PROCESSES AND COMPOUNDS FOR THE PREPARATION OF TOPOISOMERASE I INHIBITOR LINKER-PAYLOADS

Cross-Reference to Related Patent Applications

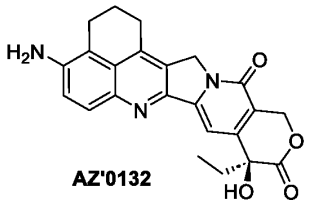
This specification claims the benefit of priority to International Application No. PCT/CN2024/081246 (filed March 12 2024). The entire text of the above-referenced patent application is incorporated by reference into this specification.

Field

This specification relates to processes and intermediate compounds involved in the preparation of Topoisomerase I inhibitor (TOPO1i) linker-payloads suitable for the synthesis of antibody conjugates.

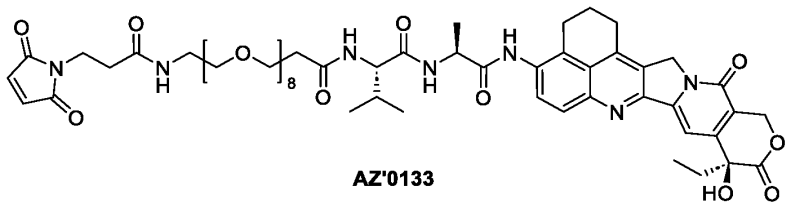
Background

Topoisomerase inhibitors are chemical compounds that block the action of topoisomerase (topoisomerase I and II), which is a type of enzyme that controls the changes in DNA structure by catalyzing the breaking and re-joining of the phosphodiester backbone of DNA strands during the normal cell cycle. Antibody Drug Conjugates (ADCs) comprising TOPO1i linker-payloads have been previously described. WO 2020/200880 discloses certain linker-payloads comprising TOPO1i drug payload AZ'0132.



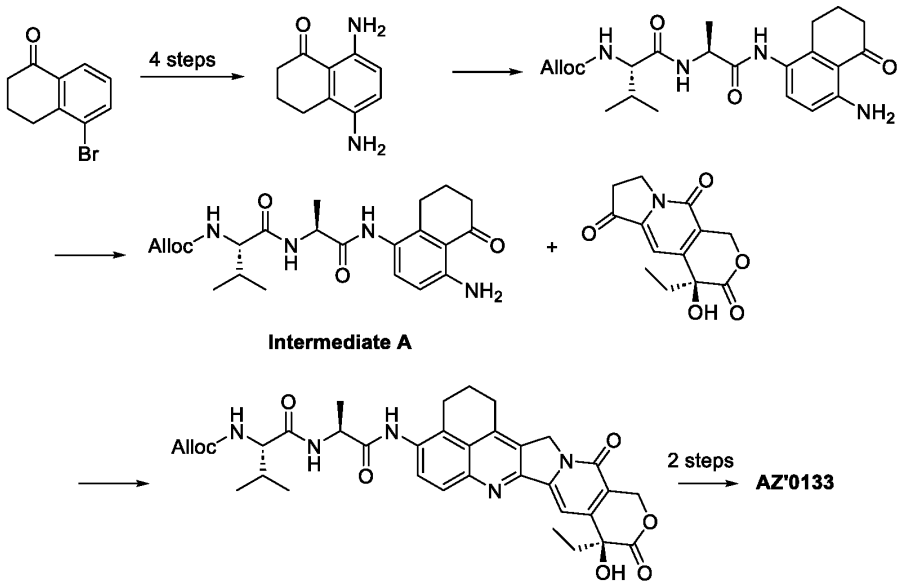
AZ'0132

Example 1 of WO 2020/200880 is a Val-Ala–PEG_8–TOPO1i linker-payload (AZ'0133). AZ'0133 has been used in the preparation of a B7-H4–directed antibody drug conjugate AZD8205 (Kinneer et al., Clin Cancer Res., 2023, 29(6), 1086-1101.) ADCs comprising AZ'0133 may undergo enzymatic cleavage in a cell lysosome to release TOPO1i drug payload AZ'0132.



AZ'0133

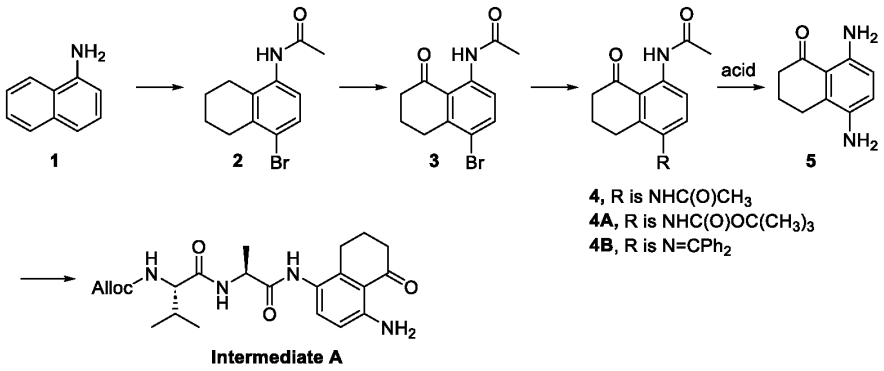
WO 2020/200880 describes a synthetic route to AZ'0133 as summarised below. This route allows **Intermediate A** to be prepared from 5 bromotetralin-1-one (where "Alloc" means N-Allyloxycarbonyl).



Although the synthetic route disclosed in WO 2020/200880 provides a reliable method for producing AZ'0133, it is desirable to improve the economy of the process for large-scale manufacture to minimise environmental impact and reduce cost of goods.

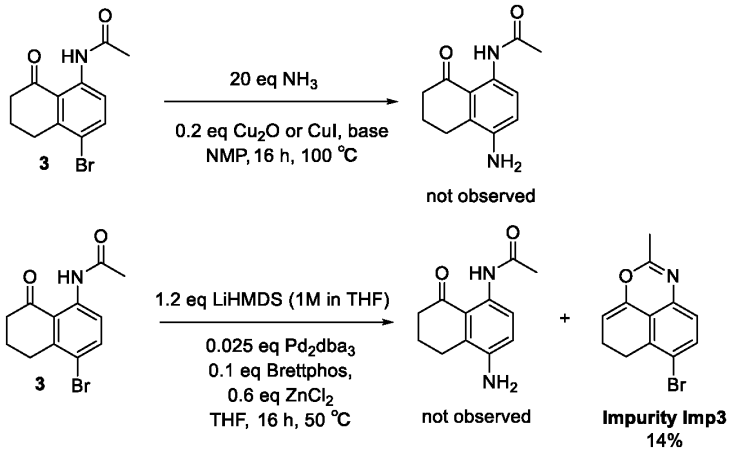
Summary

Disclosed herein is a new synthetic route for the synthesis of AZ'0133. This includes a new route for the synthesis of **Intermediate A** from naphthalen-1-amine **1**.

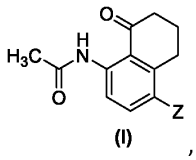


The conversion of compound **3** into compound **5** involves a Buchwald–Hartwig amination followed by deprotection. This transformation proved to be sensitive to the choice of amine source. The use

of NH_3 as an amine source in the presence of Cu_2O or CuI did not result in the desired amination reaction. Using lithium bis(trimethylsilyl)amide (LiHMDS) as an amine source resulted in significant formation of Impurity **Imp3** without observation of the desired amination reaction.

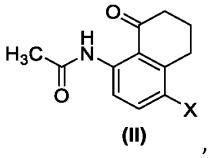


Therefore, in a first aspect there is provided a process for the production of a compound of Formula (I):



(I) ,

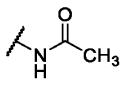
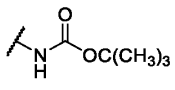
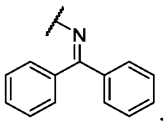
or a salt thereof, comprising a reaction of a compound of Formula (II):



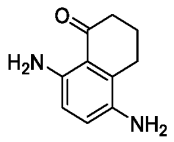
(II) ,

or a salt thereof, and H-Z, or a salt thereof, wherein the reaction is performed in the presence of a palladium catalyst and a base,

wherein X is Br, I or Cl, and

Z is  ,  or  .

In a further aspect there is provided a process for the production of a compound of Formula (III)



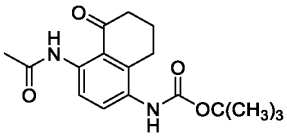
(III)

or a salt thereof, comprising

(i) the production of a compound of Formula (I), or a salt thereof, using a process as described above; and

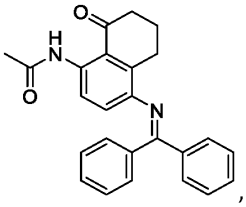
(ii) the production of the compound of Formula (III), of a salt thereof, comprising the reaction of the compound of Formula (I), or a salt thereof, and an acid.

