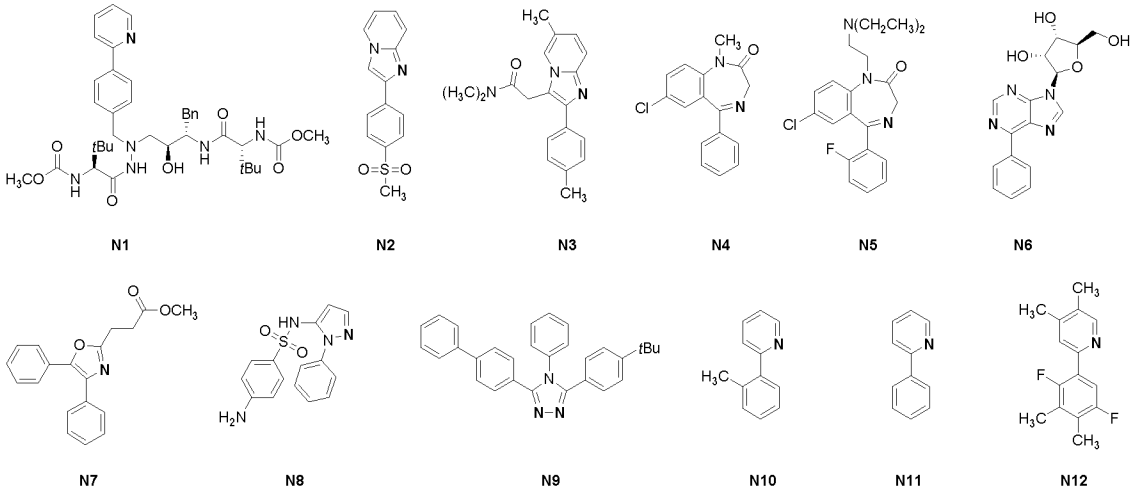


First compound | Second compound | Coupled compound

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 include (but are not limited to):

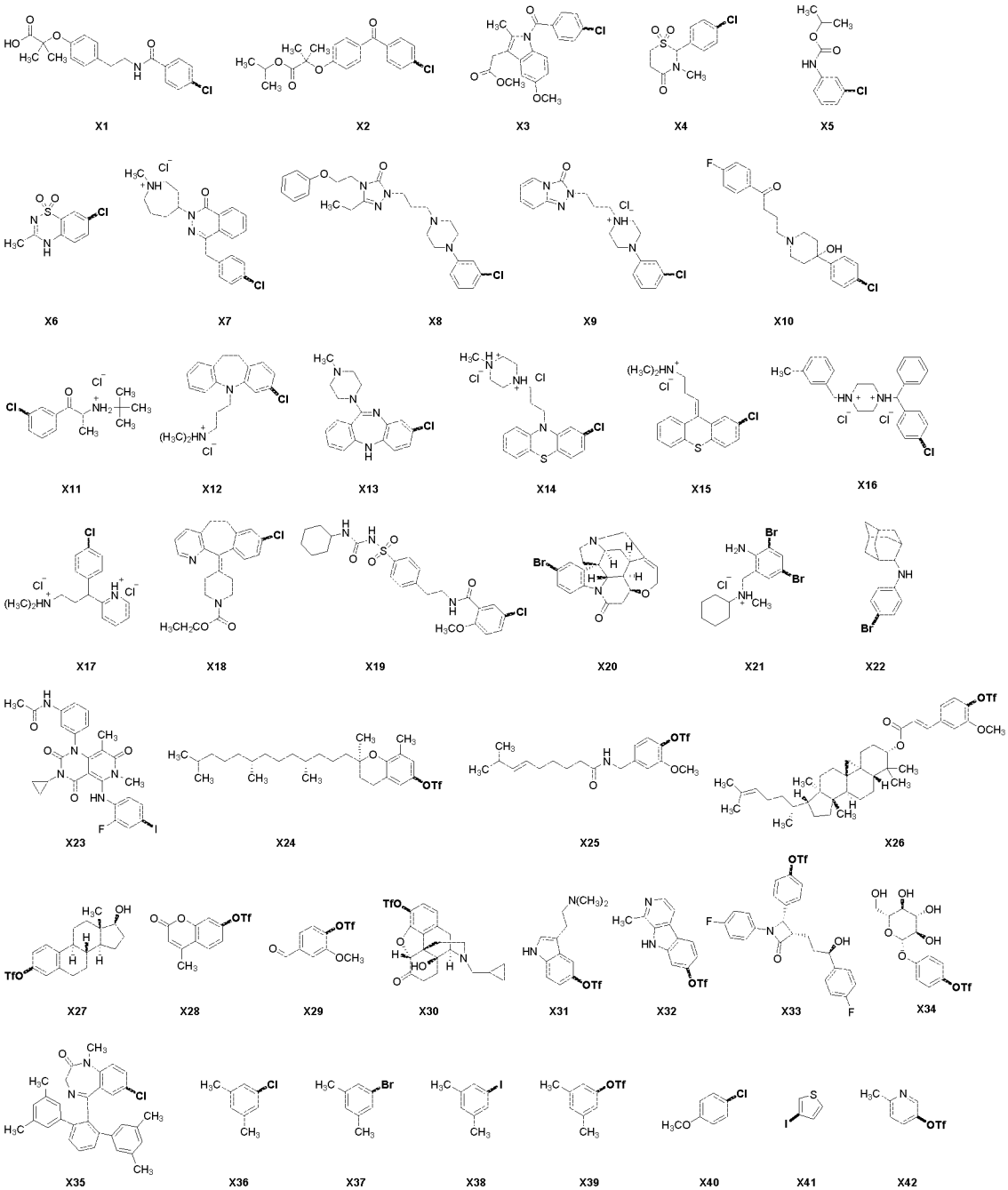


wherein *t*Bu represents *tert*-butyl, and Bn represents benzyl.

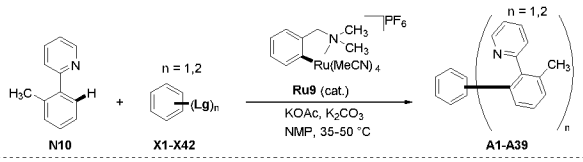
Examples of suitable first compounds include (but are not limited to) 2-(o-tolyl)pyridine and 2-phenyl pyridine. In particular, the first compound may be 2-(*o*-tolyl)pyridine (N10 above).

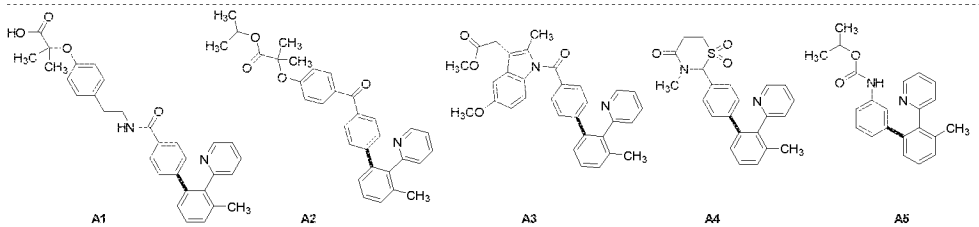
The second compound comprises an aryl or heteroaryl group having a first ring atom having a leaving group bonded thereto. Examples of suitable leaving groups include (but are not limited to) chloro, bromo, iodo, trifluoromethanesulfonate (OTf) *p*-toluenesulfonate (OTs) and methanesulfonate (OMs) (suitably chloro, bromo, iodo and trifluoromethanesulfonate).

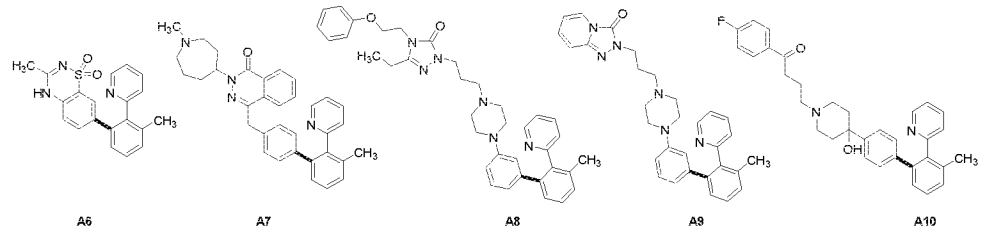
The second compound may be any suitable compound having a leaving group bonded to a first ring atom in the aryl group. Examples of suitable second compounds include (but are not limited to):

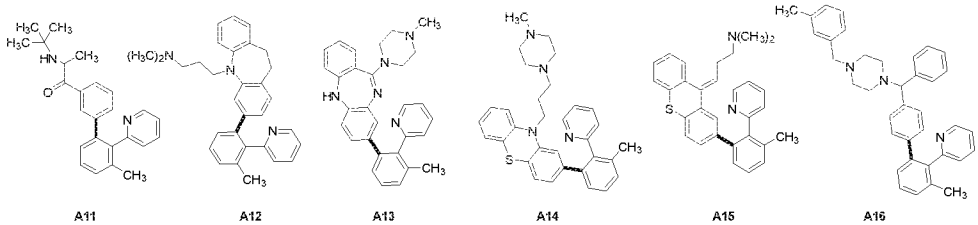


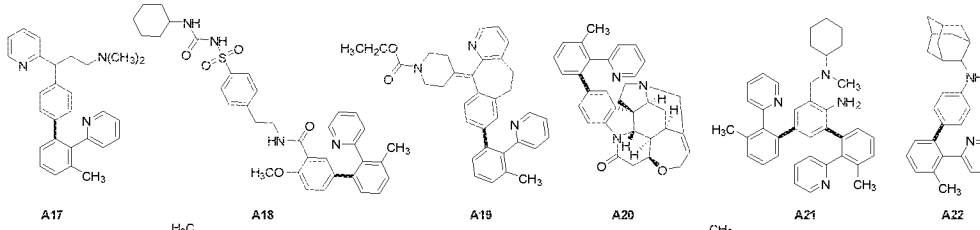
Examples of suitable processes for forming carbon-carbon bonds according to the present invention that can be conducted are (but are not limited to) as follows:

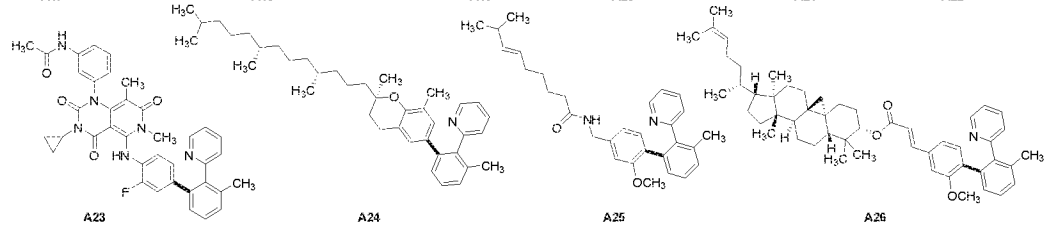

n = 1,2
PF6
Ru(MeCN)4
Ru9 (cat.)
KOAc, K2CO3
NMP, 35-50 °C
n = 1,2
N10
X1-X42
A1-A39

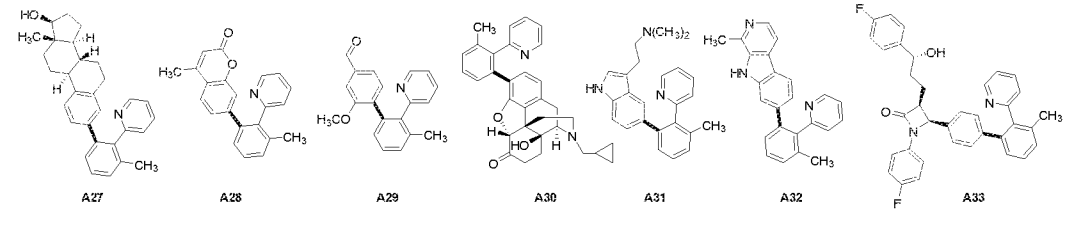

A1
A2
A3
A4
A5

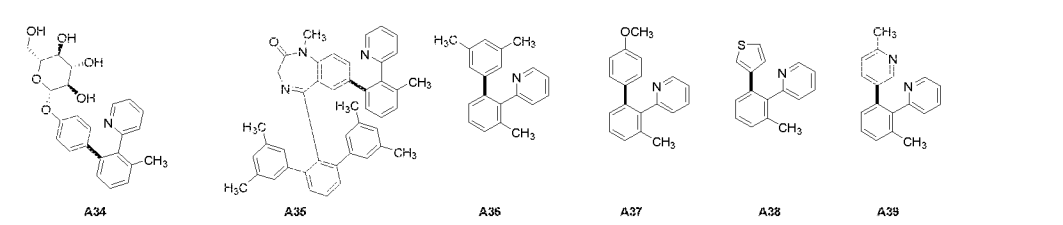

A6
A7
A8
A9
A10


A11
A12
A13
A14
A15
A16

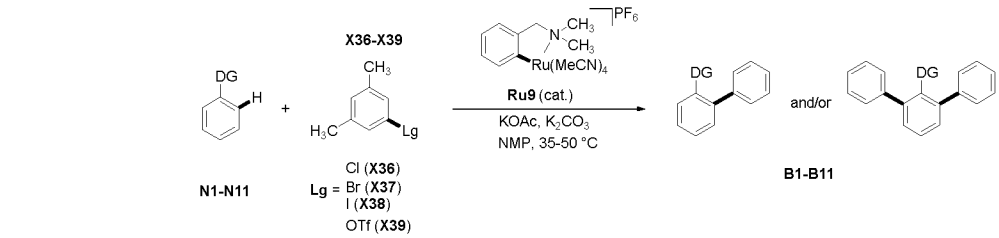

A17
A18
A19
A20
A21
A22

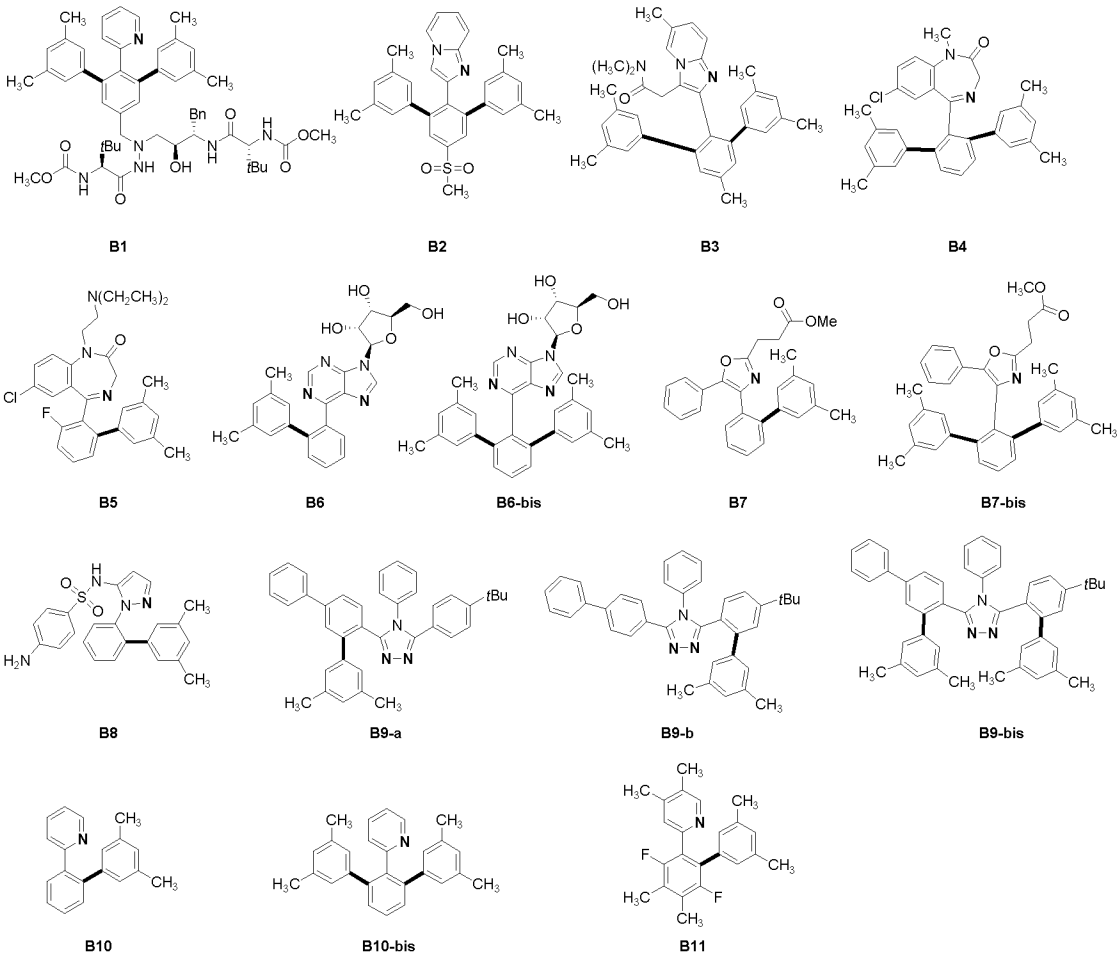

A23
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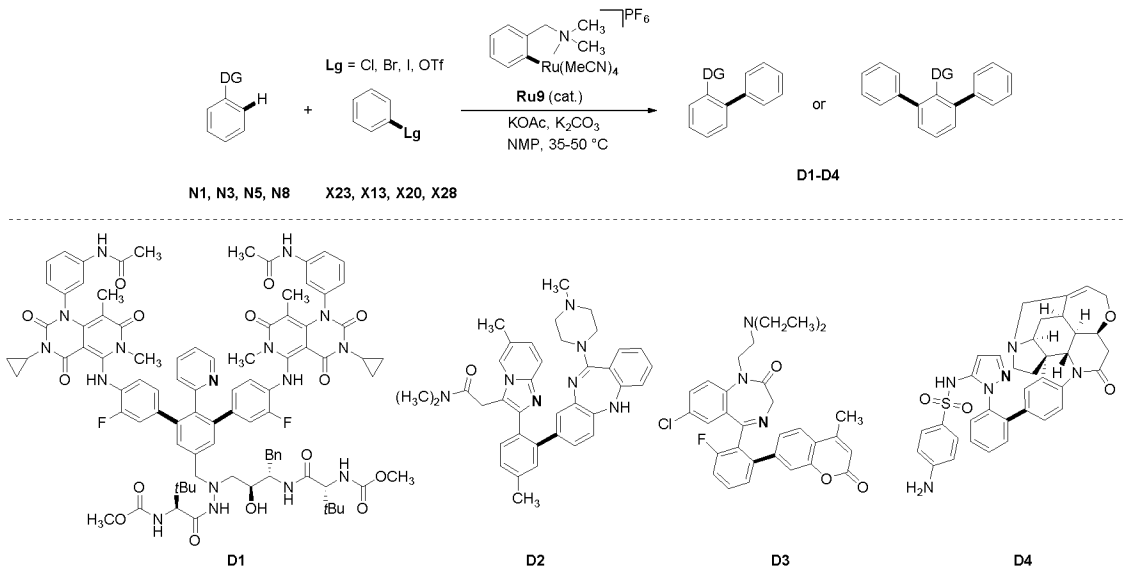
Examples of suitable processes for forming carbon-carbon bonds according to the present invention that can be conducted are (but are not limited to) as follows:





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

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:



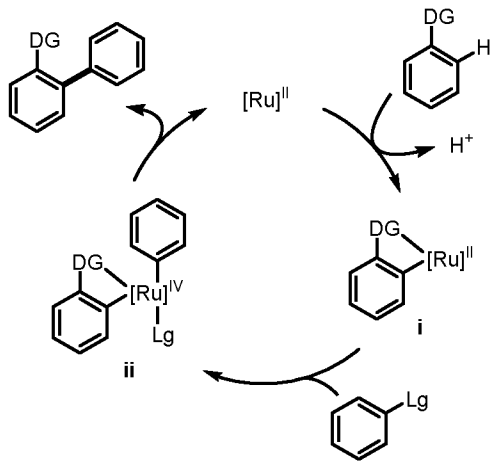
wherein *t*Bu represents *tert*-butyl, and Bn represents benzyl.

The process may be conducted at any suitable temperature, for example at a temperature from 25 to 60°C.

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.

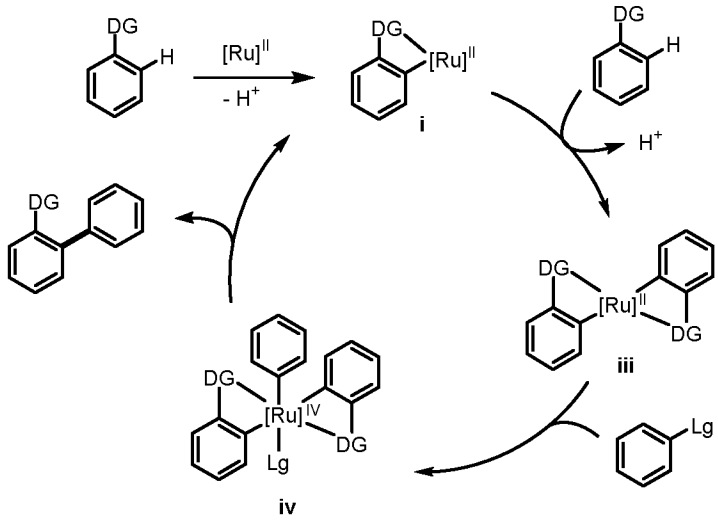
The process may be conducted in any suitable solvent. Examples of suitable solvents include tetrahydrofuran, toluene, gamma-valerolactone, propylene carbonate, ethylacetate, acetone, gamma-butyrolactone, dioxane and *N*-methyl pyrrolidone.

The mechanism of Ru(II)-catalyzed processes for forming C-C bonds as discussed herein (for example C–H arylation of DG-containing (hetero)arenes with (hetero)aryl (pseudo)halides) was previously proposed to operate via a catalytic cycle as shown in Scheme 1 below, involving an initial C–H activation step to form cycloruthenated species **i**, which was believed to undergo oxidative addition with the aryl (pseudo)halide (Ar-Lg) generating the Ru(IV) intermediate **ii**. The latter, after the reductive elimination step, was understood to then release the biaryl product restarting the cycle (see *Adv. Organomet. Chem.* **2017**, *67*, 299–399; *ACS Catal.* **2017**, *7*, 5721–5745):



Scheme 1

The present inventors have determined that a second C–H activation event is required to form the bis-cyclometalated Ru(II) complex **iii**, prior to the oxidative addition step leading to the Ru(IV) species **iv** as shown in Scheme 2 below. Thus, the present inventors have identified the new key catalytic species **iii** in the arylation reaction.



Scheme 2

This understanding of the mechanism enabled the development of cycloruthenated complexes of formula (I), which are able to catalyse the C–H arylation process at remarkably low temperatures, with equimolar amounts of the (hetero)aryl (pseudo)halide.

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.

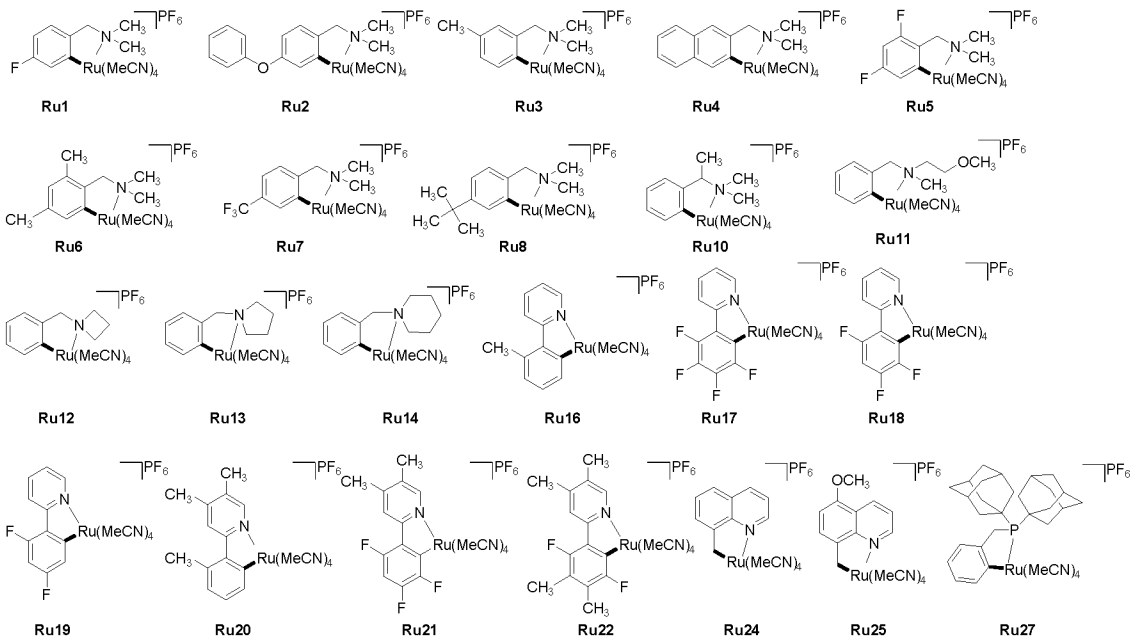
According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IB'''') as defined above.

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.

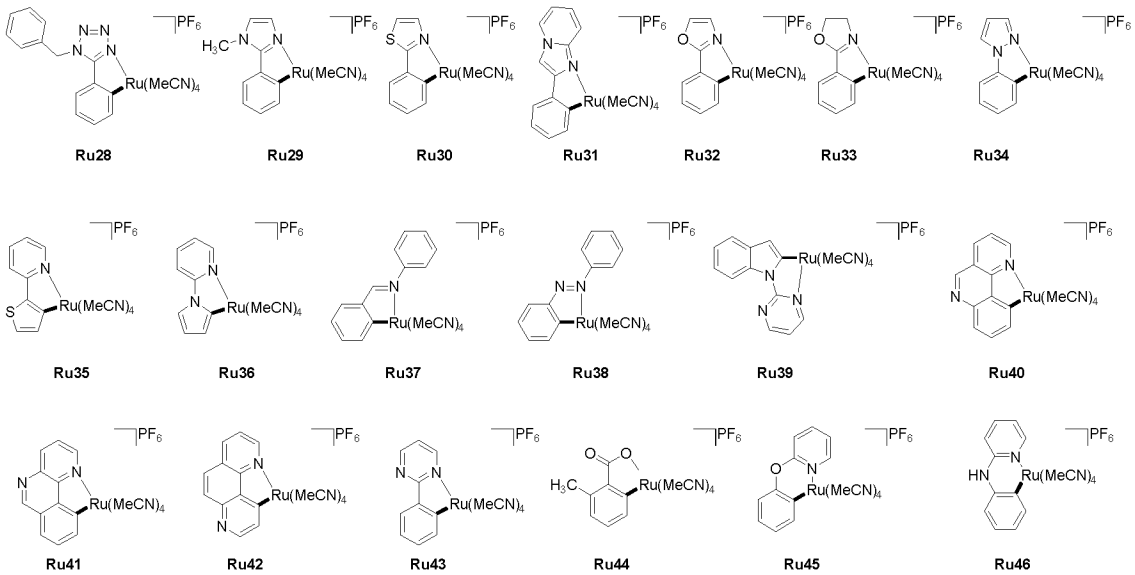
According to a second aspect of the invention, there is provided a neutral or cationic (preferably cationic) ruthenium(II) catalyst of formula (IC) as defined above.

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.

For a better understanding of the invention, and to show how exemplary embodiments of the same may be carried into effect, reference will be made, by way of example only, to the accompanying diagrammatic Figures, in which:

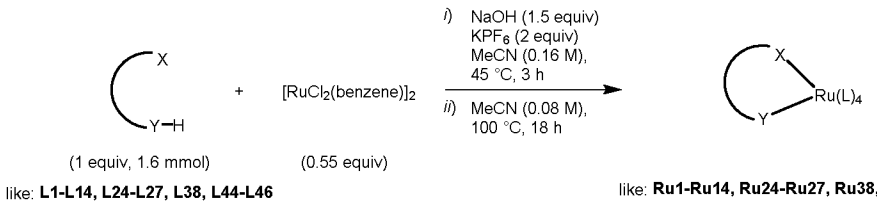
Figures 1a and 1b show the reaction scheme and ^{1}H and ^{19}F NMR spectra for the reaction of cyclometalated complex **Ru22** with 2-arylpyridine **L22**.

Figure 2 shows a comparison of the catalytic activity of the system constituted by cycloruthenated **Ru16** catalyst and KOAc with respect to **cym-Ru1** and **cym-Ru1** catalysts.

