Abstract: The present invention relates to methods of preparing compounds of formula (I) comprising the step of reacting the corresponding amide with the corresponding substituted aryl in the presence of a catalyst, which catalyst comprises copper and a ligand, \( \text{Y} \) is \( \text{CHCHR} \) or \( \text{C} = \text{C}(\text{A})\text{Z} \), \( \text{CY} \times \text{R}(\text{R})\text{Y}(\text{R}) \), \( \text{C} = \text{N}-\text{NR}(\text{R}) \); \( \text{Y}^2 \) and \( \text{Y}^3 \) are, independently, \( \text{O, S, N} \); \( \text{R} \) and \( \text{Z} \) are, independently, \( \text{CF}_x \) alkyl; \( \text{R}^1 \) is \( \text{CF}_x \) or \( \text{CF}_x \); \( \text{R}^2 \) and \( \text{R}^3 \) are, independently, \( \text{C}s \) alkyl; \( \text{B} \) is a single bond or a double bond; \( \text{R}^4 \) and \( \text{R}^7 \) are, independently, hydrogen or \( \text{C}_x \) alkyl.
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The present invention relates to methods for the preparation of pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides and also to intermediates for use in such methods.

Pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides, for example 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid (9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide, are valuable fungicides. These are described in WO 04/035589.

WO 04/035589 describes processes for the preparation of pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides, as shown in schemes 1 and 2 below. Het, R', R¹ R², R³, R⁴, R⁵, R⁶, R⁷, X and Y are as described in WO 04/035589.
According to the process shown in Scheme 1, a compound of formula (Ia) may be prepared by reacting an ester of formula (Ha) with an aniline of formula (Iiia) in the presence OfNaN(TMS)₂. According to the first process shown in Scheme 2, a compound of formula (Ia) may be prepared by reacting an acid of formula (Ifa) with an aniline of formula (Iiia) in the presence of an activating agent, such as BOP-Cl, and two equivalents of a base, such as triethylamine. According to the second process shown in Scheme 2, a halo-acid chloride of formula (II'a) is obtained from an acid of formula (Ifa) by treatment with a halogenating agent such as thionyl chloride, which is then reacted with an aniline of formula (Iiia) in the presence of a base to give a compound of formula (Ia). There are some technical issues associated with reactions involving halo-acids due to their sensitivity to water.

WO 2007/031323 describes improvements in the process for the preparation of the pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides but the improvements relate to earlier steps of the synthetic pathway described in WO 04/035589.


To facilitate large-scale production of pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides it would be desirable to find alternative synthetic pathways that allow production in high yield, preferably on a large scale.

Surprisingly, it has now been found that pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides may be prepared in high yield by reacting an ortho-substituted benzonorbornene compound with a pyrazolyl-4-amide in the presence of a catalyst comprising a metal and a ligand.

This finding was unexpected for a number of reasons. First, the bulky fused tri-cyclic ring system of the benzonorbornene compound places a high degree of steric hindrance at the ortho position of the aromatic ring, making access to the ortho position difficult.
In addition, in light of the proposed reaction mechanisms for metal catalysed aryl-amide coupling, one would expect the fused ring system of norbornene to occupy a large amount of coordination space around the metal atom, thereby significantly reducing the likelihood of effective chelation of both the reactants and ligand to the metal atom.

Accordingly, in a broad aspect, this invention relates to the synthesis of pyrazolyl-4-carboxylic acid benzonorbornen-5-yl-amides by reacting an ortho-substituted benzonorbornene compound with a pyrazolyl-4-amide in the presence of a catalyst comprising a metal.

In a first aspect of the invention there is provided a method of preparing a compound of formula (I):

![Formula (I)](image)

wherein

Y is CHCHR₆(R₇), C=C(A)Z, CY²(R²)Y³(R³), or C=N-NR⁴(R⁵);

Y² and Y³ are, independently, O, S, N;

A and Z are, independently, C₆ alkyl;

R¹ is CF₃ or CF₂H;

R² and R³ are, independently, C₈ alkyl, wherein R² and R³ are optionally joined to form a 5-8 membered ring;

R⁴ and R⁵ are, independently, C₅ alkyl;

B is a single bond or a double bond;

R⁶ and R⁷ are, independently, hydrogen or C₆ alkyl;

comprising the step of reacting a compound of formula (II):
wherein
X is F, Cl, Br, I or a sulphonate;
Y and B are as defined for the compound of formula (I);
with a compound of formula (III):
any stereoisomers, geometric isomers, tautomers, and salts of the compound unless otherwise stated.

When $Y$ is $C Y^2 (R^2) Y^3 (R^3)$, $Y^2$ and $Y^3$ are both directly bonded to the carbon atom. $R^2$ is directly bonded to $Y^2$ and $R^3$ is directly bonded to $Y^3$.

The following preferred substituent definitions apply to all aspects of the invention and may be combined in any combination.

Preferably, $A$ and $Z$ are each, independently, $C_{i-4}$ alkyl.

Preferably, $A$ and $Z$ are each, independently, CH3.

Preferably, $Y^2$ and $Y^3$ are each, independently, O or S.

Preferably, $Y^2$ and $Y^3$ are each, independently, O.

Preferably, $B$ is a single bond.

Preferably, $R^1$ is CF3, CHF2 or CH2F.

Preferably, $R^1$ is CF3 or CHF2.

Preferably, $R^1$ is CHF2.

Preferably $R^2$ and $R^3$ are each, independently, $C_{i-4}$ alkyl; or $R^2$ and $R^3$ are together a 4-6 membered ring.

Preferably, $R^2$ and $R^3$ are each, independently, methyl or ethyl; or $R^2$ and $R^3$ are together an ethylene or propylene group.

Preferably, $R^2$ and $R^3$ are each, independently, methyl or $R^2$ and $R^3$ are together an ethylene group.

Preferably, $R^4$ and $R^5$ are each, independently, $C_{i-4}$ alkyl.

Preferably, $R^4$ and $R^5$ are each, independently, methyl or ethyl, preferably methyl.

Preferably, $R^6$ and $R^7$ are each, independently, methyl or ethyl, preferably methyl.

Preferably, $Y$ is CHCHR 6($R^7$) or C=C(A)Z.

Preferably, $Y$ is CHCH(CH3)CH3 or C=C(CH3)CH3.

Preferably, $Y$ is CHCH(CH3)CH3.

Preferably, $X$, e.g. in formula (II), is Cl, Br, or I, more preferably Cl, e.g. the compound of formula (II) may be a benzonorbornen-5-yl-chloride.
The term 'sulphonate' is art recognized and includes a moiety that can be represented by the general formula:

\[-S\text{-OR}^*\]

in which \(R^*\) is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl. For example, \(X\) may be triflate, tosylate, mesylate, or nonaflate, e.g. it may be trifluoromethanesulfonate ester, \(p\)-toluenesulfonate ester, methanesulfonate, or nonafluorobutanesulfonate ester. In particular, \(X\) may be tosylate or mesylate.

Carbon chains, e.g. alkyl, may be branched or unbranched.

In a further embodiment, there is provided a method of preparing a compound of formula (IA):

\[
\begin{align*}
&\text{R}^1 &\text{R}^6 &\text{R}^7 &\text{Y} &\text{B} \\
&\text{N} &\text{N} &\text{C} &\text{H} &\text{N} \text{C} &\text{B} \\
&\text{CH}_3 &\text{N} &\text{C} & &
\end{align*}
\]

(IA)

which are compounds of formula I wherein:

\(Y\) is \(\text{CHCHR}^6(\text{R}^7)\) or \(\text{C}=\text{C}(\text{A})Z\);
\(B\) is a single bond or a double bond;
\(A\) and \(Z\) are, independently, \(\text{C}_6\) alkyl;
\(\text{R}^1\) is \(\text{CF}_3\) or \(\text{CF}_2\text{H}\); and
\(\text{R}^6\) and \(\text{R}^7\) are, independently, hydrogen or \(\text{C}_1\) alkyl;

comprising the step of reacting a compound of formula (HA):
wherein

X is F, Cl, Br, I or a sulphonate;

Y and B are as defined for the compound of formula (IA);

with a compound of formula (IIIA):

wherein R₁ is as defined for the compound of formula (IA);

in the presence of a catalyst, which catalyst comprises copper and a ligand.