In a further aspect there is provided *tert*-Butyl (4-acetamido-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate,



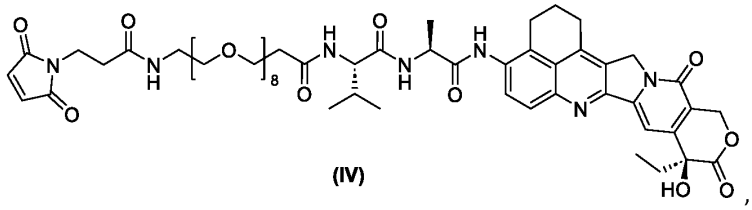
, or a salt thereof.

In a further aspect there is provided *N*-(4-((Diphenylmethylene)amino)-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide,



, or a salt thereof.

In a further aspect there is provided a process for the production of a compound of Formula (IV)



(IV)

,

comprising any of the (i) processes, or (ii) compounds, or salts thereof, described above.

In a further aspect there is provided a process for the production of a conjugate of Formula (V)

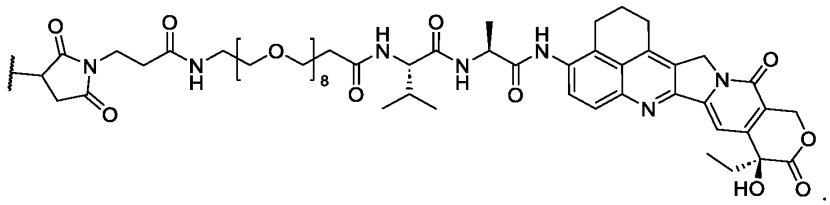
$$Ab - (LP)_k \qquad (V)$$

or a pharmaceutically acceptable salt thereof, any of the (i) processes, or (ii) compounds, or salts thereof, described above, wherein

Ab is an antibody or antigen-binding fragment thereof,

k is an integer from 1 to 10, and

LP is



For the avoidance of doubt, the use of "⊥" in formulas of this specification denotes the point of covalent attachment to a group.

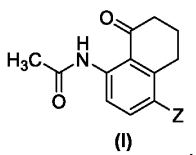
For a process for the production of a compound of Formula (I), the term "molar equivalents" refers to molar equivalents relative to the compound of Formula (II), or salt thereof.

Units, prefixes, and symbols are denoted in their International System of Units (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary of Biochemistry and Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

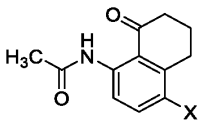
Detailed Description

As noted above, in a first aspect there is provided a process for the production of a compound of Formula (I):



(I)

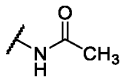
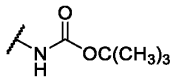
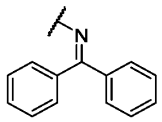
or a salt thereof, comprising a reaction of a compound of Formula (II):



(II) ,

or a salt thereof, and H-Z, or a salt thereof, wherein the reaction is performed in the presence of a palladium catalyst and a base,

wherein X is Br, I or Cl, and

Z is  ,  or  .

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein X is Br or Cl. In further embodiments, X is Br.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of at least 1.0 equivalents of base. In further embodiments, the reaction is performed in the presence of at least 1.5 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 5.0 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 3.0 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 2.5 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 2.0 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.5 to 2.5 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.5 to 2.0 equivalents of base. In further embodiments, the reaction is performed in the presence of 1.7 to 1.9 equivalents of base. In further embodiments, the reaction is performed in the presence of about 1.8 equivalents of base.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of at least 1.0 molar equivalents of base. In further embodiments, the reaction is performed in the presence of at least 1.5 molar equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 5.0 molar equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 3.0 molar equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 2.5 molar equivalents of base. In further embodiments, the reaction is performed in the presence of 1.0 to 2.0 molar equivalents of base. In further embodiments, the reaction is performed in the presence of 1.5 to 2.5 molar equivalents of base. In further embodiments, the reaction is performed in the presence of 1.5 to 2.0 molar equivalents of base. In further embodiments, the reaction is

performed in the presence of 1.7 to 1.9 molar equivalents of base. In further embodiments, the reaction is performed in the presence of about 1.8 molar equivalents of base.

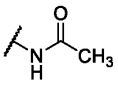
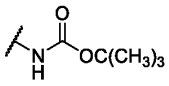
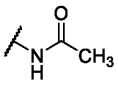
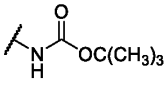
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the base is caesium carbonate (Cs_2CO_3), tripotassium phosphate (K_3PO_4), potassium *tert*-butoxide ($KOC(CH_3)_3$), potassium carbonate (K_2CO_3), potassium hydrogen carbonate ($KHCO_3$), sodium carbonate (Na_2CO_3), sodium hydrogen carbonate ($NaHCO_3$), sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH), caesium hydroxide (CsOH), calcium hydroxide ($Ca(OH)_2$), calcium carbonate ($CaCO_3$), or barium hydroxide ($Ba(OH)_2$). In further embodiments, the base is caesium carbonate (Cs_2CO_3). In further embodiments, the base is tripotassium phosphate (K_3PO_4).

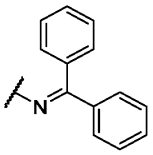
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of at least 1.0 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of at least 1.5 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 5.0 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 3.0 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 2.5 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 2.0 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.5 to 2.5 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.5 to 2.0 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.7 to 1.9 equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of about 1.8 equivalents of K_3PO_4.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of at least 1.0 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of at least 1.5 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 5.0 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 3.0 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 2.5 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.0 to 2.0 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.5 to 2.5 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.5 to 2.0 molar equivalents of K_3PO_4. In further embodiments, the reaction is performed in the presence of 1.7 to 1.9 molar equivalents of K_3PO_4. In

further embodiments, the reaction is performed in the presence of about 1.8 molar equivalents of K_3PO_4.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed using at least 1.0 molar equivalents of Z-H. In further embodiments, the reaction is performed using 1.0 to 2.0 molar equivalents of Z-H. In further embodiments, the reaction is performed using 1.0 to 1.4 molar equivalents of Z-H. In further embodiments, the reaction is performed using 1.1 to 1.3 molar equivalents of Z-H. In further embodiments, the reaction is performed using about 1.2 molar equivalents of Z-H.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or . In further embodiments, Z is . In further embodiments, Z is .

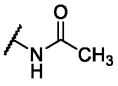
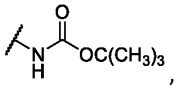
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is .

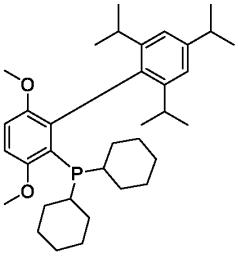
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of a ligand. Example ligands include

Ligand	Chemical Name
PPh_3	triphenylphosphine
PCy_3HBF_4	tricyclohexylphosphine tetrafluoroborate
$BuPAd_2$	di(1-adamantyl)-n-butylphosphine
XPHOS	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
tBuXPHOS	2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl
BRETTPHOS	dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine
RUPHOS	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
JOHNPHOS	(2-biphenyl)di-tert-butylphosphine
JOSIPHOS	(R)-1-[(SP)-2-(di-tert-butylphosphino)ferrocenyl]ethylbis(2-methylphenyl)phosphine
DPPP	1,3-bis(diphenylphosphino)propane

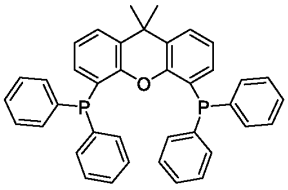
DPPF	1,1’-Ferrocenediyl-bis(diphenylphosphine)
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthalene
XANTPHOS	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of a phosphine ligand.

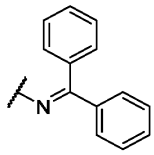
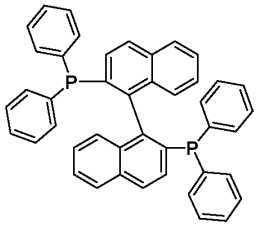
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or , and the reaction is performed in the presence of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine



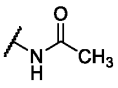
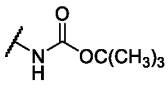
or 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

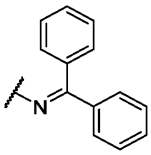


. In further embodiments, the reaction is performed in the presence of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  and the reaction is performed in the presence of 2,2’-Bis(diphenylphosphino)-1,1’-binaphthalene .

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of at least 0.01 molar equivalents of a ligand. In further embodiment, the reaction is performed in the presence of at least 0.02 molar equivalents of a ligand. In further embodiments, there the reaction is performed in the presence of 0.01 to 0.15 molar equivalents of a ligand. In further embodiment, the reaction is performed in the presence of 0.01 to 0.10 molar equivalents of a ligand. In further embodiment, the reaction is performed in the presence of 0.01 to 0.06 molar equivalents of a ligand. In further embodiment, the reaction is performed in the presence of 0.02 to 0.06 molar equivalents of a ligand. In further embodiment, the reaction is performed in the presence of 0.03 to 0.05 molar equivalents of a ligand. In further embodiment, the reaction is performed in the presence of about 0.04 molar equivalents of a ligand.

