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(54) Title: A VERSATILE LIGAND FOR PALLADIUM-CATALYZED META-C-H FUNCTIONALIZATIONS

(57) Abstract: A class of mono-protected 3-amino-2- hydroxypyridine (MPAHP) ligands that enable the *meta*- C-H arylation of anilines, phenols, phenylacetic acids, and biologically relevant heterocyclic compounds using norbornene as a transient mediator is disclosed. The applicability of this *meta*-arylation methodology in the pharmaceutical industry is illustrated for heteroaryl substrates and heteroaryl iodide coupling partners, a feat made possible by using the MPAHP ligand. The enabling nature of MPAHP ligands to achieve other *meta*-C-H functionalization processes is also illustrated by the development of a *meta*-C-H amination reaction and a *meta*-C-H alkylation reaction.



**A VERSATILE LIGAND FOR PALLADIUM-CATALYZED
META-C-H FUNCTIONALIZATIONS**

Description

GOVERNMENTAL SUPPORT

This invention was made with governmental support under NIGMS 1R01 GM102265 awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

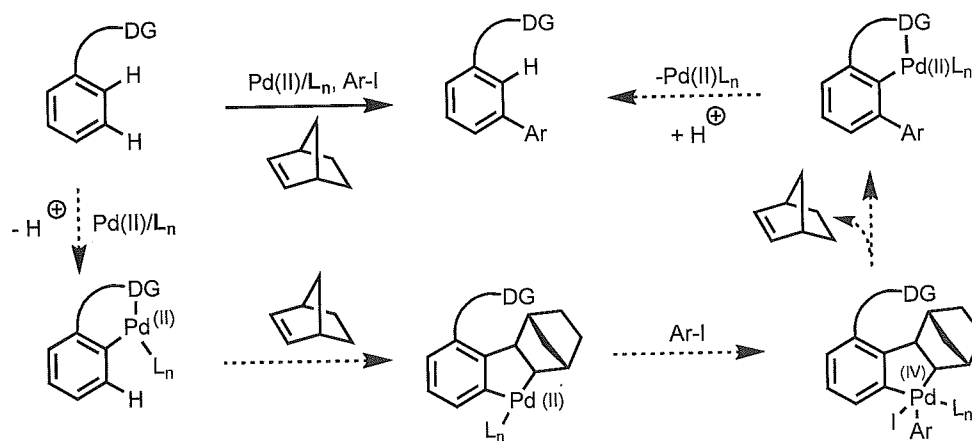
The present invention contemplates a method for forming a carbon-to-carbon (C-C) bond between a reactive substrate and an aromatic or heteroaromatic iodide, and the reagents that facilitate that electrophilic bond-formation reaction. More particularly, the new C-C bond is formed on an aromatic or heteroaromatic substrate molecule that would normally direct electrophilic substitutions to *ortho* or *para* positions instead to a position *meta* to a substituent already present on the substrate through the use of a palladium catalyst, a directing group bonded as part of the substrate, a directing ligand that is dissolved or dispersed in the reaction mixture.

BACKGROUND ART

Cyclopalladation reactions have been extensively studied since 1965.³ Recently, Pd(II)-catalyzed C-H activation reactions have been shown to

be compatible with a wide range of carbon-carbon and carbon-heteroatom bond-forming reactions through Pd(II)/Pd(0), Pd(II)/Pd(IV) and Pd(II)/Pd(II) catalytic cycles.⁴⁻⁶ However, versatile ligands that can promote both C-H cleavage and the subsequent functionalization steps remain scarce and are largely limited to mono-protected amino acids (MPAAs) and pyridine/quinoline based ligands.⁷

As effective C-H functionalization often requires a synergistic relationship between ligand and substrate coordinated to the metal center, it is essential to develop ligands that match with a variety of directing groups so that the assembled complexes are reactive in cleaving C-H bonds of a number of substrate classes.⁷ This fact is exemplified in recent efforts towards developing broadly useful norbornene-mediated meta-selective C-H functionalizations, where previously developed ligand scaffolds have proven insufficient at promoting reactivity with two important classes of substrates: anilines and phenols. A general pathway for meta-arylation using norbornene as a mediator is shown schematically below, where "DG" is a directing group, L_n is a ligand, and Ar-I is an aryl iodide coupling partner.



The norbornene insertion step from the Catellani reaction^{8,9} has previously been successfully combined with palladium catalyzed C-H activation to achieve selective C-H functionalization of indoles.^{10,11} Recently, this key step was combined with *ortho*-directed C-H activation to achieve a net *meta*-functionalization via a relay process.¹²⁻¹⁴ Further development of this newly emerging *meta*-C-H functionalization strategy remains a significant, yet important challenge as it is complementary to other approaches for the direct *meta*-functionalization of arenes.¹⁵⁻²³

BRIEF SUMMARY OF THE INVENTION

The present invention contemplates method of forming a reaction product containing carbon-to-carbon (C-C) bond to an aryl or heteroaryl substituent at a position *meta* to a substituent previously present on the ring of an aromatic reactive substrate compound, and particularly a substituted 3-amino-2-hydroxy-pyridine ligand useful in that reaction. A contemplated method comprises the steps of heating a reaction mixture to a temperature of about 70° to about 120° C. The

structural formula is shown in Formula IA



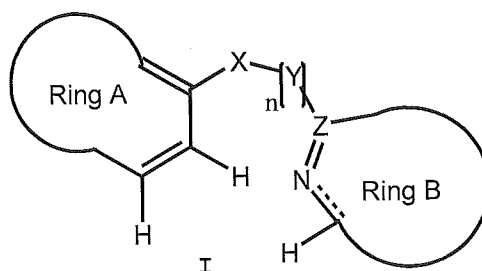
substituted

a) at the *meta* and *para* positions with one or two substituents independently selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), C₁-C₇-hydrocarbyl that is straight, branched or cyclic, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), cyano, nitro, perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarboyl (acyl), protected hydroxyl, protected hydroxyl-substituted C₁-C₇-hydrocarbyl that is straight, branched or cyclic, di-(C₁-C₇-hydrocarbyl) C₁-C₇-hydrocarbylphosphonate, protected amino wherein the protecting group(s) contains up to 10 carbon atoms and the amine nitrogen has no reactive hydrogen, and a fused ring that includes 3 or 4 added ring atoms, and

b) substituted at the *ortho* position by a carboxy C₁-C₇-hydrocarbyl or NH-C₁-C₇-hydrocarboyl group.

An iodo-substituted heteroaryl coupling agent can be further substituted with one or two substituents independently selected from the group consisting of halogen other than iodo, C₁-C₇-hydrocarbyl that is straight, branched or cyclic, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarboyl (acyl), a fused ring that includes 3 or 4 added ring atoms and in which any nitrogen atom present is free of reactive hydrogens.

The aromatic reactive substrate compound has a structural formula shown in Formula I, below:



wherein, Ring A is a heteroaromatic or carbocyclic aromatic ring structure in which the bond shown to X is at the 1-position of the ring and the substituent bonded at the 1-position constitutes the substituent previously present on the ring. The ring position rotated clock-wise from the 1-position is the *ortho*-position at which a hydrogen (H) is bonded, and the next position clock-wise from the *ortho*-position at which another hydrogen (H) is bonded is the *meta*-position and is the position at which the new C-C bond is formed.

The Ring A contains a single ring or two fused rings having a total of 5 to 10 ring atoms and in which the ring bonded to X is aromatic and any other ring fused to that aromatic ring is independently aromatic or aliphatic. A heteroaromatic ring structure that is all or a part of Ring A contains one, two or three heteroatoms that can independently be nitrogen, oxygen or sulfur atoms.

The Ring A optionally further contains 1, 2 or 3 substituents other than hydrido (H) bonded to the ring atoms. Those optional substituents when present are selected from the group consisting of halo other than iodo (fluoro, chloro or bromo), C₁-C₇-hydrocarbyl that is straight, branched or includes

a 4- to 6-membered ring bonded to a straight or branched chain, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), C₁-C₂-hydrocarbyldioxy, cyano, nitro, perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarboyl (acyl), protected amino wherein the protecting group(s) contains up to 10 carbon atoms, and a fused ring.

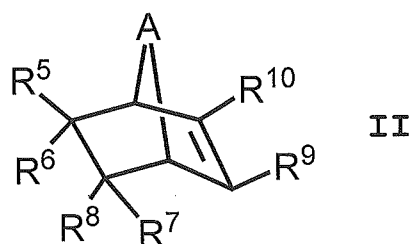
In structural Formula I, n is zero (0) or one, such that the methylene group Y within the brackets is absent when n is zero, and present when n is one.

X is O (oxygen) or NPG (a nitrogen bonded to a protecting group) when n is 1, and NPG or CH₂ (methylene) when n is zero.

Ring B is a heteroaromatic single 6-membered ring or a fused 6,6- or 5,6-membered ring system containing the depicted nitrogen atom and 1 or 2 other nitrogen ring atoms. Z is carbon when n is zero or 1. Z is nitrogen (a) when n is zero, and (b) the double bond depicted is absent and replaced by a double bond at the position of the dashed line.

Ring B optionally further contains 1, 2 or 3 substituents other than hydrido (H) bonded to the ring atoms. Those optional substituents when present are selected from the group consisting of C₁-C₇-hydrocarbyl that is straight, branched or includes a 4- to 6-membered ring bonded to a straight or branched chain C₁-C₃-substituent, C₁-C₇-hydrocarbyloxy, trifluoromethyl-C₁-C₃-hydrocarbyl, trifluoromethyl-C₁-C₃-hydrocarbyloxy, and a fused ring.

The reaction mixture also contains a transient mediator that is an ethylenically unsaturated bicyclic compound of Formula II

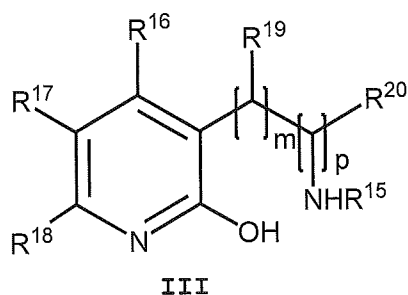


wherein

A is CH₂, C=O or O,

each of R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ is independently H, C₁-C₆-hydrocarbyl, C₁-C₆-hydrocarbyloxy, C₁-C₆-hydrocarbyl carboxylate, C₁-C₆-hydrocarboyl, one or both of R⁵ plus R⁶ and R⁷ plus R⁸ together with the carbon atom to which they are bonded form one or two carbonyl groups, or one each of R⁵ and R⁶, or R⁷ and R⁸ together with the atoms to which they are bonded form a further 4- to 6-membered aliphatic or aromatic ring that itself can be independently substituted with one or two substituent groups selected from the group consisting of a C₁-C₆-hydrocarbyl, a C₁-C₆-hydrocarbyloxy, a C₁-C₆-hydrocarbyl carboxylate and a nitro group.