It has been found that reactions involving benzonorbornen-5-yl-chlorides also proceed with up to effectively quantitative yields. Aryl C-Cl bonds are much less reactive compared to the corresponding aryl C-Br or aryl C-I bonds; indeed, it is recognised in the art that the high stability of aromatic carbon-chlorine bonds makes aryl chlorides very difficult to utilise (Grushin and Alper, Chem. Rev., 1994, 1047-1062). Although there are a small number of reports of metal catalysed amidation of chloro-substituted aryls, steric hindrance at the chloro position was not a significant consideration and yields were low when the aryl chlorides were functionalised (Klapars et al. J. Am. Chem. Soc, 2002, 124, 7421-7428; Ikawa et al., J. Am. Chem. Soc, 2007, 129, 13001-
13007). The present case differs from these reports in that there is a high degree of steric hindrance at the chloro position, as discussed above. In light of this and the inert nature of aryl C-Cl bonds, this result was highly unexpected.

The copper may be a copper atom or ion and, for example, may be derived from any copper salt, such as Cu(I) or Cu(II). For example, the copper may be CuCl, CuBr, CuI, CuCl₂, Cu₂O, CuBr₂, CuI₂, CuO, CuSCN, CuSO₄, Cu(OAc)₂, Cu(acac)₂ (acac = acetylacetonate), or a mixture thereof. Preferably, the catalyst of the invention comprises CuCl, CuBr, CuI or a mixture of two or more thereof.

The ligand comprised by the catalyst may be a chelating ligand, e.g. a bidendate ligand. The one or more atoms on the ligand mediating chelation, usually Lewis basic atoms, may be independently selected from nitrogen, oxygen, phosphorus or arsenic, and preferably are nitrogen. For the avoidance of doubt, where reference is made to a catalyst comprising "a ligand", the catalyst may comprise more than one type of ligand. Likewise, where reference is made to a catalyst comprising "the ligand", the catalyst may comprise one or more other types of ligand in addition to the ligand referred to.

Examples of suitable ligands include alkyl alcohol, aryl alcohol e.g. phenol, alkyl amine, diamine e.g. 1,2-diamine or 1,3-diamine, 1,2-aminoalcohol, 1,2-aminoether e.g. tris(3,6-dioxahexyl)amine, 1,2-aminoacid e.g. picolinic acid, 1,2-diol, imidazolium carbene, pyridine, 1,10-phenanthroline, 1,3-diketone e.g. 2,4-pentadione; each optionally substituted. Preferably the ligand is a diamine, e.g. an optionally substituted 1,2-diamine and/or an optionally substituted 1,10-phenanthroline.

For example, the ligand or ligands may be 1,2-diaminoalkane, 1,3-diaminoalkane, 1,2-diaminocyclohexane, 1,10-phenanthroline, 2-hydroxyethyl amine, or 1,2-diaminoethane, each optionally substituted. Preferably the ligand is optionally substituted 1,2-diaminocyclohexane or optionally substituted 1,2 ethylenediamine such as 1,2-diaminocyclohexane, N,N'-dimethyl-1, 2-diaminocyclohexane, N-tolyl-1, 2-diaminocyclohexane, 1, 2 ethylenediamine, N,N'-dimethyl ethylenediamine. Preferably the ligand is N, N' dimethyl 1,2 diamine cyclohexane, N, N' dimethyl 1,2 diethylamine,
or N1-methyl-propane-1,3-diamine. Preferably the ligand is N, N’-dimethyl 1,2 diamine cyclohexane or N, N’-dimethyl 1,2 diethyiamine.

Other suitable ligands include 2-phenylphenol, 2,6-dimethylphenol, 2-isopropylphenol, 1-naphthol, EDTA, 8-hydroxyquinoline, 8-aminoquinoline, DBU, 2-(dimethylamino)ethanol, ethylene glycol, N, N-diethylsalicylamide, 2-(dimethylamino)glycine, N, N, N’, N’-tetramethyl-1,2-diaminoethane, 4,7-diphenyl-1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 5-methyl-1, 10-phenanthroline, 5-chloro-1,10-phenanthroline, 5-nitro-1, 10-phenanthroline, 4- (dimethylamino)pyridine, 2-(aminomethyl)pyridine, (methylimino)diacetic acid, ethanolamine, 1,2-diaminoethane, N, N’-dimethyl-1, 2-diaminoethane, N,N’-dimethylethylenediamine, ethylenediamine, N-methylethylenediamine, N-butylethylenediamine, N,N,N’-trimethylethylenediamine, tetra-n-butalammoniumfluoride, and/or tris(3,6-trioxahexyl)amine.

Preferably the ligand is trans-N,N’-dimethyl-1,2-diaminocyclohexane. Preferably the molar ratio of trans-N,N’-dimethyl-1,2-diaminocyclohexane to cis-N,N’-dimethyl-1,2-diaminocyclohexane in the reaction mixture is at least 55% to 45%, at least 60% to 40%, at least 70% to 30%, at least 80% to 20%, at least 90% to 10%, at least 95% to 5%, at least 99% to 1%. In some cases the ligand may be substantially all trans- N,N’-dimethyl-1,2-diaminocyclohexane, e.g. 100% trans-N,N’-dimethyl-1,2-diaminocyclohexane.

For the avoidance of doubt, the general term "optionally substituted" means substituted or not substituted with one or more groups. For example "optionally substituted 1,2-diamine" means 1,2-diamine or substituted 1,2-diamine. "Substituted 1,2-diamine" includes 1,2-diamines substituted with one or more (functional) groups.

Where isomers of a particular ligand are possible, e.g. cis-trans isomers and/or stereoisomers, the ligand may be one particular isomer, e.g. a cis or trans isomer, or a mixture of isomers may be employed. For example, where the ligand comprised by the catalyst is 1,2-diaminocyclohexane, the ligand may be cis-1,2-diaminocyclohexane, trans- 1,2-diaminocyclohexane, or a mixture of cis- and trans- 1,2 diaminocyclohexane.
The method may comprise initiating the reaction by providing the compound of formula III in liquid form prior to contacting the compound of formula III with the catalyst. For example, the method may comprise initiating the reaction by contacting the copper with the ligand in the presence of the compound of formula III, the compound of formula III being present in liquid form when the copper is contacted with the ligand. The compound of formula III is in liquid form, for example, when dissolved in solvent or when melted. Experimental results suggest that heating the catalyst in the absence of the compound of formula III can reduce the effectiveness of the catalyst. Preferably the catalyst is not heated in the absence of the compound of formula III.

The invention may comprise bringing the copper into contact with the ligand in the presence of the compound of formula III, e.g. to form the catalyst, wherein the compound of formula III is provided such that it is capable of forming a complex with the copper and/or catalyst, e.g. when the copper is brought into contact with the ligand to form the catalyst. Prior to performing the step of bringing the copper into contact with the ligand the copper and ligand will be separate, i.e. not in contact.

The period during which the reaction is initiated, for example, includes the period prior to the formation of the compound of formula I during which the reagents and catalyst are combined.

For example, the invention may comprise the steps:

a) providing the compound of formula III in liquid form,

b) contacting the copper with the compound of formula III,

c) contacting the ligand with the compound of formula III,

wherein step b) or step c) may be performed prior to step a), but preferably at least one of steps b) and c) is performed after step a). Step a) may comprise contacting, e.g. dissolving, the compound of formula III in solvent. This may or may not result in all the compound of formula III used being dissolved in the solvent. Providing at least some compound of formula III is dissolved in solvent the compound of formula III will then be available for complexing with the catalyst. Preferably, at least 0.5, 0.7, 1.0, 1.5, 2, 3, 4, or even 5 molar equivalents of compound of formula III are dissolved, relative to the
amount of copper, prior to contact of the compound of formula III with the catalyst.
More preferably at least one molar equivalent of compound of formula III is dissolved relative to the amount of copper.