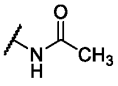
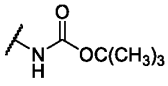
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or , and the reaction is performed in the presence of at least 0.01 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine. In further embodiment, the reaction is performed in the presence of 0.01 to 0.15 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine. In further embodiment, the reaction is performed in the presence of 0.01 to 0.10 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine. In further embodiment, the reaction is performed in the presence of 0.01 to 0.06 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine. In further embodiment, the reaction is performed in the presence of 0.02 to 0.06 molar equivalents of a dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine. In further embodiment, the reaction is performed in the presence of 0.03 to 0.05 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine. In further embodiment, the reaction is performed in the presence of about 0.04 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine.

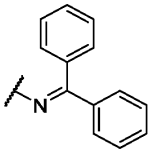
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is , and the reaction is performed in the presence of at least 0.02 molar equivalents of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. In further embodiments, the reaction is performed in the presence of 0.02 to 0.4 molar equivalents of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

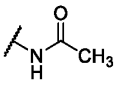
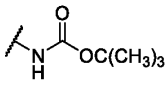
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the palladium catalyst is a palladium(0) catalyst. Examples of palladium(0) catalysts include tris(dibenzylideneacetone)dipalladium(0), tetrakis(triphenylphosphine)palladium(0) and bis(tri-tert-butylphosphine)palladium(0).

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the palladium catalyst is a palladium(II) catalyst. Examples of palladium(II) catalysts include palladium(II) acetate, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II), palladium (II) chloride, Bis(triphenylphosphine)palladium (II) dichloride, palladium (II) hydroxide and palladium (II) acetylacetonate

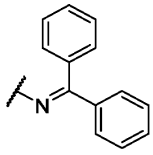
In embodiments, the palladium catalyst contains at least 0.001 molar equivalents of palladium. In further embodiments, the palladium catalyst contains at least 0.002 molar equivalents of palladium. In further embodiments, the palladium catalyst contains 0.001 to 0.05 molar equivalents of palladium. In further embodiments, the palladium catalyst contains 0.002 to 0.003 molar equivalents of palladium. In further embodiments, the palladium catalyst contains about 0.0025 molar equivalents of palladium.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or , and the palladium catalyst is tris(dibenzylideneacetone)dipalladium(0).

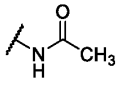
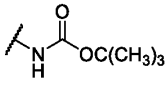
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is , and wherein the palladium catalyst is palladium(II) acetate.

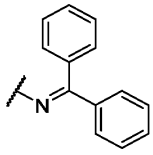
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or , and the reaction is performed in the presence of at least 0.005 molar equivalents of tris(dibenzylideneacetone)dipalladium(0). In further embodiments, the reaction is performed in the presence of at least 0.01 molar equivalents of tris(dibenzylideneacetone)dipalladium(0). In further embodiments, the reaction is performed in the presence of 0.005 to 0.04 molar equivalents of tris(dibenzylideneacetone)dipalladium(0). In further embodiments, the reaction is performed in the presence of 0.01 to 0.04 molar equivalents of

tris(dibenzylideneacetone)dipalladium(0). In further embodiments, the reaction is performed in the presence of 0.01 to 0.02 molar equivalents of tris(dibenzylideneacetone)dipalladium(0). In further embodiments, the reaction is performed in the presence of 0.010 to 0.013 molar equivalents of tris(dibenzylideneacetone)dipalladium(0). In further embodiments, the reaction is performed in the presence of about 0.015 molar equivalents tris(dibenzylideneacetone)dipalladium(0).

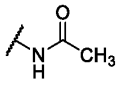
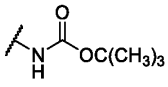
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is , and wherein the reaction is performed in the presence of at least 0.01 molar equivalents of palladium(II) acetate. In further embodiments, the reaction is performed in the presence of 0.01-0.2 molar equivalents of palladium(II) acetate.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed in the presence of a solvent. In further embodiments, the solvent is toluene, 1,4-dioxane, 2-methylbutan-2-ol (tAmylOH), dimethylformamide or 2-methyltetrahydrofuran.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or , and the reaction is performed in the presence of toluene or 2-methyltetrahydrofuran. In further embodiments, is performed in the presence of toluene.

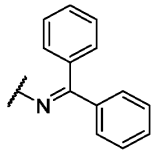
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  and the reaction is performed in the presence of 1,4-dioxane.

In embodiments, there is provided a process for the production of a compound of Formula (I) wherein the reaction is performed at a temperature of at least 60 °C.

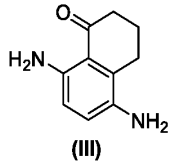
In embodiments, there is provided a process for the production of a compound of Formula (I) wherein Z is  or , and the reaction is performed at a temperature of at least 60 °C. In further embodiments, the reaction is performed at a temperature of 60 to 100 °C. In

further embodiments, the reaction is performed at a temperature of 70 to 90 °C. In further embodiments, the reaction is performed at a temperature of about 80 °C.

In embodiments, there is provided a process for the production of a compound of Formula (I)

wherein Z is , and the reaction is performed at a temperature of at least 60 °C. In further embodiments, the reaction is performed at a temperature of at least 80 °C. In further embodiments, the reaction is performed at a temperature of 80 to 120 °C. In further embodiments, the reaction is performed at a temperature of 90 to 110 °C. In further embodiments, the reaction is performed at a temperature of about 100 °C.

In a further aspect, there is provided a process for the production of a compound of Formula (III)



(III)

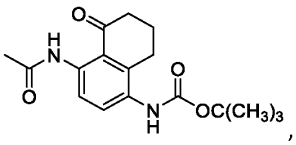
or a salt thereof, comprising

(i) the production of a compound of Formula (I), or a salt thereof, using any process described herein; and

(ii) the production of the compound of Formula (III), of a salt thereof, comprising the reaction of the compound of Formula (I), or a salt thereof, and an acid.

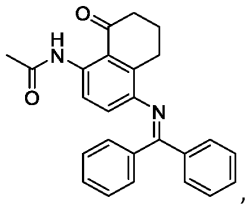
In embodiments, there is provided a process for the production of a compound of Formula (III), wherein the acid is a mineral acid. In further embodiments, acid is hydrochloric acid, sulfuric acid or phosphoric acid. In further embodiments, the acid is hydrochloric acid.

In a further aspect there is provided a compound that is *tert*-Butyl (4-acetamido-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate,



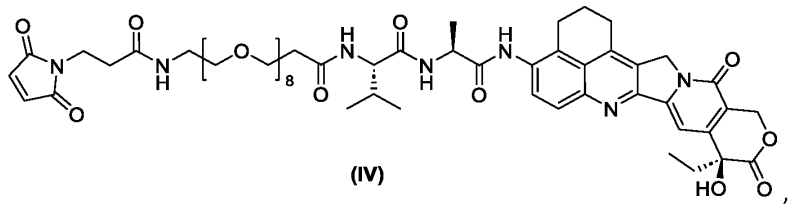
, or a salt thereof. In embodiments, there is provided *tert*-Butyl (4-acetamido-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate.

In a further aspect there is provided a compound that is *N*-(4-((Diphenylmethylene)amino)-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide,



, or a salt thereof. In embodiments, there is provided *N*-(4-((Diphenylmethylene)amino)-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide.

In a further aspect there is provided a process for the production of a compound of Formula (IV)



(IV)

,

comprising (i) any process described herein, or (ii) the use of tert-Butyl (4-acetamido-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate, or a salt thereof, or N-(4-((Diphenylmethylene)amino)-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide, or a salt thereof.

In a further aspect there is provided a process for the production of a conjugate of Formula (V)

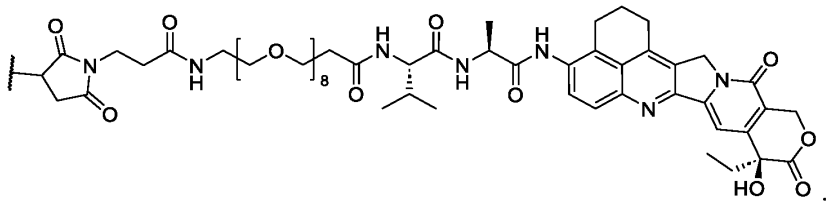
$$Ab - (LP)_k \qquad (V)$$

or a pharmaceutically acceptable salt thereof, comprising (i) any process described herein or (ii) the use of tert-Butyl (4-acetamido-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate, or a salt thereof, or N-(4-((Diphenylmethylene)amino)-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide, or a salt thereof, wherein

Ab is an antibody or antigen-binding fragment thereof,

k is an integer from 1 to 10, and

LP is



.

In embodiments, there is provided a process for the production of a conjugate of Formula (V), wherein k is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. In further embodiments k is an integer from 2 to 10. In

further embodiments k is an integer from 2 to 8. In further embodiments k is 4. In further embodiments k is 8.