The substituted 3-amino-2-hydroxypyridine ligand present in the reaction mixture has the structure of Formula **III**

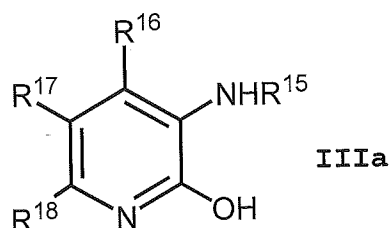


wherein R^{15} is an acyl group containing 2 to about 12 carbon atoms or a perfluorinated acyl group containing 2 to about 6 carbon atoms, R^{16} is hydrido or C_1 - C_6 -hydrocarbyl, R^{17} is hydrido, C_1 - C_6 -hydrocarbyl or trifluoromethyl, R^{18} is hydrido or C_1 - C_6 -hydrocarbyl, or R^{16} and R^{17} or R^{17} and R^{18} together with the carbon atoms to which they are bonded form a 6-membered ring with the depicted pyridine ring, m and p are the same and are zero or 1 such that m and p are zero, the bracketed carbon atoms are absent and the NHR^{15} group is bonded directly to the depicted pyridine ring, and when m and p are both one, R^{19} and R^{20} together with the carbons to which they are bonded form a phenyl ring. When R^{16} and R^{17} form a 6-membered ring with the depicted pyridine ring, it is preferred that R^{18} be hydrido.

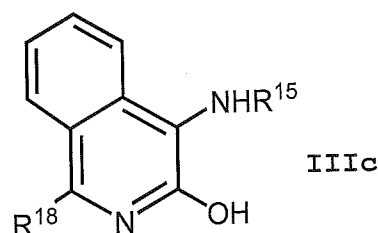
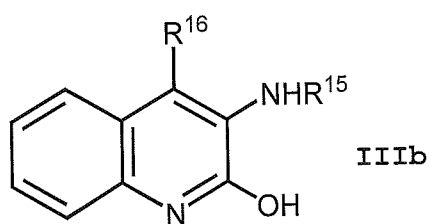
In preferred embodiments, at least one of R^{16} and R^{17} is other than hydrido. In one aspect of a preferred embodiment, R^{17} is trifluoromethyl. More preferably, R^{15} is acetyl, 1-adamantoyl or trifluoroacetyl and R^{16} is hydrido. In another preferred aspect, one of R^{16} and R^{17} is C_1 - C_6 -

hydrocarbyl and the other is hydrido. In this aspect, R¹⁵ is more preferably acetyl.

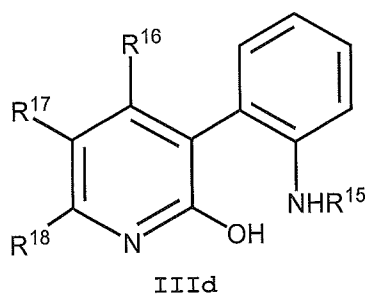
In some embodiments, m and p are both zero. In some preferred aspects of this embodiment, R¹⁶, R¹⁷, R¹⁷ and R¹⁸ are independently hydrido, C₁-C₆-hydrocarbyl or trifluoromethyl as defined above so that the ligand is a 2-hydroxypyridine derivative as is shown in Formula **IIIa**, below. In other preferred



aspects of this embodiment, R¹⁶ and R¹⁷, or R¹⁷ and R¹⁸ together with their bonded carbons form a 6-membered aromatic ring so that the ligand is a derivative of a quinoline or isoquinoline, as are shown in Formulas **IIIb** and **IIIc**, respectively, below.



In a still further embodiment, m and p are both one and R¹⁹ and R²⁰ together with the carbons to which they are bonded form a phenyl ring. In this case, the ligand is a 3-(ortho-aminophenyl)-2-hydroxypyridine derivative as is shown in Formula **IIId**, below.



The present invention has several benefits and advantages.

One benefit is that it provides a new route to the preparation of *meta*-substituted aromatics that are either not possible to readily synthesize by other means or can be synthesized but require the presence of a chemically bonded directing ligand.

An advantage of the invention is that one can prepare *meta*-substituted aromatic compounds using aromatic reactive substrates whose substituent group(s) would usually direct a new C-C bond to an *ortho* position.

Another benefit of the invention is that the *meta*-directing ligand not being bonded to the aromatic substrate need not be removed by a separate reaction as compared to removal by physical separation.

Another advantage of the invention is that the desired products can often be prepared in yields that are greater than about 50%.

Still further benefits and advantages of the invention will be apparent to the skilled worker from the discussion that follows.

DEFINITIONS

In the context of the present invention and the associated claims, the following terms have the following meanings:

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The words "ortho", "meta" and "para" are used in their usual manner to describe benzenoid compounds that are substituted "1-2", "1-3" and "1-4", respectively. Those same words are also used herein as a convenience to describe those same substitution patterns in aliphatic compounds.

The word "hydrocarbyl" is used herein as a short hand term for a non-aromatic group that includes straight and branched chain aliphatic as well as alicyclic groups or radicals that contain only carbon and hydrogen. Thus, alkyl, alkenyl and alkynyl groups are contemplated, whereas aromatic hydrocarbons such as phenyl and naphthyl groups, which strictly speaking are also hydrocarbyl groups, are referred to herein as aryl groups or radicals, as discussed hereinafter.

Where a specific aliphatic hydrocarbyl substituent group is intended, that group is recited; i.e., C₁-C₄ alkyl, methyl or hexenyl. Exemplary hydrocarbyl groups contain a chain of 1 to about 7 carbon atoms, and preferably 1 to about 4 carbon atoms.

A particularly preferred hydrocarbyl group is an alkyl group. As a consequence, a generalized,

but more preferred substituent can be recited by replacing the descriptor "hydrocarbyl" with "alkyl" in any of the substituent groups enumerated herein.

Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. Examples of suitable alkenyl radicals include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, decenyl and the like. Examples of alkynyl radicals include ethynyl, 2-propynyl, 3-propynyl, decynyl, 1-butyne, 2-butyne, 3-butyne, and the like.

Usual chemical suffix nomenclature is followed when using the word "hydrocarbyl" except that the usual practice of removing the terminal "yl" and adding an appropriate suffix is not always followed because of the possible similarity of a resulting name to one or more substituents. Thus, a hydrocarbyl ether is referred to as a "hydrocarbyloxy" group rather than a "hydrocarboxy" group as may possibly be more proper when following the usual rules of chemical nomenclature. Illustrative hydrocarbyloxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, cyclohexenyloxy groups and the like. On the other hand, a hydrocarbyl group containing a $-C(O)O-$ functionality is referred to as a hydrocarboyl (acyl) group inasmuch as there is no ambiguity in using that suffix. Exemplary hydrocarboyl and hydrocarboyl groups include acyl and acyloxy groups, respectively, such as acetyl and acetoxy, acryloyl and acryloyloxy.

As a skilled worker will understand, a substituent that cannot exist such as a C₁ alkenyl group is not intended to be encompassed by the word "hydrocarbyl", although such substituents with two or more carbon atoms are intended.

A "carboxyl" substituent is a -C(O)OH group. A C₁-C₆ hydrocarbyl carboxylate is a C₁-C₆ hydrocarbyl ester of a carboxyl group [-C(=O)-O-C₁-C₆ hydrocarbyl].

The term "aryl", alone or in combination, means a phenyl or naphthyl or other aromatic radical. An aryl group can be carbocyclic, containing only carbon atoms in the ring(s) or heterocyclic as a heteroaryl group discussed hereinafter. A "heteroaryl" group is an aromatic heterocyclic ring substituent that preferably contains one, or two, up to three or four, atoms in the ring other than carbon. Those heteroatoms can be nitrogen, sulfur or oxygen. A heteroaryl group can contain a single 5- or 6-membered ring or a fused ring system having two 6-membered rings or a 5- and a 6-membered ring. Exemplary heteroaryl groups include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as 1,3,5-, 1,2,4- or 1,2,3-triazinyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl groups; 6-/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl and anthranilyl groups; and 6-/6-membered fused rings such as 1,2-, 1,4-, 2,3- and 2,1-

benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl groups.

The term "halogen" means fluorine, chlorine or bromine. The term perfluorohydrocarbyl means a hydrocarbyl group wherein each hydrogen is replaced by a fluorine atom. Examples of such perfluorohydrocarbyl groups, in addition to trifluoromethyl, which is preferred, are perfluorobutyl, perfluoroisopropyl, perfluorododecyl and perfluorodecyl.

The terms "amino-protecting group" and "amine-protecting group" as used herein refer to one or more selectively removable substituents on the amino group commonly employed to block or protect the amino functionality. Examples of such amine-protecting groups include the formyl ("For") group, the trityl group ("Trt"), the phthalimido group ("Phth"), the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups. Urethane blocking groups, such as t-butoxy-carbonyl ("Boc"), 2-(4-biphenyl)propyl-(2)oxycarbonyl ("Bpoc"), 2-phenylpropyl(2)oxycarbonyl ("Poc"), 2-(4-phenyl)-isopropoxycarbonyl, 1,1-diphenyl-ethyl(1)oxycarbonyl, 1,1-diphenylpropyl(1)-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl(2)oxycarbonyl ("Ddz"), 2-(p-5-toluy)-propyl(2)oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluy)sulfonyl)ethoxycarbonyl, 2-(methyl-sulfonyl)-ethoxycarbonyl, 2-(triphenylphosphino)-ethoxy-carbonyl, 9-fluoroenylmethoxycarbonyl

("Fmoc"), 2-(trimethyl-silyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethyl-silylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalyl-methoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl(2) propoxy-carbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Z"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, α -2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyl-oxycarbonyl, 4-chlorobenzylloxycarbonyl, 3-chloro-benzylloxycarbonyl, 2-chlorobenzylloxycarbonyl, dichlorobenzylloxycarbonyl, 4-bromobenzylloxycarbonyl, 3-bromobenzylloxycarbonyl, 4-nitrobenzylloxycarbonyl, 4-cyanobenzylloxycarbonyl, 4-(decyloxy)benzyloxy-carbonyl, and the like, the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts'") group, the 2-(nitro)-phenylsulfonyl group ("Nps'"), the 2- or 4-nitro-phenylsulfonyl ("Nos") group, 4-toluenesulfonyl ("Ts"), the diphenylphosphine oxide group, and like amino-protecting groups.

The species of amine-protecting group employed is usually not critical so long as the derivatized amino group is stable to the conditions of the subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the compound. A preferred amine-protecting group is a phthalimido group.