5 Step a) may comprise heating the compound of formula III. Preferably the compound of formula III is heated to at least 40, 50, 60, 70, 80, 90, 100, 105, or even at least 110⁰C in step a) e.g. prior to contacting the compound of formula III with both the copper and the ligand.

10 The reaction may be performed in a solvent, preferably an organic polar solvent. The compound of formula II and/or the ligand may serve as the solvent, or the solvent may be a different component. In some cases, the compound of formula III may serve as the solvent.

15 The method may comprise contacting the compound of formula III with solvent, e.g. the compound of formula II, and heating prior to contacting both of the ligand and the copper with the solvent. Heating may facilitate solvation of the compound of formula III, thereby allowing more compound of formula III to be available for complexing with the catalyst. Preferably the solvent and compound of formula III is heated to at least 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, or even at least 140⁰C, e.g. 50-200⁰C, 80 to 180⁰C 100-170⁰C, 130-160⁰C⁰C in step a) e.g. prior to contacting both of the copper and ligand in the solvent. The solvent and compound of formula III may be heated at any of the foregoing temperatures for any desired length of time, e.g. 1 second to 24 hours, e.g. 1-1000 minutes, e.g. 10 to 500 minutes, e.g. 30 to 300 minutes. The solvent and compound of formula III may be heated at any of the foregoing temperatures for at least 1, 10, 30, 60, or even at least 200 minutes. Preferably, the solvent with compound of formula III dissolved therein is heated at least at 100⁰C for at least 100 minutes before the copper and ligand are both contacted with the solvent.

30 When the solvent is the compound of formula II, the method may include the additional step of melting the compound of formula II prior to contacting with the compound of formula III.
The compound of formula II may be combined with the other reagents at any stage.

Generally, the molar ratio of ligand to copper in the catalyst may be at least 10 to 1, at least 5 to 1, at least 3 to 1, at least 2.5 to 1, at least 2 to 1, at least 1.5 to 1, at least 1 to 1, at least 0.5 to 1, at least 0.1 to 1. For example, the molar ratio of ligand to copper in the catalyst may be less than 10 to 1, less than 5 to 1, less than 3 to 1, less than 2.5 to 1, less than 2 to 1, less than 1.5 to 1, or less than 1 to 1. For example, the molar ratio of ligand to copper in the catalyst may be in the range from 10:0.1 to 0.1:10, 5:1 to 1:5, 3:1 to 1:3, 2.5:1 to 1:2.5, 2:1 to 1:2, or 1.5:1 to 1:1.5. For example, the molar ratio of ligand to copper in the catalyst is preferably at least 1 to 1, e.g. at least 2 to 1, e.g. about 2.2 to 1.

Additional ligand may be added to the reaction mixture after the reaction has commenced, e.g. at one or more time points after commencement. Additional ligand may be added batch-wise, continuously or by a combination of both methods.

Additional ligand may be added, for example, after at least 10, at least 20, at least 30, at least 40, at least 50, or at least 60 minutes, e.g. after at least 1, at least 2, at least 3, at least 4, or at least 5, hours after commencement. The molar amount of additional ligand added during the course of the reaction may be at least 0.1, at least 0.5, at least 1, at least 2, at least 3, at least 4, at least 5, at least 8, or even at least 10 times the molar amount of copper present at reaction commencement. For example, at commencement of the reaction the ligand may be present at about the same molar concentration as the copper, with additional ligand added during the reaction so that the final molar concentration of the ligand is at least 2, at least 2.5, at least 3, at least 3.5, at least 4, at least 4.5, at least 5, at least 8, or even at least 10 times the molar concentration of the copper.

Likewise, additional copper may be added to the reaction mixture after the reaction has commenced, e.g. at one or more time points after commencement. Additional copper may be added batch-wise, continuously or by a combination of both methods.

Additional copper may be added, for example, after at least 10, at least 20, at least 30, at least 40, at least 50, or at least 60 minutes, e.g. after at least 1, at least 2, at least 3, at least 4, or at least 5, hours after commencement. The molar amount of additional copper
added during the course of the reaction may be at least 0.1, at least 0.5, at least 1, at least 2, at least 3, at least 4, at least 5, at least 8, or even at least 10 times the amount of copper present at commencement of the reaction. The final molar concentration of the copper may be at least 2, at least 2.5, at least 3, at least 3.5, at least 4, at least 4.5, at least 5, at least 8, or even at least 10 times the molar concentration of the copper at reaction commencement.

In the same way, additional copper and ligand may be added to the reaction mixture after the reaction has commenced, e.g. simultaneously, sequentially or separately. For additional reaction safety the compound of formula (II) may be slowly added to the reaction. The solvent and/or water may be distilled off during the reaction. The solvent may then be recharged, e.g. to maintain reaction mobility.

The reaction of the invention may be performed in a solvent, particularly solvents in which the reactants and catalyst are substantially soluble. Examples of solvents include ethers, such as diethylether, 1,2-dimethoxyethane, diethoxymethane, diglyme, t-butyl methyl ether, THF, 2-methyl-THF, dioxane; halogenated solvents such as chloroform, dichloromethane, dichloroethane, monochlorobenzene, dichlorobenzene, trichlorobenzene, 4-fluorotoluene; aliphatic (linear branched or cyclic) or aromatic hydrocarbon solvents such as benzene, xylene, toluene, benzene, ligroin, octane, heptane, hexane, pentane, methylcyclohexane, cyclohexane; esters and ketones such as ethyl acetate, acetone 2-butanone, methylisobutylketone; amines such as anisole, polar aprotic solvents such as acetonitrile, dimethylsulfoxide, dimethylformamide, N-methylpyrrolidone, dimethylacetamide; and alcohols, such as methanol, ethanol, isopropanol, t-BuOH, diethyleneglycol. A combination of more than one solvent may be employed.

Preferably, the solvent is an organic polar solvent, i.e. the solvent contains at least one carbon atom. The solvent may be protic or aprotic. Examples of solvents include ethers, such as diethylether, 1,2-dimethoxyethane, diethoxymethane, diglyme, t-butyl methyl ether, THF, 2-methyl-THF, dioxane; halogenated solvents such as chloroform, dichloromethane, dichloroethane, monochlorobenzene, dichlorobenzene, trichlorobenzene, 4-fluorotoluene; esters and ketones such as ethyl acetate, acetone 2-
butanone, methylisobutylketone; amines such as anisole, polar aprotic solvents such as acetonitrile, dimethylsulfoxide, dimethylformamide, N-methylpyrrolidone, dimethylacetamide; and alcohols, such as methanol, ethanol, isopropanol, t-BuOH, cyclohexanol, heptanol, octanol, or longer chain alcohols, and diethyleneeglycol. The solvent may be the compound of formula II. A combination of more than one solvent may be employed, which may include one or more non-polar solvents.

When X is halide the solvent may be one in which halide salts have low solubility, e.g. the non-polar solvents mentioned above in which salts are substantially insoluble so that the halide ions released during the reaction are substantially removed from the reaction solution. Alternatively a combination of solvents may be used to tune the bulk solvent polarity verses halide salt solvation whereby one or more polar solvents, particularly polar aprotic solvents, and one or more non-polar solvent from the list above are combined. An example is a mixture of DMF with xylene, which may in some cases contain about 50% v/v of each solvent.

The solvent may, for example, be DMF, diglyme, xylene, or mixtures thereof, e.g. diglyme and xylene.

The reaction of the invention may be performed using a solvent that has a boiling point (as determined under standard conditions) above 100°C, above 100°C, above 120°C, above 130°C, above 140°C, above 150°C, above 160°C, or even above 170°C, particularly when the copper is copper. Preferably, the reaction of the invention is performed using a solvent that has a boiling point above 150°C.