Examples

The specification will now be illustrated by the following non-limiting Examples.

Abbreviations:

EtOH – Ethanol
DCM – Dichloromethane
HCl – Hydrochloric acid
THF – Tetrahydrofuran
DMSO – Dimethylsulfoxide
MTBE – Methyl *tert*-butyl ether
t-BuOH – *tert*-Butanol
2-MeTHF – 2-Methyltetrahydrofuran
MeOH – Methanol
2-PrOH – 2-Propanol
1,2-DME – 1,2-Dimethoxyethane
DMF – *N*,*N*-Dimethylformamide
w/w – weight/weight
weq. – weight equivalents
v/v – volume/volume
veq. – volume equivalents

IUPAC names were generated using Biovia Draw 2020 version 20.1

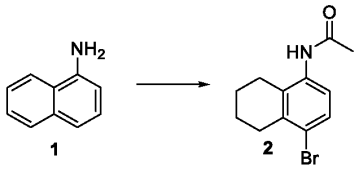
All NMR data were recorded on a Bruker Avance Neo spectrometer fitted with a QCI cryoprobe with an operating frequency of 499.90 MHz for proton.

LC-MS data were collected using a a Water ACQUITY UPLC H-Class system, equipped with a single quad mass spectrometer.

Reagent charges, weight equivalents and volume equivalents are relative to the limiting reagent which is the starting material in each process description.

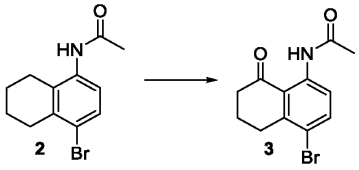
Example 1: Preparation of Intermediate A

Preparation of *N*-(8-bromotetralin-5-yl)acetamide 2



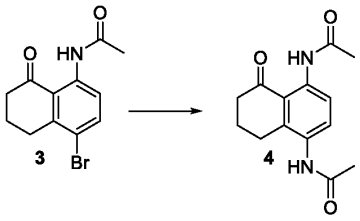
Naphthalen-1-amine **1** (80.0 kg, 559 mol) and EtOH (1200 L) were heated to 45-65°C and then acetic anhydride (62.7 kg, 615 mol) was added. The mixture was stirred until reaction completion, then cooled and purged with nitrogen to reach an oxygen content ≤0.1%. Raney nickel (80.0 kg, 1.0 wt equivalents) was added and then the mixture was purged with hydrogen and pressurised to 2.5-3.5 MPa. Upon reaction completion the mixture was filtered, and the filter cake was washed with EtOH. *N*-Bromosuccinimide (109.4 kg, 615 mol) was added portionwise to the combined filtrate. Upon reaction completion water (1600 L) was added and the mixture stirred at 0-10°C for 2 hours. The mixture was filtered and the filter cake was washed with water. The isolated product was dried to give *N*-(8-bromotetralin-5-yl)acetamide **2** as a solid in approximately 85% yield. ^{1}H NMR (500 MHz, DMSO, 27°C) 9.20 (1H, s), 7.38 (1H, d), 7.19 (1H, d), 2.65 (2H, t), 2.58 (2H, q), 2.04 (3H, s), 1.70 (4H, dddd); m/z (ES$^+$) $[M+H]^+$=268

Preparation of *N*-(8-Bromo-4-oxo-tetralin-5-yl)acetamide 3



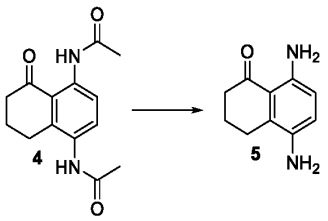
N-(8-bromotetralin-5-yl)acetamide **2** (80.0 kg, 298 mol) was mixed with acetonitrile (800 L) and *t*-BuOH (800 L) and cooled to 15-25°C before addition of 15% aqueous $MgSO_4$ (49.6 kg, 412 mol). $KMnO_4$ (165.0 kg, 1044 mol) was then added portionwise over 2-3 hours. Upon reaction completion, 20% (w/w) aqueous H_2SO_4 (584.8 kg, 1194 mol) and oxalic acid dihydrate (150.4 kg, 1194 mol) were added until absence of oxidation by starch-KI test and pH ≤7 was reached. The mixture was filtered, and the isolated solid was washed with water then dissolved in DCM (800 L). Water (400 L) was added, and the mixture was stirred for 2 hours and filtered. The separated organic layer was washed sequentially with aqueous $NaHCO_3$ and saturated aqueous NaCl then concentrated to a volume of approximately 200-240 L. MeOH (720 L) was added and the subsequent precipitate was collected by filtration and dried to give *N*-(8-Bromo-4-oxo-tetralin-5-yl)acetamide **3** as a solid in approximately 67% yield. ^{1}H NMR (500 MHz, DMSO, 27°C) 11.95 (1H, s), 8.42 (1H, d), 7.83 (1H, d), 2.96 (2H, t), 2.66 – 2.74 (2H, m), 2.15 (3H, s), 2.03 (2H, p); m/z (ES$^+$) $[M+H]^+$=282

Preparation of *N*-(8-Acetamido-1-oxo-tetralin-5-yl)acetamide 4



N-(8-Bromo-4-oxo-tetralin-5-yl)acetamide **3** (57.0 kg, 202 mol) was mixed with toluene (1140 L), K_3PO_4 (77.2 kg, 363.6 mol) and acetamide (14.3 kg, 242 mol, 1.2 eq) and purged with nitrogen to an oxygen content ≤0.1%. Dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (4.34 kg, 8.1 mol, 0.04 eq) and tris(dibenzylideneacetone)dipalladium(0) (2.28 kg, 3.03 mol, 0.015 eq) were added and the mixture was heated to 80°C. Upon reaction completion, the mixture was cooled and then water (570 L) was added and the mixture stirred for 2 hours. The resulting suspension was filtered, and the filter cake washed with water. After drying, the isolated solid was stirred in EtOH (142.5 L) at 60°C for 2 hours then cooled. The resulting suspension was filtered, and the isolated product was washed with ethanol (114 L) and dried to give *N*-(8-Acetamido-1-oxo-tetralin-5-yl)acetamide **4** as a solid in approximately 77% yield. ^{1}H NMR (500 MHz, DMSO, 27°C) 11.95 (1H, s), 9.46 (1H, s), 8.41 (1H, d), 7.51 (1H, d), 2.80 (2H, t), 2.64 – 2.71 (2H, m), 2.14 (3H, s), 2.05 (3H, s), 1.95 (2H, p); m/z (ES$^+$) $[M+H]^+$=261.

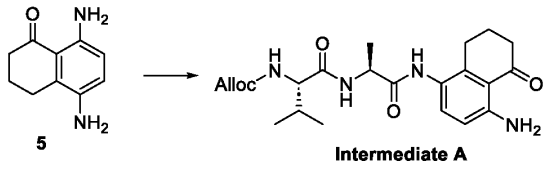
Preparation of 5,8-diaminotetralin-1-one 5



N-(8-Acetamido-1-oxo-tetralin-5-yl)acetamide **4** (40.3 kg, 154.9 mol) was mixed with 36% aqueous HCl (123.3 kg, 1214 mol) then heated to 70-75°C. Upon reaction completion the mixture was cooled to 20-30°C and then water (80 L) and SMA905 (palladium scavenger, 2.4 kg, 0.06 w/w) were added. The mixture was stirred for 3 hours and additional SMA905 added if required. The mixture was filtered and the filter cake washed with water (40 L). The pH of the filtrate was adjusted to 8-10 at 0-10°C with 30% (w/w) aqueous NaOH (63.6 kg, 1595 mol). The resulting suspension was filtered, washed with water and the isolated product dried to give 5,8-Diaminotetralin-1-one **5** as a solid in

approximately 87% yield ^{1}H NMR (500 MHz, DMSO, 27°C) 6.77 (1H, d), 6.52 – 6.84 (2H, m), 6.43 (1H, d), 4.17 (2H, s), 2.56 (2H, t), 2.46 (2H, dd), 1.90 (2H, p); m/z (ES$^+$) $[M+H]^+$=177.

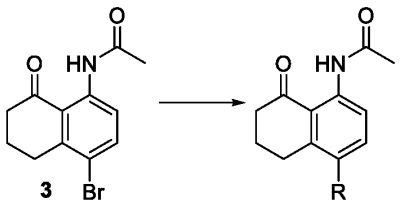
Preparation of allyl ((S)-1-(((S)-1-((4-amino-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate Intermediate A



Intermediate A may be prepared from compound **5** according to the process described in WO 2020/200880, the contents of which are incorporated by reference.

Example 2: Reaction Screening of Buchwald–Hartwig amination with acetamide, Boc-NH_2 and ammonium sulfate

General procedure



4, R is $NHC(O)CH_3$
4A, R is $NHC(O)OC(CH_3)_3$
4C, R is NH_2

The starting material **3** (20mg, 0.083mmol, 1 eq) was charged to a vial followed by acetamide or $(NH_4)_2SO_4$ or $BocNH_2$ (1.2 eq), base (1.5 eq), catalyst, e.g. Pd_2dba_3 (0.025 eq) and either monodentate ligand (0.1 eq) or bidentate ligand (0.05 eq) under a nitrogen atmosphere. Solvent (10 vol, degassed) was added at 20°C and the mixture was heated to 100°C for 16h.