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

Examples

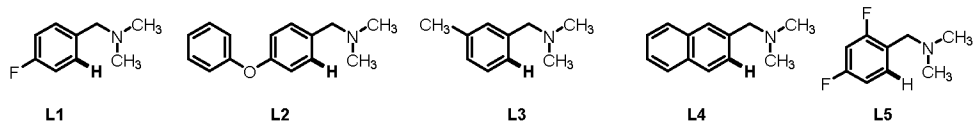
General Procedure A: preparation of cyclometalated ruthenium(II) catalysts



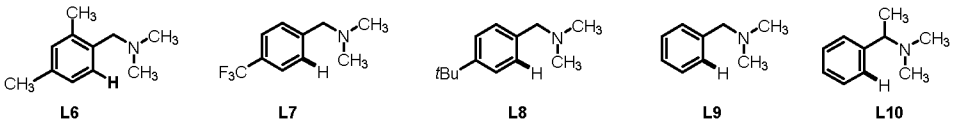
(1 equiv, 1.6 mmol) (0.55 equiv)

like: **L1-L14, L24-L27, L38, L44-L46**

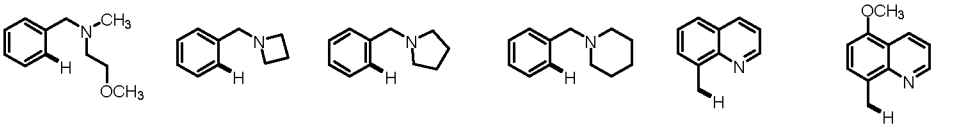
like: **Ru1-Ru14, Ru24-Ru27, Ru38, Ru44-Ru46**



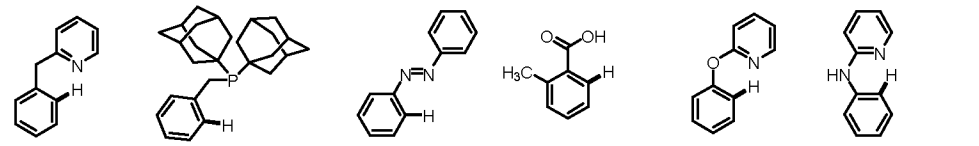
L1 **L2** **L3** **L4** **L5**



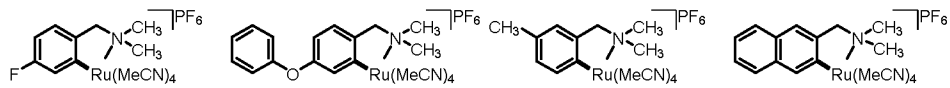
L6 **L7** **L8** **L9** **L10**



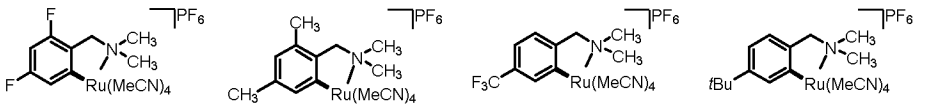
L11 **L12** **L13** **L14** **L24** **L25**



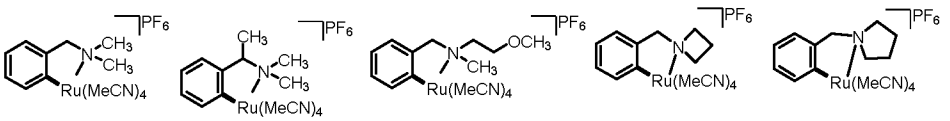
L26 **L27** **L38** **L44** **L45** **L46**



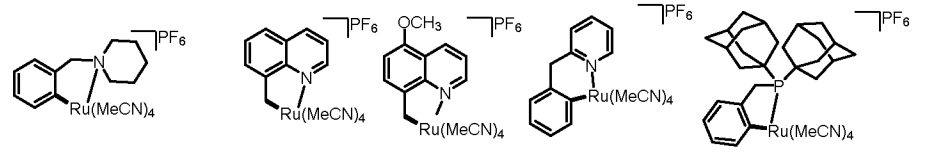
Ru1 **Ru2** **Ru3** **Ru4**



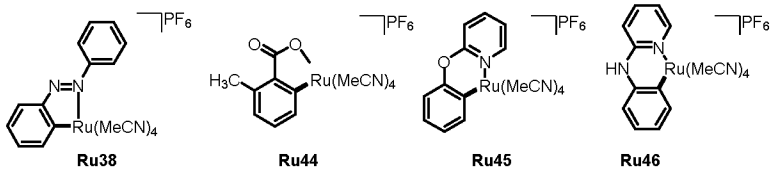
Ru5 **Ru6** **Ru7** **Ru8**



Ru9 **Ru10** **Ru11** **Ru12** **Ru13**



Ru14 **Ru24** **Ru25** **Ru26** **Ru27**

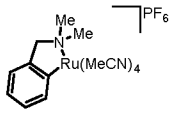


Ru38 **Ru44** **Ru45** **Ru46**

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).

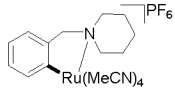
The General Procedure A was applied with *N*,*N*-dimethylbenzylamine **L9** (216.3 mg, 1.6 mmol, 1 equiv.) affording **Ru9** as an off white solid (653.3 mg, 75%).



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 **Ru24** as an off white solid (598.5 mg, 64%).

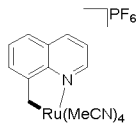


Ru14

^{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.

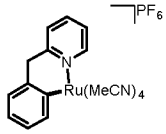
The General Procedure A was applied with 8-methylquinoline **L24** (229.1 mg, 1.6 mmol, 1 equiv.) affording **Ru24** as a red solid (123.9 mg, 14%). However, the reaction time for the first step was extended from 3 to 48 hours.



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.

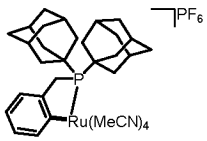
The General Procedure A was applied with 2-benzylpyridine **L26** (270.7 mg, 1.6 mmol, 1 equiv.) affording **Ru26** as a yellow solid (219.1 mg, 22%). However, the reaction time for the first step was extended from 3 to 72 hours. Spectroscopic data matched those previously reported (Organometallics **1999**,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

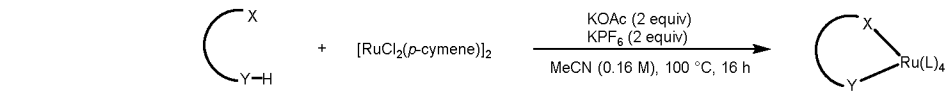


Ru27

^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,

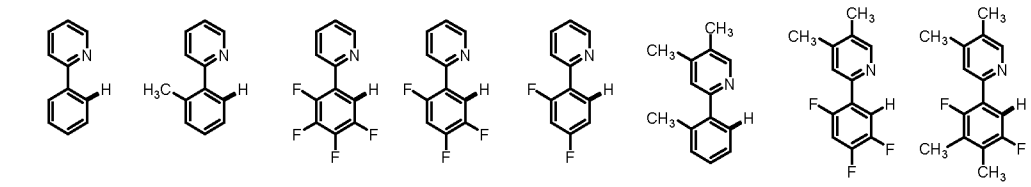
125.0 (2C), 124.1, 123.3 (d, *J* = 14.4 Hz), 121.8, 42.3 (d, *J* = 14.2 Hz), 40.2, 37.5, 31.8 (d, *J* = 24.6 Hz), 29.7 (d, *J* = 7.7 Hz), 4.9, 4.6; ^{19}F NMR (471 MHz, CD_3CN) δ -72.2, -73.7; ^{31}P NMR (202 MHz, CD_3CN) δ 89.7; ESI-MS calcd for $C_{33}H_{45}N_3PRu$ $[M - PF_6 - MeCN]^+$: 616.2, found 616.2.

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

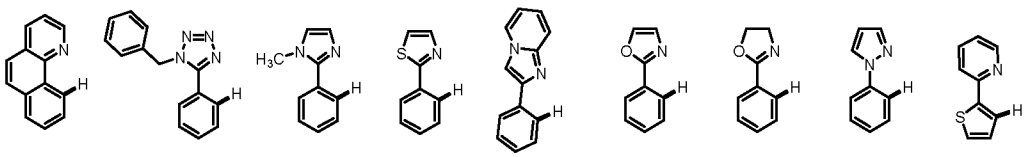


(1 equiv, 1.6 mmol) (0.5 equiv.)

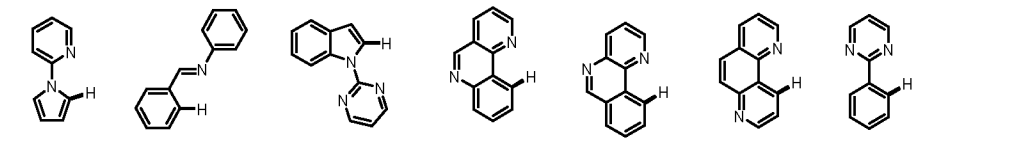
like: **L15-L23, L28-L37, L39-L43** like: **Ru15-Ru23, Ru28-Ru37, Ru39-Ru43**



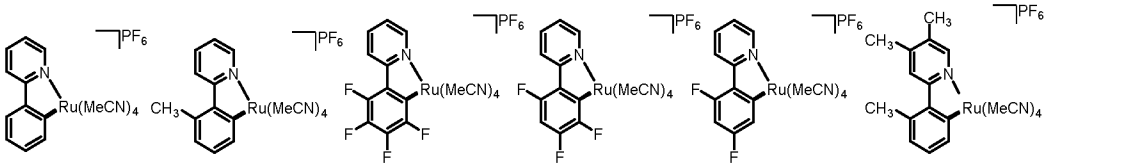
L15 **L16** **L17** **L18** **L19** **L20** **L21** **L22**



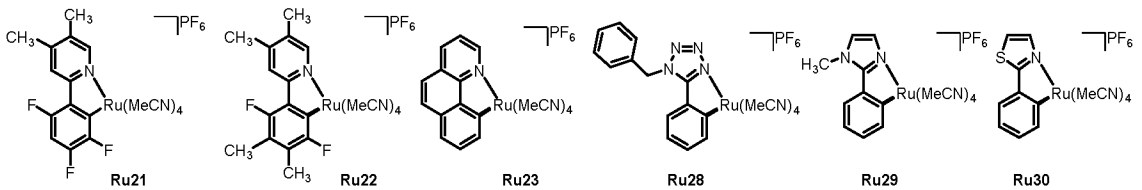
L23 **L28** **L29** **L30** **L31** **L32** **L33** **L34** **L35**



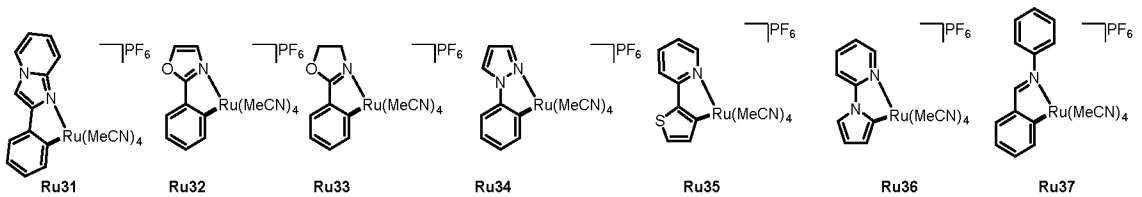
L36 **L37** **L39** **L40** **L41** **L42** **L43**



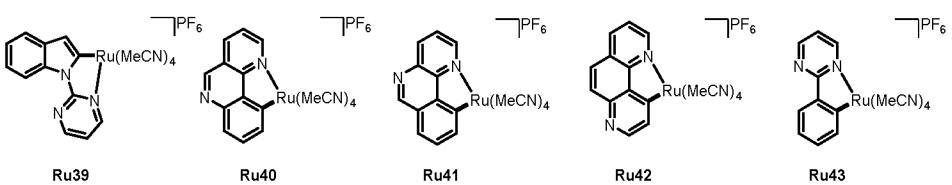
Ru15 **Ru16** **Ru17** **Ru18** **Ru19** **Ru20**



Ru21 **Ru22** **Ru23** **Ru28** **Ru29** **Ru30**



Ru31 **Ru32** **Ru33** **Ru34** **Ru35** **Ru36** **Ru37**

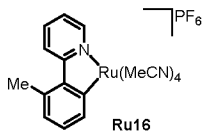


Ru39 **Ru40** **Ru41** **Ru42** **Ru43**

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).

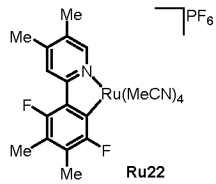
The General Procedure B was applied with 2-(*o*-tolyl)pyridine **L16** (270.8 mg, 1.6 mmol, 1 equiv.) affording **Ru16** as an orange solid (879.3 mg, 95%).



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%).

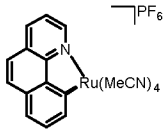


Ru22

^{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.

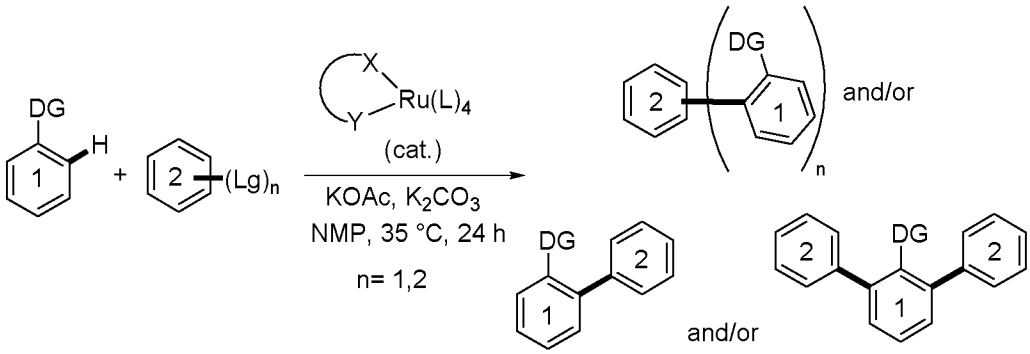
The General Procedure B was applied with benzo[*h*]quinoline **L23** (286.7 mg, 1.6 mmol, 1 equiv.) affording **Ru23** as a light orange solid (782.1 mg, 81%). Spectroscopic data matched those previously reported (*Inorganica Chim. Acta* **2010**, *363*, 567–573).



Ru23

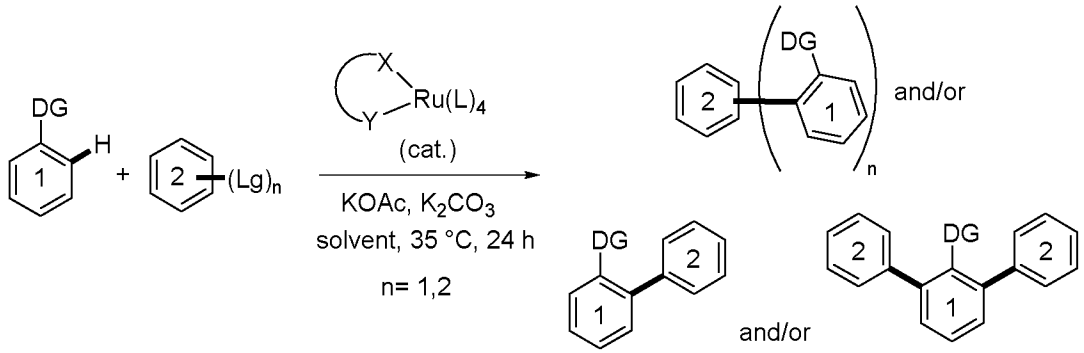
^{1}H NMR (500 MHz, CD_3CN) δ 9.18 (dd, J = 5.3, 1.4 Hz, 1H), 8.27 (dd, J = 8.0, 1.3 Hz, 1H), 8.17 (dd, J = 6.4, 1.8 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.57 – 7.44 (m, 3H), 2.58 (s, MeCN), 2.14 (s, MeCN) 1.91 (s, 2xMeCN) The signals of the coordinated acetonitriles integrate 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: arylation of DG-containing (hetero)arenes with (hetero)aryl (pseudo)halides using cyclometalated ruthenium(II) catalysts



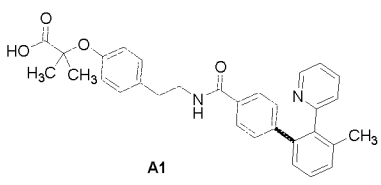
Unless otherwise stated, in an Argon filled glove-box a crimp-cap microwave vial equipped with a magnetic stirring bar was charged with the appropriate cyclometalated Ru(II)-catalyst (like **Ru1-Ru46**, from 3 mol % to 10 mol %), KOAc (5.9 mg, 0.06 mmol, 30 mol %), K_2CO_3 (2.0 – 4.0 equiv.), the appropriate DG-containing arene (like **N1-N12**, 0.20 mmol, 1.0 equiv.), the appropriate (hetero)aryl (pseudo)halide (like **X1-X42**, 0.2 mmol, 1.0 equiv) and *N*-methyl-2-pyrrolidone (NMP) (200 µL, 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 arylation of DG-containing (hetero)arenes with (hetero)aryl (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). Unless otherwise stated, 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 3 mol % to 10 mol %), KOAc (5.9 mg, 0.06 mmol, 30 mol %), K_2CO_3 (2.0 – 4.0 equiv.) and if solid the appropriate (hetero)aryl (pseudo)halide (like **X1-X42**, 0.20 mmol, 1.0 equiv.). The tube was evacuated and back-filled with nitrogen three times, then the appropriate DG-containing arene (like **N1-N12**, 0.20 mmol, 1.0 equiv.), if liquid the appropriate (hetero)aryl (pseudo)halide (like **X1-X42**, 0.20 mmol, 1.0 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 24 hours. Upon completion, the crude mixture was loaded on a silica gel column and purified by flash chromatography.

Characterization data for arylated compounds



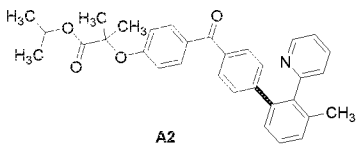
A1

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Bezafibrate **X1** (72.4 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) for 48 h. The crude reaction mixture was diluted with H_2O (20 mL) and extracted with Et_2O (3×20 mL). Acetate buffer was added to the aqueous phase (pH ≈ 4.5) and the mixture was extracted with EtOAc (3×20 mL). The organic phases were reunited, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOAc/pentane at 4 °C to afford **A1** as an off-white powder (89.0 mg, 90%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 6 H), 2.13 (s, 3 H), 2.75 (t, *J* = 7.1 Hz, 2 H), 3.50 (q, *J* = 6.6 Hz, 2 H), 6.31-6-48 (m, 1 H), 6.75 (d, *J* = 8.2 Hz, 2 H), 6.90 (d, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 7.11-7.17 (m, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 7.29 (d,

J = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 7.50 (td, *J* = 7.7, 1.7 Hz, 1 H), 8.61 (d, *J* = 5.2 Hz, 1 H), 10.92 (bs, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.5, 25.4, 34.7, 41.3, 79.4, 119.8, 122.3, 126.2, 126.5, 127.5, 128.6, 129.5, 129.8, 130.0, 132.4, 132.5, 137.1, 137.2, 138.0, 140.5, 144.7, 148.0, 154.1, 158.4, 167.7, 176.8 ppm; mp > 114 °C (decomposition); IR ν_{max} (neat/cm^{-1}): 3338, 3060, 2992, 2847, 1726, 1642, 1604, 1513, 1459, 1300, 1231, 1148, 851, 767; HRMS calcd for $C_{31}H_{29}O_4N_2$ [M–H]$^-$: 493.2133, found 493.2134.

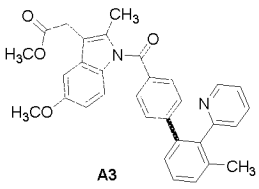
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Fenofibrate **X2** (72.2 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/Et_2O, from 7:3 to 4:6) afforded **A2** as an off-white solid (88.8 mg, 90%).



A2

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.4 Hz, 6 H), 1.65 (s, 6 H), 2.20 (s, 3 H), 5.09 (hept, *J* = 6.4 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 7.12 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.18 (d, *J* = 8.2, 2 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 7.2 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.48 (td, *J* = 7.6, 1.9, 1 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 8.63 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 21.5, 25.3, 69.3, 79.3, 117.0, 121.5, 125.6, 127.4, 128.2, 129.3, 129.4, 130.0, 130.6, 131.9, 135.7, 135.9, 136.9, 139.3, 140.2, 145.7, 148.9, 159.1, 159.4, 173.1, 195.3 ppm; mp 135-137 ºC; IR ν_{max} (neat/cm^{-1}): 3058, 2982, 2938, 1729, 1651, 1597, 1286, 1249, 1176, 1147, 1102; HRMS calcd for $C_{32}H_{32}O_4N$ [M+H]$^+$: 494.2326, found 494.2322.

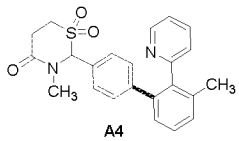
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Indometacin methyl ester **X3** (74.4 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/Et_2O, 4:6) afforded **A3** as a pale yellow solid (92.8 mg, 92%).



A3

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3 H), 2.32 (s, 3 H), 3.66 (s, 2 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 6.63 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 1 H), 6.95 (d, *J* = 2.6 Hz, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 7.16 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.30-7.38 (m, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.47-7.57 (m, 3 H), 8.62 (d, *J* = 4.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.2, 20.4, 30.1, 52.1, 55.6, 100.8, 111.5, 112.0, 114.9, 121.6, 125.6, 127.2, 128.2, 129.1, 129.9, 130.1, 130.4, 130.8, 133.1, 135.8, 136.0, 136.9, 139.2, 140.0, 146.6, 149.0, 155.8, 159.0, 169.2, 171.3 ppm; mp 58-62 ºC; IR ν_{max} (neat/cm^{-1}): 2952, 2928, 2834, 1736, 1680, 1477, 1456, 1356, 1313, 1262, 1224; HRMS calcd for $C_{32}H_{28}O_4N_2Na$ [M+Na]$^+$: 527.1941, found 527.1942.

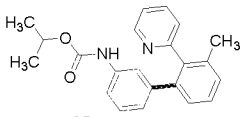
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Chlormezanone **X4** (54.7 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/EtOAc, from 2:8 to 1:9) afforded **A4** an off-white wax (75.6 mg, 93%).



A4

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 2.89 (s, 3 H), 2.98-3.32 (m, 4 H), 5.18 (d, *J* = 1.2 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 7.08-7.21 (m, 5 H), 7.25-7.31 (m, 1 H), 7.34 (d, *J* = 6.8 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.46 (td, *J* = 7.6, 1.6 Hz, 1 H), 8.61 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 30.5, 36.1, 43.2, 80.3, 121.5, 125.6, 127.3 (2×C), 127.8, 128.3, 130.1, 130.5, 135.7, 136.9, 139.3, 139.9, 144.1, 149.0, 159.1, 166.1 ppm; IR v_{max} (neat/cm^{-1}): 3057, 2926, 2855, 1651, 1331, 1322, 1131; HRMS calcd for $C_{23}H_{22}O_3N_2NaS$ $[M+Na]^+$: 429.1243, found 429.1235.

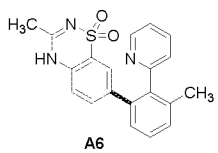
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Chlorpropham **X5** (42.7 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/Et_2O, 1:1) afforded **A5** as a white solid (63.7 mg, 92%).



A5

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.2, 6 H), 2.17 (s, 3 H), 4.99 (hept, *J* = 6.2, 1 H), 6.59 (bs, 1 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 7.03 (s, 1 H), 7.10 (ddd, *J* = 7.4, 5.0, 1.2 Hz, 1 H), 7.22-7.36 (m, 4 H), 7.47 (td, *J* = 7.6, 2.0 Hz, 1 H), 8.63 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 22.1, 68.6, 116.4, 119.6, 121.3, 124.7, 125.6, 127.5, 128.0, 128.1, 129.5, 135.8, 136.6, 137.6, 139.1, 140.7, 142.4, 148.7, 153.1, 159.4 ppm; mp 65-68 ºC; IR v_{max} (neat/cm^{-1}): 3311, 3059, 2979, 2934, 1724, 1704, 1590, 1550, 1222, 1112; HRMS calcd for $C_{22}H_{23}O_2N_2$ $[M+H]^+$: 347.1754, found 347.1762.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Diazoxide **X6** (46.1 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) for 48 hours. Column chromatography (acetone/EtOAc, 2:8) afforded **A6** as a white solid (66.1 mg, 91%).

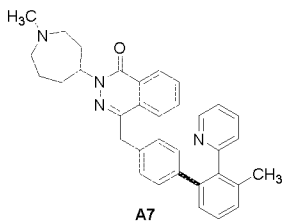


A6

^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 3 H), 2.25 (s, 3 H), 7.03-7.11 (m, 2 H), 7.24 (dd, *J* = 6.8, 5.2 Hz, 1 H), 7.26-7.32 (m, 2 H), 7.32-7.36 (m, 1 H), 7.38 (d, *J* = 7.4 Hz, 1 H), 7.44 (d, *J* = 7.4 Hz, 1 H), 7.66 (td, *J* = 7.6, 1.6 Hz, 1 H), 8.57 (d, *J* = 4.8 Hz, 1 H), 11.96 (s, 1 H) ppm; ^{13}C-NMR (125 MHz, DMSO-d_6) δ 20.1, 22.5, 116.7, 120.6, 122.0, 123.5, 125.3, 127.2, 128.3,

129.7, 133.5, 133.7, 136.4 (2 × C), 138.5, 138.9, 139.3, 149.0, 157.1, 158.0 ppm; mp > 250 ºC; IR ν_{max} (neat/cm^{-1}): 3534, 3270, 3170, 2924, 2853, 1698, 1625, 1583, 1520, 1498, 1461, 1301, 1161; HRMS calcd for $C_{20}H_{17}O_2N_3NaS$ $[M+Na]^+$: 386.0920, found 386.0921.

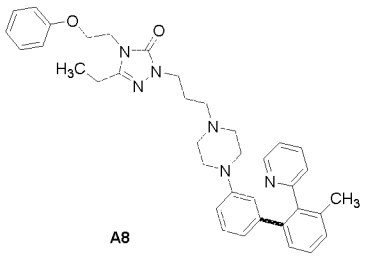
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Azelastine • HCl **X7** (83.7 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) for 72 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A7** as a light brown solid (92.6 mg, 90%).



A7

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.72-1.87 (m, 1 H), 1.93-2.21 (m, 7 H), 2.21-2.34 (m, 1 H), 2.42 (s, 3 H), 2.57-2.70 (m, 2 H), 2.71-2.81 (m, 1 H), 2.82-2.91 (m, 1 H), 4.20 (s, 2 H), 5.30-5.41 (m, 1 H), 6.83 (d, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 7.01-7.09 (m, 3 H), 7.22 (d, *J* = 7.6 Hz, 1 H), 7.26-7.30 (m, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.38 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.58-7.73 (m, 3 H), 8.44-8.47 (m, 1 H), 8.57-8.62 (m, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 24.7, 32.2, 33.2, 38.8, 47.0, 54.5, 56.1, 58.9, 121.2, 124.8, 125.6, 127.4, 127.4, 127.7, 128.0, 128.2, 128.7, 129.4, 129.9, 130.9, 132.5, 135.6, 135.9, 136.7, 139.3, 140.0, 140.8, 144.9, 148.8, 158.4, 159.5 ppm; mp 60-63 ºC; IR ν_{max} (neat/cm^{-1}): 3060, 2926, 2852, 2793, 1650, 1585, 1460, 1322; HRMS calcd for $C_{34}H_{34}ON_4Na$ $[M+Na]^+$: 537.2625, found 537.2618.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Nefazodone **X8** (94.0 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A8** as a light brown solid (110.9 mg, 92%).



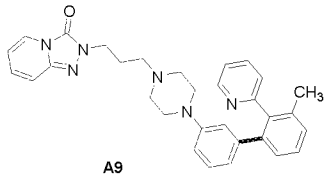
A8

The General Procedure D was applied was applied with encapsulated **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), (33.9 mg, 0.20 mmol, 1 equiv.), Nefazodone **X8** (94.0 mg, 0.20 mmol, 1 equiv.), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) in NMP (300 µL) and toluene (500 µL). Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A8** as a light brown solid (78.4 mg, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.4 Hz, 3 H), 1.97 (quint, *J* = 7.2 Hz, 2 H), 2.18 (s, 3 H), 2.48 (t, *J* = 7.4 Hz, 2 H), 2.49-2.57 (m, 4 H), 2.70 (q, *J* = 7.4 Hz, 2 H), 2.90-3.02 (m, 4 H), 3.82 (t, *J* = 7.0 Hz, 2 H), 4.01 (t, *J* = 5.0 Hz, 2 H), 4.19 (t, *J* = 5.0 Hz, 2 H), 6.53-6.57 (m, 1 H), 6.63-3.71 (m, 2 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 6.96 (t, *J* = 7.4 Hz, 1 H), 7.04-7.13 (m, 2 H), 7.23-7.32 (m, 4 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.45 (td, *J* = 7.6, 1.6 Hz, 1 H), 8.63 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.1, 19.1, 20.2, 25.9, 41.2, 43.3,

48.7, 52.9, 55.4, 65.3, 114.0, 114.2, 118.0, 121.0, 121.2, 121.3, 125.6, 127.4, 128.0, 128.4, 129.3, 129.6, 135.9, 136.7, 139.2, 141.5, 142.3, 147.9, 148.6, 150.2, 153.7, 158.0, 159.8 ppm; mp 57-60 ºC; IR ν_{max} (neat/cm^{-1}): 2943, 2879, 2820, 1699, 1599, 1574, 1465, 1455, 1241; HRMS calcd for $C_{37}H_{43}O_2N_6$ $[M+H]^+$: 603.3442, found 603.3440.

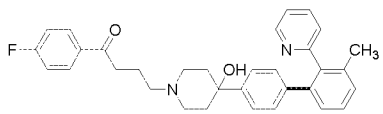
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Trazodone • HCl **X9** (81.7 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) at 50 ºC. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A9** as an off-white solid (93.9 mg, 93%).