The reaction may be carried out at a temperature of 0 to 200°C, in particular at least 100°C, at least 120°C, at least 130°C, at least 140°C, at least 150°C, at least 160°C, at least 170°C, at least 180°C, or even at least 190°C. The reaction may be performed in the range of from 0°C-200°C, 100°C-200°C, 110-200°C, 120°C-200°C, 130°C-200°C, 140°C-200°C, 150°C-200°C, 160°C-200°C, 170°C-200°C, 180°C-200°C, 190°C-200°C, 100°C-190°C, 100°C-180°C, 100°C-170°C, 120°C-160°C,
130°C-190°C, 140°C-180°C, 140°C-170°C, 140°C-160°C, or in the range from 145°C - 155°C.

It has been found, surprisingly, that when the metal is copper, generally there are no observed side reactions, e.g. no observed dehalogenation of the benzonorbornene, even when harsh conditions are employed, such as a reaction temperature above 140°C.

The reaction of the invention may be performed at a higher pressure than atmospheric pressure. For example, the reaction may be performed at a pressure of about 1 bar or at least 1.1 bar, at least 1.2 bar, at least 1.3 bar, at least 1.4 bar, at least 1.5 bar, at least 1.6 bar, at least 1.7 bar, at least 1.8 bar, at least 1.9 bar, at least 2 bar, at least 3 bar, at least 4 bar, or even at least 5 bar, e.g. less than 10 bar, less than 5 bar, less than 2 bar, e.g. in the range of from 1 bar to 10 bar, 1 bar to 5 bar, 1 bar to 4 bar, 1 bar to 3 bar, 1 bar to 2 bar, 1 bar 1.9 bar, 1 bar to 1.8 bar, 1 bar to 1.7 bar, 1 bar to 1.6 bar, 1 bar to 1.5 bar, 1 bar to 1.4 bar, 1 bar to 1.3 bar, 1 bar to 1.2 bar, or even from 1 bar to 1.1 bar. A higher pressure than 1 bar may be used when the solvent chosen has a boiling point less than the desired reaction temperature. For the present purposes 1 bar may be generally considered to represent atmospheric pressure.

Preferably, the reaction is performed in the presence of a base. The base may be any Bronsted base, e.g. a carbonate, carboxylate, phosphate, oxide, hydroxide, alkoxide, aryloxide, amine, copper amide, fluoride, or guanidine, or a mixture of one or more thereof. The base may be a metal salt of a carboxylic acid, e.g. sodium acetate, potassium phosphate, potassium carbonate, caesium carbonate, sodium tert-butoxide, sodium hydroxide, or mixtures thereof. Examples of suitable bases include K3PO4, K2CO3, Na2CO3, Ti2CO3, Cs2CO3, K(OtBu), Li(OtBu), Na(OtBu), K(OPh), Na(OPh), or mixtures thereof. Preferably the base is a carbonate, e.g. potassium carbonate. Generally, about 1 to 2 molar equivalents of potassium carbonate, preferably about one molar equivalent (e.g. 1.1), will be used based on the amount of compound (II).

 Provision may be made for removal, e.g. continuous removal, of water from the reaction mixture. A suitable method is azeotropic removal of water. Suitable apparatus for conducting azeotropic removal of water will be known to those skilled in the art.
The amount of copper employed may be less than 50 mol % based on the amount of compound (II), e.g. less than 25 mol%, less than 20 mol%, less than 10 mol %, less than 5 mol %, less than 2 mol %, less than 1 mol %, less than 0.5 mol %, or less than 0.1 mol % based on the amount of compound (II). The amount of copper employed may be at least 0.01 mol % based on the amount of compound (II), e.g. at least 0.1 mol %, at least 1, at least 2, at least 5, or at least 10 mol % based on the amount of compound (II). The amount of copper employed may be in the range from 0.01 to 50 mol % based on the amount of compound (II), in the range from 0.1 to 25 mol %, 1 to 20 mol %, or in the range from 5 to 15 mol % based on the amount of compound (II). Preferably, the amount of copper is about 1 mol % based on the amount of compound (II), but may be up to 10 mol %.

The amount of copper employed may be less than 50 mol % based on the amount of compound (III), e.g. less than 25 mol%, less than 20 mol%, less than 10 mol %, less than 5 mol %, less than 2 mol %, less than 1 mol %, less than 0.5 mol %, or less than 0.1 mol % based on the amount of compound (III). The amount of copper employed may be at least 0.01 mol % based on the amount of compound (III), e.g. at least 0.1 mol %, at least 1, at least 2, at least 5, or at least 10 mol % based on the amount of compound (III). The amount of copper employed may be in the range from 0.01 to 50 mol % based on the amount of compound (III), in the range from 0.1 to 25 mol %, 1 to 20 mol %, or in the range from 5 to 15 mol % based on the amount of compound (III). Preferably the amount of copper is about 1 mol % based on the amount of compound (III), but may be up to 10 mol %.

The amount of ligand employed may be less than 100 mol %, based on the amount of compound (II), e.g. less than 50 mol %, less than 25 mol%, less than 20 mol%, less than 10 mol %, less than 5 mol %, less than 2 mol %, less than 1 mol %, less than 0.5 mol %, or even less than 0.1 mol % based on the amount of compound (II). The amount of ligand employed may be at least 0.01 mol % based on the amount of compound (II), e.g. at least 0.1 mol %, at least 1 mol %, at least 2 mol %, at least 5 mol %, at least 10 mol %, at least 20 mol %, or at least 50 mol % based on the amount of compound (II). The amount of ligand employed may be in the range from 0.01 to 100 mol % based on the
amount of compound (II), in the range from 1 to 50 mol %, 5 to 40 mol %, 10 to 30 mol %, or in the range from 15 to 25 mol % based on the amount of compound (II).

The amount of ligand employed may be less than 100 mol %, based on the amount of compound (III), e.g. less than 50 mol %, less than 25 mol%, less than 10 mol %, less than 5 mol %, less than 2 mol %, less than 1 mol %, less than 0.5 mol %, or even less than 0.1 mol % based on the amount of compound (III). The amount of ligand employed may be at least 0.01 mol % based on the amount of compound (III), e.g. at least 0.1 mol %, at least 1 mol %, at least 2 mol %, at least 5 mol %, at least 10 mol %, at least 20 mol %, or at least 50 mol % based on the amount of compound (III). The amount of copper employed may be in the range from 0.01 to 100 mol % based on the amount of compound (III), in the range from 1 to 50 mol %, 5 to 40 mol %, 10 to 30 mol %, or in the range from 15 to 25 mol % based on the amount of compound (III).

In the reaction of the invention, the molar ratio of compound (II) to (III) may be in the range of from 10:1 to 1:10, 5:1 to 1:5, 2:1 to 1:2 or 1:2:1 to 1:1:2. In particular, the molar ratio of compound (II) to compound (III) may be in the range of from 1.1:1 to 1:1.1, e.g. about 1:1. Generally, when the catalyst comprises copper or palladium, at reaction commencement, the reactant ratio will be about 1:1. However, a slight excess of the amide may be desired to ensure the entire norbornene compound has reacted as it is harder to separate from the product in subsequent work up. However, the reactants may be fed one to the other over the course of the reaction in which case the ratio of reactants may vary considerably during the course of the reaction.