The reaction mixture was diluted with a mixture of acetonitrile and water, then sampled for HPLC analysis. Tables 1 to 3 set out the HPLC area% of starting material, product and impurities.

Tables 1 to 3 make reference to the following impurities;

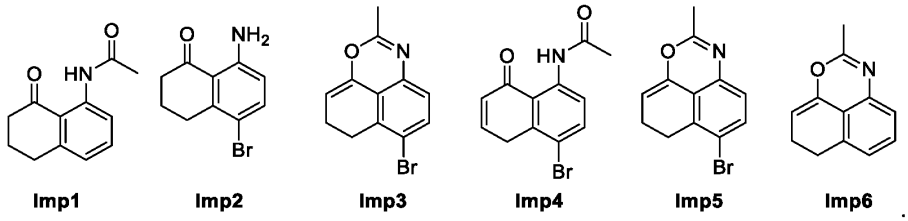
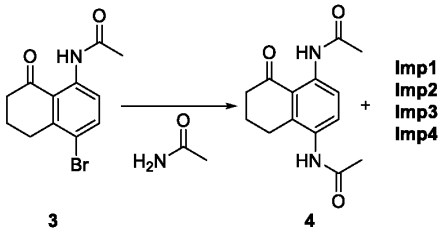


Table 1: Reaction screening with acetamide



Ligand	Base	Solvent	3/%	4/%	Imp1/%	Imp2/%	Imp3%	Imp4%
PPh_3	Cs_2CO_3	Toluene	43.68	0.00	14.64	9.67	20.38	6.77
PCy_3HBF_4	Cs_2CO_3	Toluene	41.66	0.00	5.61	10.98	22.53	15.94
$BuPAd_2$	Cs_2CO_3	Toluene	45.74	0.00	5.78	1.57	1.70	1.66
Xphos	Cs_2CO_3	Toluene	67.15	0.00	3.89	7.06	19.83	1.68
tBuXphos	Cs_2CO_3	Toluene	71.75	0.00	2.56	6.28	16.52	1.07
Brettphos	Cs_2CO_3	Toluene	0.58	75.93	2.43	3.01	0.00	0.25
Ruphos	Cs_2CO_3	Toluene	78.10	0.00	3.07	4.80	16.31	1.36
Johnphos	Cs_2CO_3	Toluene	70.57	0.00	2.67	7.81	22.50	0.44
Josiphos	Cs_2CO_3	Toluene	74.44	0.17	3.01	6.37	17.02	0.85
DPPP	Cs_2CO_3	Toluene	73.09	0.00	0.19	7.51	17.86	0.00
DPPF	Cs_2CO_3	Toluene	70.14	0.15	1.90	3.78	16.19	0.76
r-Binap	Cs_2CO_3	Toluene	78.00	0.22	0.35	3.66	14.21	0.28
Xantphos	Cs_2CO_3	Toluene	36.45	4.45	12.30	0.64	15.92	28.84
PPh_3	K_3PO_4	Toluene	41.28	0.00	17.77	10.20	15.42	20.35
PCy_3HBF_4	K_3PO_4	Toluene	61.13	0.00	6.46	2.94	6.52	15.90
$BuPAd_2$	K_3PO_4	Toluene	5.27	0.00	6.15	7.05	1.23	0.00
Xphos	K_3PO_4	Toluene	59.15	0.00	3.03	16.04	20.10	0.87
tBuXphos	K_3PO_4	Toluene	70.29	0.00	3.14	10.90	13.41	1.29
Brettphos	K_3PO_4	Toluene	0.32	78.98	1.87	2.79	0.00	0.00
Ruphos	K_3PO_4	Toluene	62.15	0.00	3.84	13.14	16.99	2.87

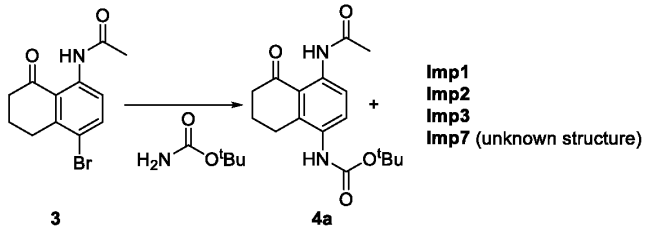
Johnphos	K_3PO_4	Toluene	60.80	0.00	2.92	14.57	19.17	0.93
Josiphos	K_3PO_4	Toluene	62.15	0.00	3.04	13.98	15.09	1.28
DPPP	K_3PO_4	Toluene	61.19	0.00	0.20	15.87	17.17	0.39
DPPF	K_3PO_4	Toluene	63.27	0.00	1.90	17.49	16.56	1.49
r-Binap	K_3PO_4	Toluene	63.43	0.12	0.38	14.03	17.50	0.54
Xantphos	K_3PO_4	Toluene	17.16	7.83	19.05	3.48	9.02	37.37
PPh_3	Cs_2CO_3	Dioxane	30.80	0.00	18.53	4.34	36.34	19.97
PCy_3HBF_4	Cs_2CO_3	Dioxane	40.78	0.00	9.41	1.78	12.67	31.10
$BuPAd_2$	Cs_2CO_3	Dioxane	15.47	0.00	1.11	0.38	1.91	3.10
Xphos	Cs_2CO_3	Dioxane	50.69	0.34	3.33	5.79	38.83	2.20
tBuXphos	Cs_2CO_3	Dioxane	6.10	0.42	0.89	4.42	25.17	21.20
Brettphos	Cs_2CO_3	Dioxane	0.20	55.05	4.86	0.56	0.00	1.23
Ruphos	Cs_2CO_3	Dioxane	57.12	0.23	2.75	4.74	32.19	1.72
Johnphos	Cs_2CO_3	Dioxane	56.54	0.24	2.89	4.69	33.27	0.91
Josiphos	Cs_2CO_3	Dioxane	61.64	1.24	3.75	3.49	24.28	1.14
DPPP	Cs_2CO_3	Dioxane	59.83	0.00	0.00	4.40	28.18	0.19
DPPF	Cs_2CO_3	Dioxane	57.65	0.31	1.43	7.79	32.68	1.27
r-Binap	Cs_2CO_3	Dioxane	63.78	0.48	0.58	4.09	32.71	0.64
Xantphos	Cs_2CO_3	Dioxane	2.62	15.03	27.75	2.29	0.00	36.93
PPh_3	K_3PO4	Dioxane	47.09	0.00	13.97	8.91	23.34	20.93
PCy_3HBF_4	K_3PO4	Dioxane	52.74	0.00	10.23	7.51	3.77	22.07
$BuPAd_2$	K_3PO4	Dioxane	0.00	0.00	4.73	1.01	0.00	0.29
Xphos	K_3PO_4	Dioxane	53.41	0.33	2.17	9.88	38.97	1.49
tBuXphos	K_3PO_4	Dioxane	54.66	2.87	4.12	7.44	29.44	6.02
Brettphos	K_3PO_4	Dioxane	0.00	55.03	3.78	0.91	0.26	0.57
Ruphos	K_3PO_4	Dioxane	51.77	0.40	2.65	7.32	30.67	1.73
Johnphos	K_3PO_4	Dioxane	63.35	0.29	2.33	10.63	41.12	0.72
Josiphos	K_3PO_4	Dioxane	56.12	1.33	2.95	6.59	33.06	2.07
DPPP	K_3PO_4	Dioxane	52.15	0.00	0.00	11.63	39.38	0.46
DPPF	K_3PO_4	Dioxane	11.77	0.27	1.10	14.43	16.27	16.14
r-Binap	K_3PO_4	Dioxane	55.33	0.79	0.00	0.38	28.41	0.59
Xantphos	K_3PO_4	Dioxane	25.22	8.64	24.63	3.89	0.00	44.40
PPh_3	Cs_2CO_3	tAmylOH	10.67	0.21	3.88	3.66	47.83	1.75