Further examples of amino-protecting groups embraced to by the above term are well known in organic synthesis and the peptide art and are described by, for example: T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd

ed., John Wiley and Sons, New York. N.Y., Chapter 7, 1991; M. Bodanzsky, *Principles of Peptide Synthesis*, 1st and 2nd revised ed., Springer-Verlag, New York, N.Y., 1984 and 1993; and Stewart and Young, *Solid Phase Peptide Synthesis*, 2nd ed., Pierce Chemical Co, Rockford, IL 1984.

The related term "protected amino" or "protected amine" defines an amino group substituted with an amino-protecting group discussed above.

The terms "hydroxy-protecting group" and "hydroxyl-protecting group" refer to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxyprop-2-yl, 1-ethoxyeth-1-yl, methoxymethyl, methylthiomethyl, β -methoxyethoxymethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl ("TMS"), t-butyldiphenylsilyl ("TBDPS"), (t-butyl)dimethylsilyl ("TBS" or "TBDMS"), triisopropylsilyl ("TIPS"), and 2,2,2-trichloroethoxycarbonyl groups, and the like. Ester groups such as C₁-C₆-hydrocarboyl esters such as acetate ("OAc"), propionate and hexanoate are also useful, as is a benzyl ether ("Bn") group. The species of hydroxyl-protecting groups is also usually not critical so long as the derivatized (protected) hydroxyl group is stable to the conditions of subsequent reaction(s) and the protecting group can be removed at the appropriate point without disrupting the remainder of the compound.

Further examples of hydroxy-protecting groups are described by C. B. Reese and E Haslam, *Protective Groups in Organic Chemistry*, J. G. W.

McOmie Ed., Plenum Press, New York, N.Y., Chapters 3 and 4, 1973, and T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley and Sons, New York, N.Y., Chapters 2 and 3, 1991.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

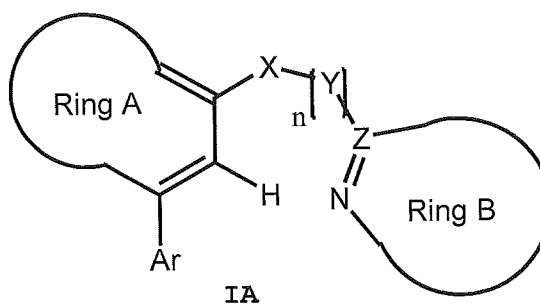
In an attempt to expand the scope of norbornene-mediated *meta*-C-H arylation reactions, aniline was selected as a model substrate. *Meta*-functionalization of this class of substrates²⁰⁻²² is highly valuable as electrophilic substitution reactions predominantly afford *ortho*- and/or *para*-substituted products due to the electronic directing effects of the aniline nitrogen atom.

Because of the multiple possible reaction pathways at several steps of the catalytic cycle, development of a ligand to orchestrate each step is a tremendous challenge. The discovery of mono-protected 3-amino-2-hydroxypyridine ligands (MPAHPs) that promote a highly efficient *meta*-C-H arylation of anilines, phenols, phenylacetic acids and heterocycles is disclosed hereinafter. This class of ligands has also enabled a *meta*-C-H amination reaction and a *meta*-C-H alkynylation reaction both of which, have not previously been achieved so far as is known.

Thus, a method of forming a reaction product containing carbon-to-carbon (C-C) bond to an aryl or heteroaryl substituent at a position *meta* to a substituent previously present on the ring of an aromatic reactive substrate compound is contemplated. Particularly contemplated in conjunction with that

reaction is a substituted 3-amino-2-hydroxy-pyridine ligand useful in that reaction.

A contemplated method comprises the steps of heating a reaction mixture to a temperature of about 70° to about 120° C. The reaction mixture contains i) an aromatic reactive substrate compound of Formula I dissolved or dispersed in a non-aqueous solvent having a boiling point at 1 atmosphere of about 40° to about 200° C. That reaction mixture further contains dissolved or dispersed therein ii) a catalytic amount of a Pd(II) catalyst, iii) a substituted 3-amino-2-hydroxy-pyridine ligand of Formula III is present at about 10 to about 50 mole percent based on the moles of reactive substrate, iv) an ethylenically unsaturated bicyclic compound of Formula II as a transient mediator present in excess over the amount of reactive substrate, v) about 1.5 to about 5 equivalents of an oxidant based on the amount of said reactive substrate, and vi) about 1.1 to about 10 equivalents of a iodo-substituted aryl or heteroaryl coupling agent (Ar-I). The temperature is maintained for a time period sufficient to carry out the C-C bond formation at a position *meta* to the substituent and form a reaction product whose structural formula is shown in Formula IA



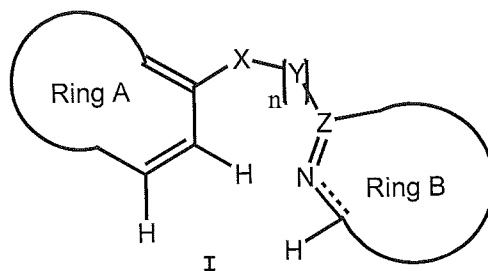
In some aspects, the reaction product is recovered from the reaction mixture. Where Y is methylene, the reacted A Ring can be separated from the B Ring by treatment with hydrogen in the presence of a catalyst such as palladium on charcoal, or by reaction with an acid such as trifluoroacetic acid. In other aspects, either treatment can be used without isolating the product from the reaction mixture.

In that reaction mixture, the iodo-substituted aryl or heteroaryl coupling agent can no further substituent that the iodo group; i.e., additionally be unsubstituted. Alternatively, the iodo-substituted aryl coupling agent can be further substituted a) at the *meta* and *para* positions with one or two substituents independently selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), C₁-C₇-hydrocarbyl that is straight, branched or cyclic, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), cyano, nitro, perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarboyl (acyl), protected hydroxyl, protected hydroxyl-substituted C₁-C₇-hydrocarbyl that is straight, branched or cyclic, di-(C₁-C₇-hydrocarbyl) C₁-C₇-hydrocarbylphosphonate, protected amino wherein the protecting group(s) contains up to 10 carbon atoms and the amine nitrogen has no reactive hydrogen, and a fused ring that includes 3 or 4 added ring atoms. That iodo-substituted aryl coupling agent can also be substituted b) at the *ortho* position by a carboxy C₁-C₇-hydrocarbyl or NH-C₁-C₇-hydrocarboyl group.

An iodo-substituted heteroaryl coupling agent can also be further substituted with one or two substituents independently selected from the group consisting of halogen other than iodo, C₁-C₇-hydrocarbyl that is straight, branched or cyclic, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarbonyl (acyl), a fused ring that includes 3 or 4 added ring atoms and in which any nitrogen atom present is free of reactive hydrogens.

The phrase "any nitrogen atom present is free of reactive hydrogens" and similar phrases are used herein to mean that a primary or secondary amine that normally contains one or two hydrogens bonded to the amine nitrogen atom are replaced by amine protecting groups (PG) that can be the same or different. Thus, a hydrogen that could otherwise react with a reactive group such as a isocyanate is absent. Illustrative protecting groups for a primary amine are benzyl (Bn) and *t*-butoxycarbonyl (Boc), and one or the other for a secondary amine.

The aromatic reactive substrate compound has a structural formula shown in Formula I, below:



In Formula I, Ring A is a heteroaromatic or carbocyclic aromatic ring structure in which the bond

shown to X is at the 1-position of the ring and the substituent bonded at the 1-position constitutes the substituent previously present on the ring that was noted above. The ring position rotated clock-wise from the 1-position is the *ortho*-position at which a hydrogen (H) is bonded, and the next position clock-wise from the *ortho*-position at which another hydrogen (H) is bonded is the *meta*-position and is the position at which the new C-C bond is formed.

The Ring A contains a single ring or two fused rings having a total of 5 to 10 ring atoms and in which the ring bonded to X is aromatic and any other ring fused to that aromatic ring is independently aromatic or aliphatic. A heteroaromatic ring structure that is all or a part of Ring A contains one, two or three heteroatoms that can independently be nitrogen, oxygen or sulfur atoms.

The Ring A optionally further contains 1, 2 or 3 substituents other than hydrido (H) bonded to the ring atoms. Those optional substituents when present are selected from the group consisting of halo other than iodo (fluoro, chloro or bromo), C₁-C₇-hydrocarbyl that is straight, branched or cyclic, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), cyano, nitro, perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarboyl (acyl), protected amino wherein the protecting group(s) contains up to 10 carbon atoms, and a fused ring. Preferably, zero or 1 additional substituent is present bonded to a ring atom of Ring A.

Illustrative ring structures of Ring A include benzene and naphthalene rings, thiophene and furan rings, as well as pyridine, pyrazine, quinoline, quinoxaline, indole, indoline, indazole, dihydrobenzodioxine, and chromen-4-one rings. It is noted that in any of the Ring A heterocyclic rings that include a nitrogen ring atom, that nitrogen atom is bonded to a C₁-C₇-hydrocarbyl group as discussed above, or to a removable nitrogen protecting group so that no reactive hydrogen is present bonded to a Ring A nitrogen.

In structural Formula I, n is zero (0) or one. Thus, the methylene group (CH₂), Y, within the depicted brackets is absent when n is zero, and present when n is one. Z is carbon when n is zero or 1. Z is nitrogen (a) when n is zero, and (b) the double bond depicted is absent and replaced by a double bond at the position of the dashed line. In preferred aspects of the invention, n is 1.

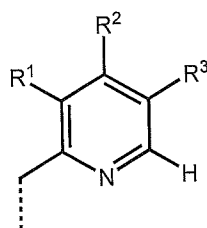
X is O (oxygen) or NPG (a nitrogen bonded to a protecting group) when n is 1, and NPG or CH₂ (methylene) when n is zero. Additionally, when n is zero, the double bond depicted is absent and is replaced by a double bond at the position of the dashed line.

Ring B is a heteroaromatic single 5- or 6-membered ring or a fused 6,6- or 5,6-membered fused ring system containing the depicted nitrogen atom and 1 or 2 other nitrogen ring atoms. Ring B is often referred to herein as a directing group (DG or DG').

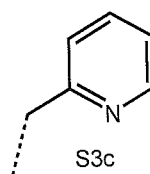
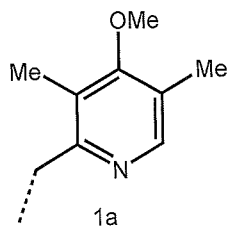
Preferably, when n is one, Ring B contains a single 6-membered ring and one nitrogen atom and up to three substituents other than hydrido (H) bonded

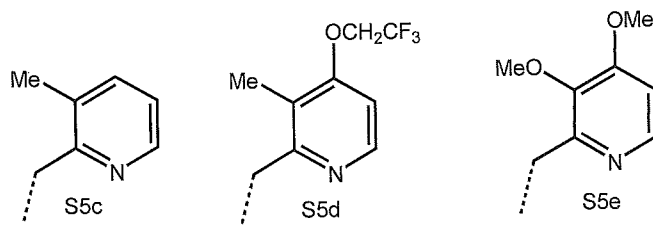
to the ring atoms at ring positions other than that shown by the hydrido (hydrogen) bonded to the carbon atom adjacent to the depicted Ring B nitrogen in Formula I. Those optional substituents, R^1 , R^2 and R^3 , when present are selected from the group consisting of C_1 - C_7 -hydrocarbyl that is straight, branched or cyclic, C_1 - C_7 -hydrocarbyloxy, trifluoromethyl- C_1 - C_3 -hydrocarbyl, trifluoromethyl- C_1 - C_3 -hydrocarbyloxy.