Workup of the reaction mixture is achieved according to well known procedures of synthetic organic chemistry. For example, an aqueous workup may be achieved by the addition of water (or other aqueous solution), and filtering the product as a precipitate or extraction of the desired product with a suitable organic solvent. Alternatively, the product may be isolated by removing any solvent present by distillation, e.g. under reduced pressure. Purification of the product may be achieved by any one of a number of methods, e.g. distillation, recrystallization and chromatography.
In a further aspect of the invention, there is provided a method of preparing a compound of formula (X):

\[
\text{HF}_2\text{C} \quad \text{O} \quad \text{N} \quad \text{Me}^\text{N} \quad \text{NH}
\]

(X)

comprising the step of reacting a compound of formula (XI):

\[
\text{HF}_2\text{C} \quad \text{O} \quad \text{NH}_2 \quad \text{N} \quad \text{Me}^\text{N}
\]

(XI)

with a compound of formula (XII):

\[
\text{X} \quad \text{N} \quad \text{Me}^\text{N}
\]

(XII)

wherein X is F, Cl, Br, I, or a sulphonate, preferably Cl;
in the presence of a catalyst, which catalyst comprises a copper and a ligand.
In a further aspect of the invention, there is provided a method of preparing a compound of formula (XIV):

![Chemical structure](image)

comprising the step of reacting a compound of formula (XI):

![Chemical structure](image)

with a compound of formula (XV):

![Chemical structure](image)

wherein X is F, Cl, Br, I, or a sulphonate, preferably Cl;
in the presence of a catalyst, which catalyst comprises a copper and a ligand.
In a further aspect of the invention, there is provided a method of preparing a compound of formula (XVII):

![Chemical structure](image)

(XVII)

comprising the step of reacting a compound of formula (XI):

![Chemical structure](image)

(XI)

with a compound of formula (XVIII):

![Chemical structure](image)

(XVIII)

wherein X is F, Cl, Br, I, or a sulphonate, preferably Cl;
in the presence of a catalyst, which catalyst comprises a copper and a ligand.

In a further aspect of the invention, there is provided a method of preparing a compound of formula XIX:

\[
\text{(XIX)}
\]

comprising the step of reacting a compound of formula XI:

\[
\text{(XI)}
\]

with a compound of formula XXVII:

\[
\text{(XXVII)}
\]

wherein X is F, Cl, Br, I or a sulphonate, preferably Cl;
in the presence of a catalyst, which catalyst comprises a copper and a ligand.
A compound of formula (II) may be a compound of formula (XXII), (XXIII) or (XXIV):

\begin{align*}
\text{(XXII)} & \\
\text{(XXIII)} & \\
\text{(XXIV)} & 
\end{align*}

wherein X is F, Cl, Br, I, or a sulphonate, preferably Cl;
A and Z are independently, hydrogen or \( \text{Ci}_6 \) alkyl.

Examples of the compounds of formula (XXII), (XXIII) and (XXIV) are the compounds of formula (XII) and (XV) and (XVIII) respectively:

\begin{align*}
\text{(XII)} & \\
\text{(XV)} & \\
\text{(XVIII)} & 
\end{align*}

wherein X is F, Cl, Br, I, or a sulphonate, preferably Cl.
These compounds represent additional aspects of the invention.

In a further aspect of the invention, there is provided a method comprising

i. preparing a compound of formula (XXX):
comprising the steps of:

(a) protecting the ketone group in the compound of formula (XXXI):

wherein X is F, Cl, Br, I, or a sulphonate;

(b) reacting the compound produced in step (a) with a compound of formula (XI):

in the presence of a catalyst, which catalyst comprises copper and a ligand; and
(c) deprotecting the ketone.

Suitable protecting groups will be apparent to the skilled person and include, for example, alcohols, such as 1,2 alcohols, thiols, such as 1,2 thiols, amines, such as 1,2 amines and hydrazines.

For example, the product of step (a) may be a compound of formula (XXXII) or (XXXIII):

![Chemical Structures](XXXII) or (XXXIII)

wherein

- $Y^2$ and $Y^3$ are independently O, S, N;
- $R^2$ and $R^3$ are independently $C_i$ alkyl, wherein $R^2$ and $R^3$ are optionally joined to form a 5-8 membered ring;
- $R^4$ and $R^5$ are independently $C_i$ alkyl;
- $X$ is F, Cl, Br, I, or a sulphonate.

For example, the product of step (b) may be a compound of formula (XXXV) or a compound of formula (XXXVI):
wherein \( Y^2, Y^3, R^2, R^3, R^4 \) and \( R^5 \) are as defined for the compounds of formula (XXXII) and (XXXIII).

The method may comprise

ii. optionally converting the compound of formula (XXX):

\[
\text{(XXX)}
\]

10
to a compound of formula (XXXIV):
e.g. by reacting the compound of formula (XXX) with a suitable reagent such as triphenylphosphine and carbon tetrachloride.

5

The invention also provides a method of preparing a compound of formula (XXXV) or (XXXVI) as described in step (b).

The present invention also relates to compounds of the formula (XXXI), (XXXII), (XXXIII), (XXVII), (XVIII), (XXXV) or (XXXVI):

(XXXI) (XXXII)
(XXXIII) (XXVII) (XVIII)
wherein

Y\textsubscript{2} and Y\textsubscript{3} are independently O, S, N;

R\textsubscript{2} and R\textsubscript{3} are independently C\textsubscript{i-8} alkyl, wherein R\textsubscript{2} and R\textsubscript{3} are optionally joined to form a 5-8 membered ring;

R\textsubscript{4} and R\textsubscript{5} are independently C\textsubscript{i-s} alkyl;

X is F, Cl, Br, I, or a sulphonate;

excluding the following compounds of formula (XXXV):

i. Y\textsubscript{2} is O, Y\textsubscript{3} is O, R\textsubscript{2} is C\textsubscript{2}H\textsubscript{5}\textsubscript{-}(n), R\textsubscript{3} is C\textsubscript{3}H\textsubscript{7}\textsubscript{-}(n);

ii. Y\textsubscript{2} is O, Y\textsubscript{3} is O, R\textsubscript{2} is C\textsubscript{2}H\textsubscript{5}, R\textsubscript{3} is C\textsubscript{2}H\textsubscript{5};

iii. Y\textsubscript{2} is O, Y\textsubscript{3} is O, R\textsubscript{2} and R\textsubscript{3} are together -CH\textsubscript{2}-CH\textsubscript{2}.

Preferably, X is Cl.

Compounds of formula (III) may be prepared, for example, according to the following scheme:

**Scheme 3**

\[
\text{Het} \overset{\text{Cl}}{\text{C}} \overset{\text{NH}_3}{\text{O}} \rightarrow \text{Het} \overset{\text{N}}{\text{O}} \overset{\text{NH}_2}{\text{Cl}}
\]
Aqueous or gaseous ammonia may be used, or an ammonium salt, such as ammonium acetate. Suitable solvents, e.g. THF, and reaction conditions may be selected by the person skilled in the art. The acid chloride may be prepared as described, for example, in WO 04/035589. Alternatively, the amide may be prepared by reacting ammonia with the ester of the corresponding heterocycle.

Compounds of formula (II) may be prepared using the methodology described in WO 04/035589, and WO 2007/068417, for example. Compounds of formula (XII) may be prepared according to the following scheme:

Scheme 4

The compounds of formula (XV), (XII) and (XVIII) may be prepared using methodology as described in WO 2007/068417. Reactions a and c may be performed as described in WO 2007/068417, e.g. using a hydrogenation catalyst such as 5% Pd/C, 5% Raney Nickel, or 5% Rhodium on carbon, in a solvent such as methanol, ethanol, THF or ethyl acetate. Reactions b may also be performed using the methodology described in WO 2007/068417 for the corresponding nitro/amine substituted norbornenes. The extent of hydrogenation may also be controlled e.g. by using Wilkinson's catalyst (RhCl(PPh₃)₃). Compound (XXVII) may be produced during the
course of reaction a or b. The compounds may be isolated according to known procedures, e.g. HPLC.

In a further aspect, the invention provides the above methods in which the catalyst is replaced by a catalyst comprising iron and a ligand or palladium and a ligand.

When the catalyst comprises palladium the palladium may be a palladium atom or ion, and, for example, may be derived from any palladium salt, such as Pd(O) or Pd(II). For example, the palladium may be Pd(OH)$_2$, PdCl$_2$, Pd(OAc)$_2$, Pd(NO$_3$)$_2$, Pd(dba)$_2$.

Pd$_2$(dba)$_3$, (dba = dibenzylidenacetone), Pd(acac)$_2$, Pd(CH$_3$CN)$_2$Cl$_2$, dichloro-bis-(triphenylphosphine) palladium(II), tetrakis-(triphenylphosphine)- palladium(O), Pd/C, Palladium nanoparticles, or a mixture of two or more thereof.