PCy_3HBF_4	Cs_2CO_3	tAmylOH	15.36	0.10	11.72	2.85	30.76	33.53
$BuPAd_2$	Cs_2CO_3	tAmylOH	7.24	0.00	0.94	1.34	20.98	4.16
Xphos	Cs_2CO_3	tAmylOH	17.64	0.34	1.27	4.19	52.03	2.14
tBuXphos	Cs_2CO_3	tAmylOH	14.19	5.15	4.47	3.05	59.20	2.88
Brettphos	Cs_2CO_3	tAmylOH	1.22	39.80	6.91	1.60	4.53	1.69
Ruphos	Cs_2CO_3	tAmylOH	21.26	0.36	1.15	0.15	44.14	1.06
Johnphos	Cs_2CO_3	tAmylOH	21.87	0.76	1.94	5.04	41.41	0.66
Josiphos	Cs_2CO_3	tAmylOH	10.49	1.14	7.27	2.09	38.75	11.48
DPPP	Cs_2CO_3	tAmylOH	23.63	0.00	0.00	5.12	43.66	0.15
DPPF	Cs_2CO_3	tAmylOH	22.86	0.13	0.00	7.87	47.34	0.30
r-Binap	Cs_2CO_3	tAmylOH	18.30	0.16	0.00	4.01	37.76	0.22
Xantphos	Cs_2CO_3	tAmylOH	5.06	0.96	3.70	2.90	42.92	0.61
PPh_3	K_3PO_4	tAmylOH	18.92	0.00	15.96	6.55	41.20	20.70
PCy_3HBF_4	K_3PO_4	tAmylOH	28.05	0.00	12.41	5.98	18.07	31.06
$BuPAd_2$	K_3PO_4	tAmylOH	0.00	0.00	1.72	4.13	0.00	0.57
Xphos	K_3PO_4	tAmylOH	47.45	0.62	2.58	11.58	40.65	2.23
tBuXphos	K_3PO_4	tAmylOH	41.51	7.09	5.60	8.86	32.14	4.93
Brettphos	K_3PO_4	tAmylOH	0.41	52.79	6.09	0.44	0.13	2.15
Ruphos	K_3PO_4	tAmylOH	19.20	0.31	1.74	10.57	30.39	11.25
Johnphos	K_3PO_4	tAmylOH	44.92	0.70	2.52	12.58	45.05	0.95
Josiphos	K_3PO_4	tAmylOH	34.94	0.75	6.25	9.84	38.85	10.30
DPPP	K_3PO_4	tAmylOH	42.46	0.00	0.00	12.82	43.54	0.75
DPPF	K_3PO_4	tAmylOH	43.02	0.00	0.00	11.90	37.73	0.35
r-Binap	K_3PO_4	tAmylOH	32.81	0.29	1.53	8.88	3.66	9.51
Xantphos	K_3PO_4	tAmylOH	32.30	2.12	10.38	1.17	35.43	23.60
PPh_3	Cs_2CO_3	DMF	2.67	0.65	13.82	27.19	36.24	22.53
PCy_3HBF_4	Cs_2CO_3	DMF	7.67	0.00	16.31	14.79	15.98	54.07
$BuPAd_2$	Cs_2CO_3	DMF	4.83	0.16	0.88	9.36	3.15	6.82
Xphos	Cs_2CO_3	DMF	9.89	0.41	10.46	24.26	27.48	21.75
tBuXphos	Cs_2CO_3	DMF	10.17	3.85	13.68	22.64	17.13	26.57
Brettphos	Cs_2CO_3	DMF	0.00	31.54	14.69	2.94	0.35	1.06
Ruphos	Cs_2CO_3	DMF	0.00	0.24	0.00	23.23	12.50	0.26
Johnphos	Cs_2CO_3	DMF	3.10	0.48	7.86	24.43	43.56	9.33

Josiphos	Cs_2CO_3	DMF	1.26	1.74	20.32	12.03	25.31	31.43
DPPP	Cs_2CO_3	DMF	3.55	0.12	9.06	26.28	48.68	1.18
DPPF	Cs_2CO_3	DMF	4.93	0.17	9.79	31.19	47.34	1.12
r-Binap	Cs_2CO_3	DMF	4.32	0.37	10.95	24.58	45.57	3.11
Xantphos	Cs_2CO_3	DMF	2.44	0.91	10.21	10.50	43.71	14.00
PPh_3	K_3PO_4	DMF	1.74	0.00	24.07	2.60	10.72	44.71
PCy_3HBF_4	K_3PO_4	DMF	17.35	0.00	15.47	3.57	16.94	45.60
$BuPAd_2$	K_3PO_4	DMF	1.06	0.00	1.32	4.62	0.53	0.38
Xphos	K_3PO_4	DMF	24.34	0.74	8.95	5.65	15.10	17.31
tBuXphos	K_3PO_4	DMF	9.64	1.09	17.88	4.67	3.61	22.60
Brettphos	K_3PO_4	DMF	0.52	15.51	19.69	7.52	0.44	1.36
Ruphos	K_3PO_4	DMF	35.25	0.31	3.85	4.03	24.01	5.31
Johnphos	K_3PO_4	DMF	28.84	0.54	6.77	4.62	30.62	9.14
Josiphos	K_3PO_4	DMF	4.30	0.21	34.77	5.73	0.00	54.60
DPPP	K_3PO_4	DMF	29.33	0.00	4.59	8.71	36.22	1.46
DPPF	K_3PO_4	DMF	30.83	0.18	6.21	8.80	34.05	1.41
r-Binap	K_3PO_4	DMF	0.25	0.40	0.00	2.93	26.71	16.57
Xantphos	K_3PO_4	DMF	0.00	10.15	25.55	1.83	0.21	38.75
PPh_3	Cs_2CO_3	2-MeTHF	66.89	0.00	3.00	1.81	18.74	6.20
PCy_3HBF_4	Cs_2CO_3	2-MeTHF	68.19	0.00	8.35	0.00	3.63	21.45
$BuPAd_2$	Cs_2CO_3	2-MeTHF	50.55	0.00	0.62	0.74	2.32	2.13
Xphos	Cs_2CO_3	2-MeTHF	64.94	0.36	2.37	1.61	14.79	1.92
tBuXphos	Cs_2CO_3	2-MeTHF	75.42	3.40	3.51	2.04	18.29	4.41
Brettphos	Cs_2CO_3	2-MeTHF	0.54	70.40	2.63	0.42	0.00	0.50
Ruphos	Cs_2CO_3	2-MeTHF	122.80	0.24	1.77	2.48	21.42	1.77
Johnphos	Cs_2CO_3	2-MeTHF	69.65	0.35	2.28	2.78	20.01	1.50
Josiphos	Cs_2CO_3	2-MeTHF	72.56	0.70	1.45	1.84	19.99	0.91
DPPP	Cs_2CO_3	2-MeTHF	70.37	0.00	0.00	2.37	19.27	0.55
DPPF	Cs_2CO_3	2-MeTHF	69.87	0.00	0.00	7.81	23.50	0.74
r-Binap	Cs_2CO_3	2-MeTHF	66.12	0.23	0.00	2.65	20.95	0.75
Xantphos	Cs_2CO_3	2-MeTHF	65.21	1.77	5.75	1.23	13.09	9.70
PPh_3	K_3PO_4	2-MeTHF	69.60	0.00	3.03	3.55	11.99	6.13
PCy_3HBF_4	K_3PO_4	2-MeTHF	65.34	0.00	7.27	1.64	2.91	18.72

$BuPAd_2$	K_3PO_4	2-MeTHF	26.68	0.00	1.01	0.18	0.43	3.89
Xphos	K_3PO_4	2-MeTHF	73.19	0.52	2.66	3.91	9.91	2.10
tBuXphos	K_3PO_4	2-MeTHF	70.66	4.06	4.93	1.87	4.86	6.61
Brettphos	K_3PO_4	2-MeTHF	0.41	70.83	2.33	1.82	0.00	0.57
Ruphos	K_3PO_4	2-MeTHF	75.78	0.29	1.89	3.17	10.33	1.76
Johnphos	K_3PO_4	2-MeTHF	78.49	0.62	3.88	2.74	7.18	1.80
Josiphos	K_3PO_4	2-MeTHF	68.86	0.69	1.43	3.84	13.14	0.95
DPPP	K_3PO_4	2-MeTHF	80.41	0.00	0.00	3.31	12.62	0.73
DPPF	K_3PO_4	2-MeTHF	62.58	0.16	0.00	9.32	10.24	0.76
r-Binap	K_3PO_4	2-MeTHF	71.72	0.26	0.00	4.18	14.96	0.82
Xantphos	K_3PO_4	2-MeTHF	45.79	7.09	17.93	0.39	0.15	34.69

Table 2: Reaction Screening with Boc-NH_2

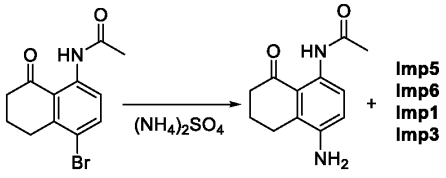


Ligand	**Base**	**Solvent**	**3/%**	**4a/%**	**Imp1/%**	**Imp2/%**	**Imp3/%**	**Imp7/%**
PPh_3	K_3PO_4	Toluene	58.39	0.00	13.04	0.00	5.79	19.87
PCy_3HBF_4	K_3PO_4	Toluene	54.29	0.00	9.05	0.00	2.00	11.59
$BuPAd_2$	K_3PO_4	Toluene	10.96	0.26	2.09	0.00	0.51	1.25
Xphos	K_3PO_4	Toluene	0.80	71.00	1.68	0.00	0.00	0.00
tBuXphos	K_3PO_4	Toluene	0.00	68.68	1.61	0.00	0.00	0.00
Brettphos	K_3PO_4	Toluene	0.00	81.10	0.31	0.00	0.00	0.00
Ruphos	K_3PO_4	Toluene	0.91	64.61	3.53	0.34	0.00	0.00
Johnphos	K_3PO_4	Toluene	22.38	41.39	4.35	0.00	0.66	0.27
Josiphos	K_3PO_4	Toluene	78.44	3.94	3.29	0.40	3.23	0.38
DPPP	K_3PO_4	Toluene	83.72	0.00	0.47	0.55	4.18	0.00
DPPF	K_3PO_4	Toluene	83.39	0.86	0.96	0.37	4.15	0.14
r-Binap	K_3PO_4	Toluene	68.16	4.39	1.19	0.00	2.87	0.00
Xantphos	K_3PO_4	Toluene	44.24	4.24	13.90	0.00	3.55	24.14