In preferred aspects of this embodiment, a Ring B is a pyridine derivative whose structural formula is shown below, where the dotted line denotes



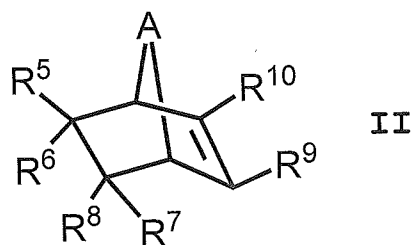
a bond to the methylene group Y of Formula I, R^1 , R^2 and R^3 are independently hydrido, C_1 - C_6 -hydrocarbyl, C_1 - C_6 -hydrocarbyloxy or trifluoromethyl- C_1 - C_3 -hydrocarbyloxy. More preferably, at least one of R^1 , R^2 and R^3 is other than hydrido. Preferred and particularly preferred Ring B groups are shown below with numerals identifying the compound of Formula I in which they are exemplified.





When n is zero, exemplary Ring B ring systems include pyridine, pyrimidine, pyrazine, pyrazole, indazole and quinolone. These B ring systems can contain one or two substituent groups such as a C_1 - C_7 -hydrocarbyl and a C_1 - C_7 -hydrocarbyloxy group.

The reaction mixture also contains a transient mediator that is an ethylenically unsaturated bicyclic compound of Formula II



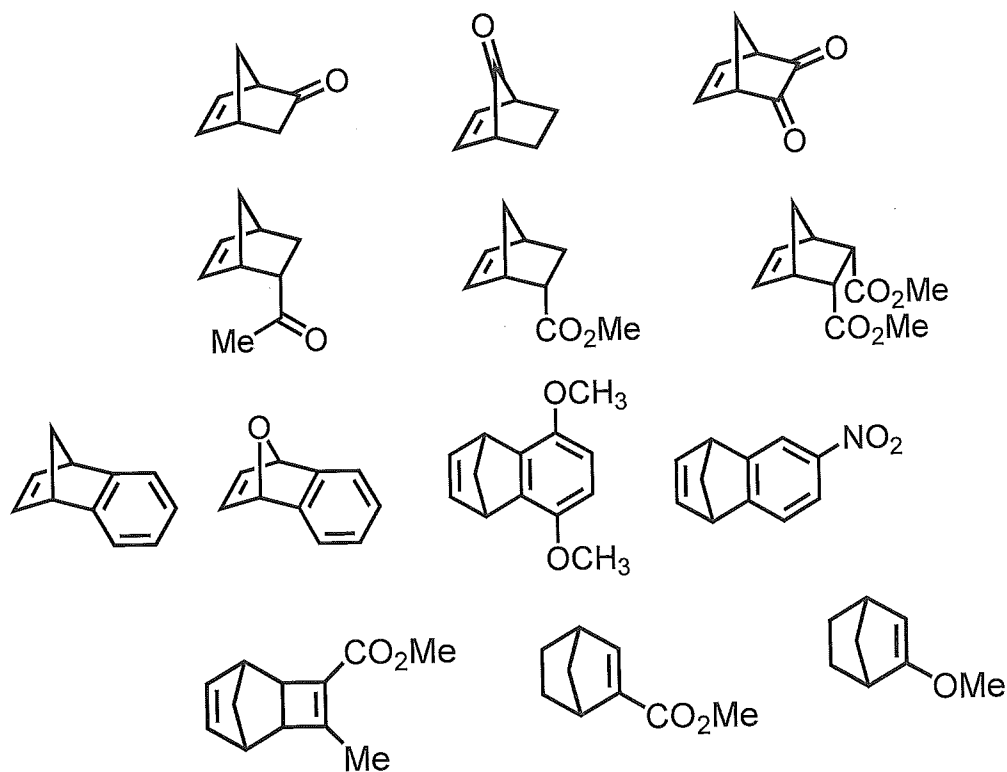
wherein

A is CH_2 , $C=O$ or O,

each of R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10} is independently H, C_1 - C_6 -hydrocarbyl, C_1 - C_6 -hydrocarbyloxy, C_1 - C_6 -hydrocarbyl carboxylate, C_1 - C_6 -hydrocarbonyl, one or both of R^5 plus R^6 and R^7 plus R^8 together with the carbon atom to which they are bonded form one or two carbonyl groups, or one each of R^5 and R^6 , or R^7 and R^8 together with the atoms to which they are bonded form a further 4- to 6-membered aliphatic or aromatic ring that itself can be independently substituted with one or two substituent

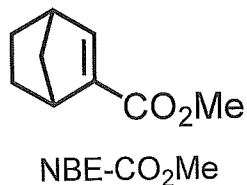
groups selected from the group consisting of a C₁-C₆-hydrocarbyl, a C₁-C₆-hydrocarbyloxy, a C₁-C₆-hydrocarbyl carboxylate and a nitro group.

A ethylenically unsaturated bicyclic transient mediator compound of Formula II is present in excess over the amount of reactive substrate used. Preferably, that compound is present in an amount of about 1.2 to about 3 equivalents relative to the reactive substrate. More preferably, that amount is about 1.5 to about 2 times the moles of reactive substrate. Structural formulas of illustrative transient mediator ethylenically unsaturated bicyclic compounds are shown below.

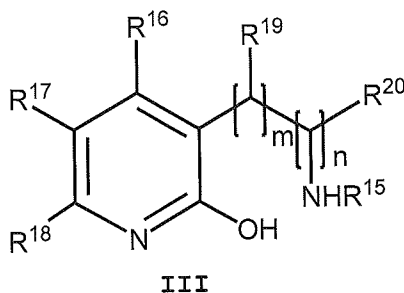


An improved transient mediator, methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate (NBE-CO₂Me), whose structural formula is shown below is preferred

in place of 2-norbornene that had been used in prior publications.¹⁴



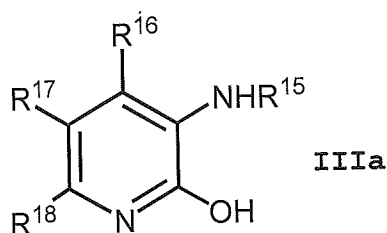
A ligand that can be viewed as a substituted 3-amino-2-hydroxypyridine is also present in the reaction mixture has the structure of Formula **III**, below,



wherein R¹⁵ is an acyl group containing 2 to about 12 carbon atoms or a perfluorinated acyl group containing 2 to about 6 carbon atoms, R¹⁶ is hydrido or C₁-C₆-hydrocarbyl, R¹⁷ is hydrido, C₁-C₆-hydrocarbyl or trifluoromethyl, R¹⁸ is hydrido or C₁-C₆-hydrocarbyl, or R¹⁶ and R¹⁷ or R¹⁷ and R¹⁸ together with the carbon atoms to which they are bonded form a 6-membered ring with the depicted pyridine ring, m and p are the same and are zero or 1. When m and p are zero, the bracketed carbon atoms are absent and the NHR¹⁵ group is bonded directly to the depicted pyridine ring. When R¹⁶ and R¹⁷ form a

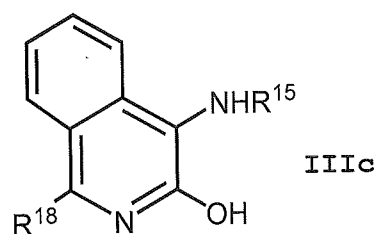
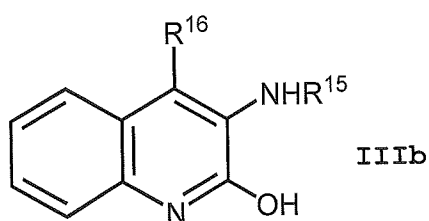
6-membered ring with the depicted pyridine ring, it is preferred that R^{18} be hydrido. When m and p are both one, R^{19} and R^{20} together with the carbons to which they are bonded form a phenyl ring.

In some embodiments, when m and p are both zero, R^{16} , R^{17} , R^{18} and R^{15} are independently hydrido, C_1 - C_6 -hydrocarbyl or trifluoromethyl as defined above so that the ligand is a 2-hydroxypyridine derivative as is shown in Formula **IIIa**, below. Here, preferably at least one of R^{16} ,

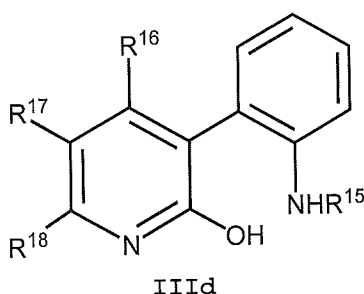


R^{17} and R^{18} is other than hydrido. In one aspect of a preferred embodiment, R^{17} is trifluoromethyl. More preferably, R^{15} is acetyl, 1-adamantoyl or trifluoroacetyl and R^{16} is hydrido. In another preferred aspect, one of R^{16} and R^{17} is C_1 - C_6 -hydrocarbyl and the other is hydrido. In this aspect, R^{15} is more preferably acetyl.

In other preferred aspects of this embodiment, R^{16} and R^{17} , or R^{17} and R^{18} together with their bonded carbons form a 6-membered aromatic ring so that the ligand is a derivative of a quinoline or isoquinoline, as are shown in Formulas **IIIb** and **IIIc**, respectively, below.

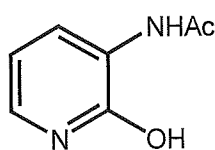
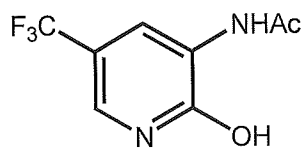
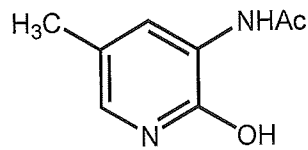
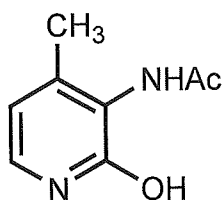
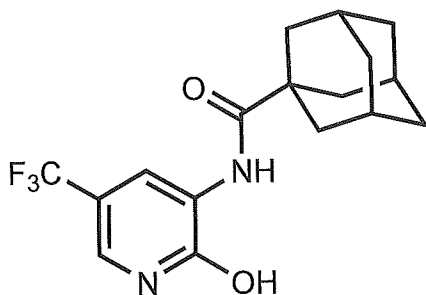
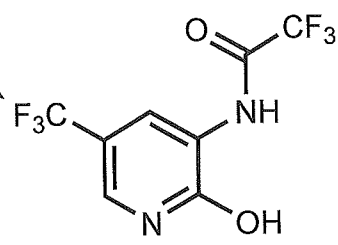


In a still further embodiment, m and p are both one and R¹⁹ and R²⁰ together with the carbons to which they are bonded form a phenyl ring. In this case, the ligand is a 3-(*ortho*-aminophenyl)-2-hydroxypyridine derivative as is shown in Formula **IIId**, below, where R¹⁶, R¹⁷ and R¹⁸ are as defined above.