When the catalyst comprises palladium, examples of suitable ligands include carbene and phosphene ligands. In particular, the ligand or ligands maybe selected from the wide range of known phosphene or carbene ligands. For example, the ligand may be a xantphos ligand, a ferrocine biphosphine ligand, a JosiPhos ligand, a biaryl monophosphine ligand, and each may be optionally substituted. For example, the ligand may one described in Ikawa et al. J. Am. chem. Soc, 2007, 129, 13001-13007, e.g. (9, 9-dimethyl-4-5-bis(diphenylphosphino)xanthene), tris(t-butyl)phosphene, 1,1'-bis(di-z-propylphosphino)ferrocene, (R)-(−)-1-[(S)-2-(dicyclohexylphosphino)ferrocenyl]ethylid-ter t-butylphosphine}, e.g. any of ligands A, B, C, D, and E.
Preferably, the ligand is A or D, more preferably D. It has been found herein that ligand D is an effective ligand when the catalyst comprises palladium and is relatively cheap.

Other suitable ligands when the catalyst comprises palladium include those described in Singer et al. Tetrahedron Letters, 2006, 47, 3727-3731, e.g. one selected from ligands F, G, H, and I:
In compound F, $R_z$ may be t-Bu or cyclohexyl; in compound G, $R_z$ may be t-Bu or i-Pr.

In particular the ligand may be I when the catalyst comprises palladium.

When the catalyst comprises iron the iron may be an iron atom or ion, and, for example, may be derived from any iron salt, e.g. Fe(II) or Fe(III), including iron oxides such as Fe$_2$O$_3$, FeO, iron halides such as FeCl$_3$, iron oxohalides, e.g. Fe(ClO$_2$)$_3$, salts such as Fe(acac)$_3$. The use of iron catalysts to form aryl C-N has been reported in the literature, e.g. Correa and BoIm, Angew. Chem. Int. Ed., 2007, 46, 8862-8865; Taillefer et al, Angew. Chem., 2007, 119, 952-954; Correa et al., Chem. Soc. Rev., 2008, 37, 1108-1117.

When the catalyst comprises iron, examples of suitable ligands include diamines, amino acids, amino alcohols, and phosphines. In particular the ligand or ligands may be one described in any of Correa and BoIm, Angew. Chem. Int. Ed., 2007, 46, 8862-8865; Taillefer et al., Angew. Chem., 2007, 119, 952-954; Correa et al., Chem. Soc. Rev.,
2008, 37, 1108-1117, e.g. an optionally substituted 1,2-dimaine, e.g. \( N_2N' \)dimethylethlenediamine (DMEDA), a dione, such as 2,2,6,6-tetramethyl-3,5-heptanedione, or acetylacetonate.

In some embodiments the catalyst may comprise a mixture of different types of metals, such as a mixture of two or all of Fe, Pd and Cu. For example, the catalyst may comprise a mixture of Cu and Fe, Cu and Pd, Pd and Fe, or Pd, Fe and Cu, in particular a mixture of Cu and Fe.

The reaction conditions described above for copper based catalysts are also appropriate for catalysts comprising palladium or ion.

The present invention will now be described by way of the following non-limiting examples. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

All references mentioned herein are incorporated by reference in their entirety. All aspects and preferred features of the invention may be combined with each other, except where this is evidently not possible.

**Examples**

**Example 1:** Ammonolysis of 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester

Solid 3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (2.05 g, 10 mmol) was added to a saturated aqueous ammonia solution (30 mL) and stirred overnight at 35-40\(^\circ\)C during which time a new white solid formed in the water. The solid was filtered off and the remaining aqueous layer was extracted using a 60/40
mixture of ethyl acetate methanol (3 x 25 mL). The combined organic extracts were dried with brine and MgSO$_4$ and concentrated in vacuo to yield a second white solid. Both white solids were combined to give an isolated product yield of 76%. The purity was 99% by GC. The solid strength was 99%.

**Example 2**: Cu-catalysed Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide

CuI (190 mg, 10 mol % wrt 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide) was charged into a dried/evacuated reaction vessel under nitrogen, followed by N,N'-Dimethylcyclohexane-1,2-diamine (340 µL, 22 mol % wrt 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide) and anhydrous DMF (4 mL). The blue suspension was stirred at room temperature, whilst adding 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide (1.76 g, 10 mmol), potassium carbonate (2.9 g, 21 mmol) and 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (2.20 g, 10 mmol). The resulting blue suspension was stirred overnight at 150°C. After this time, the suspension was cooled and diluted with acetone (15 mL), and the reaction mass filtered through a pad of Celite, washing with acetone (25 mL). The resulting solution was concentrated in vacuo to give a pale brown-brown solid. The product yield was 80%; the solid strength was 92%.
Example 3: Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide which was partially dissolved before addition of N,N'-Dimethyl-trans-l,2-cyclohexanediamine / CuBr catalyst

An oven-dried multi-necked flask was evacuated and refilled with nitrogen three times. 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide (1.75g, 10 mmol), 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (2.20 g, 10 mmol), potassium carbonate (0.77 g, 5.5 mmol) and solvent ethylene glycol diethyl ether (5 mL) were charged into the flask, and the flask evacuated and refilled with nitrogen once more. This suspension was heated to 150°C, with stirring, over 20 minutes. Once at temperature, the mixture was stirred for a further two hours, before adding pre-mixed copper I bromide (280 mg, 20 mol %) and N,N'-Dimethylcyclohexanediamine (0.69 mL, 44 mol %) and stirring for a further 12 hours at 150°C, in situ product yield = 92%, rest remaining starting materials. The resulting suspension was cooled to room temperature, and a small volume of acetone (1-2 mL) was added to improve the mobility of the suspension. Water with 0.1% H₃PO₄ was added to the suspension until solids started to crash out. The resulting suspension was left for 1.5 hours to allow the solid product to crash out of the (blue) aqueous solution. The solid product was filtered off under vacuum, and washed with toluene (5-10 mL), which removed a large amount of the dark colour from the recovered solids. The isolated product yield (not optimised) was 86%.

Example 4: Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide with N,N'-Dimethyl-trans-l,2-cyclohexanediamine / CuBr catalyst when either 3-
Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide or 5-Chloro-9-isopropyl-l,2,3,4-tetrahydro-1,4-methano-naphthalene added last

An oven-dried multi-necked flask was evacuated and refilled with nitrogen three times. 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide (1.75g, 10 mmol) or 5-Chloro-9-isopropyl-l,2,3,4-tetrahydro-1,4-methano-naphthalene (2.20 g, 10 mmol), with potassium carbonate (0.77 g, 5.5 mmol) and diethylene glycol diethyl ether (5 mL) were charged into the flask, and the flask evacuated and refilled with nitrogen once more. This suspension was heated to 150°C, with stirring, over 20 minutes. Once at temperature, the mixture was stirred for a further two hours, before adding pre-mixed copper I bromide (280 mg, 20 mol %) and N,N'-Dimethylcyclohexanediamine (0.69 mL, 44 mol %) and stirring for a further 1 hour at 150°C. The remaining reagent, aryl chloride, or amide, was added to the reaction mixture and the suspension stirred for a further 12 hours at 150°C. The in situ product yield was 88% when 5-Chloro-9-isopropyl-l,2,3,4-tetrahydro-1,4-methano-naphthalene added last and 26% when 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide added last, the remainder being starting materials.