A9

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.07 (quint, *J* = 7.2 Hz, 2 H), 2.17 (s, 3 H), 2.42-2.56 (m, 6 H), 2.87-2.99 (m, 4 H), 4.08 (t, *J* = 7.2 Hz, 2 H), 6.44-6.51 (m, 1 H), 6.54 (s, 1 H), 6.62-6.70 (m, 2 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.02-7.13 (m, 4 H), 7.24-7.31 (m, 2 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.44 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.75 (d, *J* = 7.2 Hz, 1 H), 8.62 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 26.0, 44.3, 48.8, 53.0, 55.5, 110.5, 113.9, 115.3, 118.0, 120.8, 121.2, 123.6, 125.5, 127.4, 127.9, 128.3, 129.2, 129.7, 135.8, 136.6, 139.1, 141.4, 141.5, 142.2, 148.5, 148.6, 150.2, 159.8 ppm; mp 60-62 ºC; IR ν_{max} (neat/cm^{-1}): 2947, 2820, 1705, 1639,1593, 1542, 1455, 1225; HRMS calcd for $C_{31}H_{33}ON_6$ $[M+H]^+$: 505.2710, found 505.2705.

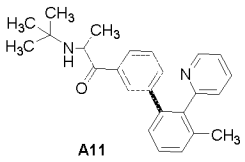
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Haloperidol **X10** (75.2 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A10** as a white solid (93.6 mg, 92%).



A10

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.69 (d, *J* = 13.5 Hz, 2 H), 2.04-2.18 (m, 5 H), 2.19-2.37 (m, 2 H), 2.62-2.89 (m, 4 H), 2.90-3.15 (m, 4 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 7.00 (d, *J* = 7.5 Hz, 2 H), 7.08-7.17 (m, 3 H), 7.18-7.25 (m, 3 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.94-8.08 (m, 2 H), 8.54 (d, *J* = 4.0 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4, 35.9, 36.7, 49.1, 57.2, 65.8, 70.0, 115.7 (d, *J* = 22.5 Hz), 121.5, 123.8, 125.6, 127.6, 128.1, 129.4, 129.5, 130.6 (d, *J* = 10.0 Hz), 133.2, 135.9, 136.8, 139.1, 140.4, 140.6, 145.1, 148.7, 159.3, 165.7 (d, *J* = 252.5 Hz), 197.6 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ −105.0 ppm; mp 140-143 ºC; IR ν_{max} (neat/cm^{-1}): 3333, 3062, 2943, 2820, 1683, 1596, 1460, 1231; HRMS calcd for $C_{33}H_{34}O_2N_2F$ $[M+H]^+$: 509.2599, found 509.2598.

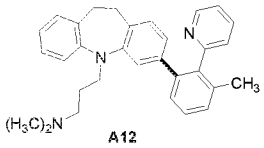
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Bupropion • HCl **X11** (55.2 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) at 50 ºC. Column chromatography (Et_2O/acetone, 9:1) afforded **A11** as an off-white wax (61.8 mg, 83%).



A11

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9 H), 1.22-1.34 (m, 3 H), 2.19 (s, 3 H), 4.12-4.26 (m, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 7.06-7.16 (m, 1 H), 7.28-7.35 (m, 1 H), 7.35-7.45 (m, 3 H), 7.45-7.55 (m, 2 H), 7.57 (s, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 8.66 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4, 21.5, 28.7, 52.3, 68.1, 121.7, 125.6, 126.6, 127.6, 128.4, 128.8, 129.7, 130.2, 133.4, 134.9, 136.1, 137.1, 139.2, 139.7, 142.4, 149.2, 159.2, 196.5 ppm; IR v_{max} (neat/cm^{-1}): 3058, 2962, 2925, 2857, 1683, 1585, 1458, 1231, 1206; HRMS calcd for $C_{25}H_{28}ON_2Na$ $[M+Na]^+$: 395.2094, found 395.2084.

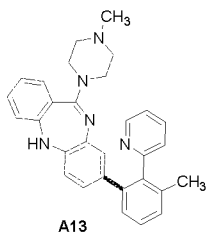
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Clomipramine • HCl **X12** (70.3 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.). Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A12** as a white solid (86.8 mg, 97%).



A12

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.63-1.82 (m, 2 H), 2.16 (s, 3 H), 2.38 (s, 6 H), 2.55-2.68 (m, 2 H), 2.98-3.13 (m, 4 H), 3.43 (bs, 2 H), 6.69 (s, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.85-6.98 (m, 4H), 7.04-7.15 (m, 2 H), 7.15-7.22 (m, 1 H), 7.22-7.31 (m, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 8.69 (d, *J* = 4.5 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4, 23.7, 31.8, 31.9, 43.8, 47.5, 56.7, 119.8, 121.5, 121.6, 123.0, 123.7, 125.5, 126.5, 127.5, 128.1, 129.3, 129.6, 129.6, 131.3, 134.7, 136.1, 136.8, 139.0, 139.8, 140.6, 146.9, 147.5, 148.9, 159.9 ppm; mp 49-51 ºC; IR v_{max} (neat/cm^{-1}): 2921, 2855, 2765, 1593, 1584, 1490, 1460, 1404; HRMS calcd for $C_{31}H_{34}N_3$ $[M+H]^+$: 448.2747, found 448.2753.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Clozapine **X13** (65.4 mg, 0.20 mmol, 1 equiv.) and (55.3 mg, 0.4 mmol, 2 equiv.) for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A13** as a yellow solid (88.2 mg, 96%).

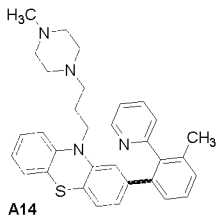


A13

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3 H), 2.38 (s, 3 H), 2.56 (bs, 4 H), 3.39-355 (m, 4 H), 4.86 (s, 1 H), 6.33 (d, *J* = 8.0 Hz, 1 H), 6.36 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 6.98 (td, *J* = 7.5, 0.8 Hz, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 7.07 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.20-7.32 (m, 5 H), 7.42 (td, *J* = 7.6, 2.0 Hz, 1 H), 8.63 (d, *J* = 5.2 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.5, 45.9, 47.1, 54.8, 118.3, 119.9, 121.1, 122.6,

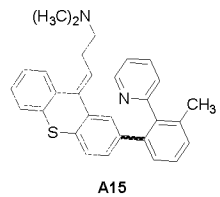
123.3, 125.7, 125.7, 127.6, 127.8, 128.3, 129.0, 130.3, 131.7, 135.8, 136.6, 137.7, 139.1, 139.8, 140.0, 140.6, 148.6, 153.1, 159.8, 162.3 ppm; mp 140-144 ºC; IR ν_{max} (neat/cm^{-1}): 3265, 2936, 2847, 2795, 1601, 1566, 1456, 1377, 1287, 1232; HRMS calcd for $C_{30}H_{30}N_5$ $[M+H]^+$: 460.2496, found 460.2490.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Prochlorperazine • 2HCl **X14** (89.4 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (110.6 mg, 0.8 mmol, 4 equiv.) at 50 ºC for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A14** as a light brown solid (86.1 mg, 85%).


A14

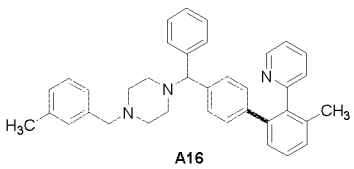
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.77 (quint, *J* = 6.8 Hz, 2 H), 2.17 (s, 3 H), 2.26-2.88 (m, 13 H), 3.57-3.72 (m, 2 H), 6.56 (s, 1 H), 6.71 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.85-6.97 (m, 3 H), 7.05-7.18 (m, 3 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.50 (td, *J* = 7.4, 2.0 Hz, 1 H), 8.66 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.5, 24.1, 45.0, 45.5, 52.6, 54.6, 55.4, 115.5, 117.3, 121.4, 122.3, 123.0, 123.7, 124.9, 125.5, 126.7, 127.1, 127.3, 127.4, 128.1, 129.5, 136.1, 136.9, 139.0, 140.7, 140.9, 144.5, 144.8, 148.8, 159.6 ppm; mp 75-78 ºC; IR ν_{max} (neat/cm^{-1}): 3056, 2932, 2795, 1584, 1456; HRMS calcd for $C_{32}H_{35}N_4S$ $[M+H]^+$: 507.2577, found 507.2588.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Chlorprothixene • HCl **X15** (70.5 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A15** as an off-white solid (80.8 mg, 90%). After purification, **A15** must be stored under inert atmosphere at low temperature to prevent olefin isomerization.


A15

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 2.29 (s, 6 H), 2.46-2.58 (m, 4 H), 5.86 (t, *J* = 6.8 Hz, 1 H), 6.88 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.93 (d, *J* = 7.5 Hz, 1 H), 7.09 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1 H), 7.16-7.21 (m, 2 H), 7.21-7.27 (m, 3 H), 7.28-7.33 (m, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.43-7.48 (m, 2 H), 8.62 (d, *J* = 5.0 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.5, 27.3, 44.9, 59.0, 121.5, 125.6, 125.7, 125.8, 126.0, 126.8, 126.9, 127.7, 128.2, 128.6, 129.1, 129.5, 129.7, 131.6, 131.7, 133.1, 136.1, 136.6, 136.9, 138.3, 139.2, 139.6, 140.3, 149.0, 159.4 ppm; mp 77-80 ºC; IR ν_{max} (neat/cm^{-1}): 3058, 2969, 2940, 2856, 2815, 2768, 1584, 1563, 1456, 1439; HRMS calcd for $C_{30}H_{28}N_2NaS$ $[M+Na]^+$: 471.1865, found 471.1855.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Meclizine • 2HCl **X16** (92.8 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (110.6 mg, 0.8 mmol, 4 equiv.) at 50 ºC.

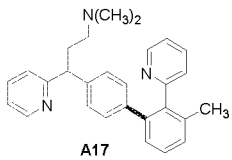


A16

Column chromatography (hexane/Et_2O, 1:1) afforded **A16** as a white solid (94.3 mg, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3 H), 2.22-2.55 (m, 11 H), 3.42 (d, *J* = 13.4 Hz, 1 H), 3.46 (d, *J* = 13.4 Hz, 1 H), 4.13 (s, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.96-7.16 (m, 8 H), 7.17, 7.26 (m, 5 H), 7.26-7.31 (m, 3 H), 8.55 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 21.3, 51.6, 53.3, 63.0, 75.5, 121.1, 125.7, 126.3, 126.7, 127.2, 127.3, 127.7, 127.9, 128.0, 128.0, 128.2, 129.3, 129.6, 129.9, 135.3, 136.5, 137.7, 137.9, 139.3, 140.2, 140.4, 141.1, 142.5, 148.6, 159.5 ppm; mp 167-169 ºC; IR ν_{max} (neat/cm^{-1}): 2956, 2806, 1585, 1453, 1136, 1007; HRMS calcd for $C_{37}H_{38}ON_3$ $[M+H]^+$: 524.3052, found 524.3051.

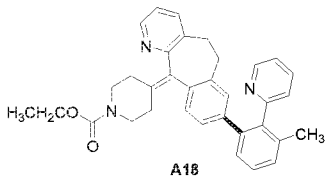
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (67.7 mg, 0.40 mmol, 2 equiv.), Chlorpheniramine • 2HCl **X17** (69.5 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (110.6 mg, 0.8 mmol, 4 equiv.) at 50 ºC for 72 hours. Column chromatography (CH_2Cl_2/MeOH, from 95:5 to 85:15) afforded **A17** as a light brown wax (66.0 mg, 81%).



A17

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 2.18-2.28 (m, 1 H), 2.29-2.40 (m, 8 H), 2.42-2.54 (m, 1 H), 4.04 (t, *J* = 7.6 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.98 (d, *J* = 7.6 Hz, 2 H), 7.04-7.11 (m, 5 H), 7.23 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.25-7.29 (m, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.41 (td, *J* = 7.6, 1.8 Hz, 1 H), 7.54 (td, *J* = 7.6, 1.8 Hz, 1 H), 8.53 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 8.60 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 31.4, 44.5, 50.5, 57.3, 121.2, 121.4, 123.0, 125.6, 127.1, 127.4, 127.9, 129.3, 129.8, 135.6, 136.4, 136.6, 139.3, 139.9, 140.8, 140.9, 148.7, 149.1, 159.5, 162.8 ppm; IR ν_{max} (neat/cm^{-1}): 3419, 3058, 2927, 2855, 2768, 1587, 1461, 1432; HRMS calcd for $C_{28}H_{30}ON_3$ $[M+H]^+$: 408.2434, found 408.2423.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (101.5 mg, 0.60 mmol, 3 equiv.) Loratadine **X18** (76.6 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 ºC for 72 hours. Column chromatography (hexane/EtOAc, 4:6) afforded **A18** as a white solid (57.8 mg, 56%).

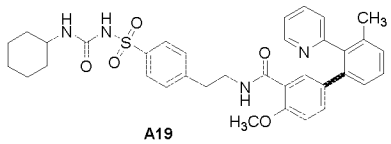


A18

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 2.19 (s, 3 H), 2.21-2.36 (m, 3 H), 2.39-2.50 (m, 1 H), 2.54-2.75 (m, 2 H), 3.05-3.18 (m, 2 H), 3.19-3.31 (m, 2 H), 3.69-3.86 (m, 2 H),

4.14 (q, *J* = 7.2 Hz, 2 H), 6.82-6.90 (m, 3 H), 6.94 (d, *J* = 7.6 Hz, 1 H), 7.05-7.12 (m, 2 H), 7.24-7.31 (m, 2 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 7.37-7.44 (m, 2 H), 8.39 (d, *J* = 4.4 Hz, 1 H), 8.61 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.7, 20.5, 30.5, 30.7, 31.7, 31.8, 44.8, 61.3, 121.2, 122.0, 125.7, 127.1, 127.3, 128.0, 128.6, 129.4, 130.4, 133.8, 135.0, 135.6, 136.7, 136.8, 136.9, 136.9, 137.3, 139.3, 140.6, 140.8, 146.4, 148.7, 155.5, 157.5, 159.6 ppm; mp 93-95 ºC; IR ν_{max} (neat/cm^{-1}): 3057, 2978, 2922, 2856, 1694, 1436, 1228; HRMS calcd for $C_{34}H_{34}O_2N_3$ $[M+H]^+$: 516.2646, found 516.2638.

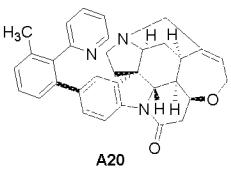
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Glyburide **X19** (98.8 mg, 0.20 mmol, 1 equiv.), KOBz (9.6 mg, 0.06 mmol, 0.3 equiv.) in replacement of KOAc, K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) and NMP (0.4 mL, 0.5 M) at 50 ºC for 72 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 97:3) afforded **A19** as a light brown solid (97.8 mg, 78%).



A19

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96-1.29 (m, 5 H), 1.41-1.61 (m, 3 H), 1.65-1.78 (m, 2 H), 2.06 (s, 3 H), 2.91 (t, *J* = 7.0 Hz, 2 H), 3.40-3.53 (m, 1 H), 3.55-3.68 (m, 5 H), 6.34 (d, *J* = 7.6 Hz, 1 H), 6.54 (d, *J* = 8.5 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.91 (dd, *J* = 8.5, 2.1 Hz, 1 H), 7.03 (dd, *J* = 7.2, 5.2 Hz, 1 H), 7.13-7.21 (m, 3 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.70-7.80 (m, 3 H), 7.97 (d, *J* = 2.1 Hz, 1 H), 8.54 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4, 24.5, 25.3, 32.9, 35.6, 40.5, 49.1, 55.8, 110.6, 120.4, 121.4, 125.8, 127.3, 127.7, 128.2, 129.5, 129.7, 132.8, 134.3, 134.8, 136.1, 136.7, 137.9, 139.1, 139.7, 145.9, 148.8, 150.5, 156.0, 159.4, 165.4 ppm; mp 140-144 ºC; IR ν_{max} (neat/cm^{-1}): 3367, 3061, 2929, 2854, 1709, 1631, 1537, 1459, 1161; HRMS calcd for $C_{35}H_{37}O_5N_4S$ $[M-H]^-$: 625.2490, found 625.2493.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Br-Strychnine **X20** (82.7 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 97:3 to 92:8) afforded **A20** as a light brown solid (91.3 mg, 91%).

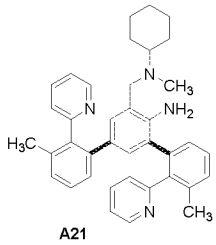


A20

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.10-1.34 (m, 3 H), 1.47-1.69 (m, 1 H), 1.71-1.84 (m, 1 H), 2.13 (s, 3 H), 2.29 (d, *J* = 13.6 Hz, 1 H), 2.61 (dd, *J* = 17.6, 2.4 Hz, 1 H), 2.79-2.99 (m, 1 H), 3.09 (dd, *J* = 17.6, 8.3 Hz, 1 H), 3.15 (bs, 1 H), 3.26-3.51 (m, 1 H), 3.61-3.91 (m, 3 H), 4.02 (dd, *J* = 13.8, 5.8 Hz, 1 H), 4.14 (dd, *J* = 13.8, 7.0 Hz, 1 H), 4.24 (dt, J = 8.3, 3.5 Hz, 1 H), 5.95-610 (m, 1 H), 6.70 (s, 1 H), 6.85-8.97 (m, 1 H), 7.03-7.13 (m, 1 H), 7.17 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.20-7.29 (m, 2 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 8.59-8.70 (m, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 26.1, 41.7, 42.2, 47.6, 50.2, 51.5, 52.3,

59.8, 60.2, 64.3, 77.2, 77.3, 115.6, 121.1, 123.8, 125.6, 127.3, 128.1, 129.3, 130.2, 130.2, 130.3, 135.8, 136.7, 137.8, 139.2, 140.1, 140.3, 149.1, 159.6, 168.9 ppm; mp > 250 ºC; IR ν_{max} (neat/cm^{-1}): 3426, 2926, 2862, 1670, 1492, 1462, 1383; HRMS calcd for $C_{33}H_{31}O_2N_3Na$ $[M+Na]^+$: 524.2308, found 524.2302.

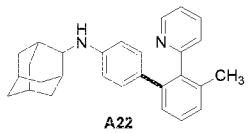
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (67.7 mg, 0.40 mmol, 2 equiv.), Bromhexine • HCl **X21** (82.5 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (110.6 mg, 0.8 mmol, 4 equiv.) at 50 ºC for 72 hours. Column chromatography (EtOAc) afforded **A21** as a light brown solid (76.3 mg, 69%).



A21

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01-1.20 (m, 4 H), 1.52-1.83 (m, 9 H), 2.09-2.23 (m, 7 H), 2.99 (d, *J* = 12.4 Hz, 1 H), 3.42-3.56 (m, 1 H), 4.53 (m, 2 H), 6.32 (d, *J* = 1.4 Hz, 1 H), 6.77 (d, *J* = 1.4 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 7.04-7.15 (m, 4 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 7.22-7.31 (m, 3 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.36-7.46 (m, 2 H), 8.55 (d, *J* = 4.4 Hz, 1 H), 8.64 (d, *J* = 4.8 Hz, 1 H), ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 20.5, 25.8, 25.9, 26.3, 28.0, 28.4, 36.0, 57.5, 61.9, 120.9, 121.1, 122.5, 125.2, 125.8, 126.7, 127.5, 127.8, 128.2, 128.3, 128.4, 129.6, 129.6, 130.5, 131.0, 135.0, 135.3, 136.5, 136.8, 138.2, 138.8, 140.1, 141.2, 143.1, 148.5, 148.6, 159.2, 160.4 ppm; mp 93-96 ºC; IR ν_{max} (neat/cm^{-1}): 3435, 3267, 3061, 2927, 2853, 2791, 1615, 1585, 1453; HRMS calcd for $C_{38}H_{41}N_4$ $[M+H]^+$: 553.3326, found 553.3313.

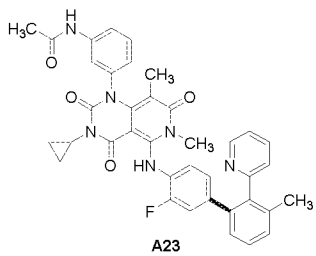
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (27.6 mg, 0.163 mmol, 1 equiv.), a grinded pill of Ladastan containing 50 mg of Bromantane (0.163 mmol, 1 equiv.), KOAc (4.8 mg, 0.049 mmol, 0.3 equiv.) and K_2CO_3 (45.1 mg, 0.326 mmol, 2 equiv.). The excipients contained in a pill of Ladasten are potato starch, magnesium stearate and microcrystalline cellulose in unknown amounts. Column chromatography (hexane/Et_2O, 7:3) afforded **A22** as a pale yellow solid (60.5 mg, 94%).



A22

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.54-1.62 (m, 2 H), 1.72-1.93 (m, 10 H), 1.97 (bs, 2 H), 2.16 (s, 3 H), 3.47 (bs, 1 H), 3.90 (bs, 1 H), 6.38 (d, *J* = 8.2 Hz, 2 H), 6.86 (d, *J* = 8.2 Hz, 2 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 7.09-7.15 (m, 1 H), 7.20-7.29 (m, 2 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.6, 27.3, 27.4, 31.6, 31.6, 37.4, 37.7, 56.7, 112.3, 121.1, 125.8, 127.6, 128.0, 128.5, 130.0, 130.6, 135.9, 136.6, 139.0, 141.3, 145.8, 148.7, 160.1 ppm; mp 220-224 ºC; IR ν_{max} (neat/cm^{-1}): 2905, 2851, 1610, 1521; HRMS calcd for $C_{28}H_{31}N_2$ $[M+H]^+$: 395.2482, found 395.2481.

The purity of Trametinib purchased from Generon was assessed to be 70% by quantitative ^{1}H-NMR with an internal standard. The impurity was not NMR-active. Trametinib was further purified by centrifuging the solid in H_2O and by removing the white particles which were not depositing at the bottom of the vial (×10 times). The purity was then assessed to be 84% by quantitative ^{1}H-NMR with an internal standard.

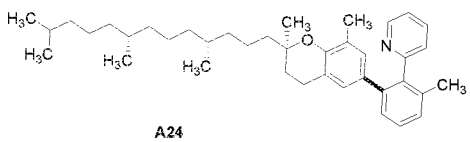


A23

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Trametinib **X23** (142.8 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (EtOAc) afforded **A23** as a white solid (110.3 mg, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.73-0.83 (m, 2 H), 1.05-1.16 (m, 2 H), 1.39 (s, 3 H), 2.13 (s, 3 H), 2.19 (s, 3 H), 2.67-2.79 (m, 1 H), 3.04 (s, 3 H), 6.75 (t, *J* = 8.2 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 6.87-7.02 (m, 3 H), 7.14-7.22 (m, 1 H), 7.22-7.31 (m, 3 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.62-7.75 (m, 2 H), 8.64 (d, *J* = 4.8 Hz, 1 H), 11.31 (s, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 8.4, 13.3, 20.4, 24.5, 25.2, 34.4, 89.3, 102.9, 117.5 (d, *J* = 19.9 Hz), 118.9, 120.3, 121.8, 123.6, 124.2, 125.5, 125.8 (d, *J* = 11.8 Hz), 126.0 (d, *J* = 3.3 Hz), 127.2, 128.3, 129.1, 130.1, 136.0, 137.0, 138.8, 139.0, 139.2, 140.3, 141.1 (d, *J* = 7.3 Hz), 144.9, 149.1, 151.8, 152.6, 154.9 (d, *J* = 247.0 Hz), 159.0, 163.0, 164.8, 168.4 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ –124.8 ppm; mp 236-240 ºC; IR ν_{max} (neat/cm^{-1}): 3311, 2924, 2855, 1630, 1605, 1551, 1422; HRMS calcd for $C_{38}H_{34}O_4N_6F$ $[M+H]^+$: 657.2620, found 657.2607.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), δ-Tocopherol-OTf **X24** (106.9 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (Et_2O/hexane, 1:9) afforded **A24** as a colourless oil (99.7 mg, 90%).



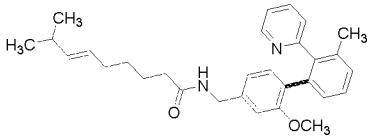
A24

The General Procedure D was applied was applied with encapsulated **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), δ-Tocopherol-OTf **X24** (106.9 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) in NMP (300 µL) and toluene (500 µL). Column chromatography (Et_2O/hexane, 1:9) afforded **A24** as a colourless oil (68.7 mg, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80-0.91 (m, 12 H), 0.96-1.59 (m, 24 H), 1.60-1.76 (m, 2 H), 2.00 (s, 3 H), 2.17 (s, 3 H), 2.45-2.58 (m, 2 H), 6.55 (d, *J* = 1.4 Hz, 1 H), 6.67 (d, *J* = 1.4 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 7.08 (ddd, *J* = 7.6, 5.2, 0.8 Hz, 1 H), 7.22 (d, *J* = 7.4 Hz, 1 H),

7.26 (d, *J* = 7.4 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 1 H), 7.45 (td, *J* = 7.6, 2.0 Hz, 1 H), 8.63 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.8, 19.6, 19.7, 20.5, 20.9, 22.1, 22.6, 22.7, 24.1, 24.4, 24.8, 28.0, 31.2, 32.7, 32.8, 37.3, 37.4 (×3), 39.3, 40.1, 75.9, 119.5, 121.0, 125.2, 125.7, 127.5, 127.9, 128.2, 128.6, 129.7, 132.0, 135.6, 136.5, 139.2, 141.3, 148.5, 150.6, 160.2 ppm; IR ν_{max} (neat/cm^{-1}): 2924, 2866, 1584, 1486, 1459, 1377, 1225, 1201, 1149, 1112; HRMS calcd for $C_{39}H_{55}ONNa$ [M+Na]$^+$: 576.4176, found 576.4176.

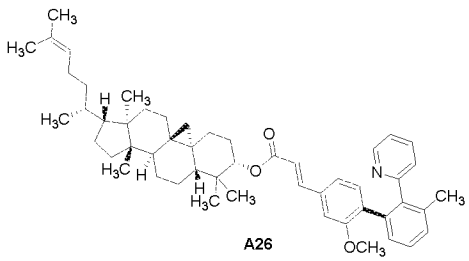
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Capsaicin-OTf **X25** (87.5 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) for 72 hours. Column chromatography (Et_2O) afforded **A25** as a pale yellow wax (64.8 mg, 71%).



A25

NMR analysis shows the product as a mixture of two amide isomers: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.81-1.00 (m, 6 H), 1.09-1.55 (m, 5 H), 1.59-1.72 (m, 2 H), 1.95-2.05 (m, 1 H), 2.14-2.27 (m, 5 H), 3.52 (bs, 3 H), 4.35 (d, *J* = 5.2 Hz, 2 H), 5.25-5.43 (m, 1 H), 5.66-5.78 (m, 1 H), 6.59 (s, 1 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 6.91-7.01 (m, 2 H), 7.04 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1 H), 7.18 (d, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 7.2 Hz, 1 H), 7.33 (t, *J* = 7.2 Hz, 1 H), 7.44 (td, *J* = 7.6, 1.1 Hz, 1 H), 8.52 (d, *J* = 4.7 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.6, 22.6, 22.7, 25.3, 25.8, 27.2, 28.0, 29.3, 29.4, 29.6, 31.0, 32.2, 36.7, 36.9, 39.0, 43.5, 55.1, 109.7, 119.1, 121.2, 125.0, 126.5, 127.7, 128.2, 129.6, 129.7, 131.9, 135.3, 136.3, 137.5, 138.1, 138.7, 139.9, 148.4, 156.4, 159.4, 172.9, 173.0 ppm; IR ν_{max} (neat/cm^{-1}): 3081, 3064, 2954, 2924, 2954, 1647, 1461; HRMS calcd for $C_{30}H_{36}O_2N_2Na$ [M+Na]$^+$: 479.2669, found 479.2663.

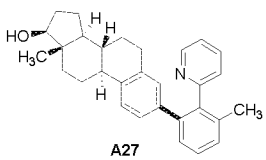
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), γ-Oryzanol-OTf **X26** (147.0 mg, 0.20 mmol, 1 equiv.), KOBz (9.6 mg, 0.06 mmol, 0.3 equiv.) in replacement of KOAc, K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) and NMP (0.4 mL, 0.5 M) at 50 ºC for 72 hours. Column chromatography (Et_2O/hexane, 4:6) afforded **A26** as a white solid (126.7 mg, 84%).



A26

The product **A26** was obtained as a mixture of isomers (^{1}H-NMR ratio 79:21) matching the isomer ratio of **X26**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.37 (d, *J* = 4.2 Hz, 1 H), 0.61 (d, *J* = 4.2 Hz, 1 H), 0.74-2.41 (m, 48 H), 3.58 (s, 3 H), 4.65-4.77 (m, 2 H), 6.31-6.42 (m, 1 H), 6.79-6.85 (m, 1 H), 6.92-7.00 (m, 2 H), 7.01-7.08 (m, 2 H), 7.21 (d, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 6.8 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.42 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.57 (d, *J* = 16.0 Hz, 1 H), 8.56 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR chemical shifts of the major isomer: ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.3, 18.0, 18.3, 19.3, 20.1, 20.5, 20.9, 21.9, 22.0, 25.5, 25.8, 26.0, 26.5, 26.9, 28.1, 31.3,

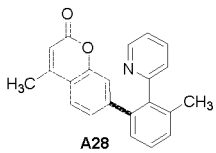
31.6, 32.8, 33.8, 35.0, 35.5, 36.1, 39.7, 45.3, 47.2, 47.8, 48.8, 52.2, 55.1, 80.7, 105.9, 109.1, 118.5, 120.4, 121.1, 124.8, 127.7, 127.9, 129.8, 132.1, 132.9, 134.6, 135.1, 136.3, 137.2, 139.9, 144.1, 148.5, 156.4, 156.8, 159.2, 166.7 ppm; mp 88-92 ºC; IR ν_{max} (neat/cm^{-1}): 2936, 2867, 1708, 1636, 1461, 1271, 1243, 1173; HRMS calcd for $C_{52}H_{67}O_3NNa$ $[M+Na]^+$: 776.5013, found 776.5509.