In preferred embodiments of a compound of Formula **IIIa**, at least one of R¹⁶ and R¹⁷ is other than hydrido. In one aspect of a preferred embodiment, R¹⁷ is trifluoromethyl. More preferably, R¹⁵ is acetyl, 1-adamantoyl or trifluoroacetyl and R¹⁶ is hydrido. In another preferred aspect, one of R¹⁶ and R¹⁷ is C₁-C₆-hydrocarbyl and the other is hydrido. In this aspect, R¹⁵ is more preferably acetyl. R¹⁸ is preferably hydrido when not part of a ring system.

Structural formulas of six of these more preferred ligand compounds are shown below along with their numerical identifiers used herein.

**L12****L14****L16****L17****L24****L25**

A ligand of Formula **III** is present in the reaction mixture in an amount of about 10 to about 50 mole percent based on the moles of reactive substrate. Preferably, that amount is about 20 to about 40 mole percent.

A contemplated method utilizes an excess, about 1.5 to about 5 equivalents (moles) of an oxidant per mole of reactive substrate, and preferably about 2 to about 4 equivalents of oxidant. A silver oxidant is typically used, although oxygen and other mild oxidants can also be used.

Illustrative catalysts include Ag(Piv), Ag(OAc), Ag₂O,

AgTFA, AgOTf, Ag₂CO₃, $\text{Et} \begin{array}{c} \text{Me} \\ \diagup \diagdown \\ \text{C} \\ \diagdown \diagup \\ \text{Me} \end{array} \text{CO}_2\text{Ag}$, $\text{Et} \begin{array}{c} \text{Me} \\ \diagup \diagdown \\ \text{C} \\ \diagdown \diagup \\ \text{Me} \end{array} \text{CO}_2\text{Ag}$, $\text{Et} \begin{array}{c} \text{Me} \\ \diagup \diagdown \\ \text{C} \\ \diagdown \diagup \\ \text{Me} \end{array} \text{CO}_2\text{Ag}$, and

Cu(OAc)₂. Ag(OAc) is a preferred oxidant.

A contemplated reaction is carried out with the ingredients dissolved or dispersed in a solvent

and with agitation as can be provided by the use of a magnetic stir bar. Additional means of agitation such as shaking can also be utilized.

The reaction is carried out at a temperature of about 70° to about 120° C. More preferably, the reaction temperature is about 90° to about 110° C. Because many useful solvents boil at a temperature less than 70° C, the reactions are typically carried out in sealed containers under pressure greater than 1 atmosphere. Thus, the pressure under which the ingredients are maintained is mostly that created by the solvent used at the reaction temperature, with some contribution from the reactants.

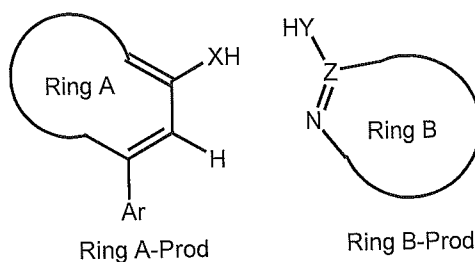
The reaction is carried out at an above elevated temperature for a time period sufficient to carry out the electrophilic insertion and form a reaction product having the new carbon-carbon (C-C) bond. Reaction times are typically about 15 to about 50 hours, with times of about 18-30 hours being usual.

A contemplated solvent is a non-aqueous solvent having a boiling point at 1 atmosphere of about 40° to about 200° C. Exemplary solvents include ^tBuCO₂Me, hexafluoro-isopropanol (HFIP), ethyl acetate (EtOAc or EA), acetonitrile, acetone, ^tBuCN, ^tBuOMe (TBME), dioxane, toluene, *t*-amylOH, ^tBu(C=O)Me, *n*-hexane, (trifluoromethyl)benzene, C₆F₆, chloroform (CClH₃), dichloromethane (DCM), and 1,2-dichloroethane (DCE). DCE, *t*-amylOH and HFIP are preferred among these materials.

Upon completion of the reaction, the desired product can be recovered by usual work-up

procedures, or can be left *in situ* and reacted further as desired. In preferred situations in which Y is methylene and Z is carbon, the Ring B portion of the molecule is a pyridine derivative as discussed previously, a reaction product of Formula IA is chemically similar to a benzyl ether or benzyl amine.

As such, the two portions of the reaction product can be severed at the bond between X and Y in the structural formula to provide Ring A-Prod and Ring B-Prod whose structural formulas are shown below. This cleavage can be carried out using



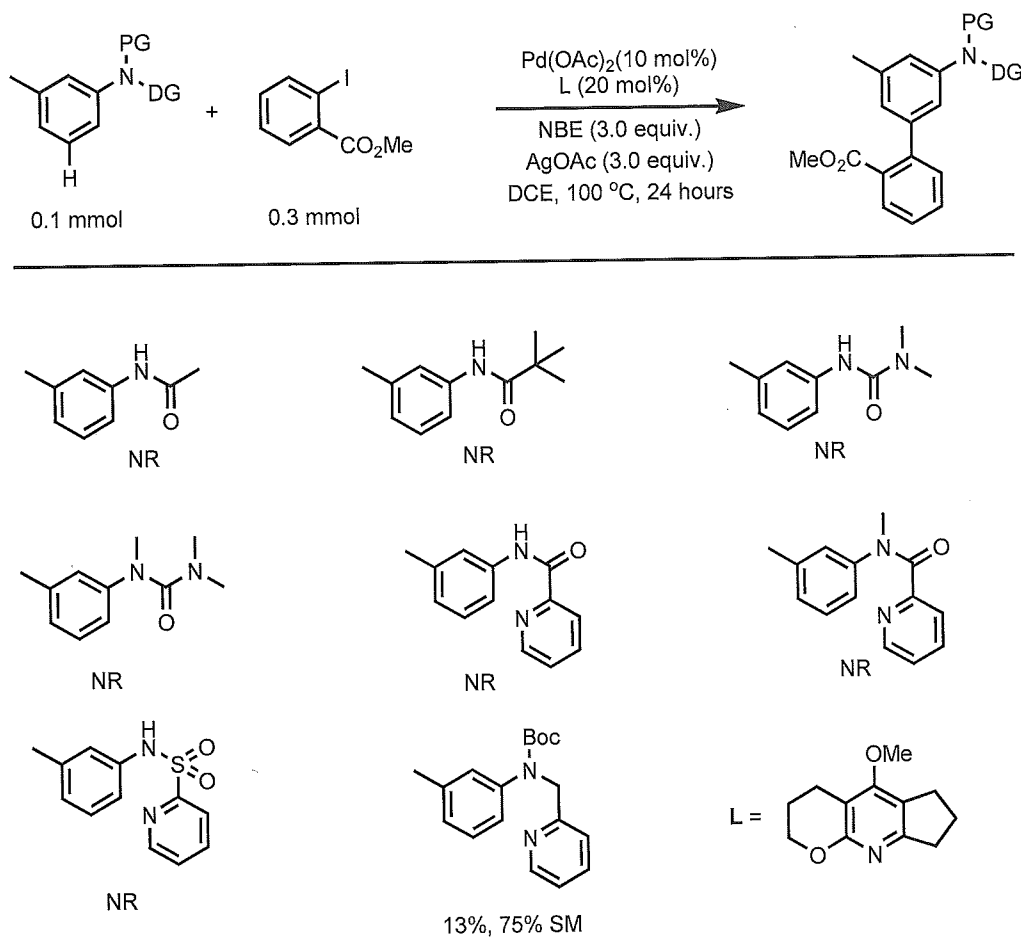
chemistry utilized for benzyl protecting group cleavage as is discussed in Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd ed. John Wiley & Sons, Inc., New York (1999). Further illustrative cleavage reactions are illustrated hereinafter.

Results and discussion

The initial evaluation of aniline substrates focused on finding a reactive and readily removable directing group that would be compatible with the desired catalytic cycle. The screening reaction used to identify a useful directing group (DG) is illustrated below in **Table 1** along with eight aniline derivatives examined.

After a survey of the several directing groups, a benzylic-pyridine based directing group bonded to the aniline amine nitrogen along with a *t*-Boc protecting group (PG) was found to provide the *meta*-arylated product in 13% yield. Other directing groups were not reactive, as is shown.

Table 1

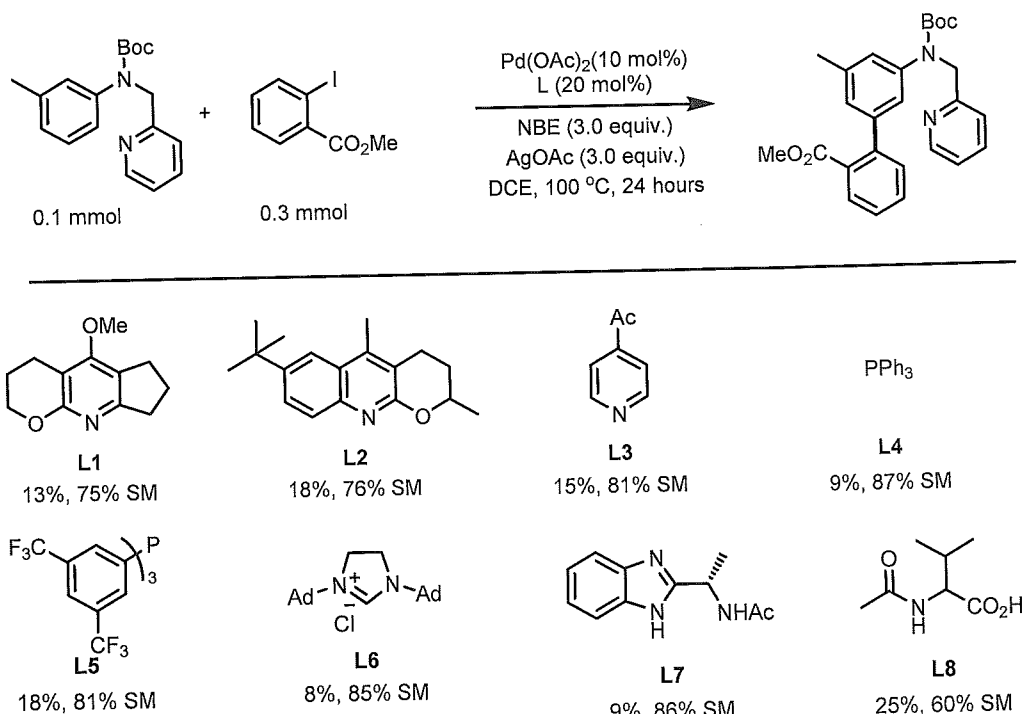


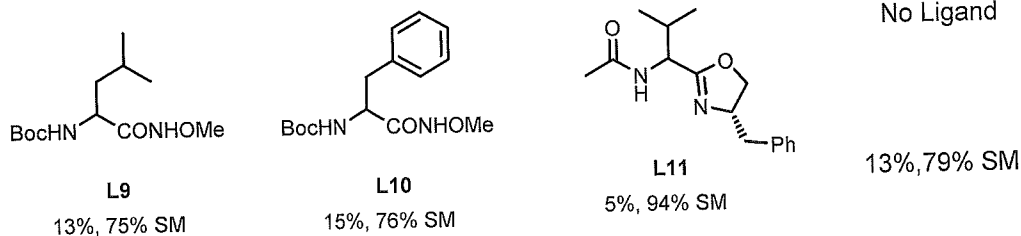
NR = no reaction; SM = starting material; The yield was determined by ¹H NMR.