PPh_3	K_3PO_4	Dioxane	52.31	0.00	10.77	1.31	18.61	23.30
PCy_3HBF_4	K_3PO_4	Dioxane	44.62	0.00	7.40	0.00	7.64	16.25
$BuPAd_2$	K_3PO_4	Dioxane	20.38	0.00	1.21	0.00	1.81	2.28
Xphos	K_3PO_4	Dioxane	3.37	43.60	6.61	0.00	0.00	0.00
tBuXphos	K_3PO_4	Dioxane	54.05	9.36	3.67	0.56	4.15	1.62
Brettphos	K_3PO_4	Dioxane	1.03	71.54	1.29	0.00	0.00	0.00
Ruphos	K_3PO_4	Dioxane	9.70	32.98	7.62	0.24	0.00	0.31
Johnphos	K_3PO_4	Dioxane	57.85	7.52	4.52	0.66	5.58	0.69
Josiphos	K_3PO_4	Dioxane	69.68	1.03	5.11	1.12	16.01	0.77
DPPP	K_3PO_4	Dioxane	79.28	0.00	0.31	1.33	16.22	0.26
DPPF	K_3PO_4	Dioxane	77.96	0.26	1.28	1.24	16.68	0.27
r-Binap	K_3PO_4	Dioxane	72.24	0.42	0.00	0.76	12.39	0.61
Xantphos	K_3PO_4	Dioxane	11.71	3.22	27.89	0.00	1.26	60.99
PPh_3	K_3PO_4	tAmylOH	32.93	0.00	3.41	11.73	54.69	7.97
PCy_3HBF_4	K_3PO_4	tAmylOH	26.66	0.00	11.77	4.67	26.72	16.16
$BuPAd_2$	K_3PO_4	tAmylOH	17.69	0.00	1.54	3.35	24.25	1.75
Xphos	K_3PO_4	tAmylOH	24.44	14.66	7.11	2.25	12.49	0.00
tBuXphos	K_3PO_4	tAmylOH	22.49	28.99	6.76	2.95	12.89	0.89
Brettphos	K_3PO_4	tAmylOH	0.66	65.70	2.85	0.00	0.00	0.00
Ruphos	K_3PO_4	tAmylOH	36.69	2.45	3.44	6.50	38.66	0.00
Johnphos	K_3PO_4	tAmylOH	27.02	22.70	5.85	2.78	16.15	0.33
Josiphos	K_3PO_4	tAmylOH	36.80	0.16	1.69	10.42	43.30	0.26
DPPP	K_3PO_4	tAmylOH	37.12	0.00	0.49	12.24	47.83	0.00
DPPF	K_3PO_4	tAmylOH	38.68	0.00	0.35	11.80	47.75	0.00
r-Binap	K_3PO_4	tAmylOH	40.78	0.00	0.73	11.29	46.84	0.34
Xantphos	K_3PO_4	tAmylOH	33.88	0.00	1.70	12.53	62.21	0.68
PPh_3	K_3PO_4	DMF	44.89	0.00	7.36	1.46	14.52	11.22
PCy_3HBF_4	K_3PO_4	DMF	52.86	0.00	5.01	1.35	13.77	3.44
$BuPAd_2$	K_3PO_4	DMF	3.39	0.00	4.97	0.00	1.33	5.91
Xphos	K_3PO_4	DMF	12.71	0.00	18.81	0.00	1.65	26.32
tBuXphos	K_3PO_4	DMF	12.15	0.00	16.30	2.40	0.00	17.92
Brettphos	K_3PO_4	DMF	7.17	0.00	12.65	1.58	0.00	12.16
Ruphos	K_3PO_4	DMF	30.95	0.00	8.09	0.00	3.94	10.74

Johnphos	K_3PO_4	DMF	18.51	0.00	22.29	2.36	1.54	34.09
Josiphos	K_3PO_4	DMF	49.15	0.00	4.59	1.74	17.29	1.65
DPPP	K_3PO_4	DMF	46.81	0.00	5.71	2.12	18.83	1.06
DPPF	K_3PO_4	DMF	51.30	0.00	4.78	1.57	14.31	0.97
r-Binap	K_3PO_4	DMF	46.93	0.00	6.99	1.75	14.48	1.54
Xantphos	K_3PO_4	DMF	34.76	0.00	12.80	1.06	12.34	17.40
PPh_3	K_3PO_4	2-MeTHF	70.41	0.00	7.87	0.39	4.54	21.50
PCy_3HBF_4	K_3PO_4	2-MeTHF	66.43	0.00	5.33	0.00	2.22	11.70
$BuPAd_2$	K_3PO_4	2-MeTHF	59.00	0.00	0.49	0.23	2.33	1.19
Xphos	K_3PO_4	2-MeTHF	53.21	13.08	4.01	0.00	1.21	1.97
tBuXphos	K_3PO_4	2-MeTHF	44.37	30.47	2.12	0.19	0.34	0.94
Brettphos	K_3PO_4	2-MeTHF	2.20	79.33	0.89	0.00	0.00	0.00
Ruphos	K_3PO_4	2-MeTHF	33.30	20.86	4.45	0.00	0.00	0.00
Johnphos	K_3PO_4	2-MeTHF	53.38	22.13	3.41	0.00	0.27	1.58
Josiphos	K_3PO_4	2-MeTHF	80.53	0.54	1.42	0.51	5.97	0.98
DPPP	K_3PO_4	2-MeTHF	76.55	0.00	0.00	0.00	4.17	1.58
DPPF	K_3PO_4	2-MeTHF	78.82	0.00	0.00	0.00	3.16	0.00
r-Binap	K_3PO_4	2-MeTHF	74.90	0.00	0.00	0.00	3.77	0.00
Xantphos	K_3PO_4	2-MeTHF	67.81	0.00	6.09	0.00	5.75	10.87

Table 3: Reaction Screening with Ammonium Sulfate ($(NH_4)_2SO_4$)

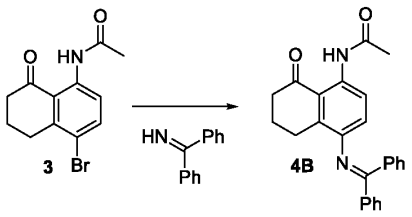


3 **4C**

Ligand	**Base**	**Solvent**	**3/%**	**4C/%**	**Imp5%**	**Imp6%**	**Imp1/%**	**Imp3%**
PPh_3	KOtBu	Dioxane	0.00	34.63	0.00	0.00	0.00	102.59
PCy_3HBF_4	KOtBu	Dioxane	0.00	13.21	0.00	1.36	0.16	110.90
$BuPAd_2$	KOtBu	Dioxane	0.23	15.75	0.00	9.28	0.00	100.25
Xphos	KOtBu	Dioxane	0.00	22.29	0.00	8.27	0.00	107.10
tBuXphos	KOtBu	Dioxane	0.00	21.30	4.60	1.69	0.00	112.43

Brettphos	KOtBu	Dioxane	0.00	18.65	18.36	16.99	0.00	56.19
Ruphos	KOtBu	Dioxane	0.00	21.56	0.00	11.66	0.00	72.88
Johnphos	KOtBu	Dioxane	0.00	21.54	1.75	3.13	0.00	101.96
Josiphos	KOtBu	Dioxane	0.00	62.81	0.00	2.51	0.00	66.18
DPPP	KOtBu	Dioxane	0.00	37.59	0.00	0.10	0.14	112.97
DPPF	KOtBu	Dioxane	0.00	29.22	0.00	0.06	0.00	85.45
r-Binap	KOtBu	Dioxane	0.00	22.72	0.00	0.37	0.00	132.52
Xantphos	KOtBu	Dioxane	0.00	38.28	0.00	2.26	0.00	100.68
PPh_3	K_3PO_4	Dioxane	33.12	0.69	0.00	1.88	22.93	5.79
PCy_3HBF_4	K_3PO_4	Dioxane	47.40	0.63	0.00	0.08	9.72	5.51
$BuPAd_2$	K_3PO_4	Dioxane	38.82	0.00	0.00	0.00	0.00	5.15
Xphos	K_3PO_4	Dioxane	38.43	0.74	0.00	0.00	2.97	49.16
tBuXphos	K_3PO_4	Dioxane	49.51	0.61	0.00	0.00	2.48	41.79
Brettphos	K_3PO_4	Dioxane	30.55	0.00	0.00	0.14	3.82	2.81
Ruphos	K_3PO_4	Dioxane	48.35	0.46	0.00	0.00	2.63	37.91
Johnphos	K_3PO_4	Dioxane	54.44	0.55	0.00	0.00	3.61	31.56
Josiphos	K_3PO_4	Dioxane	46.94	1.00	0.00	0.00	3.93	46.52
DPPP	K_3PO_4	Dioxane	49.88	0.00	0.00	0.00	0.43	46.53
DPPF	K_3PO_4	Dioxane	56.96	0.00	0.00	0.00	2.43	23.95
r-Binap	K_3PO_4	Dioxane	49.27	0.14	0.00	0.00	1.49	13.40
Xantphos	K_3PO_4	Dioxane	18.22	0.22	0.00	2.62	26.82	2.38