A27

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Estradiol-OTf **X27** (80.9 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (Et_2O/hexane, 7:3) afforded **A27** as a white solid (82.2 mg, 97%).

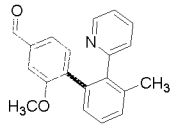
^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.76 (s, 3 H), 1.06-1.76 (m, 9 H), 1.78-1.86 (m, 1 H), 1.89-1.96 (m, 1 H), 2.03-2.21 (m, 5 H), 2.21-2.29 (m, 1 H), 2.60-2.77 (m, 2 H), 3.71 (t, J = 8.5 Hz, 1 H), 6.78-6.85 (m, 2 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.09-7.14 (m, 1 H), 7.24-7.30 (m, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 8.65 (d, *J* = 4.5 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.0, 20.5, 23.1, 25.9, 27.2, 29.3, 30.6, 36.7, 38.5, 43.2, 44.2, 50.2, 81.8, 121.2, 124.5, 125.6, 126.8, 127.6, 128.0, 129.1, 130.3, 135.8, 135.8, 136.7, 138.2, 138.7, 139.2, 141.0, 148.7, 159.8 ppm; mp decomposes above 200 ºC; IR ν_{max} (neat/cm^{-1}): 3327, 2927, 2868, 1594, 1462, 1424, 1055, 909; HRMS calcd for $C_{30}H_{33}ONNa$ $[M+Na]^+$: 446.2454, found 446.2450.



A28

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Hymechromone-OTf **X28** (61.7 mg, 0.20 mmol, 1 equiv.), KOBz (9.6 mg, 0.06 mmol, 0.3 equiv.) in replacement of KOAc, and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 ºC for 48 hours. Column chromatography (Et_2O/hexane, 1:1) afforded **A28** as an off-white solid (60.2 mg, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 2.37 (s, 3 H), 6.22 (s, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 7.01 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.09 (d, *J* = 1.6 Hz, 1 H), 7.12-7.17 (m, 1 H), 7.24-7.31 (m, 1 H), 7.32-7.44 (m, 3 H), 7.52 (td, *J* = 7.6, 1.6 Hz, 1 H), 8.63 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.5, 20.4, 114.6, 117.8, 118.1, 121.7, 123.6, 125.5, 125.9, 127.5, 128.3, 130.3, 136.1, 137.1, 139.2, 139.3, 145.8, 149.1, 152.2, 153.0, 158.8, 161.0 ppm; mp 70-72 ºC; IR ν_{max} (neat/cm^{-1}): 3061, 2922, 1716, 1614, 1387, 1162; HRMS calcd for $C_{22}H_{18}O_2N$ $[M+H]^+$: 328.1332, found 328.1328.



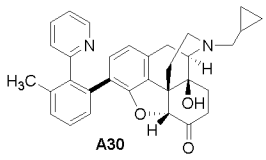
A29

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (101.5 mg, 0.60 mmol, 3 equiv.), Vanillin-OTf **X29**

(56.8 mg, 0.20 mmol, 1 equiv.), KOBz (9.6 mg, 0.06 mmol, 0.3 equiv.) in replacement of KOAc, and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 ºC for 72 hours. Column chromatography (Et_2O/hexane, 1:1) afforded **A29** as an off-white wax (37.6 mg, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 3.62 (s, 3 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 7.04 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.18-7.25 m, 3 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.32-7.35 (m, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.43 (d, *J* = 7.6, 1.6 Hz, 1 H), 8.53 (d, *J* = 4.4 Hz, 1 H), 9.89 (s, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.5, 55.3, 108.4, 121.3, 123.8, 124.8, 127.6, 127.8, 130.2, 132.3, 135.2, 136.4, 136.5, 136.8, 137.7, 139.8, 148.6, 156.9, 159.0, 191.9 ppm; IR ν_{max} (neat/cm^{-1}): 3060, 3002, 2928, 2850, 2732, 1689, 1548, 1460, 1412, 1387, 1266, 1154, 1034; HRMS calcd for $C_{20}H_{18}O_2N$ $[M+H]^+$: 304.1332, found 304.1321.

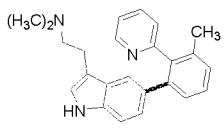
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Naltrexone-OTf **X30** (94.7 mg, 0.20 mmol, 1 equiv.) and (55.3 mg, 0.4 mmol, 2 equiv.) for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **A30** as a pale yellow wax (70.0 mg, 71%).



A30

^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.17 (bs, 2 H), 0.58 (d, *J* = 7.5 Hz, 2 H), 0.79-0.99 (m, 2 H), 1.27-1.43 (m, 2 H), 1.50-1.65 (m, 1 H), 1.82-1.97 (m, 1 H), 1.98-2.10 (m, 1 H), 2.17 (s, 3 H), 2.29 (dt, *J* = 14.5, 3.0 Hz, 1 H), 2.35-2.51 (m, 2 H), 2.52-2.64 (m, 1 H), 2.64-2.80 (m, 1 H), 2.93-3.049 (m, 2 H), 3.12-3.35 (m, 1 H), 4.62 (s, 1 H), 6.38 (d, *J* = 7.8 Hz, 1 H), 6.59 (d, *J* = 7.8 Hz, 1 H), 6.99-7.07 (m, 2 H), 7.27 (d, *J* = 7.0 Hz, 1 H), 7.32-7.48 (m, 3 H), 8.56 (d, *J* = 4.0 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 3.8, 4.1, 9.2, 20.4, 23.2, 30.6, 31.6, 36.1, 43.6, 50.3, 59.1, 61.8, 70.2, 89.7, 118.1, 121.1, 122.6, 125.7, 127.3, 127.8, 128.0, 129.7, 131.5, 135.4, 135.5, 136.5, 139.7, 148.4, 154.6, 159.6, 208.3 ppm; IR ν_{max} (neat/cm^{-1}): 3390, 3060, 3001, 2925, 2850, 1726, 1585, 1461, 1426, 1407; HRMS calcd for $C_{32}H_{32}O_3N_2Na$ $[M+Na]^+$: 515.2305, found 515.2294. ∞

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Bufotenin-OTf **X31** (67.3 mg, 0.20 mmol, 1 equiv., for its preparation see: *J. Med. Chem.* **1996**, *39*, 4717–4726), and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) for 72 hours. Column chromatography (CH_2Cl_2/MeOH, from 9:1 to 8:2) afforded **A31** as a white solid (55.5 mg, 78%).

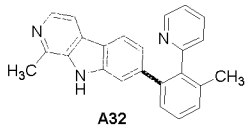


A31

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 2.35 (s, 6 H), 2.50-2.59 (m, 2 H), 2.76-2.85 (m, 2 H), 6.82-6.92 (m, 2 H), 6.94 (dd, *J* = 8.4 Hz, 1 H), 7.04 (ddd, *J* = 7.4, 5.0, 1.2 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 7.24-7.32 (m, 2 H), 7.33-7.41 (m, 3 H), 8.33 (bs, 1 H), 8.65 (d, *J* = 4.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.6, 23.2, 45.2, 59.8, 110.3, 113.9, 120.0, 121.1,

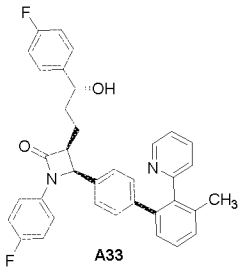
121.9, 124.1, 125.7, 126.9, 127.9, 128.2, 128.7, 132.6, 134.9, 135.8, 136.6, 139.4, 142.2, 148.6, 160.2 ppm; mp 128-131 ºC; IR v_{max} (neat/cm^{-1}): 3142, 3043, 2924, 2855, 2820, 2777, 1592, 1456; HRMS calcd for $C_{24}H_{25}N_3Na$ [M+Na]$^+$: 378.1941, found 378.1932.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Harmol-OTf **X32** (66.1 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 ºC for 48 hours. Column chromatography (EtOAc) afforded **A32** as a pale yellow solid (48.9 mg, 70%).


A32

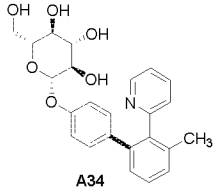
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3 H), 2.73 (s, 3 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 7.05-7.11 (m, 1 H), 7.21 (s, 1 H), 7.30-7.35 (m, 2 H), 7.36-7.44 (m, 2 H), 7.73 (d, *J* = 5.2 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 8.28 (d, *J* = 5.2 Hz, 1 H), 8.59 (d, *J* = 4.4 Hz, 1 H), 9.34 (bs, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.0, 20.5, 112.7, 112.8, 120.1, 120.8, 121.4, 122.4, 125.7, 127.9, 128.1, 128.2, 129.6, 134.9, 135.9, 136.7, 137.7, 139.3, 140.2, 141.4, 141.5, 142.2, 148.8, 159.5 ppm; mp 90-93 ºC; IR v_{max} (neat/cm^{-1}): 3147, 3062, 2956, 2924, 2854, 1629, 1593, 1567, 1446, 1421, 1325, 1260; HRMS calcd for $C_{24}H_{19}N_3Na$ [M+Na]$^+$: 372.1471, found 372.1466.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Ezetimibe-OTf **X33** (108.3 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (Et_2O/hexane, 8:2) afforded **A33** as a white solid (102.0 mg, 91%).


A33

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.76-2.05 (m, 4 H), 2.17 (s, 3 H), 2.87-3.07 (m, 2 H), 4.51 (d, *J* = 2.0 Hz, 1 H), 4.59-4.67 (m, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 7.02-7.10 (m, 5 H), 7.11-7.17 (m, 2 H), 7.21-7.32 (m, 4 H), 7.33-7.43 (m, 2 H), 8.55 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4, 25.1, 36.6, 60.1, 61.1, 72.8, 115.2 (d, *J* = 21.3 Hz), 115.6 (d, *J* = 22.5 Hz), 118.3 (d, *J* = 7.8 Hz), 121.4, 125.2, 125.6, 127.3, 127.3 (d, *J* = 7.9 Hz), 128.1, 129.7, 130.4, 133.8 (d, *J* = 2.6 Hz), 135.3, 135.7, 136.8, 139.1, 140.3 (d, *J* = 3.0 Hz), 140.4, 142.0, 148.7, 158.9 (d, *J* = 241.8 Hz), 159.2, 162.1 (d, *J* = 243.9 Hz), 167.4 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ −118.1, −115.0 ppm; mp 80-84 ºC; IR v_{max} (neat/cm^{-1}): 3353, 3059, 2924, 2856, 1741, 1508, 1385, 1219; HRMS calcd for $C_{36}H_{30}O_2N_2F_2Na$ [M+Na]$^+$: 583.2186, found 583.2157.

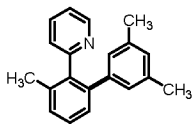
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), Arbutin-OTf **X34** (80.9 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2


A34

equiv.) for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 97:3 to 92:8) afforded **A34** as an off-white solid (74.5 mg, 88%).

^{1}H-NMR (400 MHz, acetone-d_6) δ 2.10 (s, 3 H), 3.36-3.53 (m, 4 H), 3.57-3.74 (m, 2 H), 3.80-3.90 (m, 1 H), 4.24 (d, *J* = 3.2 Hz, 1 H), 4.28-4.33 (m, 1 H), 4.53 (d, *J* = 3.6 Hz, 1 H), 4.89 (d, *J* = 7.6 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 1 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 7.19 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.58 (td, *J* = 7.6, 1.6 Hz, 1 H), 8.61 (d, *J* = 4.8 Hz, 1 H), ppm; ^{13}C-NMR (100 MHz, acetone-d_6) δ 20.6, 62.6, 71.3, 74.7, 77.7, 78.0, 101.7, 116.4, 122.3, 126.3, 128.3, 128.7, 129.7, 131.3, 136.4, 136.6, 137.5, 140.7, 141.5, 149.7, 157.4, 160.7 ppm; mp 85-88 ºC; IR ν_{max} (neat/cm^{-1}): 3358, 2923, 2854, 1511, 1460, 1231, 1072, 1045; HRMS calcd for $C_{24}H_{25}O_6NNa$ [M+Na]$^+$: 446.1574, found 446.1568.

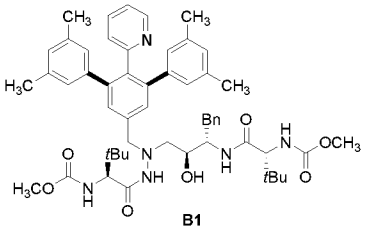
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (29.0 µL, 0.2 mmol, 1 equiv.), and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/Et_2O, 9:1) afforded **A36** as a white solid (53.0 mg, 97%).



A36

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 6 H), 2.21 (s, 3 H), 6.73 (s, 2 H), 6, 78 (s, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 7.10 (dd, *J* = 7.5, 5.1 Hz, 1 H), 7.25-7.32 (m, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 8.66 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 21.1, 121.1, 125.5, 127.4, 127.5, 127.7, 127.9, 129.1, 135.6, 136.5, 136.8, 139.2, 141.3, 141.3, 148.6, 159.7 ppm; mp 58-60 ºC; IR ν_{max} (neat/cm^{-1}): 3013, 2912, 2868, 1600, 1460, 1024, 792, 748, 704; HRMS calcd for $C_{20}H_{20}N$ [M+H]$^+$: 274.1596, found 274.1583.

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.



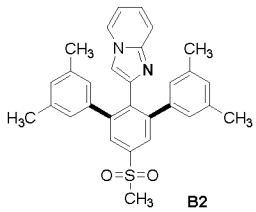
B1

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Atazanavir **N1** (152.3 mg, 0.20 mmol, 1 equiv.), 5-bromo-*m*-xylene **X37** (54.5 µL, 0.4 mmol, 2 equiv.), K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) and NMP (0.4 mL, 0.5 M) for 72 hours. Column chromatography (EtOAc/hexane, 6:4) afforded **B1** as an off-white solid (146.1 mg, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 9 H), 0.86 (s, 9 H), 2.14 (s, 12 H), 2.63 (dd, *J* = 12.0, 2.4 Hz, 1 H), 2.90-3.01 (m, 3 H), 3.56-3.71 (m, 8 H), 3.80 (d, *J* = 8.0 Hz, 1 H), 3.96 (d, *J* = 14.0 Hz, 1 H), 4.09 (q, *J* = 8.4 Hz, 1 H), 4.17 (d, *J* = 14.0 Hz, 1 H), 4.94 (bs, 1 H), 5.25 (d, *J* = 8.4 Hz, 1 H), 5.42 (d, *J* = 8.8 Hz, 1 H), 6.44-6.59 (m, 1 H), 6.67 (s, 4 H), 6.76 (s, 2 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 6.88-6.97 (m, 2 H), 7.08-7.17 (m, 1 H), 7.18-7.25 (m, 4 H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1

H), 7.41 (bs, 2 H), 8.34 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 26.2, 26.5, 33.8, 34.3, 38.7, 52.0, 52.3, 52.4, 61.4, 61.4, 62.5, 63.6, 67.3, 120.7, 126.2, 126.6, 127.5, 127.9, 128.2, 129.3, 129.5, 134.7, 135.7, 136.9, 138.0, 140.9, 142.2, 148.1, 156.8, 156.9, 159.0 170.6, 170.9 ppm, 1 × C not observed; mp 135-138 ºC; IR ν_{max} (neat/cm^{-1}): 3449, 3365, 3240, 2955, 2913, 1715, 1669, 1651, 1510, 1249; HRMS calcd for $C_{54}H_{68}O_7N_6Na$ $[M+Na]^+$: 935.5042, found 935.5026.

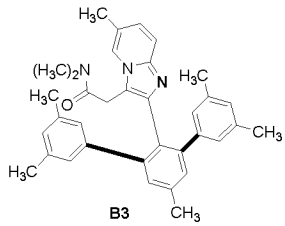
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Zolimidine **N2** (54.5 mg, 0.20 mmol, 1 equiv., for its preparation see: *Chin. Chem. Lett.* **2015**, *26*, 881–884), 5-bromo-*m*-xylene **X37** (54.5 µL, 0.4 mmol, 2 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) for 72 hours. Column chromatography (Et_2O/hexane, 8:2) afforded **B2** as a pale yellow solid (78.8 mg, 82%).



B2

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 12 H), 3.13 (s, 3 H), 6.60-6.69 (m, 1 H), 6.80 (s, 2 H), 6.89 (s, 4 H), 6.98 (s, 1 H), 7.02-7.10 (m, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 6.8 Hz, 1 H), 7.96 (s, 2 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 44.6, 112.0, 112.3, 117.3, 124.0, 125.4, 127.2, 127.2, 128.7, 137.1, 137.4, 139.8, 139.9, 142.4, 143.9, 145.1 ppm; mp 245-248 ºC; IR ν_{max} (neat/cm^{-1}): 3021, 2920, 2857, 1602, 1499, 1358, 1312, 1143; HRMS calcd for $C_{30}H_{29}O_2N_2S$ $[M+H]^+$: 481.1917, found 481.1929.

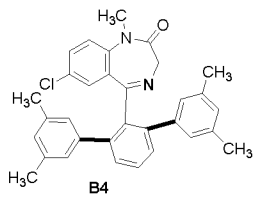
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Zolpidem **N3** (61.5 mg, 0.20 mmol, 1 equiv.), 5-bromo-*m*-xylene **X37** (54.5 µL, 0.4 mmol, 2 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) for 72 hours. Column chromatography (EtOAc/hexane, 4:6) afforded the title product as a light brown solid (88.7 mg, 86%).



B3

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 12 H), 2.24 (s, 3 H), 2.47 (s, 3 H), 2.57 (s, 3 H), 2.79 (s, 3 H), 3.14 (s, 2 H), 6.73 (s, 2 H), 6.85 (s, 4 H), 6.90 (d, *J* = 9.2 Hz, 1 H), 7.26 (s, 2 H), 7.37 (d, *J* = 9.2 Hz, 1 H), 7.83 (s, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.4, 21.1, 21.3, 29.1, 35.4, 37.3, 115.9, 116.2, 120.7, 122.2, 126.4, 127.3, 128.0, 128.4, 129.8, 136.7, 138.0, 141.5, 142.0, 143.1, 143.7, 168.5 ppm; mp 211-213 ºC; IR ν_{max} (neat/cm^{-1}): 3023, 2919, 2861, 1647, 1599, 1395, 1377; HRMS calcd for $C_{35}H_{37}ON_3Na$ $[M+Na]^+$: 538.2829, found 538.2818.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Diazepam **N4** (56.9 mg, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (58.0 µL, 0.4 mmol, 2 equiv.) and K_2CO_3 (82.9 mg, 0.6

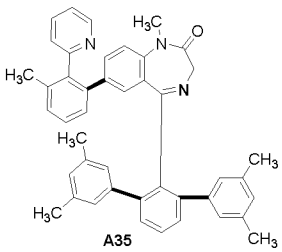


B4

mmol, 3 equiv.) for 72 hours. Column chromatography (Et_2O/hexane, 6:4) afforded the title product as a white solid (93.7 mg, 95%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 6 H), 2.30 (s, 6 H), 2.90 (s, 3 H), 3.32 (d, *J* = 10.8 Hz, 1 H), 4.52 (d, *J* = 10.8 Hz, 1 H), 6.57 (bs, 2 H), 6.76 (bs, 1 H), 6.81 (d, *J* = 8.8 Hz, 1 H), 6.93 (bs, 1 H), 7.01-7.09 (m, 3 H), 7.15-7.21 (m, 1 H), 7.24 (dd, *J* = 8.8, 6.8 Hz, 1 H), 7.44-7.52 (m, 2 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 21.3, 34.4, 56.0, 121.3, 127.2, 127.5, 128.0, 128.5, 128.6, 128.7, 129.0, 129.5, 130.4, 131.8, 136.7, 136.9, 137.1, 140.6, 140.9, 141.2, 142.2, 142.5, 168.2, 169.1 ppm; mp 173-175 ºC; IR ν_{max} (neat/cm^{-1}): 2916, 2856, 1677, 1602, 1482, 1399, 1342; HRMS calcd for $C_{32}H_{29}ON_2ClNa$ [M+Na]$^+$: 515.1861, found 515.1856.

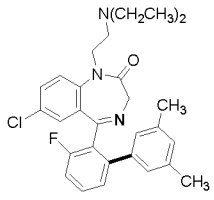
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Diazepam **N4** (56.9 mg, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (58.0 µL, 0.4 mmol, 2 equiv.), K_2CO_3 (110.6 mg, 0.8 mmol, 4 equiv.) and NMP (0.4 mL, 0.5 M) for 72 hours. After this time, 2-(*o*-tolyl)pyridine **N10** (50.8 mg, 0.3 mmol, 1.5 equiv.) was added and the reaction was stirred for additional 72 hours. Column chromatography (EtOAc/hexane, 6:4) afforded **A35** as a white solid (118.9 mg, 95%).



A35

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.06-2.22 (m, 9 H), 2.30 (s, 6 H), 2.78 (s, 3 H), 3.30 (d, *J* = 10.4 Hz, 1 H), 4.54 (d, *J* = 10.4 Hz, 1 H), 6.51 (bs, 2 H), 6.58 (d, *J* = 8.4 Hz, 1 H), 6.76 (bs, 1 H), 6.79-6.86 (m, 2 H), 6.88-6.99 (m, 2 H), 7.02 (d, *J* = 2.0 Hz, 1 H), 7.06-7.20 (m, 4 H), 7.30 (d, *J* = 7.4 Hz, 1 H), 7.35 (d, *J* = 7.4 Hz, 1 H), 7.40-7.50 (m, 3 H), 8.58 (bs, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 21.3, 34.4, 55.9, 119.1, 121.6, 125.2, 127.4, 127.6, 128.2, 128.2, 128.4, 128.4, 128.9, 129.3, 129.8, 129.8, 130.2, 132.0, 135.8, 136.7, 136.8, 136.9, 137.1, 137.3, 139.1, 139.4, 140.6, 141.0, 141.6, 141.9, 149.2, 159.2, 168.5, 170.2 ppm; mp 115-118 ºC; IR ν_{max} (neat/cm^{-1}): 2916, 2857, 1677, 1602, 1459, 1327; HRMS calcd for $C_{44}H_{39}ON_3Na$ [M+Na]$^+$: 648.2985, found 648.2978.

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Flurazepam **N5** (77.6 mg, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (29.0 µL, 0.2 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 ºC for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 95:5) afforded **B5** as a pale yellow wax (90.5 mg, 92%).

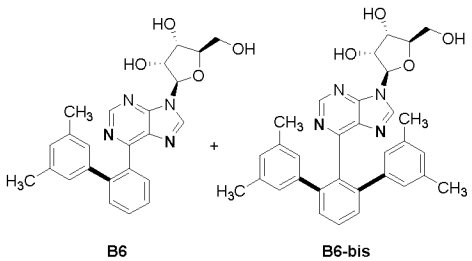


B5

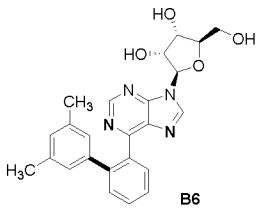
NMR analysis at 25 ºC shows the product as a mixture of conformers (73:27 ratio) as determined from ^{19}F-NMR (see, *Tetrahedron* **2013**, *69*, 10783–10795). Spectra were also recorded at 120 ºC to observe the product as a single species. ^{1}H-NMR (500 MHz, DMSO-d_6, 120 ºC) δ 0.69-1.10 (m, 8 H), 1.23 (3, 2 H), 2.18 (s, 6 H), 2.52-2.64 (m, 4 H), 3.18-4.40 (m, 2 H), 6.65 (bs, 2 H), 6.88 (s, 1 H), 6.92 (s, 1 H), 7.10-7.19 (m, 1 H), 7.31 (t, *J* = 9.0 Hz, 1 H),

7.47-7.61 (m, 3 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$, 25 ºC) δ 11.9, 21.2, 29.7, 47.7, 51.0, 57.2, 114.6 (d, *J* = 22.0 Hz), 123.2, 125.9, 126.2 (d, *J* = 1.9 Hz), 126.9 (2 × C), 128.6 (d, *J* = 39.6 Hz), 129.0, 130.4, 130.7 (d, *J* = 65.1 Hz), 130.7, 137.2, 139.1, 141.2, 144.2, 157.7 (d, *J* = 244.8 Hz), 165.6, 166.5 ppm; ^{19}F-NMR (470 MHz, DMSO-d_6, 25 ºC) δ −136.6 (bs, 1F), 117.4 ppm (bs, 1F); ^{19}F-NMR (470 MHz, DMSO-d_6, 120 ºC) δ −116.3 (bs, 1F) ppm; IR ν_{max} (neat/cm^{-1}): 2968, 2931, 1678, 1482, 1458, 1406; HRMS calcd for $C_{29}H_{32}ON_3ClF$ $[M+H]^+$: 492.2212, found 492.2200.

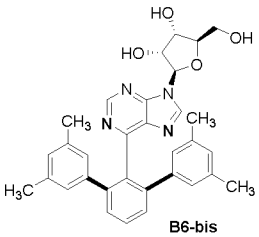
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 6-phenylpurine riboside **N6** (65.7 mg, 0.20 mmol, 1 equiv., for its preparation see: *Eur. J. Med. Chem.* **2014**, *85*, 418–437), 5-iodo-*m*-xylene **X38** (58.0 µL, 0.4 mmol, 2.0 equiv) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) at 50 °C for 48 hours. Column chromatography (CH_2Cl_2/MeOH, 95:5) afforded the **B6** (12.1 mg, 14%) and **B6-bis** (64.4 mg, 60%) as pale yellow solids.



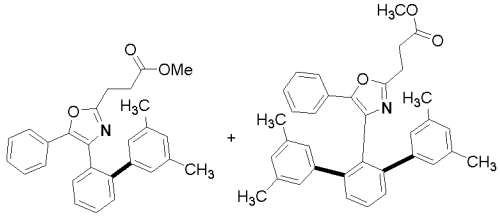
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 6 H), 2.19 (s, 1 H), 2.64 (s, 1 H), 3.70-3.84 (m, 1 H), 3.96 (d, *J* = 12.0 Hz, 1 H), 4.34 (s, 1 H), 4.43 (d, *J* = 5.2 Hz, 1 H), 4.73 (dd, *J* = 6.8, 5.2 Hz, 1 H), 5.51 (d, *J* = 10.4 Hz, 1 H), 5.78 (d, *J* = 7.2 Hz, 1 H), 6.73 (s, 2 H), 6.76 (s, 1 H), 7.48-7.66 (m, 4 H), 7.89 (s, 1 H), 8.81 (s, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.2, 63.1, 72.4, 73.5, 87.8, 91.6, 127.1, 127.3, 128.4, 130.2, 130.9, 130.9, 133.4, 133.5, 137.3, 140.6, 142.1, 144.1, 149.8, 151.4, 160.4 ppm; mp 90-93 ºC; IR ν_{max} (neat/cm^{-1}): 3331, 2922, 2855, 1599, 1586, 1502, 1456, 1391, 1332, 1212; HRMS calcd for $C_{24}H_{23}O_4N_4$ $[M-H]^-$: 431.1725, found 431.1721.



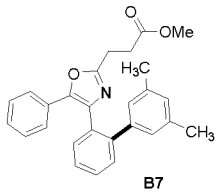
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 6 H), 2.07 (s, 6 H), 3.46 (bs, 1 H), 3.65 (t, *J* = 11.6 Hz, 1 H), 3.75-3.96 (m, 2 H), 4.22 (s, 1 H), 4.32 (d, *J* = 4.0 Hz, 1 H), 4.67-4.80 (m, 1 H), 5.46 (d, *J* = 10.4 Hz, 1 H), 5.68 (d, *J* = 6.8 Hz, 1 H), 6.61-6.80 (m, 6 H), 7.37-7.46 (m, 2 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.81 (s, 1 H), 8.66 (s, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.0, 20.1, 62.8, 71.9, 73.8, 87.5, 91.2, 127.0, 127.0, 128.3, 128.4, 129.0 (2 × C), 129.2, 132.5, 135.6, 136.9, 137.0, 140.5, 140.6, 142.1, 142.1, 144.1, 149.3, 150.6, 161.0 ppm; mp 130-133 ºC; IR ν_{max} (neat/cm^{-1}): 3281, 2919, 2861, 1595, 1332, 1209, 1109, 1083, 1052; HRMS calcd for $C_{32}H_{32}O_4N_4Na$ $[M+Na]^+$: 559.2316, found 559.2312.



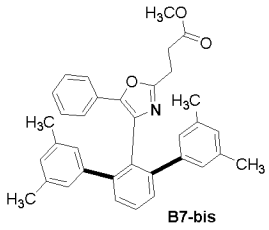
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Oxaprozin methyl ester **N7** (61.5 mg, 0.20 mmol, 1 equiv.), 5-bromo-*m*-xylene **X37** (28.5 µL, 0.2 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 °C for 72 hours. Column chromatography (Et_2O/hexane, 3:7) afforded **B7** as a white wax (51.9 mg, 63%) and **B7-bis** as a white solid (4.1 mg, 4%).