Ligands that could match with this directing group and promote the reaction were sought, starting with both amino acid- and heterocyclic base-derived ligands that have been shown to promote C-H activation reactions^{7,12}. Unexpectedly, there was no significant improvement of the yield when

utilizing either of these previously established ligand classes. These results are surprising given the enabling role of the pyridine-derived ligand **L1** in the norbornene-mediated *meta*-C-H arylation of phenylacetic acid derived substrates previously reported by the inventor and co-workers.¹² Phosphine (**L4** and **L5**) and *N*-heterocyclic carbene (**L6**) ligands were also evaluated, but neither class provided a significant improvement of the yield. This indicated that design of a new ligand would be crucial for developing broadly useful *meta*-C-H functionalizations of anilines utilizing this approach. See **Table 2** below for results with ligands **L1-L11**.

Table 2*



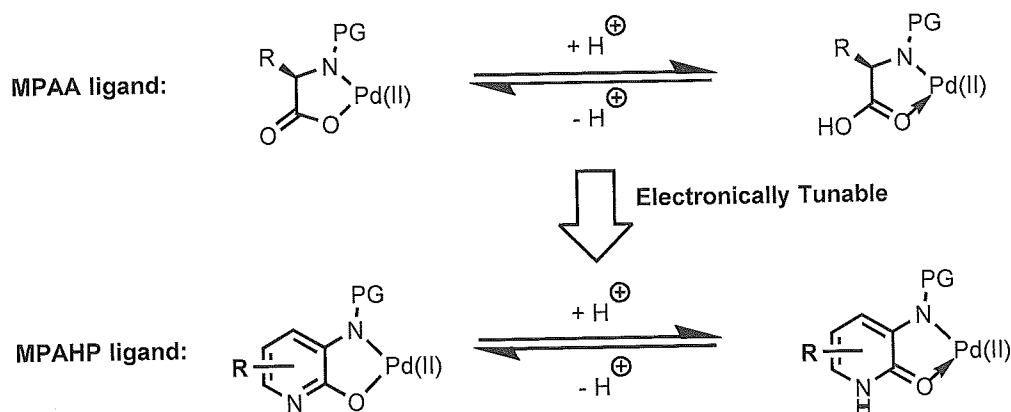


*The yields were determined by ^1H NMR; SM = starting material.

Considering that the MPAAAs have been shown to be highly versatile ligands that promote palladium(II) catalyzed C-H functionalization reactions of $\text{C}(\text{sp}^2)\text{-H}$ and in some cases $\text{C}(\text{sp}^3)\text{-H}$ bonds,^{24,25} the vital structural features of this ligand were sought to be incorporated into other backbones that would enable new reactivity. Although varying the side chain of MPAA ligands permits tuning of their steric properties, modulation of the electronic properties of the C- and N-termini (COOH and NHPG, respectively, PG = protecting group such as Ac, Boc) remains limited. Notably, both computational studies and experimental investigations indicated the NHAc and COOH moieties are essential for forming a bis-dentate complex with Pd(II), generating the active catalytic species.^{26,27}

Computational work has also identified a transition state in which the Pd-NAc or Pd-NBoc moiety can assist C-H deprotonation in the C-H cleavage step.^{26,27} Recognizing the similarity of 2-hydroxypyridine and 2-pyridone tautomers with the various coordination modes of a carboxylate in MPAA ligands (below), MPAHP ligands were designed and prepared based on a hydroxypyridine scaffold that also incorporates the NHAc group from the MPAAAs. A schematic that illustrates these ligands and their

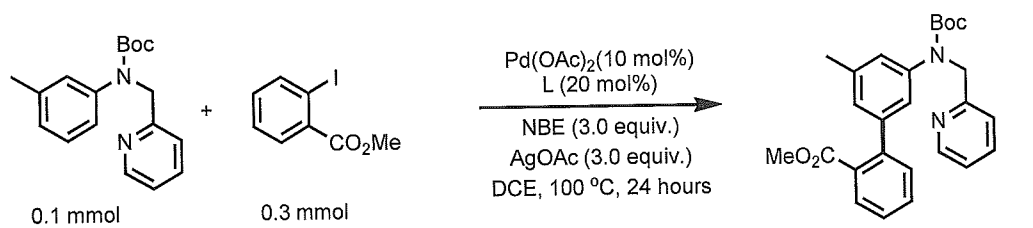
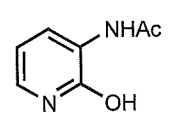
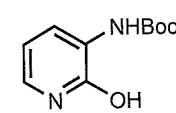
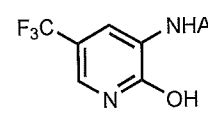
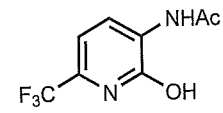
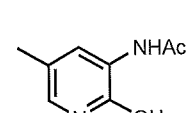
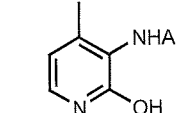
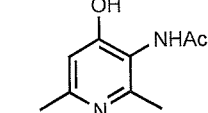
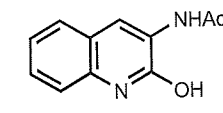
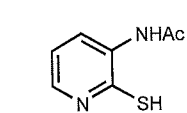
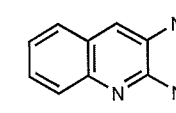
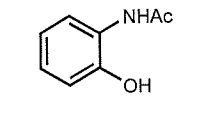
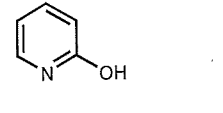
structural differences is shown below, where PG is a protecting group.



It is important to emphasize that MPAHP ligands were not only designed to act as structural mimics of the MPAA's but also to address the limited opportunities for electronic tuning of the latter ligand class. Specifically, as indicated above, substitution of the aromatic ring of MPAHP ligands permits significant modulation of electronic properties and hence, binding of the OH and NHAc groups (owing to their conjugation to the aromatic ring) to the Pd(II) catalyst. Illustrative ligands examined are shown in **Table 3** below along with yield data for the use of each in the model ligand screening reaction shown in the previous table.

With these newly prepared ligands in hand, their use in a model system was investigated, and it was found that the yield approximately tripled with the introduction of **L12**.

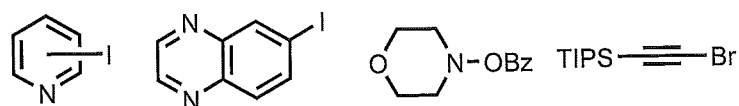
Table 3*

			
0.1 mmol	0.3 mmol		
			
L12	L13	L14	L15
42%, 58% SM	21%, 74% SM	35%, 65% SM	20%, 65% SM
			
L16	L17	L18	L19
27%, 71% SM	34%, 62% SM	19%, 66% SM	20%, 74% SM
			
L20	L21	L22	L23
NR	17%, 69% SM	11%, 81% SM	18%, 78% SM

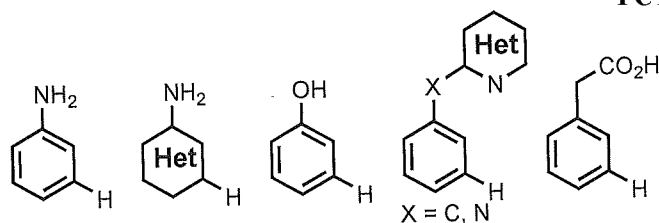
*The yields were determined by ^1H NMR; SM = starting material.

The use of a MPAHP ligand permits the use of a wide range of coupling partners such as a heteroaryl iodide, an alkynyl bromide and an N-OBz amine as are exemplarily illustrated below.

Coupling Partners Enabled by use of a MPAHP Ligand

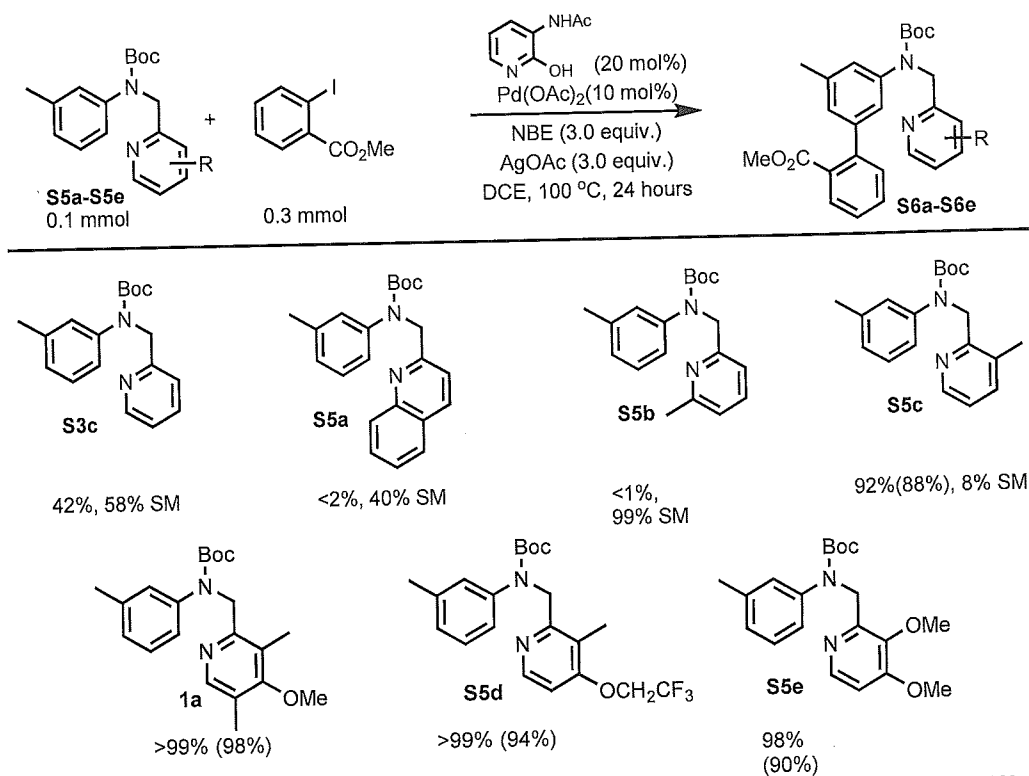


Similarly, use of a MPAHP ligand permits the use a wide range of substrates as are exemplarily shown below.