Example 5: Amidation of 5-Chloro-9-isopropyl-l,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide with N,N'-Dimethyl-trans-l,2-cyclohexanediamine / CuBr catalyst when either CuBr or N,N'-Dimethyl-trans-l,2-cyclohexanediamine added last

(i) CuBr salt last

An oven-dried Schlenk was charged with 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide (1.39 g, 8 mmol), 5-Chloro-9-isopropyl-l,2,3,4-tetrahydro-1,4-methano-naphthalene (1.75 g, 8 mmol), potassium carbonate (600 mg, 4.4 mmol), evacuated and back filled with nitrogen 3 times. Diglyme (4 mL) was added and the mixture was stirred magnetically under nitrogen at 150°C for two hours. N,N'-Dimethyl-trans-l,2-cyclohexanediamine (500 mg, 3.4 mmol, 44 mol%) was then added to the reaction at 150°C and was allowed to stir for 5 minutes. Solid copper (I) bromide (230 mg, 1.6 mmol, 20 mol%) was then added to the reaction mixture at 150°C and the resultant deep green/brown reaction was stirred at 150°C for a further 18 hours. GC analysis after 18 hours indicated 84% conversion.
(ii) N,N’-Dimethyl-trans-1,2-cyclohexanediamine last

An oven-dried Schlenk was charged with 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide (1.39 g, 8 mmol), 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (1.75 g, 8 mmol), potassium carbonate (600 mg, 4.4 mmol), evacuated and back filled with nitrogen 3 times. Diglyme (4 mL) was added and the mixture was stirred magnetically under nitrogen at 150°C for two hours. Solid copper (I) bromide (230 mg, 1.6 mmol, 20 mol%) was then added to the reaction at 150°C and was allowed to stir for 5 minutes to afford a deep orange mixture. N,N'-Dimethyl-trans-1,2-cyclohexanediamine (500 mg, 3.4 mmol, 44 mol%) was then added to the reaction mixture at 150°C and the resultant deep green/brown reaction was stirred at 150°C for a further 18 hours. GC analysis after 18 hours indicated 90% conversion.

**Example 6: Solvent effect on the Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide**

The method described in Example 3 was repeated in a range of solvents at different temperatures, see Table 1.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature / °C</th>
<th>In Situ Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diglyme</td>
<td>150</td>
<td>92%</td>
</tr>
<tr>
<td>Ethyl diglyme</td>
<td>180</td>
<td>80%</td>
</tr>
<tr>
<td>DMF</td>
<td>150</td>
<td>98%</td>
</tr>
<tr>
<td>NMP</td>
<td>150</td>
<td>96%</td>
</tr>
<tr>
<td>Cyclohexanol</td>
<td>150</td>
<td>88%</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>150</td>
<td>48% (note all starting materials reacted, many side products)</td>
</tr>
<tr>
<td>Anisole</td>
<td>140</td>
<td>22%</td>
</tr>
<tr>
<td>Amyl acetate</td>
<td>130</td>
<td>0%</td>
</tr>
<tr>
<td>Butyl acetate</td>
<td>120</td>
<td>0%</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>70</td>
<td>0%</td>
</tr>
<tr>
<td>4-Fluorotoluene</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>Toluene</td>
<td>120</td>
<td>0%</td>
</tr>
</tbody>
</table>
Example 7: Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide using N, N'-dimethylethylenediamine as ligand

An oven-dried multi-necked flask was evacuated and refilled with nitrogen three times. 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide (1.75 g, 10 mmol), 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (2.20 g, 10 mmol), potassium carbonate (0.77 g, 5.5 mmol), copper bromide (280 mg, 20 mol %) and cyclohexanol (5 mL) were charged into the flask, and the flask evacuated and refilled with nitrogen once more. This suspension was heated to 150°C, with stirring, over 20 minutes. Once at temperature, the mixture was stirred for a further two hours, before adding N, N'-Dimethylethylenediamine (0.47 mL, 44 mol %) subsurface and stirring for a further 12 hours at 150°. The in situ product yield was 88%, the remainder being starting materials.

Repeating in a sealed tube to avoid loss of the volatile ligand resulted in a much faster reaction and 78% conversion after only 5 hours, the remainder being starting materials.

Example 8: Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid amide with N,N'-Dimethyl-trans-1,2-cyclohexanediamine / CuBr catalyst

5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (2.2 g, 10 mmol) was weighed into a round bottomed flask and heated with stirring, allowing it to fully melt. 1-Methyl-3-difluoromethyl-1H-pyrazole-4-carboxylic acid amide (0.44 g, 2.5 mmol), and K2CO3 (0.2 g, 1.4 mmol) were then added, and the suspension allowed to heat to 150°C, and kept at this temperature for two hours. Copper bromide (70 mg, 20 mol %) and N,N'-Dimethylethylenediamine (0.12 mL, 44 mol %) were then added to the suspension and the reaction stirred overnight at 150°C under a slight positive pressure of nitrogen. After this time, a sample was removed from the reaction for analysis by HPLC. Conversion by as measured by HPLC was 89% (based on DFP-amide).
**Example 9: Amidation of 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene with 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid amide with N1-methyl-propane-l,3-diamine / CuBr catalyst**

An oven-dried flask was evacuated and refilled with nitrogen three times before adding 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (2.20 g, 10 mmol), 1-Methyl-3-difluoromethyl-lH-pyrazole-4-carboxylic acid amide (1.75 g, 10 mmol), potassium carbonate (0.8 g, 5.7 mmol), and CuBr (280 mg, 20 mol %) and diglyme (5 mL). The suspension was heated with stirring to 150°C, and allowed to stir at this temperature for 2 hours prior to adding ligand N1-methyl-propane-1,3-diamine (0.31 mL, 44 mol %) and stirring at 150°C overnight. After this time, a sample was removed for analysis by HPLC. Conversion was 64% as measured by HPLC.

**Example 10: Preparation of 3-Difluoromethyl-l-methyl-lH-pyrazole-4-carboxylic acid (9-dichloromethylene-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide**

(a) **Preparation of 5-Chloro-9,9-dimethoxy-1,2,3,4-tetrahydro-1,4-methano-naphthalene (compound 2)**

An oven-dried 50 mL 3-neck flask was charged with compound 1 (4 g, 20.8 mmol), trimethyl orthoformate (2.9 mL, 28.2 mmol) followed by methanol 5 mL under nitrogen and the mixture was stirred at 60°C. Sulfuric acid (200 uL, 50% w/v) was then added dropwise and the mixture was stirred for 20 minutes. Low levels of product precipitation were evident after 10 minutes (white solid). The reaction mixture was cooled at 0°C for 20 and the precipitate is collected via vacuum filtration and washed with cold methanol (10 mL) to afford compound 2 as a white solid in 95% yield (4.7 g).
Residual starting material can be recovered via extraction of the filtrate into diethyl ether followed by concentration in vacuo (150 mg, 4%).

Other potential protecting group are for example:

![Chemical Structures]

in which n is for example 1 to 4.

(b) Preparation of 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid (9,9-dimethoxy-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide (compound 4)

An oven-dried Schlenk was charged with compound 3 (1.39 g, 8 mmol), compound 2 (1.89 g, 8 mmol), K2CO3 (600 mg, 4.4 mmol), evacuated and back filled with nitrogen 3 times. Diglyme (4 mL) was added and the mixture was stirred magnetically under nitrogen at 150°C for two hours. Solid copper (I) bromide (230 mg, 1.6 mmol, 20 mol%) was then added to the reaction mixture at 150°C followed by N,N'-Dimethyl-trans-1,2-cyclohexanediamine (500 mg, 3.4 mmol, 44 mol%). The resultant deep green/brown reaction was stirred at 150°C for a further 18 hours. GC analysis after 18 hours indicated 81% conversion to compound 4.
(c) Preparation of 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid (9-oxo-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide (compound 5)

An oven-dried Schlenk was charged with compound 4 (100 mg, 0.26 mmol) and dissolved in acetone (1 mL). Hydrochloric acid was added (37%, 2 drops) and the mixture was stirred under nitrogen for 30 minutes at 50°C. GCMS analysis indicated complete conversion of starting material and water was added to mixture (5 mL). Extraction into ethyl acetate (3 x 5mL) followed by concentration in vacuo affords compound 5 (quantitative conversion).

(d) Preparation of 3-Difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid (9-dichloromethylene-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide (compound 6)

A suspension of compound 5 (400 mg, 1.2 mmol) and triphenylphosphine (mg, 2.7 mmol 2.2 eq) in acetonitrile (2.5 mL) was stirred at room temperature. Carbon tetrachloride (mg, mmol, eq) was then added dropwise over 5 minutes. The reaction mixture was then stirred at 60°C and quickly became a deep orange solution. After 6 hours the reaction was stopped and cooled to room temperature (adjudged complete via GCMS). The chemical yield of compound 6 in this step was calculated as 76%.
Anyone skilled in the art will readily appreciate that Examples 10a, 10b and 10c can readily be telescoped into a single stage with protection/deprotection done in situ.