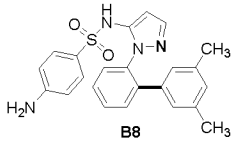
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 6 H), 2.84 (t, *J* = 7.6 Hz, 2 H), 3.14 (t, *J* = 7.6 Hz, 2 H), 3.72 (s, 3 H), 6.65 (s, 2 H), 6.72 (s, 1 H), 7.09-7.21 (m, 5 H), 7.35-7.49 (m, 3 H), 7.53 (d, *J* = 7.2 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 23.4, 31.0, 51.9, 125.3, 126.9, 127.4, 127.5, 128.0, 128.1, 128.3, 128.7, 130.2, 130.7, 131.1, 134.8, 136.8, 140.6, 142.4, 146.0, 161.0, 172.4 ppm; IR ν_{max} (neat/cm^{-1}): 2951, 2923, 2854, 1741, 1437, 1223, 1201, 1167; HRMS calcd for $C_{27}H_{25}O_3NNa$ [M+Na]$^+$: 434.1727, found 434.1725.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 12 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 2.99 (t, *J* = 7.6 Hz, 2 H), 3.68 (s, 3 H), 6.63-6.86 (m, 6 H), 6.98-7.10 (m, 2 H), 7.11-7.23 (m, 3 H), 7.38 (d, *J* = 7.2 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 23.3, 31.3, 51.8, 124.8, 127.1, 127.3, 128.0, 128.1, 128.4, 128.7, 129.1, 129.6, 133.6, 136.7, 141.1, 143.8, 146.8, 160.1, 172.3 ppm; mp 116-118 ºC; IR ν_{max} (neat/cm^{-1}): 2950, 2920, 2853, 1742, 1602, 1571, 1437, 1224, 1167; HRMS calcd for $C_{35}H_{33}O_3NNa$ [M+Na]$^+$: 538.2353, found 538.2351.



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.

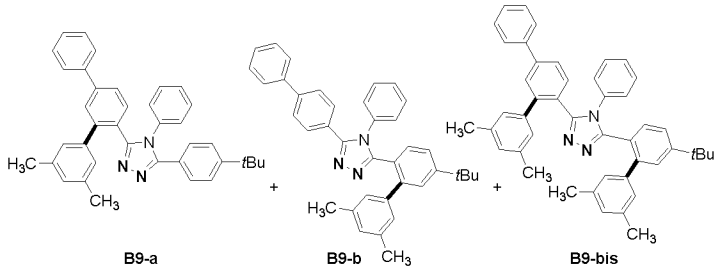


The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Sulfaphenazole **N8** (71.7 mg, 0.20 mmol, 1 equiv.), 5-bromo-*m*-xylene **X37** (28.5 µL, 0.2 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 °C for 72 h. Column chromatography (CH_2Cl_2/Et_2O, 9:1) afforded the title product as a pale yellow solid (72.0 mg, 86%).

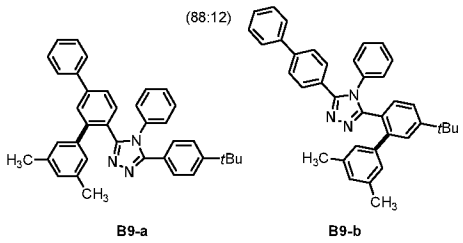
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6 H), 4.12 (bs, 2 H), 5.52 (bs, 1 H), 6.12 (d, *J* = 1.6 Hz, 1 H), 6.44 (d, *J* = 8.2 Hz, 2 H), 6.65 (s, 2 H), 6.91-6.99 (m, 2 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 7.27-7.34 (m, 1 H), 7.42-7.50 (m, 2 H), 7.56 (d, *J* = 2.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 102.3, 113.7, 125.7, 126.4, 128.2, 128.3, 129.1, 129.4, 129.9, 130.1, 134.8, 135.1, 137.1, 137.9, 138.8, 139.9, 150.9 ppm; mp 133-135 ºC; IR ν_{max} (neat/cm^{-1}): 3475, 3381, 2921,

1628, 1595, 1503, 1373, 1318, 1154; HRMS calcd for $C_{23}H_{22}O_2N_4NaS$ $[M+Na]^+$: 441.1356, found 441.1349.

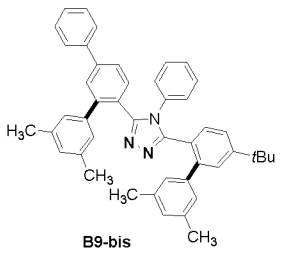
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), TAZ **N9** (85.9 mg, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (58.0 µL, 0.4 mmol, 2 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) at 50 °C for 72 hours. Column chromatography (acetone/Et_2O/hexane, 2:2:6) afforded a 88:12 mixture of **B9-a**:**B9-b** as a white solid (35.2 mg, 33%) and **B9-bis** as a pale yellow solid (53.6 mg, 42%).



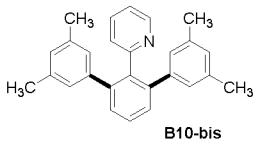
NMR data for the major isomers: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9 H), 2.07 (s, 6 H), 6.16 (d, *J* = 7.6 Hz, 2 H), 6.35 (s, 2 H), 6.71 (s, 1 H), 6.85-6.94 (m, 2 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 7.12-7.18 (m, 4 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 7.34-7.41 (m, 3 H), 7.53-7.58 (m, 2 H), 7.62 (dd, *J* = 8.0, 2.2 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 31.1, 34.7, 124.1, 124.9, 125.2, 125.8, 126.5, 126.5, 127.1, 127.6, 127.8, 128.2, 128.3, 128.5, 128.7, 128.8, 132.6, 133.9, 137.7, 139.6, 140.0, 142.1, 143.0, 152.6, 153.7, 155.2 ppm; mp decomposes above 200 ºC; IR ν_{max} (neat/cm^{-1}): 2962, 2922, 2868, 1599, 1499, 1477, 1451, 1424; HRMS calcd for $C_{38}H_{36}N_3$ $[M+H]^+$: 534.2904, found 534.2890.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 2.09 (s, 12 H), 5.35 (s, 1 H), 5.37 (s, 1 H), 6.15 (s, 2 H), 6.21 (s, 2 H), 6.53 (t, *J* = 8.0 Hz, 2 H), 6.68-6.74 (m, 2 H), 6.86 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 2.0 Hz, 1 H), 7.34-7.40 (m, 2 H), 7.41-7.51 (m, 3 H), 7.59-7.65 (m, 2 H), 7.67-7.73 (m, 2 H), 7.84 (d, *J* = 8.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1, 31.2, 34.8, 123.2, 124.5, 124.7, 125.2, 125.6, 126.0, 126.1, 126.1, 126.6, 127.1, 127.4, 127.8 , 128.2, 128.5, 128.9, 131.2, 132.1, 132.8, 137.4, 137.5, 139.5, 140.1, 140.1, 141.1, 141.9, 142.9, 153.5, 154.3, 154.7 ppm; mp 240-245 ºC; IR ν_{max} (neat/cm^{-1}): 3030, 2962, 2916, 2866, 1600, 1499, 1450, 1418; HRMS calcd for $C_{46}H_{44}N_3$ $[M+H]^+$: 638.3530, found 638.3513.



The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-phenylpyridine **N11** (28.6 µL, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (58.0 µL, 0.4 mmol, 2 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.). Column chromatography (hexane/Et_2O, 9:1) afforded **B10-bis** as a white solid (69.8 mg, 96%).



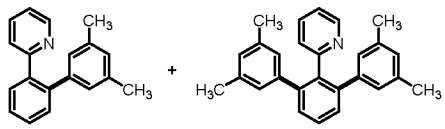
B10-bis

The General Procedure D was applied with encapsulated **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-phenylpyridine **N11** (28.6 µL, 0.20 mmol, 1 equiv.), 5-bromo-*m*-xylene **X37** (55.0 µL, 0.4 mmol, 2 equiv.) and K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) in EtOAc (400 µL) at 45 °C. Column chromatography (hexane/Et_2O, 9:1) afforded **B10-bis** as a white solid (68.3 mg, 94%).

Spectroscopic data for **B10-bis** matched those previously reported (*J. Am. Chem. Soc. 2016* **138,** 3596−3606).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 12 H), 6.73 (s, 4 H), 6.78 (s, 2 H), 6.88-6.95 (m, 2 H), 7.33 (td, *J* = 7.6, 2.0 Hz, 1 H), 7.40-7.45 (m, 2 H), 7.49 (dd, *J* = 8.8, 6.4 Hz, 1 H), 8.35 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.1, 120.6, 126.7, 127.6, 127.8, 127.9, 129.1, 134.7, 136.9, 138.4, 141.4, 141.8, 148.1, 159.3 ppm.

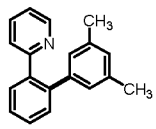
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-phenylpyridine **N11** (28.6 µL, 0.20 mmol, 1 equiv.), 5-chloro-*m*-xylene **X36** (28.1 mg, 0.2 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/Et_2O, 9:1) afforded **B10** as a clear oil (28.5 mg, 55%) and **B10-bis** as white solid (14.5 mg, 20%).



B10 B10-bis

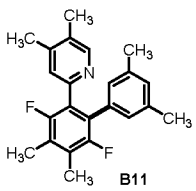
Spectroscopic data for **B10** matched those previously reported (*J. Am. Chem. Soc. 2016* **138,** 3596−3606).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 6 H), 6.78 (bs, 2 H), 6.87 (bs, 1 H), 6.92 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.11 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.37-7.48 (m, 4 H), 7.66-7.75 (m, 1 H), 8.65 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 121.2, 125.3, 127.4, 127.5, 128.2, 128.4, 130.3, 130.4, 135.0, 137.4, 139.4, 140.8, 141.1, 149.2, 159.4 ppm.



B10

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), 2-arylpyridine **N12** (49.5 mg, 0.20 mmol, 1 equiv.), 5-iodo-*m*-xylene **X38** (29.0 µL, 0.2 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.). Column chromatography (hexane/Et_2O, 9:1) afforded **B11** as a white solid (66.1 mg, 94%).

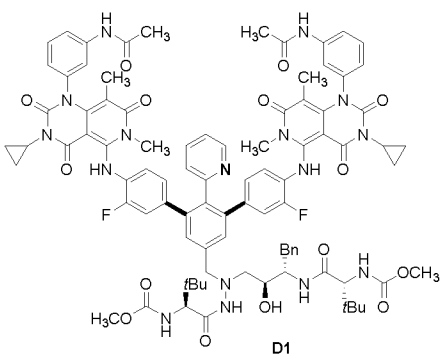


B11

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3 H), 2.14-2.23 (m, 9 H), 2.24-2.33 (m, 6 H), 6.74 (s, 2 H), 6.80 (s, 2 H), 8.36 (s, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.3 (dd, *J* = 5.4, 2.1 Hz), 11.4 (dd, *J* = 5.5, 2.3 Hz), 16.1, 19.0, 21.1, 124.2 (dd, *J* = 19.1, 4.5 Hz), 125.0 (dd, *J* = 19.6, 4.8 Hz), 126.1 (dd, *J* = 18.9, 3.3 Hz), 126.7, 126.9 (dd, *J* = 19.8, 3.4 Hz), 128.3 (d, *J* = 1.1 Hz), 128.6, 130.3, 133.5 (d, *J* = 2.0 Hz), 136.8, 145.0, 149.2, 151.3 (d, *J* = 2.4 Hz), 153.8 (dd, *J* = 236.8, 1.9 Hz), 154.4 (dd, *J* = 237.9, 2.1 Hz) ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ −124.2 (d, *J* = 17.9 Hz), −123.6 (d, *J* = 18.3 Hz) ppm; mp 109-110 ºC; IR ν_{max} (neat/cm^{-1}): 3008, 2946, 2920, 2863, 1604, 1593, 1444, 1410, 1377, 1342, 1228, 1086; HRMS calcd for $C_{23}H_{24}NF_2$ $[M+H]^+$: 352.1871, found 352.1877.

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.

The purity of Trametinib purchased from Generon was assessed to be 70% by quantitative ^{1}H-NMR with an internal standard. The impurity was not NMR-active. Trametinib was further purified by centrifuging the solid in H_2O and by removing the white particles which were not depositing at the bottom of the vial (×10 times). The purity was then assessed to be 84% by quantitative ^{1}H-NMR with an internal standard.

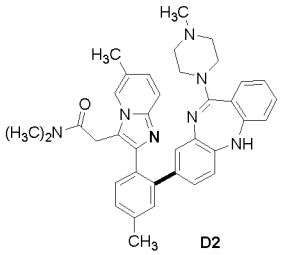


D1

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Atazanavir **N1** (152.3 mg, 0.20 mmol, 1 equiv.), Trametinib **X23** (285.4 mg, 0.4 mmol, 2 equiv.), K_2CO_3 (82.9 mg, 0.6 mmol, 3 equiv.) and NMP (0.4 mL, 0.5 M) for 72 hours. Column chromatography (acetone/hexane 6:4) afforded **D1** as a pale yellow solid (218.4 mg, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.70-0.75 (m, 13 H), 0.83-0.95 (m, 9 H), 0.95-1.03 (m, 4 H), 1.34 (s, 7 H), 2.10 (s, 6 H), 2.62-2.70 (m, 2 H), 2.74-2.82 (m, 1 H), 2.90-2.95 (m, 2 H), 2.99-3.08 (m, 7 H), 3.57 (s, 3 H), 3.59 (s, 3 H), 3.73-3.83 (m, 2 H), 3.94 (d, *J* = 8.4 Hz, 1 H), 4.13-4.24 (m, 2 H), 4.29 (d, *J* = 14.0 Hz, 1 H), 5.03 (bs, 1 H), 6.04-6.18 (m, 2 H), 6.91-7.01 (m, 4 H), 7.02-7.10 (m, 5 H), 7.10-7.18 (m, 2 H), 7.18-7.27 (m, 4 H), 7.34 (t, *J* = 8.0 Hz, 2 H), 7.52 (td, *J* = 8.0, 1.6 Hz, 1 H), 7.64-7.69 (m, 4 H), 7.73-7.78 (m, 2 H), 8.42 (d, *J* = 4.8 Hz, 1 H), 8.52 (bs, 1 H), 9.39 (s, 2 H), 11.43 (s, 2 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 8.9, 13.6, 24.3, 25.7, 26.8, 27.2, 34.3, 34.4, 34.8, 39.4, 52.2, 52.3, 52.7, 55.5, 62.3, 62.4, 64.7, 68.8, 90.6, 102.9, 118.2 (d, *J* = 20.0 Hz), 119.1, 121.2, 122.5, 124.3, 125.0, 126.8, 127.3 (d, *J* = 2.6 Hz), 127.5 (d, *J* = 11.8 Hz), 127.6, 129.0, 129.4, 130.2, 130.9, 136.3, 139.0, 139.1, 139.9, 140.7, 140.9, 141.1 (d, *J* = 7.3 Hz), 141.8, 146.1, 149.5, 152.1, 153.3, 155.5 (d, *J* = 244.1 Hz), 157.5, 157,6, 159.2, 164.0, 165.0, 169.2, 171.3, 172.3 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ −127.8 ppm; mp >250 ºC; IR ν_{max} (neat/cm^{-1}): 3435, 2958, 2924, 2854, 1704, 1628, 1548, 1423, 1234; HRMS calcd for $C_{90}H_{96}O_{15}N_{16}F_2Na$ $[M+Na]^+$: 1701.7101, found 1701.7101.

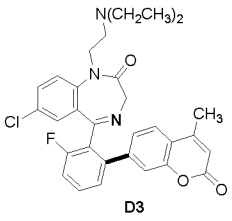
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Zolpidem **N3** (61.5 mg, 0.20 mmol, 1 equiv.), Clozapine **X13** (65.4 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.40 mmol, 2 equiv.) for 144 hours. Column chromatography (CH_2Cl_2/MeOH, from 9:1 to 8:2) afforded **D2** as a pale yellow solid (90.9 mg, 76%).



D2

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 2.40 (s, 6 H), 2.49-2.62 (m, 4 H), 2.66 (s, 3 H), 2.75 (s, 3 H), 3.30 (s, 2 H), 3.37-3.59 (m, 4 H), 4.86 (s, 1 H), 6.35 (d, *J* = 8.0 Hz, 1 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.94-7.04 (m, 2 H), 7.14-7.22 (m, 2 H), 7.22-7.30 (m, 3 H), 7.48-7.57 (m, 2 H), 7.85 (s, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.5, 21.2, 29.5, 35.6, 37.2, 46.0, 47.2, 54.9, 114.5, 116.3, 119.1, 120.0, 121.1, 122.7, 122.8, 123.4, 125.5, 126.9, 127.0, 127.9, 129.9, 130.2, 130.6, 131.7, 132.2, 137.1, 137.9, 140.2, 140.2, 140.3, 143.2, 144.3, 153.1, 162.3, 167.6 ppm; mp decomposes at 168-171 ºC; IR ν_{max} (neat/cm^{-1}): 3294, 2926, 2845, 2361, 2191, 1641, 1601, 1462, 1153, 907, 762; HRMS calcd for $C_{37}H_{39}ON_7Na$ $[M+Na]^+$: 620.3108, found 620.3108.

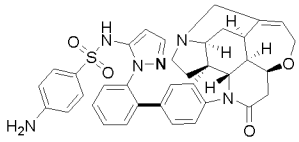
The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Flurazepam **N5** (77.6 mg, 0.20 mmol, 1.0 equiv), Hymechromone-OTf **X28** (61.7 mg, 0.20 mmol, 1 equiv.), KOBz (9.6 mg, 0.06 mmol, 0.3 equiv.) in replacement of KOAc, and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 ºC for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 99:1 to 97:3) afforded the title product as a white wax (98.3 mg, 90%).



D3

NMR analysis at 25 ºC shows the product as a mixture of conformers (72:28 ratio) as determined from ^{19}F-NMR (see, *Tetrahedron* **2013**, *69*, 10783–10795). Spectra were also recorded at 120 ºC to acquire spectra with sharper signals. ^{1}H-NMR (500 MHz, DMSO-d_6, 120 ºC) δ 0.93 (t, *J* = 7.3 Hz, 6 H), 1.38 (s, 3 H), 2.39-2.58 (m, 8 H), 3.71+4.55 (2 × bs, 2 H), 6.33-6.43 (m, 1 H), 6.82-7.21 (m, 3 H), 7.23-7.34 (m, 1 H), 7.37-7.60 (m, 3 H), 7.61-7.73 (m, 2 H) ppm; ^{13}C-NMR (125 MHz, DMSO-d_6, 70 ºC) δ 11.8, 17.5, 30.2, 46.8, 50.2, 56.7, 114.4, 115.4 (d, *J* = 22.0 Hz), 116.1, 118.4, 123.7, 124.5, 124.7, 125.6 (d, *J* = 15.1 Hz), 125.8, 126.9, 131.1 (d, *J* = 9.1 Hz), 131.3, 138.7, 140.7, 141.2, 142.3, 151.1, 152.1, 152.2, 159.0, 159.3 (d, *J* = 246.4 Hz), 163.6, 165.9 ppm; ^{19}F-NMR (470 MHz, DMSO-d_6, 25 ºC) δ –113.5 (bs, 1F), –116.6 (bs, 1F) ppm ^{19}F-NMR (470 MHz, DMSO-d_6, 120 ºC) δ –116.2 (bs, 2F) ppm; IR ν_{max} (neat/cm^{-1}): 2969, 2801, 1723, 1674, 1614, 1405, 1162, 893, 798; HRMS calcd for $C_{31}H_{30}ClFN_3O_3$ $[M+H]^+$: 546.1960, found 546.1936.

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.

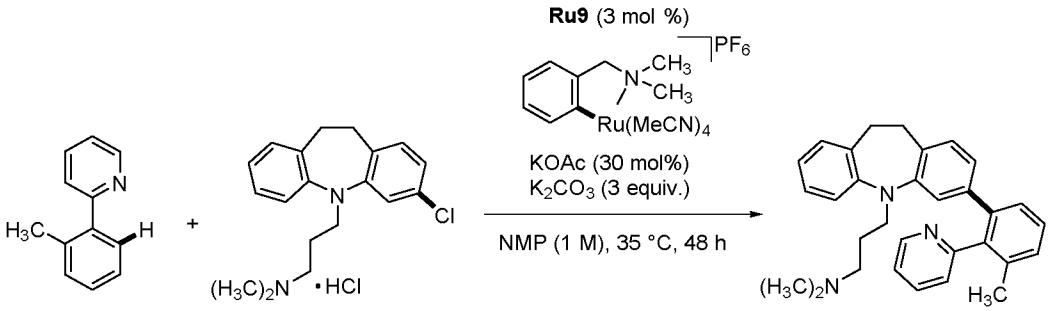


D4

The General Procedure C was applied with **Ru9** (10.9 mg, 0.02 mmol, 10 mol %), Sulfaphenazole **N8** (71.7 mg, 0.20 mmol, 1 equiv.), Br-Strychnine **X20** (82.7 mg, 0.20 mmol, 1 equiv.) and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) at 50 °C for 48 hours. Column chromatography (CH_2Cl_2/MeOH, from 9:1 to 8:2) afforded the title product as a white solid (86.7 mg, 67%).

^{1}H-NMR was recorded both on $CDCl_3$ and DMSO-d_6. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.18-1.24 (m, 3 H), 1.64-1.88 (m, 2 H), 2.22-2.36 (m, 1 H), 2.59-2.72 (m, 1 H), 2.75-2.97 (m, 2 H), 3.07-3.22 (m, 2 H), 3.24-3.48 (m, 1 H), 3.77 (d, *J* = 13.6 Hz, 1 H), 3.84 (d, *J* = 10.0 Hz, 1 H), 4.06 (dd, *J* = 13.4, 5.8 Hz, 1 H), 4.13-4.4 (m, 2 H), 4.27-4.35 (m, 1 H), 5.31 (s, 3 H), 5.96-6.06 (m, 2 H), 6.50 (d, *J* = 8.0 Hz, 2 H), 6.61 (bs, 1 H), 7.12-7.26 (m, 3 H), 7.33-7.41 (m, 1 H), 7.44-7.57 (m, 3 H), 8.07 (d, *J* = 7.2 Hz, 1 H) ppm; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.11-1.23 (m, 3 H), 1.46-1.63 (m, 1 H), 1.78-1.91 (m, 1 H), 2.15-2.26 (m, 1 H), 2.60 (dd, *J* = 13.2, 3.2 Hz, 1 H), 2.75-2.88 (m, 1 H), 2.90-3.04 (m, 2 H), 3.16 (bs, 1 H), 3.21-3.28 (m, 1 H), 3.66-3.80 (m, 2 H), 3.84 (d, *J* = 10.8 Hz, 1 H), 4.01-4.13 (m, 2 H), 4.28-4.39 (m, 1 H), 5.50 (d, *J* = 0.8 Hz, 1 H), 5.68-6.36 (m, 3 H), 6.45-6.66 (m, 3 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 7.26-7.39 (m, 4 H), 7.43-7.50 (m, 1 H), 7.53-7.61 (m, 2 H), 7.87 (d, *J* = 8.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6) δ 25.2, 30.4, 41.1, 41.6, 46.9, 50.1, 50.9, 51.7, 59.6, 60.0, 63.4, 76.3, 112.5, 114.9, 121.9, 125.2, 127.4, 128.7, 128.9, 129.1, 129.2, 130.1, 131.6, 133.9, 135.9, 138.4, 138.8 (2 × C), 141.0, 152.7, 169.0 ppm, 1 C was not observed; mp > 210 ºC; IR ν_{max} (neat/cm^{-1}): 3399, 2917, 2851, 1660, 1594, 1481, 1382, 1136, 1107, 766, 682; HRMS calcd for $C_{36}H_{35}O_4N_6S$ $[M]^+$: 646.2362, found 646.2335.

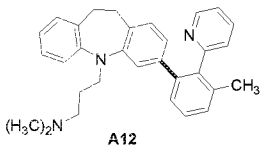
10 g scale arylation reaction of 2-(*o*-tolyl)pyridine (N10) with Clomipramine • HCl (X12)



N10, 1.03 equiv. **X12**, 1 equiv. **A12**, 95%

In a glove box, an oven-dried 250 mL round-bottom flask equipped with a magnetic stirring bar was charged with **Ru9** (496.1 mg, 0.911 mmol, 3 mol%,), Clomipramine • HCl **X12** (10.671 g, 30.374 mmol, 1.0 equiv), 2-(*o*-tolyl)pyridine **N10** (5.294 g, 31.285 mmol, 1.03 equiv.), KOAc (894.4 mg, 9.112 mmol, 0.3 equiv.), K_2CO_3 (12.594 g, 91.122 mmol, 3 equiv.) and NMP (30.4

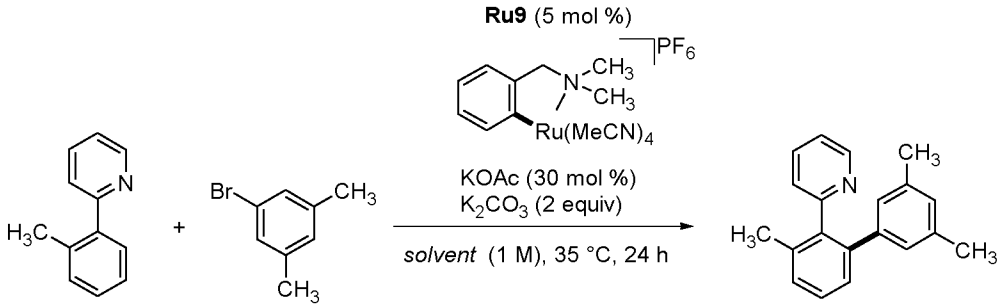
mL, 1 M). The flask was sealed with a septa and the reaction was stirred at 35 °C for 48 hours. Upon completion, the flask was transferred out of the glove box, the crude mixture was diluted with Et_2O (400 mL) and filtered with a short plug of Celite®. The resulting organic mixture was washed with H_2O (200 mL, ×3 times) and the combined aqueous phases were extracted with Et_2O (200 mL, ×2 times). The combined organic phases were acidified with HCl (1M, 200 mL) and the aqueous layer was washed with EtOAc (150 mL, ×2 times), CH_2Cl_2 (150 mL, ×4 times), and Et_2O (150 mL, ×2 times). Then, the aqueous phase was basified with NaOH solution (1M, 300 mL), extracted with Et_2O (200 mL, ×4 times), washed with brine, dried over $MgSO_4$, and evaporated to dryness to afford **A12** as an off-white solid (12.916 g, 95%).



A12

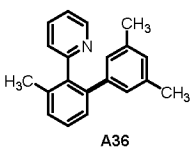
^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.63-1.82 (m, 2 H), 2.16 (s, 3 H), 2.38 (s, 6 H), 2.55-2.68 (m, 2 H), 2.98-3.13 (m, 4 H), 3.43 (bs, 2 H), 6.69 (s, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.85-6.98 (m, 4H), 7.04-7.15 (m, 2 H), 7.15-7.22 (m, 1 H), 7.22-7.31 (m, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 8.69 (d, *J* = 4.5 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4, 23.7, 31.8, 31.9, 43.8, 47.5, 56.7, 119.8, 121.5, 121.6, 123.0, 123.7, 125.5, 126.5, 127.5, 128.1, 129.3, 129.6, 129.6, 131.3, 134.7, 136.1, 136.8, 139.0, 139.8, 140.6, 146.9, 147.5, 148.9, 159.9 ppm; mp 49-51 ºC; IR ν_{max} (neat/cm^{-1}): 2921, 2855, 2765, 1593, 1584, 1490, 1460, 1404; HRMS calcd for $C_{31}H_{34}N_3$ $[M+H]^+$: 448.2747, found 448.2749.

Solvent screening for the arylation reaction of 2-(*o*-tolyl)pyridine (N10) with 5-bromo-*m*-xylene (X37)



N10 (1 equiv) **X37** (1 equiv) **A36**

The General Procedure C was applied with **Ru9** (5.5 mg, 0.01 mmol, 5 mol %), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), 5-bromo-*m*-xylene **X37** (29.0 µL, 0.2 mmol, 1 equiv.), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.), and the appropriate solvent (if needed, see Table 1 below, 200 µL, 1 M) Column chromatography (hexane/Et_2O, 9:1) afforded **A36** as a white solid (yield, see Table 1 below)



A36

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 6 H), 2.21 (s, 3 H), 6.73 (s, 2 H), 6.78 (s, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 7.10 (dd, *J* = 7.5, 5.1 Hz, 1 H), 7.25-7.32 (m, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 8.66 (d, *J* = 4.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 21.1, 121.1, 125.5, 127.4,

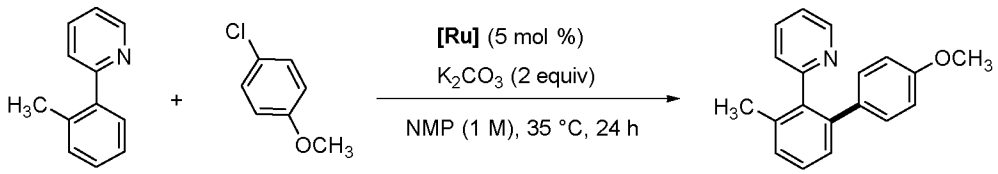
127.5, 127.7, 127.9, 129.1, 135.6, 136.5, 136.8, 139.2, 141.3, 141.3, 148.6, 159.7 ppm; mp 58-60 ºC; IR ν_{max} (neat/cm^{-1}): 3013, 2912, 2868, 1600, 1460, 1024, 792, 748, 704; HRMS calcd for $C_{20}H_{20}N$ $[M+H]^+$: 274.1596, found 274.1583.

entry	***Solvent***	**A36 (%)**
1	THF	89
2	Toluene	92
3	Gamma-valerolactone	87
4	Propylene carbonate	88
5	EtOAc	95
6	Acetone	87
7	GBL	89
8	Dioxane	87
9	No solvent	12
10	NMP	97

Table 1

The results from Table 1 indicate that cycloruthenated catalysts of formula (I) retain their exceptional catalytic activity in a wide range of organic solvents.