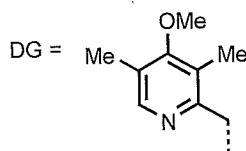
Given the importance of synergy between directing group and ligand for efficient C-H functionalization, the directing groups were re-examined. The effects of several directing groups were examined under standardized conditions as is shown in **Table A**, below. As shown by the data, it was

Table A



The yield was determined by ^1H NMR; SM = starting material; The yields in parentheses are isolated yields.

found that electron rich benzylic pyridine-based directing groups matched well with this ligand scaffold, with a commercially available directing group (DG, shown below) cooperating with the ligand

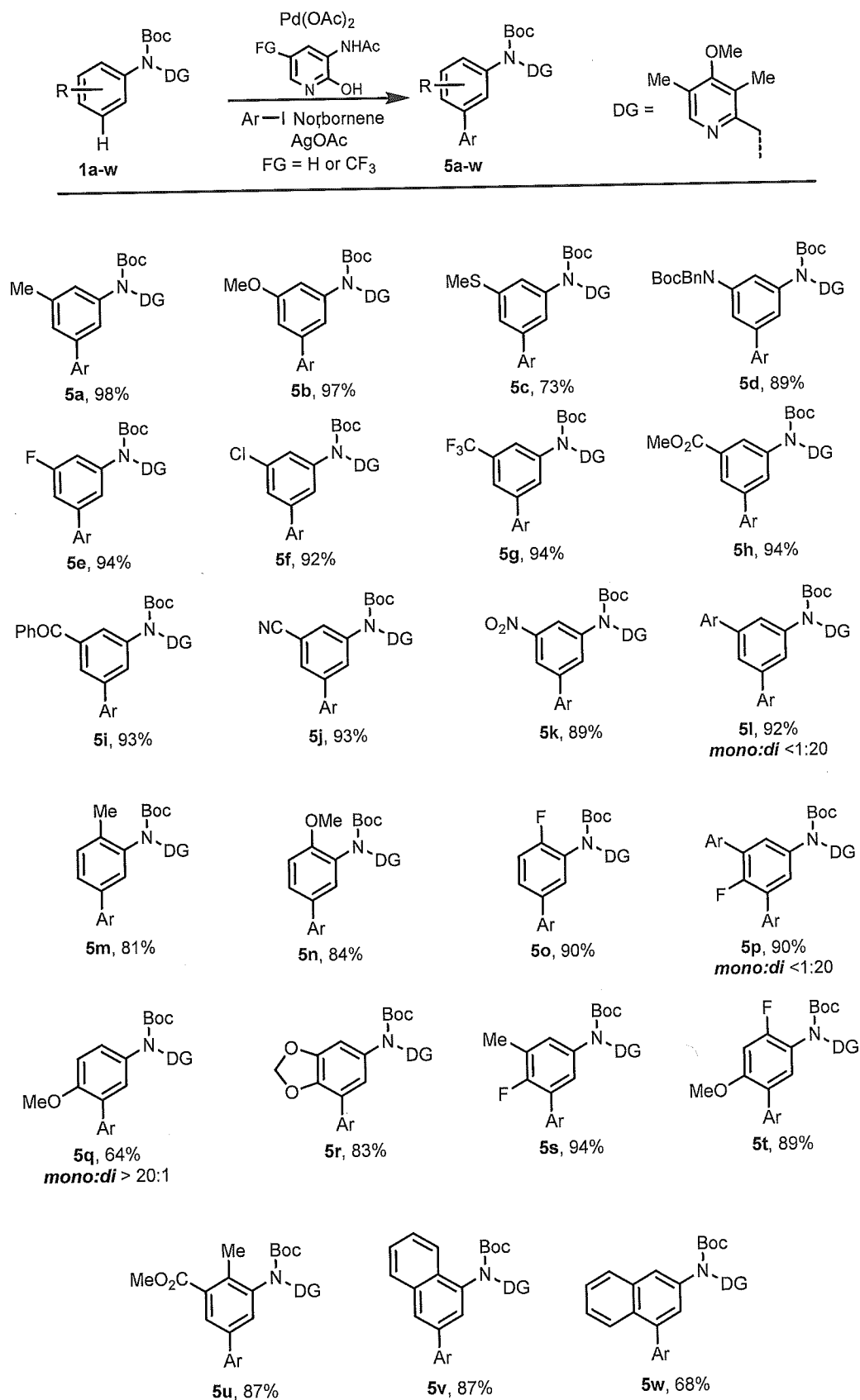


to provide the desired product in 98% isolated yield. With the optimized reaction conditions in hand, the scope of substrate reaction was examined.

As can be seen in **Tables 4-7** below, the substrate scope of this transformation is very broad. Electron-donating and electron-withdrawing groups (**5a-o**) are well tolerated at both the *ortho*- and *meta*-positions of the aniline. It is noteworthy that the commonly troublesome cyano and nitro functionalities (**5j**, **5k**) are well tolerated in this reaction when utilizing an improved transient mediator, methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate (NBE-CO₂Me), in place of 2-norbornene.¹⁴

Interestingly, unsubstituted aniline **1j** and *para*-substituted substrate **1p** showed high selectivity for the di-substituted product, whereas 4-methoxy substituted aniline **1q** showed high mono-selectivity. It is hypothesized that after the initial arylation of substrate **1q**, a conformational change is induced wherein the methyl group on the methoxy is primarily positioned away from the newly installed aryl ring, blocking the alternative *meta*-position which prevents di-arylation.

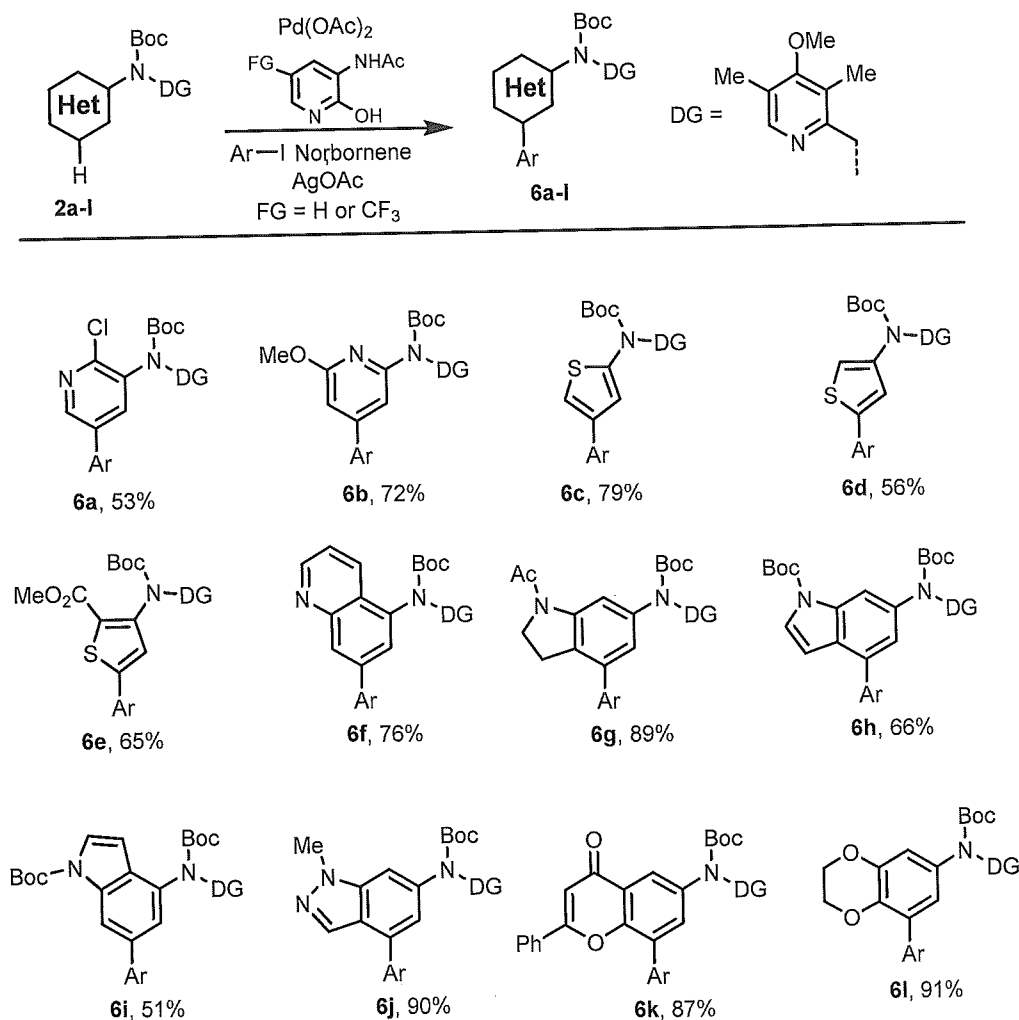
Table 4*



*In the above and following three tables: DG = directing group;
Ar-I = methyl 2-iodobenzoate; Ar = 2-(carboxymethyl)phenyl; NBE-
CO₂Me = methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate; Boc =
tert-butyloxycarbonyl; Ac = acetyl; Bn = benzyl. The values
under each structure indicate isolated yields. Substrates **1a-w**
and **2a-1** were arylated using **L12** in 1,2-dichloroethane. For
substrates **1g**, **1j**, **1k**, **2a**, **2d** and phenol substrates **3a-1**, NBE-
CO₂Me was used; other substrates were arylated using 2-
norbornene as mediator. The selectivity of the mono- and di-
arylated products was determined by ¹H NMR analysis using CH₂Br₂
as an internal standard.

A deeper investigation into the scope of
this reaction revealed that heterocyclic substrates
(**2a-1**), which are commonly incompatible with C-H
cross-coupling methodology, were well tolerated in
this reaction providing good to excellent yields of
products **6a-1**, as shown in **Table 5** below.
Importantly, the yield of product **6b** was reduced to
4% in the absence of **L12**, thus indicating the
importance of the ligand to achieve a broad substrate
scope for this transformation.