**Example 11: Preparation of 1-methyl-3-difluoromethyl-1H-pyrazole-4-carboxylic acid (9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide via palladium catalysis**

An oven-dried Schlenk was charged with 1-methyl-3-difluoromethyl-1H-pyrazole-4-carboxylic acid amide (175 mg, 1 mmol), 5-Chloro-9-isopropyl-1,2,3,4-tetrahydro-1,4-methano-naphthalene (220 mg, 1 mmol), NaO\(^{t}\)Bu (202 mg, 2.1 mmol) Pd\(_{2}\)(dba)\(_3\) (92 mg, 0.1 mmol) and 2-Di-ter\(t\)-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (65 mg, 0.11 mmol), evacuated and back filled with nitrogen 3 times, \(t\)-Butanol (4 mL) was added and the mixture was stirred magnetically under nitrogen at 80°C overnight. LC analysis after 18 hours indicated 21% conversion.
Claims:

1. A method of preparing a compound of formula (I):

\[
\text{(I)}
\]

wherein:
- \( Y \) is \( \text{CHCHR}_6(\text{R}_7) \), \( \text{C=C(A)Z} \), \( \text{CY}_2(\text{R}_2)\text{Y}_3(\text{R}_3) \), or \( \text{C=N-NR}_4(\text{R}_5) \);
- \( \text{Y}_2 \) and \( \text{Y}_3 \) are, independently, \( \text{O}, \text{S}, \text{N} \);
- \( \text{A} \) and \( \text{Z} \) are, independently, \( \text{Ci}_6 \text{alkyl} \);
- \( \text{R}_1 \) is \( \text{CF}_3 \) or \( \text{CF}_2\text{H} \);
- \( \text{R}_2 \) and \( \text{R}_3 \) are, independently, \( \text{Ci}_8 \text{alkyl} \), wherein \( \text{R}_2 \) and \( \text{R}_3 \) are optionally joined to form a 5-8 membered ring;
- \( \text{R}_4 \) and \( \text{R}_5 \) are, independently, \( \text{Ci}_5 \text{alkyl} \);
- \( \text{B} \) is a single bond or a double bond;
- \( \text{R}_6 \) and \( \text{R}_7 \) are, independently, hydrogen or \( \text{Ci}_6 \text{alkyl} \);

comprising the step of reacting a compound of formula (II):

\[
\text{(H)}
\]

wherein
- \( \text{X} \) is \( \text{F}, \text{Cl}, \text{Br}, \text{I} \) or a sulphonate;
Y and B are as defined for the compound of formula (I);

with a compound of formula (III):

\[
\begin{align*}
\text{III} & \\
\begin{array}{c}
\text{R}^1 \text{CH}_3 \\
\text{N} \quad \text{O} \quad \text{NH}_2 \\
\end{array}
\end{align*}
\]

wherein \( R^1 \) is as defined for the compound of formula (I);

in the presence of a catalyst, which catalyst comprises copper and a ligand.

2. The method of claim 1, wherein X is Cl.

3. The method of any one of the preceding claims, wherein the catalyst comprises CuI, CuBr and/or CuCl.

4. The method of any one of the preceding claims, wherein the ligand is a 1,2 diamine or a 1,3 diamine.

5. The method of any one of the preceding claims, wherein the ligand is \( N,N' \) dimethyl 1,2 diamine cyclohexane, \( N,N' \) dimethyl 1,2 diethylamine or \( N1 \)-methyl-propane-1,3-diamine.

6. The method of any one of the preceding claims, wherein the method comprises initiating the reaction by providing the compound of formula III in liquid form prior to contacting the compound of formula III with the catalyst.
7. The method of claim 6, wherein the method comprises the steps:
   a) providing the compound of formula III in liquid form,
   b) contacting the copper with the compound of formula III,
   c) contacting the ligand with the compound of formula III,
wherein at least one of steps b) and c) is performed after step a).

8. The method of any one of the preceding claims, wherein the reaction is performed in an organic polar solvent.

9. The method of claim 8, wherein the solvent is the compound of formula II.

10. The method of any one of the preceding claims, wherein the copper is present at less than 5 mol% with respect to the compound of formula II or formula III.

11. The method of any one of the preceding claims, wherein the reaction is performed at a temperature of at least 100°C.

12. The method of any one of the preceding claims, wherein the method is a method of preparing a compound of formula (X):

\[
\text{comp}(X)
\]

comprising the step of reacting a compound of formula (XI):
with a compound of formula (XI):

\[
\begin{align*}
\text{HF}_2C & \text{C} \text{=C} \text{N} \\
\text{N} & \text{Me}
\end{align*}
\]

(XI)

wherein \( X \) is F, Cl, Br, I, or a sulphonate; or

wherein the method is a method of preparing a compound of formula (XIV):

\[
\begin{align*}
\text{HF}_2C & \text{C} \text{=C} \text{N} \\
\text{N} & \text{Me}
\end{align*}
\]

(XIV)

comprising the step of reacting a compound of formula (XI):
with a compound of formula (XV):

wherein \( X \) is F, Cl, Br, I, or a sulphonate; or

wherein the method is a method of preparing a compound of formula (XVII):

comprising the step of reacting a compound of formula (XI):
with a compound of formula (XVIII):

wherein X is F, Cl, Br, I, or a sulphonate; or

wherein the method is a method of preparing a compound of formula (XIX):
with a compound of formula (XXVII):

\[
\text{(XXVII)}
\]

wherein \(X\) is \(F, Cl, Br, I\) or a sulphonate.

13. A method comprising

10

i. preparing a compound of formula (XXX):

\[
\text{(XXX)}
\]

comprising the steps of:

(a) protecting the ketone group in the compound of formula (XXXI)
wherein X is F, Cl, Br, I, or a sulphonate,

using a suitable protecting reagent;

(b) reacting the compound produced in step (a) with a compound of formula (XI)

(c) deprotecting the ketone; and

ii. optionally converting the compound of formula (XXX) to a compound of formula (XXXIV):
14. A method according to claim 13, wherein the compound produced in step (a) is a compound of formula (XXXII) or (XXXIII):

wherein

Y² and Y³ are independently O, S, N;
R² and R³ are independently C₈ alkyl, wherein R² and R³ are optionally joined to form a 5-8 membered ring;
R⁴ and R⁵ are independently C₅ alkyl;
X is F, Cl, Br, I, or a sulphonate.

15. A compound of formula (XXXI), (XXXII), (XXXIII), (XXVII), (XVIII), (XXXV) or (XXXVI):
wherein

10  \(Y^2\) and \(Y^3\) are independently \(O, \ S, \ N\);

\(R^2\) and \(R^3\) are independently \(\text{Ci}_8\) alkyl, wherein \(R^2\) and \(R^3\) are optionally joined to form a 5-8 membered ring;

\(R^4\) and \(R^5\) are independently \(\text{Ci}_s\) alkyl;

\(X\) is \(F, \ \text{Cl}, \ \text{Br}, \ \text{I}, \) or a sulphonate;

15  excluding the following compounds of formula (XXXV):
i. \( Y^2 \) is O, \( Y^3 \) is O, \( R^2 \) is \( C_3H_7-(n) \), \( R^3 \) is \( C_3H_7-(n) \);

ii. \( Y^2 \) is O, \( Y^3 \) is O, \( R^2 \) is \( C_2H_5 \), \( R^3 \) is \( C_2H_5 \);

iii. \( Y^2 \) is O, \( Y^3 \) is O, \( R^2 \) and \( R^3 \) are together \(-CH_2-CH_2-\).
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D231/12

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

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 practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

**C DOCUMENTS CONSIDERED TO BE RELEVANT**

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**Date of the actual completion of the international search**

12 February 2010

**Date of mailing of the international search report**

04/03/2010

**Name and mailing address of the ISA/Office**

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