Cyclometalated ruthenium(II) catalysts screening for the arylation reaction of 2-(*o*-tolyl)pyridine (N10) with 4-chloroanisole (X40)

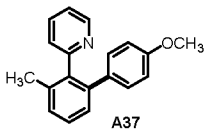


N10 (1 equiv) **X40** (1 equiv) **A37**

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]**: **Ru1**, 5.7 mg; **Ru2**, 6.5 mg; **Ru3**, 5.7 mg; **Ru4**, 6.1 mg; **Ru5**, 5.9 mg; **Ru6**, 5.9 mg; **Ru7**, **6.3** mg; **Ru8**, 6.2 mg; **Ru9**, 5.6 mg; **Ru10**, 5.7 mg; **Ru11**, 6.0 mg; **Ru12**, 5.6 mg; **Ru13**, 5.7 mg; **Ru14**, 5.8 mg; **Ru15**, 5.6 mg; **Ru16**, 5.8 mg; **Ru17**, 6.4 mg; **Ru18**, 6.2 mg; **Ru19**, 6.0 mg; **Ru20**, 6.2 mg; **Ru21**, 6.5 mg; **Ru22**, 6.6 mg; **Ru23**, 6.0 mg; **Ru24**, 5.5 mg; **Ru25**, 6.0 mg; **Ru26**, 5.8 mg; or **Ru27**, 8.2 mg), 2-(*o*-tolyl)pyridine **N10** (33.9 mg, 0.20 mmol, 1 equiv.), 4-chloroanisole **X40** (24.5 µL, 0.2 mmol, 1 equiv.),and K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.) without KOAc. Column

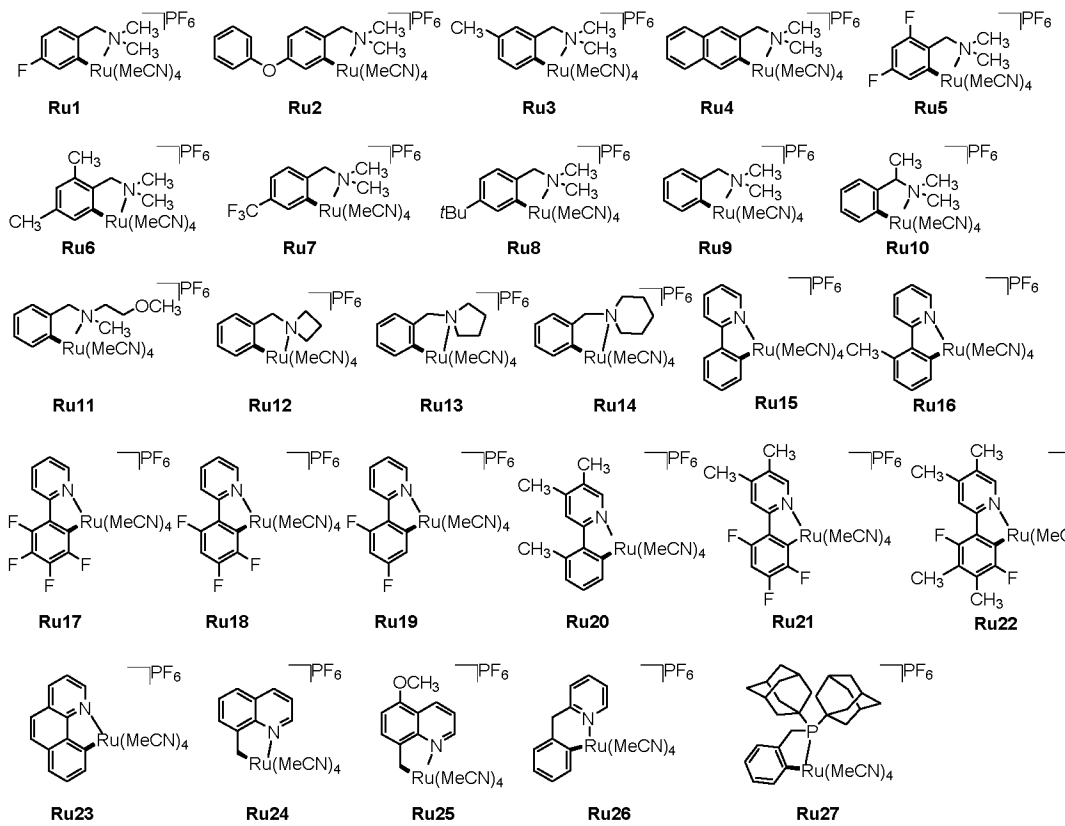
chromatography (hexane/Et_2O, 9:1) afforded **A37** as a light yellow oil (yield, see Table 2 below).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3 H), 3.72 (s, 3 H), 6.68 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 7.8 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 7.08-7.11 (m, 1 H), 7.27 (d, *J* = 5.7 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.45-7.48 (m, 1 H), 8.64 (d, *J* = 4.8 Hz, 1 H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.5, 55.0, 113.0, 121.2, 125.5, 127.5, 128.0, 129.0, 130.6, 134.0, 135.8, 136.6, 139.2, 140.7, 148.8, 158.0, 159.7 ppm; IR ν_{max} (neat/cm^{-1}): 3000, 2846, 2898, 1598, 1460, 1026, 715; HRMS calcd for $C_{19}H_{18}NO$ $[M+H]^+$: 276.1388, found 276.1382.



A37

[Ru]



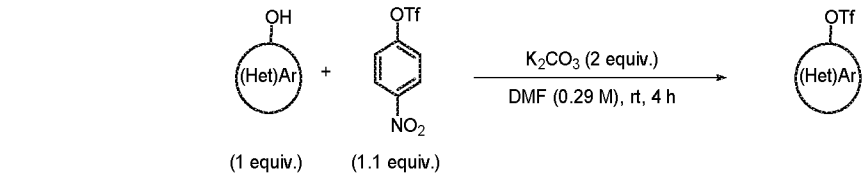
. entry	[Ru]	A37 (%)	entry	[Ru]	A37 (%)
1	**Ru1**	63	15	**Ru15**	63
2	**Ru2**	62	16	**Ru16**	65
3	**Ru3**	65	17	**Ru17**	56
4	**Ru4**	68	18	**Ru18**	55
5	**Ru5**	64	19	**Ru19**	59
6	**Ru6**	62	20	**Ru20**	64
7	**Ru7**	64	21	**Ru21**	56
8	**Ru8**	63	22	**Ru22**	59

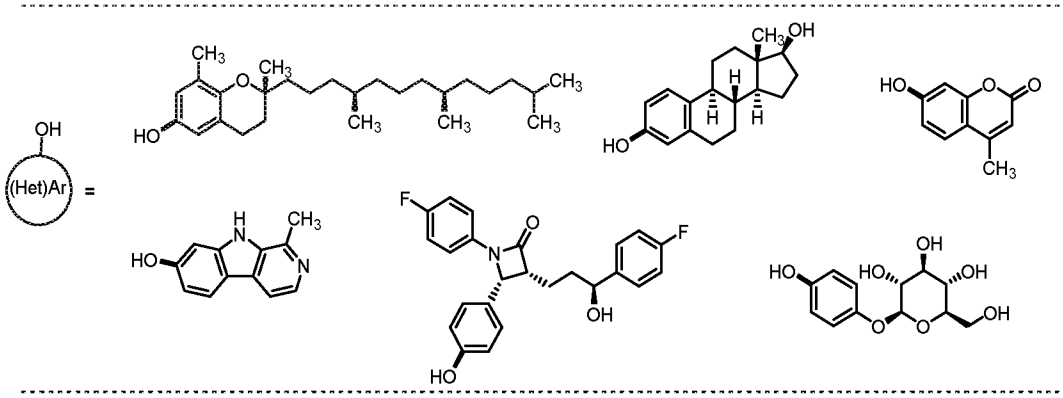
9	**Ru9**	64	23	**Ru23**	60
10	**Ru10**	60	24	**Ru24**	62
11	**Ru11**	55	25	**Ru25**	69
12	**Ru12**	58	26	**Ru26**	66
13	**Ru13**	61	27	**Ru27**	32
14	**Ru14**	62			

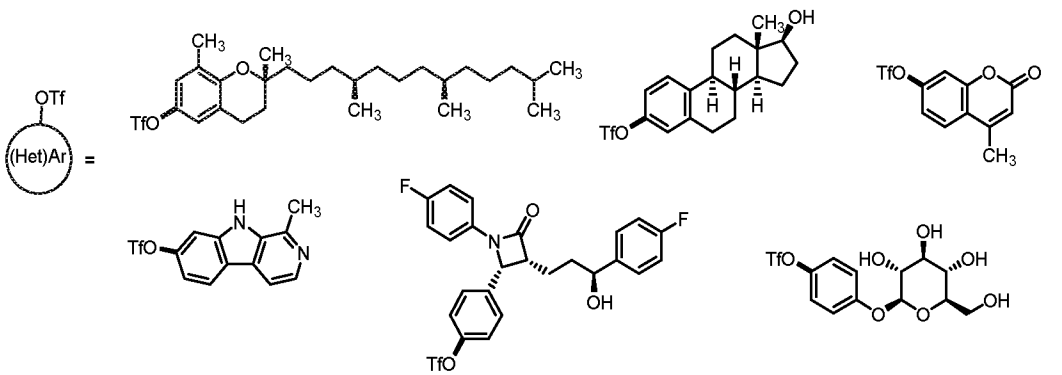
Table 2

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 (hetero)aryl (pseudo)halides.

General Procedure E: preparation of triflate-containing drug derivatives



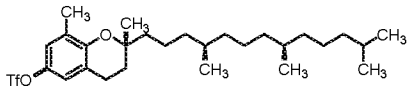




A 25 mL round bottom flask equipped with a magnetic stirring bar was charged with the appropriate phenol derivative (2.0 mmol, 1 equiv.), K_2CO_3 (552.8 mg, 4.0 mmol, 2 equiv.) and

DMF (7 mL, 0.29 M). The reaction mixture was stirred at room temperature for 5 min, then 4-nitrophenyltriflate (596.6 mg, 2.2 mmol, 1.1 equiv.) was added in one portion and the reaction was stirred for additional 4 h. Upon completion, the reaction mixture was diluted with H_2O (60 mL) and extracted with Et_2O (3×60 mL). The intense yellow organic phases were combined and repeatedly washed with saturated K_2CO_3 solution and H_2O until a colourless aqueous phase was obtained. The organic phase was further washed with brine, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography or by trituration with a suitable solvent.

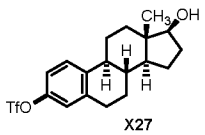
The General Procedure E was applied with δ-Tocopherol (805.3 mg, 2.0 mmol, 1 equiv.). Column chromatography hexane/CH_2Cl_2 (95:5) afforded δ-Tocopherol-OTf **X24** as a colourless oil (802.1 mg, 75%).



X24

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84-0.94 (m, 12 H), 1.01-1.68 (m, 24 H), 1.72-1.91 (m, 2 H), 2.19 (s, 3 H), 2.71-2.84 (m, 2 H), 6.83 (d, *J* = 2.8 Hz, 1 H), 6.88 (d, *J* = 2.8 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.2, 19.6, 19.7, 20.9, 22.4, 22.6, 22.7, 24.1, 24.5, 24.8, 28.0, 30.7, 32.7, 32.8, 37.3, 37.4, 37.4, 37.5, 39.4, 40.1, 76.8, 118.8 (q, *J* = 320.0 Hz), 119.1, 120.7, 121.7, 128.4, 141.5, 151.7 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ –73.1 ppm; IR ν_{max} (neat/cm^{-1}): 2926, 2868, 1472, 1421, 1206, 1142; HRMS calcd for $C_{28}H_{46}O_4F_3S$ $[M+H]^+$: 535.3063, found 535.3063

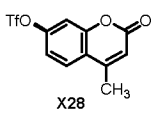
The General Procedure E was applied with Estradiol (544.8 mg, 2.0 mmol, 1 equiv.). Column chromatography (hexane/CH_2Cl_2, 95:5) afforded t Estradiol-OTf (**X27**) as a white solid (792.7 mg, 98%).



X27

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 1.14-1.62 (m, 8 H), 1.66-1.79 (m, 1 H), 1.86-2.04 (m, 2 H), 2.07-2.39 (m, 3 H), 2.84-2.97 (m, 2 H), 3.70-3.81 (m, 1 H), 6.98 (d, *J* = 2.4 Hz, 1 H), 7.03 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.0, 23.1, 26.1, 26.7, 29.5, 30.5, 36.6, 38.2, 43.1, 44.1, 50.5, 81.7, 118.1, 118.8 (q, *J* = 320.0 Hz), 121.1, 127.1, 139.5, 140.9, 147.4 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ –73.0 ppm; mp 115-118 ºC; IR ν_{max} (neat/cm^{-1}): 3376, 2930, 2870, 1418, 1207, 1139, 919; HRMS calcd for $C_{19}H_{23}O_4ClF_3S$ $[M+Cl]^-$: 439.0963, found 439.0956.

The General Procedure E was applied with Hymechromone (352.4 mg, 2.0 mmol, 1 equiv.). Column chromatography (hexane/Et_2O, 9:1) afforded Hymechromone-OTf **X28** as a white solid (548.7 mg, 89%).

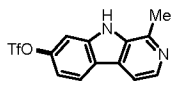


X28

^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.47 (d, *J* = 1.3 Hz, 3 H), 6.37 (q, *J* = 1.4 Hz, 1 H), 7.25 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.29 (d, *J* = 2.5 Hz, 1 H), 7.71 (d, *J* = 9.0 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz,

$CDCl_3$) δ 18.7, 110.5, 116.0, 117.4, 118.6 (q, *J* = 319.0 Hz), 120.0, 126.3, 150.7, 151.2, 154.1, 159.4 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ –72.6 ppm; mp 92-94 ºC; IR ν_{max} (neat/cm^{-1}): 3053, 1747, 1608, 1429, 1419, 1241, 1207, 1138, 1112, 977; HRMS calcd for $C_{11}H_8O_5F_3S$ $[M+H]^+$: 309.0039, found 309.0036.

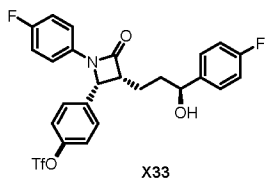
The General Procedure E was applied with Harmol (396.5 mg, 2.0 mmol, 1 equiv.). Column chromatography (EtOAc/CH_2Cl_2, 7:3) afforded Harmol-OTf **X32** as a light brown solid (363.3 mg, 55%).



X32

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 3 H), 7.20 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.45 (d, *J* = 2.0 Hz, 1 H), 7.84 (d, *J* = 5.2 Hz, 1 H), 8.15 (d, *J* = 8.8 Hz, 1 H), 8.44 (d, *J* = 5.2 Hz, 1 H), 9.34 (bs, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.3, 104.9, 113.0, 113.4, 118.8 (q, *J* = 318.7 Hz), 121.9, 123.3, 127.4, 135.5, 139.3, 140.0, 142.3, 149.1 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ –72.7 ppm; mp 184-187 ºC; IR ν_{max} (neat/cm^{-1}): 3065, 2924, 2854, 1632, 1421, 1220, 1140, 1100; HRMS calcd for $C_{13}H_8O_3N_2F_3S$ $[M–H]^–$: 329.0213, found 329.0209.

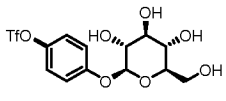
The General Procedure E was applied with Ezetimibe (818.9 mg, 2.0 mmol, 1 equiv.). Column chromatography (hexane/Et_2O, 7:3) afforded Ezetimibe-OTf **X33** as a white solid (953.0 mg, 88%).



X33

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.85-2.12 (m, 4 H), 2.27 (bs, 1 H), 3.09 (td, *J* = 7.5, 2.0 Hz, 1 H), 4.68 (d, *J* = 2.0 Hz, 1 H), 4.73 (t, *J* = 5.5 Hz, 1 H), 6.97 (t, *J* = 8.8 Hz, 2 H), 7.03 (t, *J* = 8.8 Hz, 2 H), 7.17-7.24 (m, 2 H), 7.28-7.34 (m, 4 H), 7.42 (d, *J* = 8.8 Hz, 2 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 25.1, 36.5, 60.3, 60.5, 73.1, 115.4 (d, *J* = 21.3 Hz), 116.0 (d, *J* = 22.5 Hz), 18.3 (d, *J* = 7.5 Hz), 118.6 (q, *J* = 318.8 Hz), 122.4, 127.3 (d, *J* = 8.8 Hz), 127.7, 133.4 (d, *J* = 3.8 Hz), 138.2, 139.9 (d, *J* = 3.8 Hz), 149.3, 159.1 (d, *J* = 242.5 Hz), 162.2 (d, *J* = 245.0 Hz), 166.8 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ –117.4, –114.7, –72.8 ppm; mp 48-51 ºC; IR ν_{max} (neat/cm^{-1}): 3433, 2922, 1745, 1509, 1421, 1216, 1139; HRMS calcd for $C_{25}H_{20}O_5NF_5NaS$ $[M+Na]^+$: 564.0875, found 564.0874.

The General Procedure E was applied with Arbutin (544.5 mg, 2.0 mmol, 1 equiv.). After removing the volatile under reduced pressure, the residue was triturated in $CHCl_3$. The insoluble material was filtered and washed with $CHCl_3$ to afford Arbutin-OTf **X34** as a white solid (477.1 mg, 59%).

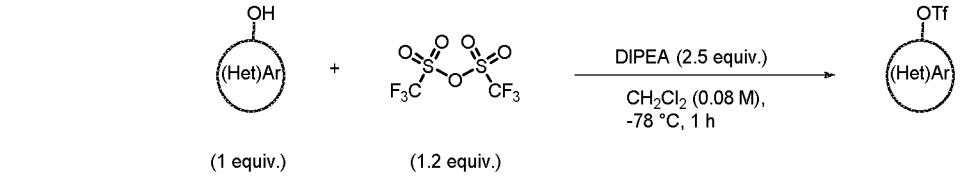


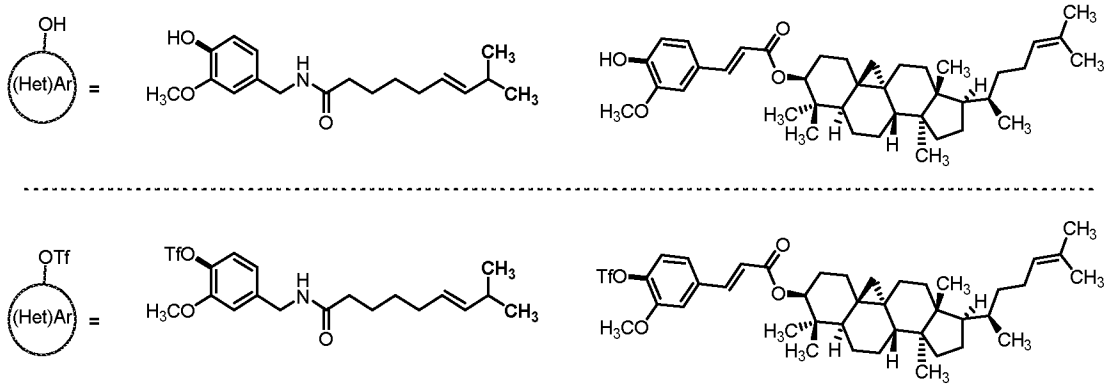
X34

^{1}H-NMR (400 MHz, acetone-d_6) δ 3.42-3.61 (m, 4 H), 3.71 (dd, *J* = 9.4, 4.4 Hz, 1 H), 3.89 (dd, *J* = 9.4, 2.0 Hz, 1 H), 4.29 (bs, 4 H), 5.02 (d, *J* = 6.0 Hz, 1 H), 7.23 (d, *J* = 7.2 Hz, 2 H), 7.37 (d, *J* = 7.2 Hz, 2 H) ppm; ^{13}C-NMR (100 MHz, acetone-d_6) δ 62.5, 71.2, 74.6, 77.8, 77.9, 102.0, 118.8, 119.6 (q, *J* = 254.0 Hz), 123.3, 144.9, 158.5 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ –74.1

ppm; mp 129-132 ºC; IR v_{max} (neat/cm^{-1}): 3352, 2889, 1499, 1418, 1210, 1138, 1071; HRMS calcd for $C_{13}H_{15}O_9ClF_3S$ $[M+Cl]^-$: 439.0083, found 439.0085.

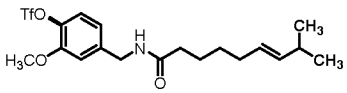
General Procedure F: preparation of triflate-containing drug derivatives





An oven-dried 25 mL Schlenk vial equipped with a magnetic stirring bar was charged with the appropriate phenol derivative (1.0 mmol, 1 equiv.), sealed with a septum, and evacuated and back-filled with N_2 three times. The vial was cooled to -78 °C, then anhydrous CH_2Cl_2 (12.5 mL, 0.08 M) and anhydrous DIPEA (435 µL, 2.5 mmol, 2.5 equiv.) were added. Triflic anhydride (202 µL, 1.2 mmol, 1.2 equiv.) was added dropwise over 5 min and the reaction was stirred at -78 °C for 1 h. After this time, the mixture was allowed to warm up to room temperature, then it was carefully poured in mixture of saturated NH_4Cl solution (50 mL) and Et_2O (50 mL). The organic phase was separated, and the aqueous phase was further extracted with Et_2O (50 mL). The combined organic phases were dried over $MgSO_4$, evaporated to dryness and the residue was purified by column chromatography.

The General Procedure F was applied with Capsaicin (305.4 mg, 1.0 mmol, 1 equiv.). Column chromatography (CH_2Cl_2/Et_2O, 95:5) afforded Capsaicin-OTf **X25** as a white solid (223.1 mg, 51%).

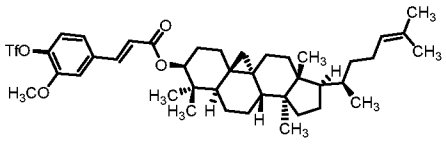


X25

NMR analysis shows the product as a mixture of two amide isomers: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79-1.03 (m, 6 H), 1.07-1.57 (m, 5 H), 1.59-1.76 (m, 2 H), 1.89-2.12 (m, 1 H), 2.14-2.30 (m, 2 H), 3.90 (s, 3 H), 4.43 (d, *J* = 6.0 Hz, 2 H), 5.20-5.46 (m, 1 H), 5.74-5.98 (m, 1 H),

6.86 (d, *J* = 8.0 Hz, 1 H), 6.97 (s, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.6, 25.2, 25.7, 27.2, 27.9, 29.3, 29.3, 29.6, 30.9, 32.2, 36.6, 36.7, 38.9, 43.0, 56.2, 112.6, 118.7 (q, *J* = 320.0 Hz), 119.8, 122.4, 126.3, 137.9, 138.1, 140.3, 151.5, 173.0, 173.1 ppm; ^{19}F-NMR (376 MHz, $CDCl_3$) δ –73.9 ppm; mp 56-58 ºC; IR ν_{max} (neat/cm^{-1}): 3292, 2957, 2929, 2866, 1647, 1505, 1422, 1209, 1142, 1109; HRMS calcd for $C_{19}H_{27}O_5NF_3S$ $[M+H]^+$: 438.1557, found 438.1543.

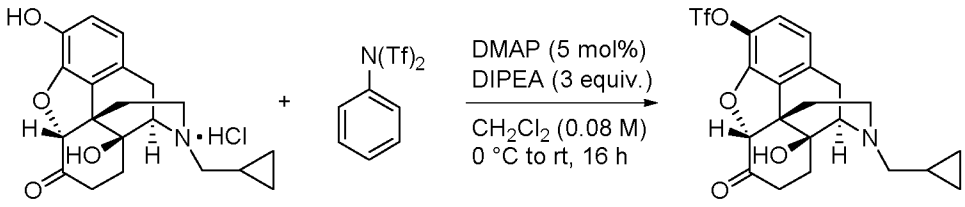
The General Procedure F was applied with γ-Oryzanol (602.9 mg, 1.0 mmol, 1 equiv.). Column chromatography (hexane/Et_2O, 9:1) afforded γ-Oryzanol-OTf **X26** as a white solid (676.2 mg, 92%).



X26

The product **X26** was obtained as a mixture of isomers (^{1}H-NMR ratio 79:21) matching the isomer ratio of γ-Oryzanol (purchased from TCI). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.38 (d, *J* = 4.0 Hz, 1 H), 0.62 (d, *J* = 4.0 Hz, 1 H), 0.74-2.45 (m, 45 H), 3.94-3.99 (m, 3 H), 4.65-4.77 (m, 2 H), 6.39-6.47 (m, 1 H), 7.11-7.19 (m, 2 H), 7.24 (d, *J* = 8.5 Hz, 1 H), 7.62 (d, *J* = 16.0 Hz, 1 H) ppm; ^{13}C-NMR chemical shifts of the major isomer: ^{13}C-NMR (125 MHz, $CDCl_3$) δ 15.3, 18.0, 18.3, 19.3, 20.2, 20.9, 21.9, 22.0, 25.5, 25.8, 25.9, 26.5, 26.9, 28.1, 29.8, 31.3, 31.6, 32.8, 33.8, 35.0, 35.5, 36.1, 39.7, 47.2, 47.8, 48.8, 52.2, 56.3, 81.1, 105.9, 111.9, 118.7 (q, *J* = 318.8 Hz), 120.9, 120.9, 122.8, 135.8, 139.6, 142.4, 151.6, 156.9, 166.2 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ –73.8 ppm; mp 150-153 ºC; IR ν_{max} (neat/cm^{-1}): 2940, 2869, 1709, 1424, 1208, 1175, 1141, 1109; HRMS calcd for $C_{41}H_{58}O_7N_5F_3S$ $[M+H]^+$: 735.3901, found 735.3875.

Preparation of triflate-containing drug derivative Naltrexone-OTf (X30)



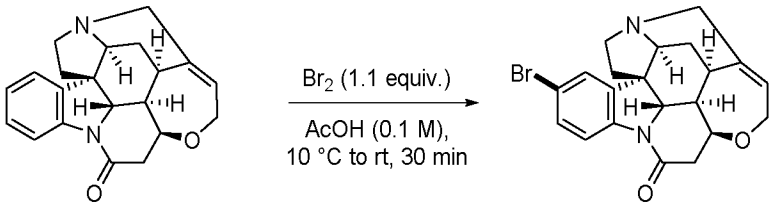
(1 equiv., 1.0 mmol) (1.1 equiv.) **X30**, 71%

An oven-dried 25 mL Schlenk vial equipped with a magnetic stirring bar was charged with Naltrexone • HCl (377.9 mg, 1.0 mmol, 1 equiv.) and DMAP (6.1 mg, 0.05 mmol, 5 mol%). The vial was sealed with a septum, evacuated and back-filled with N_2 three times, cooled to 0 °C, and anhydrous CH_2Cl_2 (12.5 ml, 0.08 M) and anhydrous DIPEA (523 µL, 3.0 mmol, 3 equiv.) were added via syringe. Under a positive flow of N_2, phenylbis(trifluoromethanesulfonimide) (393.0 mg, 1.1 mmol, 1.1 equiv.) was added. The mixture was stirred at 0 °C for 2 h and then at room temperature for additional 16 h. After this time, the reaction was diluted with 50 mL of Et_2O and washed with 7% NH_4OH solution (2×20 mL). The combined organic phases were further washed with K_2CO_3 (2 M) until disappearance of phenylbis(trifluoromethanesulfonimide)

(10×20 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness to afford Naltrexone-OTf **X30** as a colourless film (336.2 mg, 71%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.11-0.21 (m, 2 H), 0.53-0.63 (m, 2 H), 0.82-0.93 (m, 1 H), 1.54 (dd, *J* = 13.0, 3.0 Hz, 1 H), 1.60 (td, *J* = 14.0, 3.5 Hz, 1 H), 1.93 (ddd, *J* = 13.5, 5.3, 3.0 Hz, 1 H), 2.09 (td, *J* = 12.5, 4.0 Hz, 1 H), 2.34 (dt, *J* = 14.5, 3.3 Hz, 1 H), 2.42 (d, *J* = 6.5 Hz, 2 H), 2.47 (td, *J* = 12.5, 5.5 Hz, 1 H), 2.63 (dd, *J* = 19.0, 6.0 Hz, 1 H), 2.74 (dd, *J* = 12.0, 5.0 Hz, 1 H), 3.04 (td, *J* = 14.5, 5.0 Hz, 1 H), 3.12 (d, *J* = 19.0 Hz, 1 H), 3.23 (d, *J* = 6.0 Hz, 1 H), 4.80 (s, 1 H), 5.17 (bs, 1 H), 6.73 (d, *J* = 8.3 Hz, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 3.8, 4.0, 9.3, 23.0, 30.8, 31.3, 36.0, 43.2, 50.9, 59.2, 61.7, 69.8, 91.4, 118.6 (q, *J* = 318.9 Hz), 119.8, 122.7, 131.2, 131.6, 133.3, 147.7, 206.3 ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ –73.1 ppm; IR ν_{max} (neat/cm^{-1}): 3006, 2928, 2829, 1730, 1450, 1423, 1221, 1140; HRMS calcd for $C_{21}H_{23}O_6NF_3S$ $[M+H]^+$: 474.1193, found 474.1180.