Example 3: Buchwald–Hartwig amination with benzophenone imine



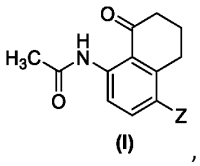
N-(8-bromo-4-oxo-tetralin-5-yl)acetamide **3** (3.5g, 12.4mmol) was mixed with benzophenone imine (2.7g, 14.9 mmol, 1.2 eq), K_3PO_4 (3.9g, 18.6mmol, 1.5 eq), $Pd(OAc)_2$ (0.28g, 1.24 mmol, 0.1 eq) and BINAP (2.48mmol, 1.54g, 0.2 eq) in 1,4-dioxane (35 mL) and heated to reflux for 18 h. The mixture was concentrated in vacuo then partitioned between water (10 vol) and ethyl acetate (10 vol). The separated organic layer was dried over sodium sulfate and concentrated under vacuum then purified

by silica gel chromatography to give N-[8-(benzhydrylideneamino)-4-oxo-tetralin-5-yl]acetamide **4B** (3.5g) in 65% yield. ^{1}H NMR (500 MHz, DMSO, 27°C) 1.98 (2H, p), 2.08 (3H, s), 2.65 (2H, t), 2.83 (2H, t), 6.69 (1H, d), 7.15 (2H, dd), 7.3 – 7.39 (3H, m), 7.48 (2H, t), 7.51 – 7.58 (1H, m), 7.68 – 7.73 (2H, m), 8.17 (1H, d), 11.77 (1H, s) ; m/z (ES+) [M+H]+=383.

The above description of illustrative embodiments is intended only to acquaint others skilled in the art with the Applicant's specification, its principles, and its practical application so that others skilled in the art may readily adapt and apply the specification in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples, while indicating embodiments of this specification, are intended for purposes of illustration only. This specification, therefore, is not limited to the illustrative embodiments described in this specification, and may be variously modified. In addition, it is to be appreciated that various features of the specification that are, for clarity reasons, described in the context of separate embodiments, also may be combined to form a single embodiment. Conversely, various features of the specification that are, for brevity reasons, described in the context of a single embodiment, also may be combined to form sub-combinations thereof.

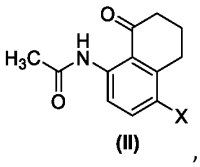
Claims

1. A process for the production of a compound of Formula (I):



(I) ,

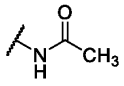
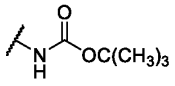
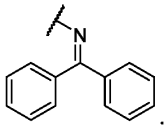
or a salt thereof, comprising a reaction of a compound of Formula (II):



(II) ,

or a salt thereof, and H-Z, or a salt thereof, wherein the reaction is performed in the presence of a palladium catalyst and a base,

wherein X is Br, I or Cl, and

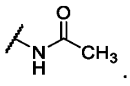
Z is  ,  or  .

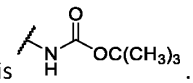
2. A process as claimed in claim 1, wherein X is Br.

3. A process as claimed in claim 1 or claim 2, wherein the reaction is performed in the presence of 1.0 to 3.0 equivalents of base.

4. A process as claimed in any one of claims 1 to 3, wherein the base is K_3PO_4.

5. A process as claimed in any one of claims 1 to 4, wherein the reaction is performed using 1.0 to 1.4 molar equivalents of Z-H.

6. A process as claimed in any one of claims 1 to 5, wherein Z is  .

7. A process as claimed in any one of claims 1 to 5, wherein Z is .

8. A process as claimed in claim 6 or claim 7, wherein the reaction is performed in the presence of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine.

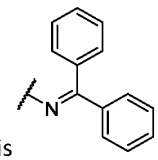
9. A process as claimed in any one of claims 6 to 8, wherein the reaction is performed in the presence of 0.01 to 0.15 molar equivalents of dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine.

10. A process as claimed in any one of claims 6 to 9, wherein the palladium catalyst is tris(dibenzylideneacetone)dipalladium(0).

11. A process as claimed in any one of claims 6 to 10, wherein the reaction is performed in the presence of 0.01 to 0.04 molar equivalents of tris(dibenzylideneacetone)dipalladium(0).

12. A process as claimed in any one of claims 6 to 11, wherein the reaction is performed in the presence of toluene.

13. A process as claimed in any one of claims 6 to 12, wherein the reaction is performed at a temperature of 60 to 100 °C.

14. A process as claimed in any one of claims 1 to 5, wherein Z is .

15. A process as claimed in claim 14, wherein the reaction is performed in the presence of 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene.

16. A process as claimed in claim 14 or claim 15, wherein the reaction is performed in the presence of 0.02 to 0.4 molar equivalents of 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene.

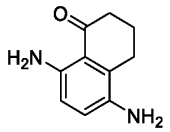
17. A process as claimed in any one of claims 14 to 16, wherein the palladium catalyst is palladium(II) acetate.

18. A process as claimed in any one of claims 14 to 17, wherein the reaction is performed in the presence of 0.01-0.2 molar equivalents of palladium(II) acetate.

19. A process as claimed in any one of claims 14 to 18, wherein the reaction is performed in the presence of dioxane.

20. A process as claimed in any one of claims 14 to 19, wherein the reaction is performed at a temperature of 80 to 120 °C.

21. A process for the production of a compound of Formula (III)



(III)

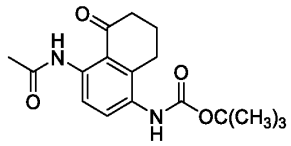
or a salt thereof, comprising

(i) the production of a compound of Formula (I), or a salt thereof, using a process as claimed in any one of claims 1 to 20; and

(ii) the production of the compound of Formula (III), of a salt thereof, comprising the reaction of the compound of Formula (I), or a salt thereof, and an acid.

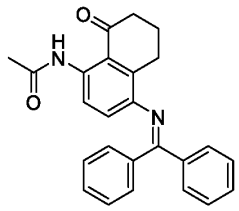
22. A process as claimed in claim 21, wherein the acid is hydrochloric acid.

23. A compound that is *tert*-Butyl (4-acetamido-5-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate,



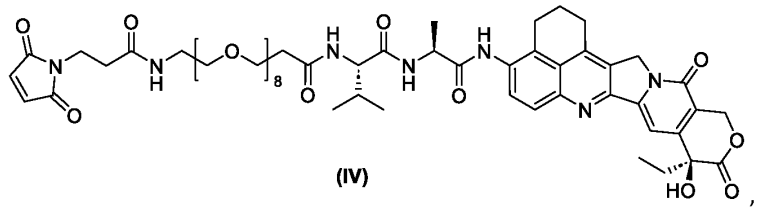
, or a salt thereof.

24. A compound that is *N*-(4-((Diphenylmethylene)amino)-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide,



, or a salt thereof.

25. A process for the production of a compound of Formula (IV)



(IV)

,

comprising a process as claimed in any one of claims 1 to 22, or a compound, or a salt thereof, as claimed in claim 23 or claim 24.

26. A process for the production of a conjugate of Formula (V)

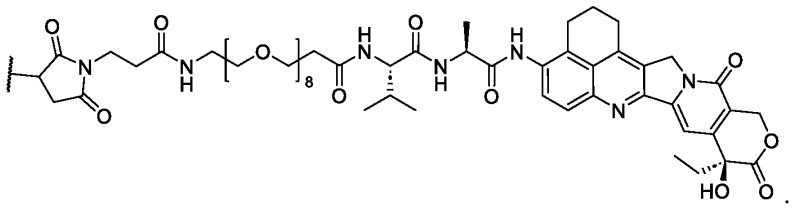
$$Ab - (LP)_k \qquad (V)$$

or a pharmaceutically acceptable salt thereof, comprising a process as claimed in any one of claims 1 to 22, or a compound, or a salt thereof, as claimed in claim 23 or claim 24, wherein

Ab is an antibody or antigen-binding fragment thereof,

k is an integer from 1 to 10, and

LP is



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