Preparation of the natural product derivative Br-Strychnine (X20)



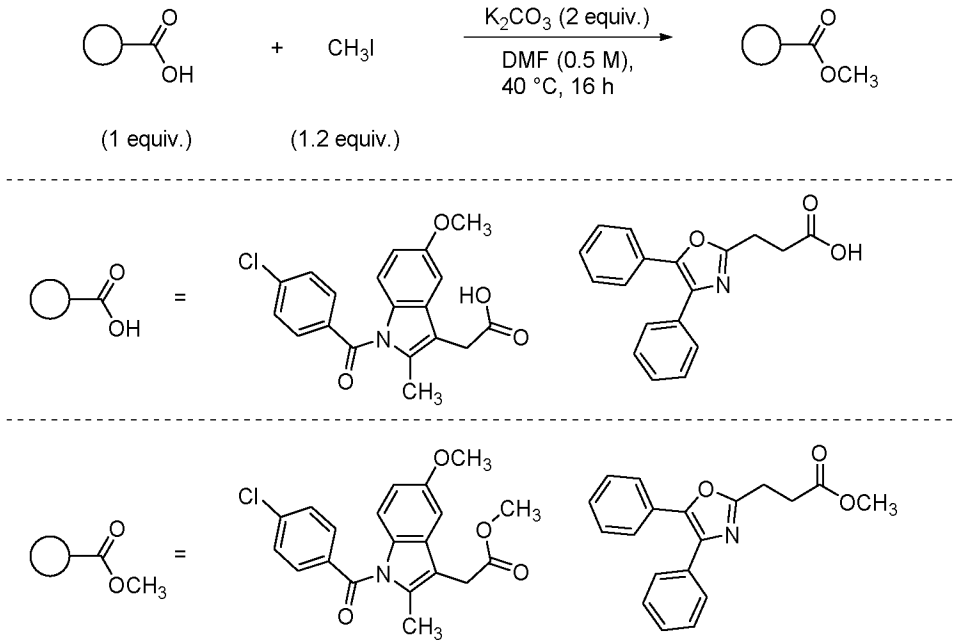
(1 equiv., 4 mmol) **X20**, 73%

In a 100 mL round-bottom flask equipped with a magnetic stirring bar, Strychnine (1.338 g, 4.0 mmol, 1 equiv.) was stirred in AcOH (40 mL, 0.1 M) until complete dissolution. Then the mixture was cooled to 10 °C and bromine (226 µL, 4.4 mmol, 1.1 equiv.) was added dropwise over 5 min. Terminated the addition, the cooling bath was removed and the stirring was continued for additional 20 min. After this time, the reaction crude was carefully poured in a vigorously stirred mixture composed by saturated K_2CO_3 solution (200 mL), saturated $Na_2S_2O_3$ solution (200 mL), ice (200 g) and EtOAc (200 mL). The mixture was stirred for 10 minutes, the organic layer separated, and the aqueous phase further extracted with 100 mL of EtOAc. The combined organic phases were dried over $MgSO_4$, evaporated to dryness, and the residue was purified by column chromatography (CH_2Cl_2/MeOH, from 99:1 to 94:6) affording the title compound as a white solid. Br-Strychnine was further purified by slow recrystallization from MeOH (1.21 g, 73%). After purification, Br-Strychnine **X20** must be stored under inert atmosphere as an impurity that makes it unsuitable for the arylation process quickly develops.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25 (dt, *J* = 10.4, 3.2 Hz, 1 H), 1.45 (d, *J* = 14.4 Hz, 1 H), 1.81-1.94 (m, 2 H), 2.36 (dt, *J* = 14.4, 4.4 Hz, 1 H), 2.64 (dd, *J* = 17.6, 3.2 Hz, 1 H), 2.72 (d, *J* = 14.8 Hz, 1 H), 2.79-2.92 (m, 1 H), 3.06-3.17 (m, 2 H), 3.18-3.26 (m, 1 H), 3.69 (d, *J* = 14.8 Hz, 1 H), 3.83-3.93 (m, 2 H), 4.04 (dd, *J* = 13.8, 6.0 Hz, 1 H), 4.14 (dd, *J* = 13.8, 6.8 Hz, 1 H), 4.28 (dt, *J* = 8.4, 3.2 Hz, 1 H), 5.91 (t, *J* = 5.8 Hz, 1 H), 7.24 (d, *J* = 2.0 Hz, 1 H), 7.34 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.8, 31.4, 42.3, 42.7, 48.0,

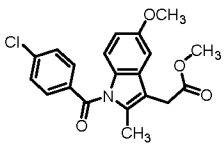
50.2, 51.8, 52.5, 60.2, 60.3, 64.5, 77.4, 116.5, 117.6, 125.5, 127.6, 131.4, 135.0, 139.9, 141.3, 169.3 ppm; mp decomposes above 200 ºC; IR v_{max} (neat/cm^{-1}): 2948, 2902, 2860, 1668, 1470, 1379, 1103; HRMS calcd for $C_{21}H_{22}O_2N_2Br$ $[M+H]^+$: 413.0859, found 413.0866.

General Procedure G: preparation of methyl ester derivatives



In a 25 mL round-bottom flask equipped with a magnetic stirring bar, the appropriate carboxylic acid derivative (2.0 mmol, 1 equiv.), K_2CO_3 (552.8 mg, 4.0 mmol, 2 equiv.) and DMF (4 mL, 0.5 M) were added. Then, methyl iodide (149 µL, 2.4 mmol, 1.2 equiv.) was added and the reaction mixture was heated at 40 °C for 16 h. Upon completion, the reaction crude was diluted with H_2O (30 mL) and Et_2O (30 mL). The organic phase was washed with H_2O (3×20 mL), saturated K_2CO_3 (3×20 mL), brine (30 mL), dried over $MgSO_4$, and evaporated to dryness to afford the desired methyl ester derivative.

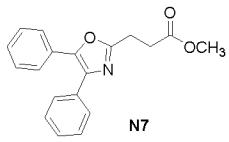
The General Procedure G was applied with Indometacin (715.6 mg, 2.0 mmol, 1 equiv.). Indometacin methyl ester **X3** was obtained as a pale yellow solid (699.0 mg, 94%).



X3

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3 H), 3.68 (s, 2 H), 3.72 (s, 3 H), 3.85 (s, 3 H), 6.68 (dd, *J* = 9.2, 2.4 Hz, 1 H), 6.87 (d, *J* = 9.2 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.3, 30.1, 52.1, 55.7, 101.3, 111.6, 112.5, 114.9, 129.1, 130.6, 130.7, 131.1, 133.8, 135.9, 139.2, 156.0, 168.2, 171.3 ppm; mp 86-87 ºC; IR v_{max} (neat/cm^{-1}): 3124, 2961, 2830, 1731, 11667, 1363, 1167, 913, 751; HRMS calcd for $C_{20}H_{19}O_4NCl$ $[M+H]^+$: 372.0996, found 372.0997.

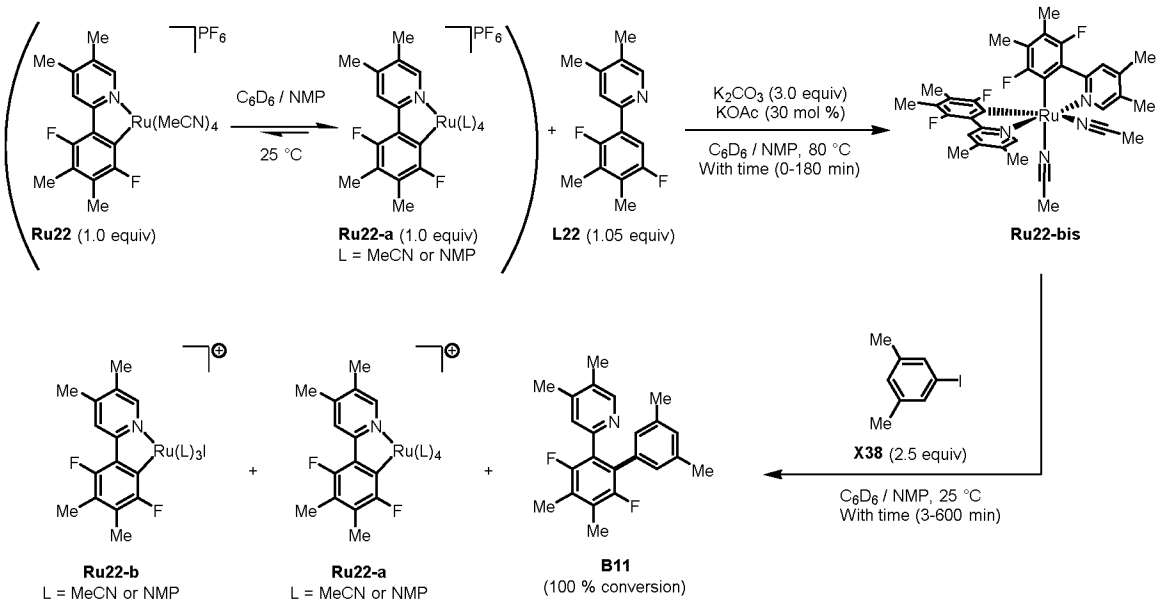
The General Procedure G was applied with Oxaprozin (586.6 mg, 2.0 mmol, 1 equiv.). Oxaprozin methyl ester **N7** was obtained as a pale yellow solid (596.3 mg, 97%).



N7

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.93 (t, *J* = 7.6 Hz, 2 H), 3.21 (t, *J* = 7.6 Hz, 2 H), 3.75 (s, 3 H), 7.29-7.42 (m, 6 H), 7.59 (d, *J* = 6.4 Hz, 2 H), 7.65 (t, *J* = 6.8 Hz, 2 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.6, 30.9, 51.9, 126.5, 127.9, 128.1, 128.5, 128.6, 128.6, 129.0, 132.5, 135.2, 145.4, 161.7, 172.5 ppm; mp 58-60 ºC; IR ν_{max} (neat/cm^{-1}): 3059, 2951, 1738, 1437, 1169; HRMS calcd for $C_{19}H_{18}O_3N$ $[M+H]^+$: 308.1281, found 308.1277.

Identification of the key bis-cyclometalated Ru(II) intermediate iii described in Scheme 2



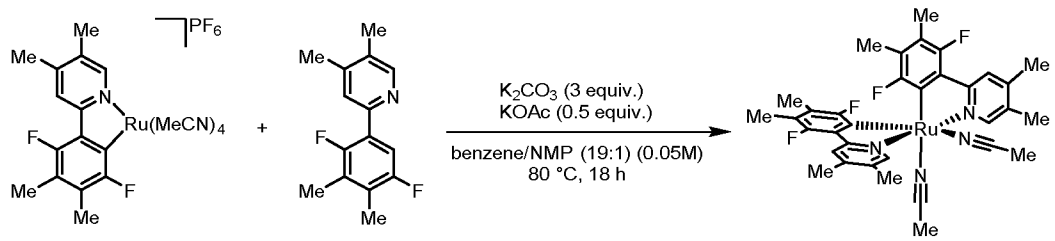
An oven dried NMR tube equipped with J. Young valve was transferred to a glove box, then **Ru22** (16.4 mg, 0.025 mmol, 1 equiv.), 2-arylpyridine **L22** (6.5 mg, 1.05 equiv.), K_2CO_3 (10.4 mg, 3 equiv.), KOAc (0.7 mg, 0.3 equiv.), benzene-d_6 (400 µL) and NMP (100 µL) were added. The tube was transferred out of the glove and analysed by NMR (time= 0 min). Then, it was placed in oil bath at 80 °C where it was periodically shaken. At 20, 40, 80, and 180 min the tube was removed from the oil bath just for the time needed for acquiring the NMR data. A change in colour from yellow/orange to deep red is associated with the formation of **Ru22-bis**. After this time, the tube was brought inside a glove and 5-iodo-*m*-xylene **X38** (9 µL, 2.5 equiv.) was added. Finally, the tube was transferred out of the glove box and the reaction was monitored at 3, 20, 60, 100, 260 and 600 min by NMR at 25 °C.

The reaction of cyclometalated complex **Ru22** with 2-arylpyridine **L22** was followed by ^{1}H and ^{19}F NMRs (see Figure 1b). A rapid ligand exchange took place at room temperature between the acetonitrile ligands of **Ru22** and NMP to produce **Ru22-a** (Figure 1b, spectra *a-c*). After 180 min

at 80 °C, **Ru22/Ru22-a** had quantitatively reacted with **L22** forming the bis-cyclometalated Ru(II) species **Ru22-bis**. Then, 5-iodo-*m*-xylene **X38** was added and the reaction was monitored at 25 °C. Over 600 min, **Ru22-bis** quantitatively reacted with **X38** forming arylated product **B11**, along with the cyclometalated complexes **Ru22-a** and **Ru22-b** deriving from reductive elimination. This experiment provides evidence that the catalytic cycle reported in Scheme 2 is, indeed, operating.

Figure 1b shows ^{1}H NMR and ^{19}F NMR expansions of the diagnostic area of the NMR spectra of: (***a***) **Ru22** in acetonitrile-d_3; (***b***) A freshly prepared sample of **Ru22** in 400 µL benzene-d_6 + 100 µL NMP showing the formation of **Ru22-a** likely due to ligand exchange of MeCN ligand(s) with NMP solvent; (***c***) **Ru22** after 12 hours at 25 °C in 400 µL benzene-d_6 + 100 µL NMP showing a different ratio between **Ru22** and **Ru22-a** with respect that present in (***b***); (***d***) **L22** in 400 µL benzene-d_6 + 100 µL NMP; (***Time 0-180 min***) Reaction between **Ru22**/**Ru22-a** and **L22** showing the formation of **Ru22-bis**. The relative intensity of the NMR peaks of **Ru22**/**Ru22-a** and **L22**are due to partial solubility of **Ru22**/**Ru22-a** in the solvent system; (***Time 3-600 min***) Reaction between **Ru22-bis** and **X38** showing the formation of **B11**, **Ru22-a** and **Ru22-b**; (***e***) **B11** in 400 µL benzene-d_6 + 100 µL NMP; (***f***) A freshly prepared sample of **Ru22** + KI (excess) in 400 µL benzene-d_6 + 100 µL NMP. **Ru22-b** was instantaneously formed after the addition of KI. The NMR samples (***a***)-(***f***) were prepared in a glove box using NMR tubes equipped with J. Young valves and their spectra are displayed in Figure 1b for clarity.

Preparation of the bis-cycloruthenated intermediate Ru22-bis described in Figure 1a

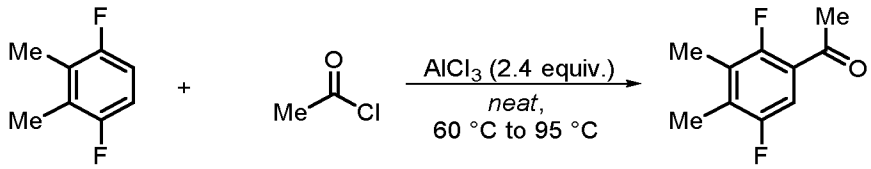


Ru22 (1.0 equiv) **L22** (1.1 equiv.) **Ru22-bis**, 72%

An oven dried crimp-cap microwave vial equipped with a stirring bar was transferred to a glove box, then **Ru22** (65.7 mg, 0.1 mmol, 1 equiv.), 2-arylpyridine **L22** (27.2 mg, 0.11 mmol, 1.1 equiv.), K_2CO_3 (41.5 mg, 0.3 mmol, 3 equiv.), KOAc (4.9 mg, 0.05 mmol, 0.5 equiv.), benzene (1.9 mL) and NMP (0.1 mL) were added. The vial was placed in a heating block at 80 °C and stirred for 18 h. Upon completion, the reaction crude was diluted with benzene and filtered through a short plug of Celite®. The solution was concentrated under reduced pressure and the resulting residue was redissolved in a minimum amount of benzene. **Ru22-bis** was precipitated after the addition pentane as a deep red solid (48.7 mg, 72%). **Ru22-bis** must be kept in a glove box as it quickly decomposes if exposed to air.

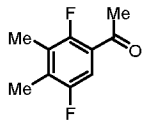
^{1}H-NMR (500 MHz, C_6D_6) δ 0.59 (s, 6 H), 1.84 (s, 6 H), 2.01 (s, 6H), 2.06 (s, 6 H), 2.10 (s, 6 H), 8.56 (s, 2 H), 9.30 (s, 2 H) ppm; ^{13}C-NMR (125 MHz, C_6D_6) δ 10.9 (dd, *J* = 7.1 Hz), 11.8-11.9 (m), 16.7, 19.4, 114.1 (dd, *J* = 20.4, 3.4 Hz), 122.4 (dd, *J* = 26.6, 4.8 Hz), 123.4 (d, *J* = 22.3 Hz), 127.4, 133.3 (dd, *J* = 21.6, 4.9 Hz), 142.0, 149.5 (d, *J* = 41.3 Hz), 151.2, 156.6 (d, *J* = 246.1 Hz), 165.1 (d, *J* = 7.6 Hz), 167.6 (d, *J* = 222.8 Hz), 170.3 (d, *J* = 54.4 Hz) ppm (Me group of the MeCN ligand is missing due to an upfield shift); ^{19}F-NMR (376 MHz, C_6D_6) δ −124.2 (d, *J* = 23.3 Hz), −123.6 (d, *J* = 23.3 Hz) ppm.

Preparation of 2-arylpyridine L22

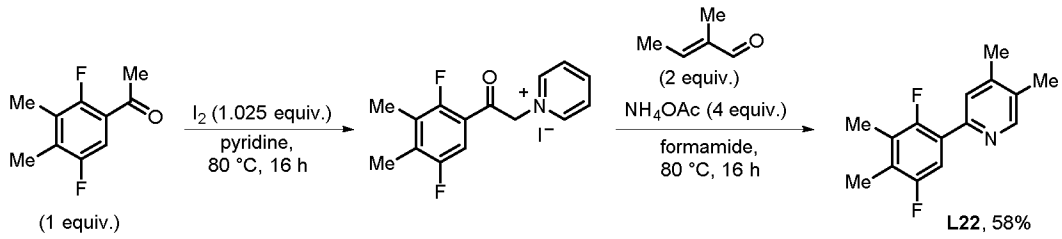


(28 mmol, 1 equiv.) (1.5 equiv.) 80%

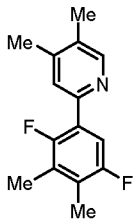
A 50 mL Schlenk flask equipped with a magnetic stirring bar was charged with 1,4-difluoro-2,3-dimethylbenzene (3.98 g, 28 mmol, 1 equiv.) and $AlCl_3$ (8.96 g, 67.2 mmol, 2.4 equiv.). The reaction was heated at 60 °C under vigorous stirring and acetyl chloride (3.0 mL, 42 mmol, 1.5 equiv.) was slowly added via syringe over 5 min. Then, the mixture was heated at 95 °C and the progression of the reaction was monitored by GC-MS. At complete conversion (about 2 h) the mixture was slowly poured onto a mixture of ice (200 g) and H_2O (200 mL). The aqueous phase was extracted with Et_2O, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (hexane/Et_2O, 9:1) affording the desired acetophenone derivative as a pale yellow oil (4.13 g, 80%).



^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.21-2.26 (m, 6 H), 2.59-2.64 (m, 3 H), 7.35 (dd, *J* = 9.5, 6.0 Hz, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.2 (dd, *J* = 6.5, 2.0 Hz), 11.7 (dd, *J* = 4.5, 2.0 Hz), 31.3 (d, *J* = 8.3 Hz), 112.7 (dd, *J* = 26.9, 3.6 Hz), 123.6 (dd, *J* = 17.0, 6.9 Hz), 126.7 (dd, *J* = 20.3, 4.1 Hz), 131.4 (dd, *J* = 18.5, 5.3 Hz), 156.4 (dd, *J* = 246.8, 2.0 Hz), 156.8 (dd, *J* = 239.6, 2.0 Hz), 195.0 (dd, *J* = 3.5, 1.1 Hz) ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ −121.0 (d, *J* = 18.8 Hz), −117.6 (d, *J* = 18.8 Hz) ppm; IR ν_{max} (neat/cm^{-1}): 3006, 2932, 1684, 1625, 1473, 1416, 1361, 1322, 1286, 1237, 1192, 1088; HRMS calcd for $C_{10}H_{11}OF_2$ $[M+H]^+$: 185.0772, found 185.0772.



A 50 mL round-bottom flask equipped with a magnetic stirring bar was charged with 1-(2,5-difluoro-34-dimethylphenyl)ethan-1-one (2.58 g, 14 mmol, 1 equiv.) and dry pyridine (3.5 mL, 4 M). A solution of Iodine (3.64 g, 14.35 mmol, 1.025 equiv.) in dry pyridine (5.6 mL, 2.56 M) was added and the mixture was stirred at 80 °C for 16 h. Upon completion, the reaction was cooled to room temperature. The precipitate was filtered, washed once with pyridine, diethyl ether, dried under vacuum and recrystallized from boiling ethanol. The corresponding pyridinium derivative was obtained as light brown powder, dried under vacuum and directly employed in the next step. A 100 mL round-bottom flask equipped with a magnetic stirring bar was loaded with the pyridinium salt (4.8 g, 12.38 mmol, 1 equiv.), ammonium acetate (3.82 g, 49.52 mmol, 4 equiv.), tiglic aldehyde (2.48 mL, 24.76 mmol, 2 equiv.), formamide (31 mL, 0.4 M) and heated at 80 °C for 16 h. After this time, the mixture was cooled to room temperature and extracted with Et_2O (3×150 mL). The ethereal phases were united, evaporated to dryness, and the residue was purified by column chromatography (hexane/Et_2O, 85:15) affording **L22** as a colourless solid (2.01 g, 58% over 2 steps).

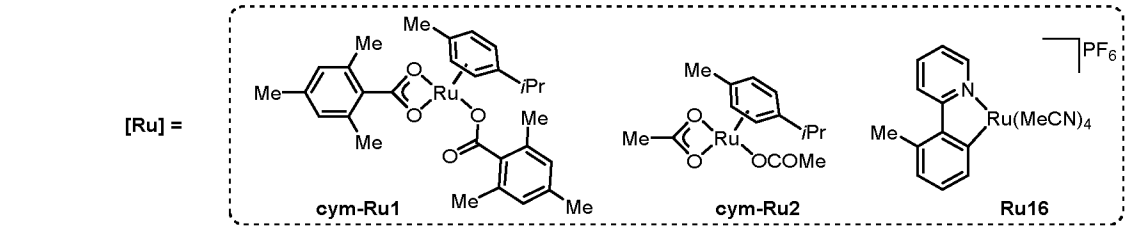


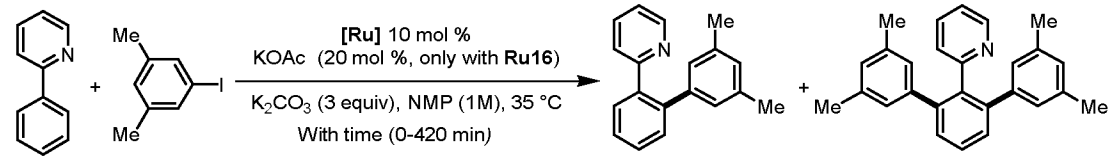
^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.24 (d, *J* = 2.0 Hz, 3 H), 2.26 (d, *J* = 2.5 Hz, 3 H), 2.29 (s, 3 H), 2.33 (s, 3 H), 7.46 (dd, *J* = 10.5, 6.5 Hz, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 8.42 (s, 1 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.3 (dd, *J* = 4.6, 2.0 Hz), 11.4 (dd, *J* = 6.5, 2.3 Hz), 16.2, 19.4, 113.3 (dd, *J* = 26.9, 4.0 Hz), 125.1 (d, *J* = 9.3 Hz), 125.3-125.9 (m, 3 C), 131.2, 145.9, 149.9, 150.7, 154.4 (dd, *J* = 240.9, 2.1 Hz), 157.1 (dd, *J* = 237.5, 2.1 Hz) ppm; ^{19}F-NMR (470 MHz, $CDCl_3$) δ −125.8 (d, *J* = 18.3 Hz), −122.3 (d, *J* = 19.3 Hz) ppm; mp 105-109 ºC; IR ν_{max} (neat/cm^{-1}): 2994, 2921, 2854, 1594, 1557, 1489, 1467, 1442, 1417, 1236, 1193, 1083; HRMS calcd for $C_{15}H_{16}NF_2$ $[M+H]^+$: 248.1245, found 248.1240.

Comparison of the catalytic activity of cyclometalated ruthenium(II) catalysts and ruthenium-catalysts cym-Ru1 and cym-Ru2

The rate of the reaction catalysed by **Ru16** and KOAc was compared to that of **cym-Ru1** and **cym-Ru2**, which are the most widely employed state-of-the-art ruthenium-catalysts (for examples see: *Adv. Organomet. Chem.* **2017**, *67*, 299–399; *ACS Catal.* **2017**, *7*, 5721–5745). Particularly, the C–H arylation of 2-phenylpyridine **N11** with 5-iodo-*m*-xylene **X38** was monitored over time at 35 °C (see Table 3 below and Figure 2). Remarkably, while the cyclometalated **Ru16** catalyst afforded a combined yield of 89% of mono (**B10**) and diarylated (**B10-bis**) adducts in 420 min, **cym-Ru1** and **cym-Ru1** were essentially inactive. These results

demonstrate that cycloruthenated catalysts of formula (I) possess a far superior catalytic activity than the commonly employed Ru(II) species like **cym-Ru1** or **cym-Ru2**, enabling reactivity to occur at unprecedentedly low temperatures.





[Ru]	cym-Ru1			cym-Ru1			Ru16		
KOAc	-			-			20 mol %		
time (min)	**N11** (%)	**B10** (%)	**B10-bis** (%)	**N11** (%)	**B10** (%)	**B10-bis** (%)	**N11** (%)	**B10** (%)	**B10-bis** (%)
1	99.5	0.0	0.0	98.7	0.0	0.0	99.8	0.0	0.0
5	99.2	0.0	0.0	98.7	0.0	0.0	96.7	0.3	0.6
10	99.0	0.0	0.0	98.5	0.0	0.0	91.5	1.0	2.5
30	99.3	0.0	0.0	98.9	0.0	0.1	72.2	3.7	15.6
45	99.0	0.0	0.0	99.2	0.0	0.0	58.8	4.9	25.0
60	99.0	0.0	0.0	98.4	0.0	0.1	48.9	5.8	33.4
75	98.7	0.0	0.0	98.7	0.0	0.0	41.2	6.2	39.6
90	98.8	0.0	0.0	98.2	0.0	0.1	35.7	6.6	44.8
120	98.2	0.0	0.0	97.3	0.0	0.1	26.7	6.8	53.6
150	98.1	0.0	0.1	97.3	0.0	0.1	19.7	6.5	60.7
180	98.3	0.0	0.1	97.6	0.0	0.2	14.5	6.3	67.0
210	98.5	0.0	0.0	97.9	0.0	0.2	9.3	5.3	72.4
240	98.5	0.0	0.0	97.2	0.1	0.3	5.1	4.5	76.7
270	98.4	0.0	0.1	98.2	0.1	0.3	3.3	3.7	80.2
300	98.5	0.0	0.1	97.8	0.1	0.3	1.8	3.2	83.1
360	98.3	0.0	0.2	98.7	0.1	0.4	0.7	2.3	86.6
420	98.3	0.0	0.2	98.6	0.1	0.4	0.7	2.3	86.6

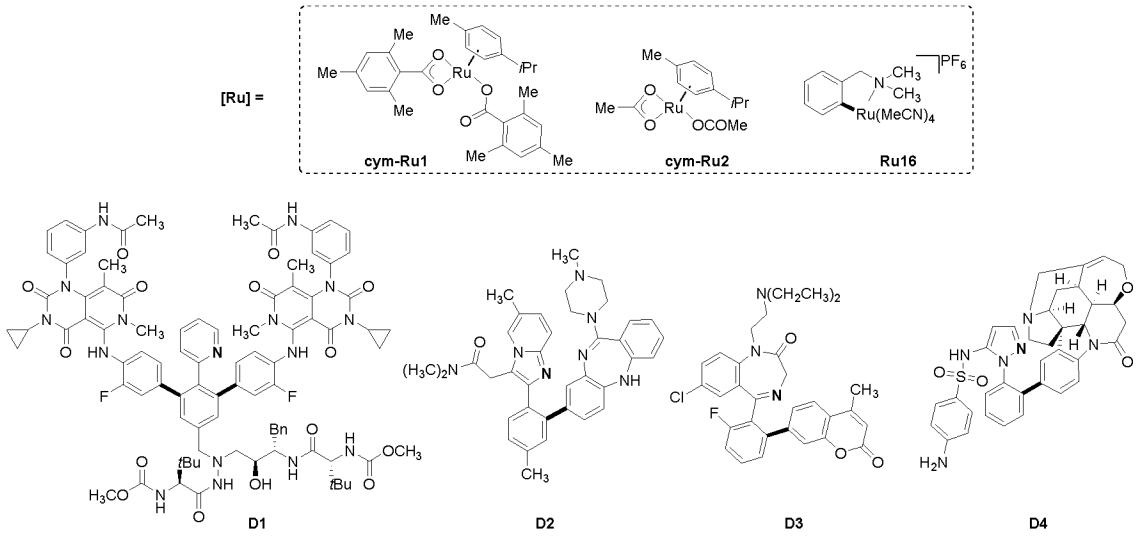
Table 3. An oven dried crimp-cap microwave vial equipped with a stirring bar was transferred to a glove box, then the appropriate Ru-catalyst denoted as [Ru] (10 mol %, 0.08 mmol: **cym-Ru1**, 45.1 mg; **cym-Ru2**, 28.3 mg; **Ru16**, 46.3 mg), K_2CO_3 (331.7 mg, 2.4 mmol, 3 equiv.), KOAc (*if needed*: 15.7 mg, 0.16 mmol, 0.2 equiv.), 2-phenylpyridine **N11** (124.2 mg, 0.8 mmol,

1 equiv.), 5-iodo-*m*-xylene **X38** (230.9 µL, 1.6 mmol, 2 equiv.) and hexadecane (internal standard:15 µL, 0.064 equiv.) were loaded. NMP (800 µL, 1 M) that had been preheated to 35 °C was added and the vial instantly placed in a heating block set at 35 °C. Aliquots (≈50-100 µL) were taken at the given time periods via syringe (1 mL disposable). Then, the syringes were transferred out of the glove box, flushed and eluted in a short silica plug with Et_2O/pyridine (99:1) directly inside a GC vial. The yields were determined by quantitative GC-FID analysis

Figure 2 shows a comparison of the catalytic activity of the system constituted by cycloruthenated **Ru16** catalyst and KOAc (filled squares) with respect to **cym-Ru1** (hollowed circles) and **cym-Ru1** (crosses) catalysts. For further information see Table 3.

Comparison of the activity of cyclometalated ruthenium(II) catalyst Ru9 with that of catalysts cym-Ru1 and cym-Ru2

To further illustrate the disparity in reactivity between cycloruthenated catalysts of formula (I) and commonly employed Ru(II) catalysts in C–H arylation, **cym-Ru1**, **cym-Ru2** and **Ru9** catalysts were used for the coupling of two heavily-functionalised substrates. While **Ru9** provided superb yield of the targeted arylated compounds **D1-D4**, catalysts **cym-Ru1** and **cym-Ru2** were essentially inactive (see Table 5 below).

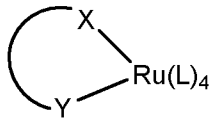


[Ru]	**D1** (%)	**D2** (%)	**D3** (%)	**D4** (%)
cym-Ru1	<1	<1	<1	<1
cym-Ru2	<1	<1	2	<1
Ru9	65	76	90	67

Table 5. Reaction conditions were identical to those described in the characterization data for arylated compounds section when the General Procedure C was successfully applied with **Ru9** to yield **D1**-**D4** (see above for details), but **cym-Ru1** and **cym-Ru2** were used instead of **Ru9** without KOAc or KOBz.

Claims

1. A process for forming a carbon-carbon bond to couple an aryl or heteroaryl group of a first compound with an aryl or heteroaryl group 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:

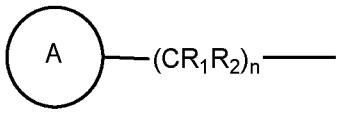
each L is independently selected from neutral and anionic ligands in any combination that balances the bonding and charge requirements of the ruthenium, and wherein any two ligands L can be linked so as to form a bidentate ligand; and

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)

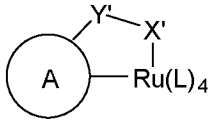
wherein

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

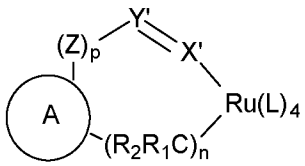
L is as defined in claim 1;

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;

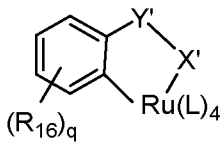
Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H or (1-4C)alkyl;

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;

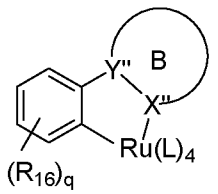
q represents 0, 1, 2, 3 or 4;

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:

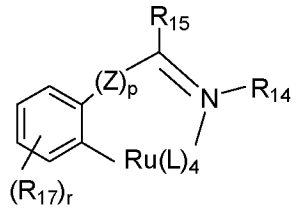
L is as defined in claim 1;

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;

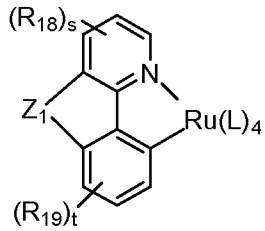
Z represents CR_3R_4, O or NR_5, wherein R_3, R_4 and R_5 each independently represent H or (1-4C)alkyl;

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;

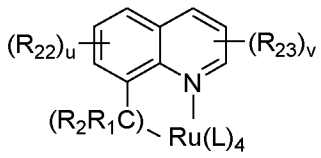
s represents 0, 1, 2 or 3;

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;

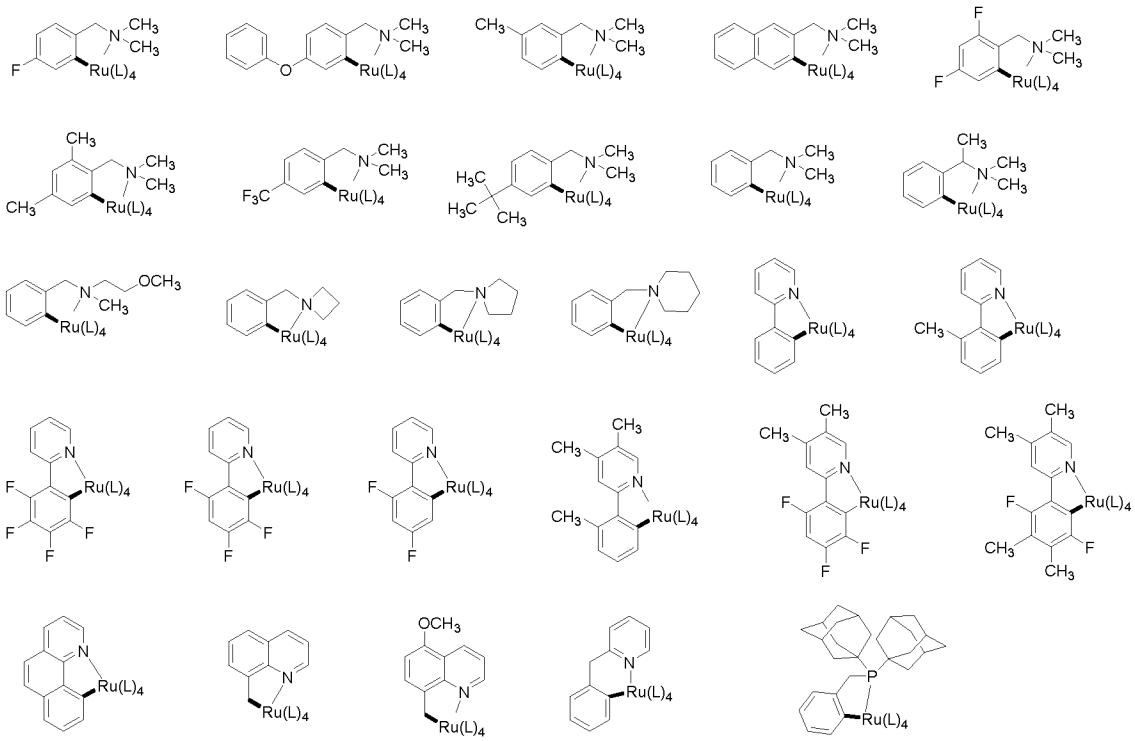
R_1 and R_2 are each independently selected from H or (1-4C)alkyl;

u represents 0, 1, 2 or 3;

v represents 0, 1, 2 or 3;

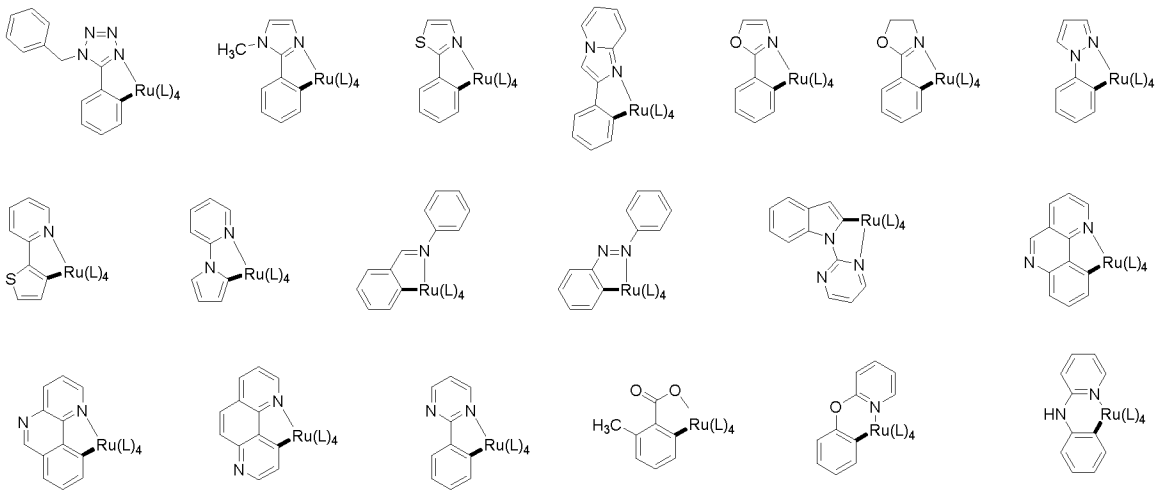
each R_{22} and R_{23} is independently selected from halo, (1-10C)alkyl, (1-10C)alkoxy, phenoxy, trifluoromethyl, (3-8C)cycloalkyl, aryl, heteroaryl, (2-10C)alkenyl, hydroxyl, amino, (1-10C)alkylamino, di[(1-10C)alkyl]amino, (1-10C)alkanoyl, (1-10C)alkylthio, amido, (1-10C)alkylamido, di[(1-10C)alkyl]amido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

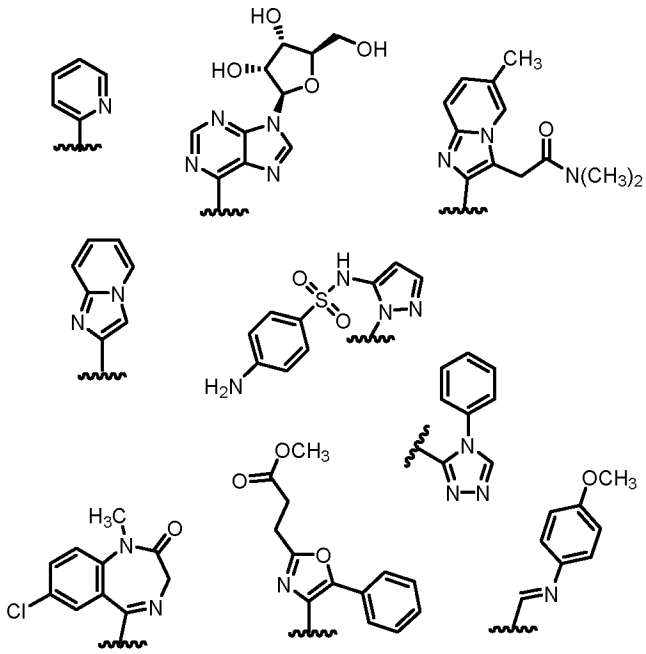


wherein L is as defined in claim 1.

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 ortho to the first ring atom and which has a nitrogen containing directing group (or a salt or protected derivative thereof) bonded thereto,

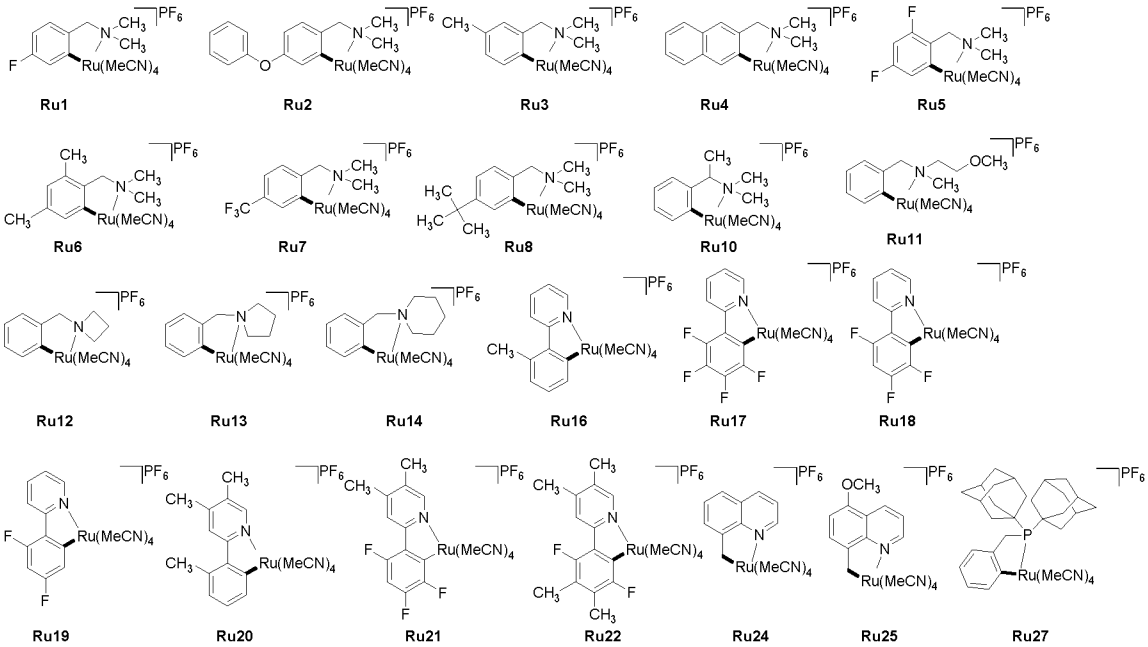
and wherein the second compound comprises an aryl or heteroaryl group having a first ring atom which is a carbon atom having a leaving group bonded thereto, such that the reaction between the first compound and the second compound results in the formation of a carbon-carbon bond between the first ring atom of the first compound and the first ring atom of the second compound.

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



17. A process according to any preceding claim which is conducted at a temperature from 25 to 60°C, preferably 25 to 50°C.

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


Ru1
Ru2
Ru3
Ru4
Ru5
Ru6
Ru7
Ru8
Ru10
Ru11
Ru12
Ru13
Ru14
Ru16
Ru17
Ru18
Ru19
Ru20
Ru21
Ru22
Ru24
Ru25
Ru27

.

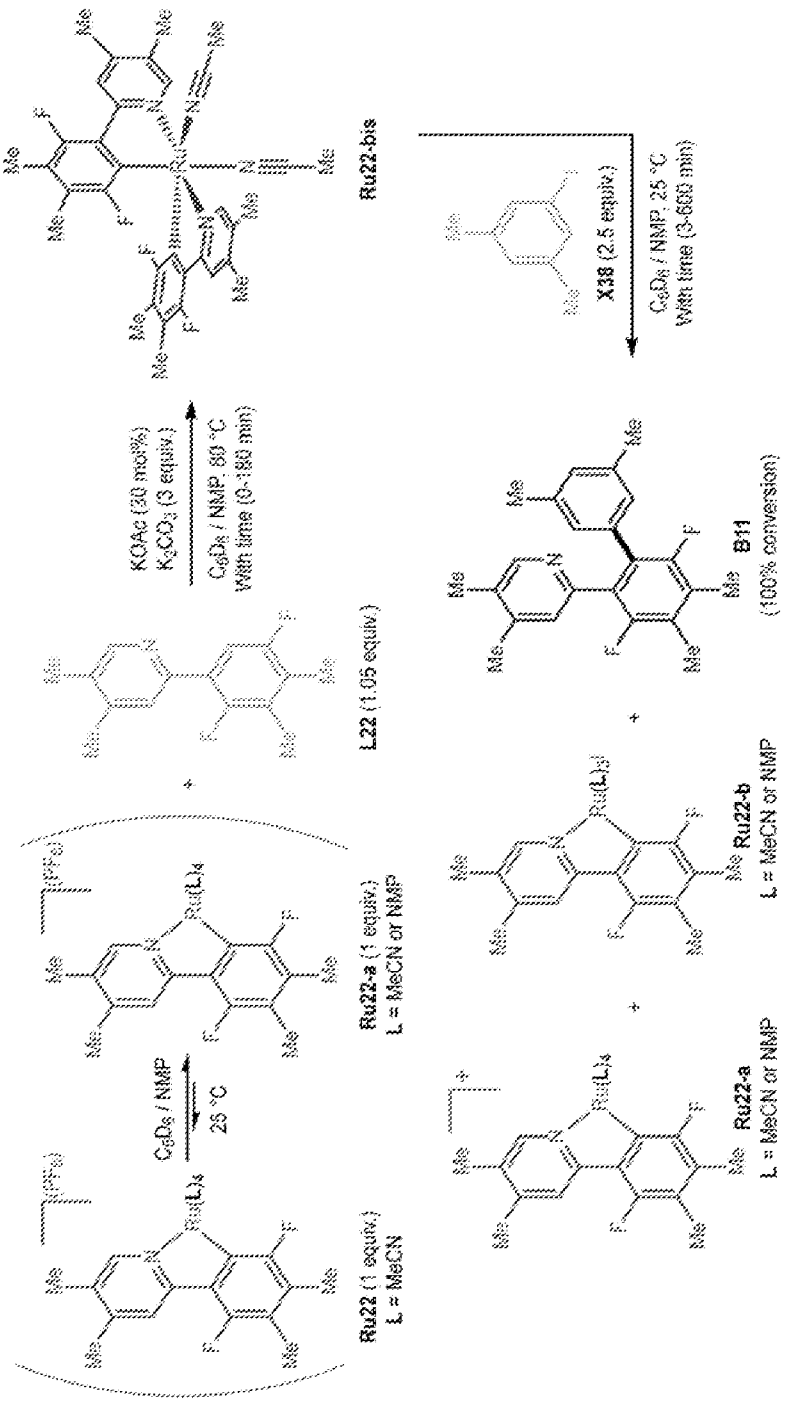

Ru22 (1 equiv.)
L = MeCN
C6D6 / NMP
25 °C
Ru22-a (1 equiv.)
L = MeCN or NMP
L22 (1.05 equiv.)
KOAc (30 mol%)
K2CO3 (3 equiv.)
C6D6 / NMP, 80 °C
With time (0-180 min)
Ru22-bis
X38 (2.5 equiv.)
C6D6 / NMP, 25 °C
With time (3-666 min)
B11
(100% conversion)
Ru22-b
L = MeCN or NMP
Ru22-a
L = MeCN or NMP

Figure 1a

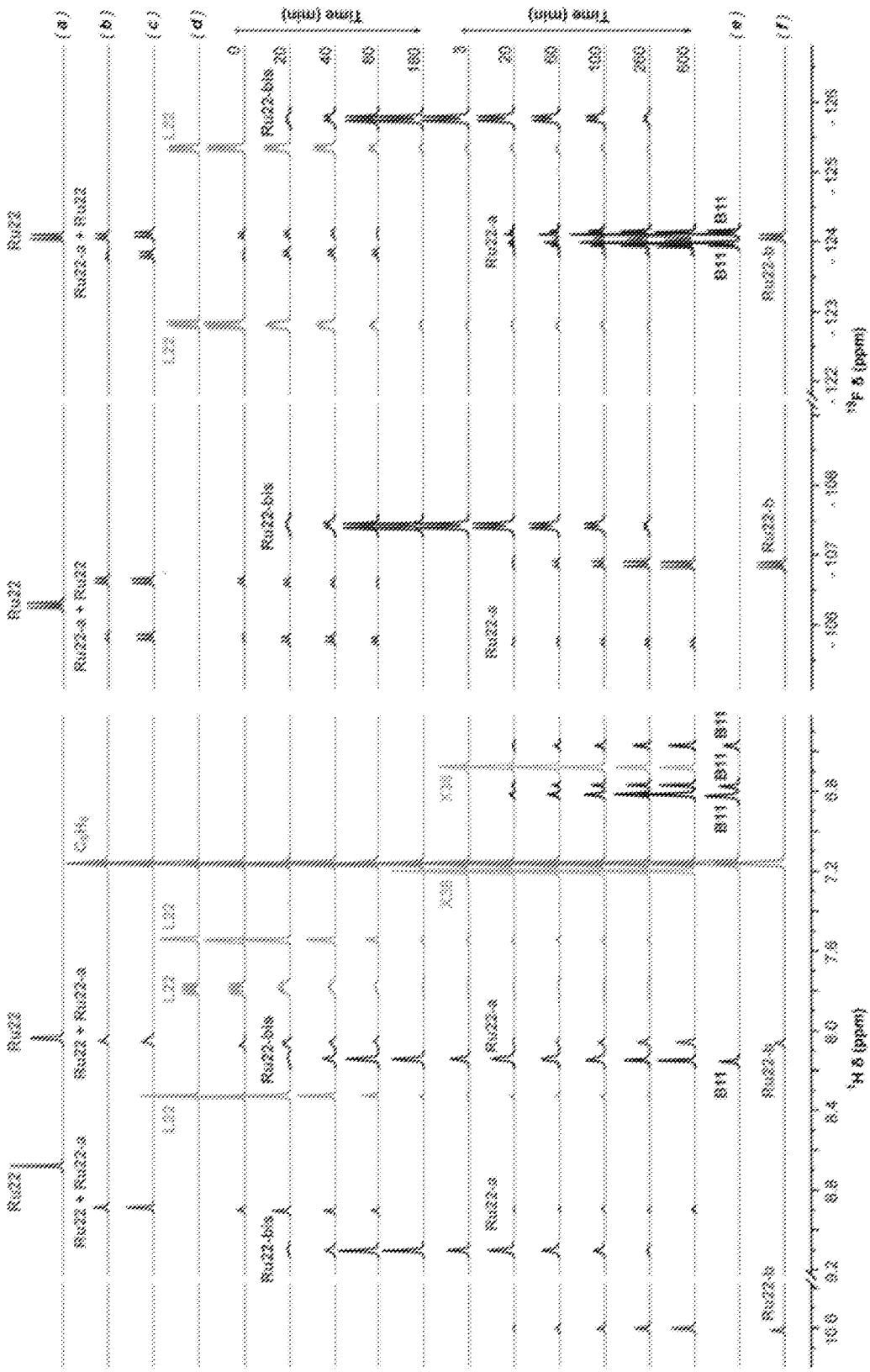
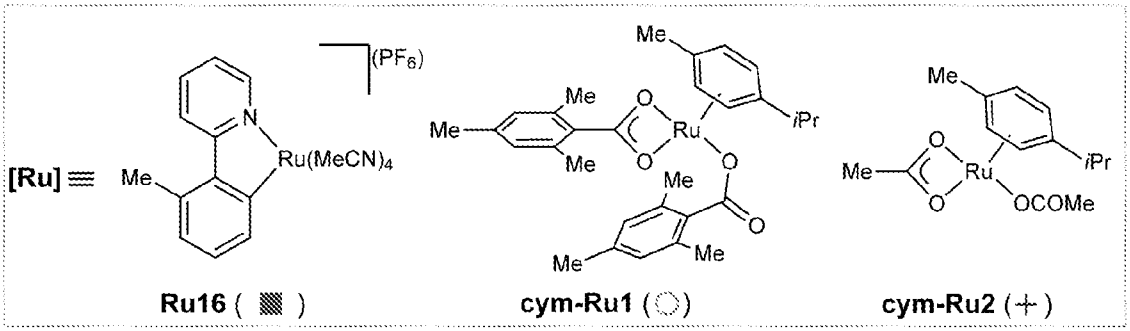
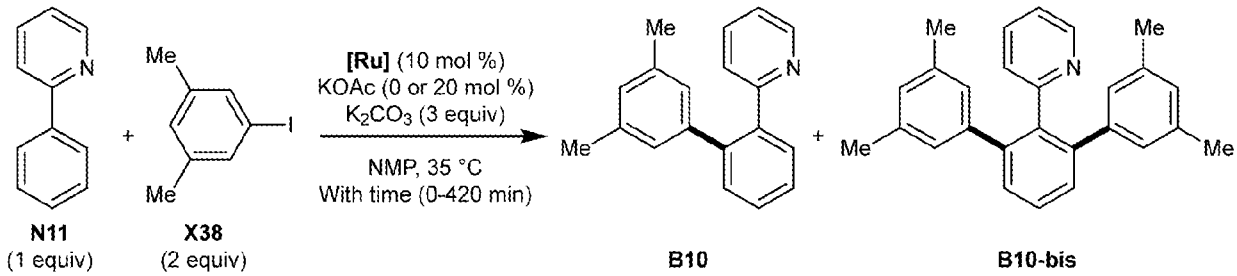


Figure 1b


[Ru] ≡
Me
N
Ru(MeCN)4
(PF6)
Ru16 ( )
Me
Me
Me
O
O
Ru
iPr
O
Me
Me
Me
O
cym-Ru1 ( )
Me
Me
O
O
Ru
iPr
OCOMe
cym-Ru2 (+)


N
N11
(1 equiv)
+
Me
I
Me
X38
(2 equiv)
[Ru] (10 mol %)
KOAc (0 or 20 mol %)
K2CO3 (3 equiv)
NMP, 35 °C
With time (0-420 min)
Me
N
Me
B10
+
Me
Me
N
Me
Me
B10-bis

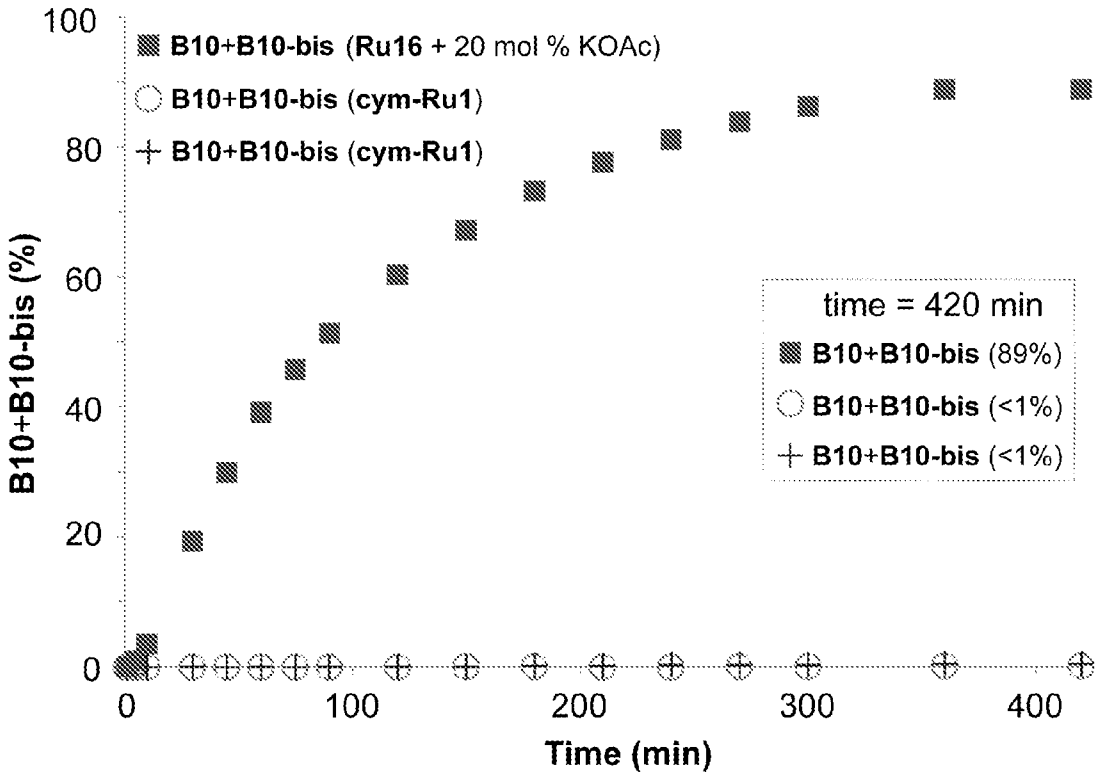

100
80
60
40
20
0
B10+B10-bis (%)
B10+B10-bis (Ru16 + 20 mol % KOAc)
B10+B10-bis (cym-Ru1)
B10+B10-bis (cym-Ru1)
time = 420 min
B10+B10-bis (89%)
B10+B10-bis (<1%)
B10+B10-bis (<1%)
0
100
200
300
400
Time (min)

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/051226

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F15/00
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)
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	SATOSHI UENO ET AL.: "Ruthenium-Catalyzed Carbon-Carbon Bond Formation via the Cleavage of an Unreactive Aryl Carbon-Nitrogen Bond in Aniline Derivatives with Organoboronates", J. AM. CHEM. SOC., vol. 129, 20 April 2007 (2007-04-20), pages 6098-6099, XP002792079, scheme 1 page 6098	1-17

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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
14 June 2019	28/06/2019

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/051226

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAVID DASTBARAVARDEH ET AL.: "Aryl Bromides and Aryl Chlorides for the Direct Arylation of Benzylic AminesMediated by Ruthenium(II)", EUR. J. ORG. CHEM., vol. 2013, no. 14, 22 March 2013 (2013-03-22), pages 2878-2890, XP002792080, table 1 page 2879	1-18
Y	LARRY N LEWIS ED - 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	1-17
X	MOTLEY TYLER C ET AL: "Excited-State Decay Pathways of Tris(bidentate) Cyclometalated Ruthenium(II) Compounds", INORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 56, no. 21, 25 October 2017 (2017-10-25), pages 13579-13592, XP002791896, ISSN: 0020-1669 page 13581	18

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