Table 5*



* Het = heteroaromatic.

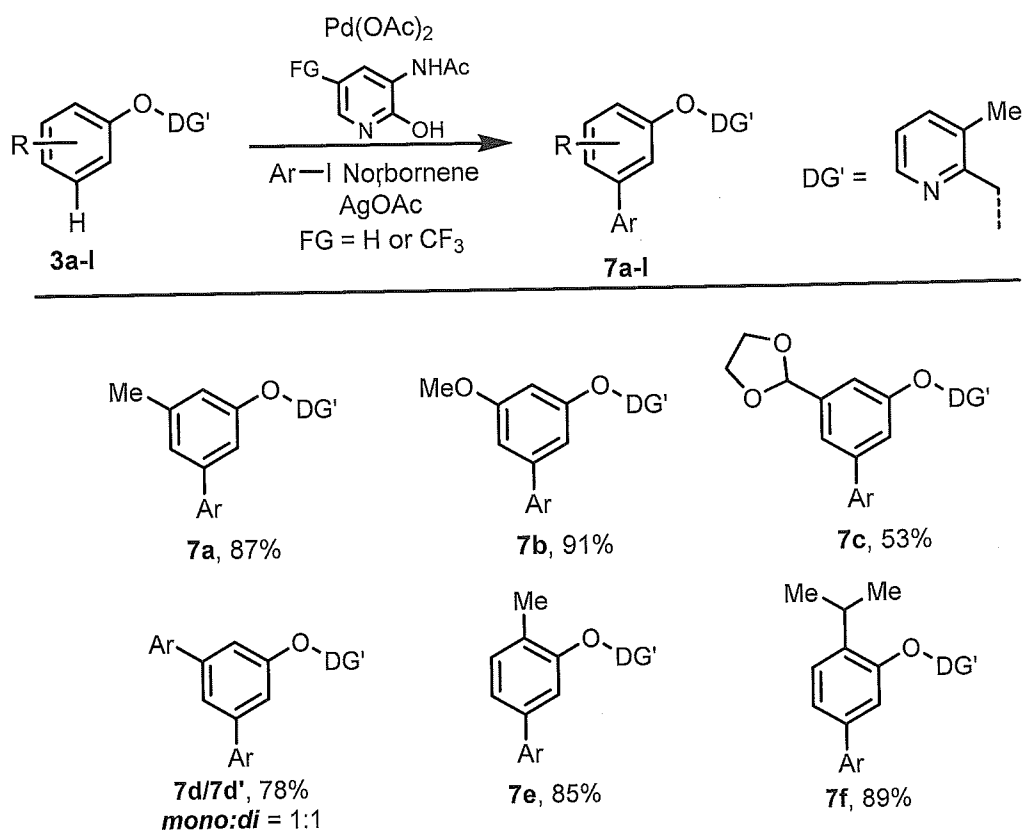
Being interested in further examining the breadth of this reaction, was next evaluated *meta*-C-H arylation of phenol^{28,29}-derived substrates bearing benzylic pyridine based directing groups was next evaluated.³⁰ Although good yields were obtained with the same directing group that was utilized for the aniline derived substrates, deprotection proved problematic. To circumvent this problem, a 2,3-lutidine derived directing group (DG' , whose structure is shown adjacent to the reaction scheme in **Table 6**) was used that is removed by hydrogenolysis

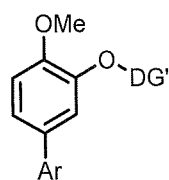
with catalytic palladium on carbon under 30 bar hydrogen.

As shown in **Table 6**, a variety of phenols could be successfully arylated at the *meta*-position utilizing methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate (NBE-CO₂Me) and a modified ligand (**L14**). Successful use of both ligand attests to the importance of being able to tune the electronics of this newly disclosed ligand scaffold.

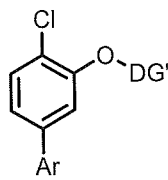
Intriguingly, although substrate **1j** shows high selectivity for di-arylated product, phenolic substrate **3d** provides a mono:di ratio of 1:1. This result is attributed to the phenolic substrates being slightly less reactive than their aniline counterparts.

Table 6*

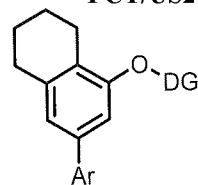




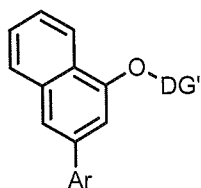
7g, 54%



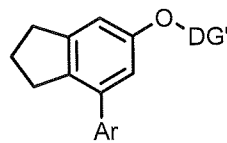
7h, 81%



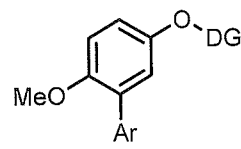
7i, 90%



7j, 87%



7k, 42%

7l, 58%
mono:di > 20:1

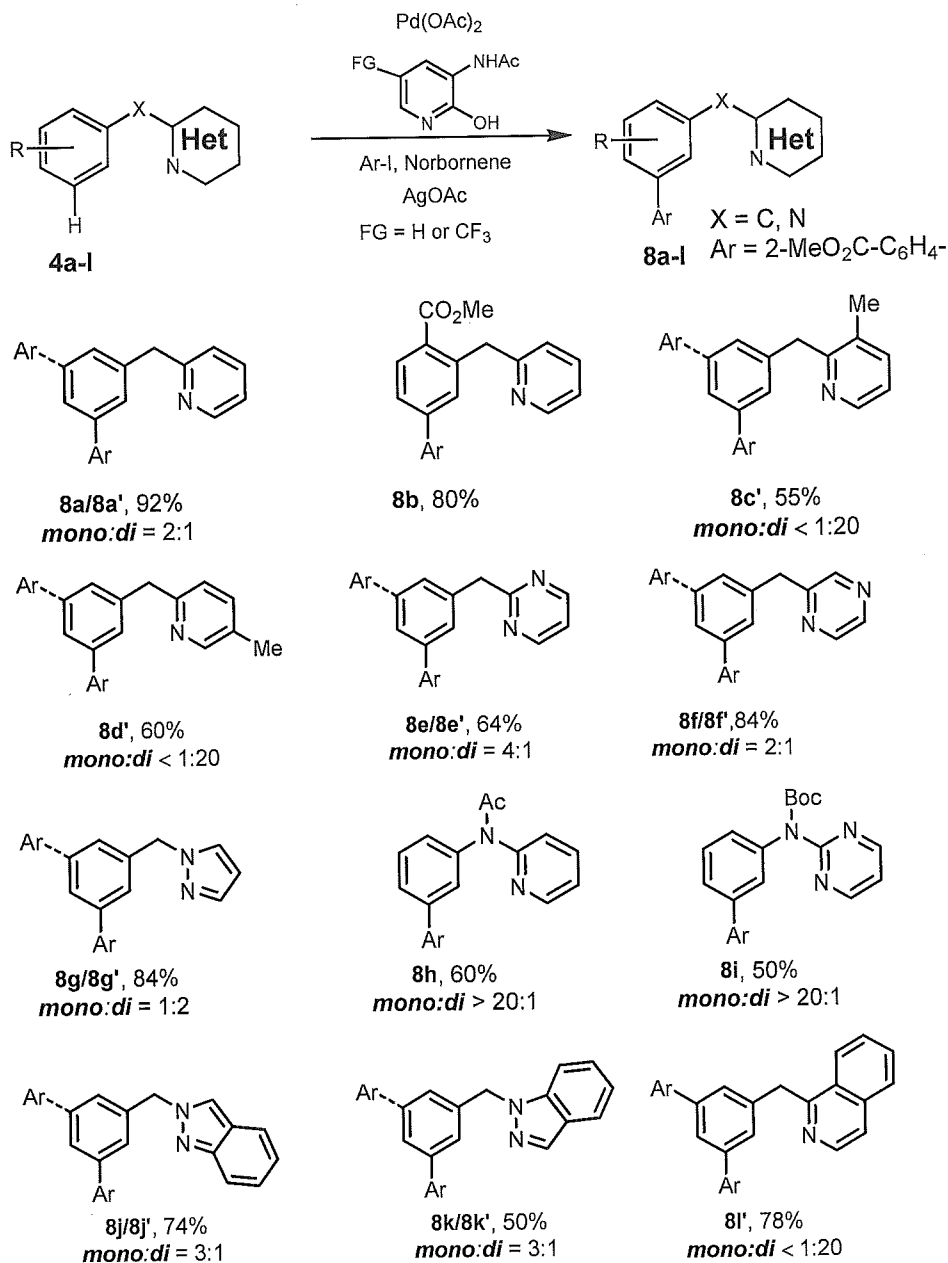
*Substrates **3a-1** and **4a-1** were arylated using **L14** in chloroform; substrate **3h** was arylated using **L12** in chloroform for 36 hours.

To more fully explore the scope of this methodology, the activity of this ligand was examined with substrates containing native heterocycles as directing groups. Gratifyingly, heterocyclic substrates that form 6-membered palladacycles upon cyclopalladation worked exceedingly well. Substrates directed by native pyridine, pyrimidine, pyrazine, pyrazole, indazole, isoindazole and isoquinoline were all successfully arylated at the previously inaccessible *meta*-positions as is seen in **Table 7**, below.

As all of these substrates are unsubstituted, the mono:di ratio appears to be loosely correlated to the coordination strength of the various heterocyclic directing groups with weaker coordinating directing groups tending away from highly di-selective arylations. Dotted bond lines in that table indicate the presence of diarylation products with the ratio of mono:di products being shown. Importantly, the ligand should be present for

this reaction to proceed in synthetically useful yields with all of the substrate classes shown in Table 7.

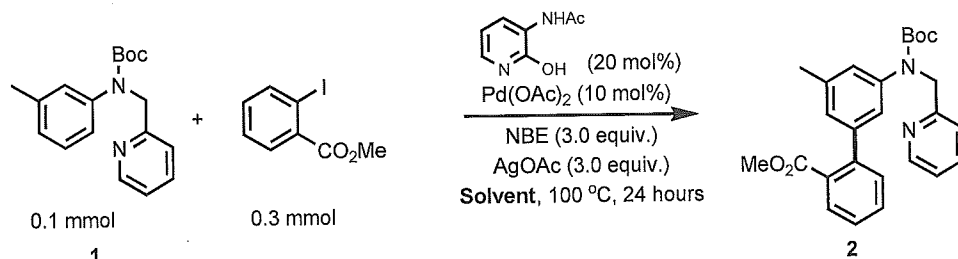
Table 7*



* Het = heteroaromatic.

The effects of solvent and oxidation on the arylation in the standard reaction were also

examined. Those results are illustrated by the reaction scheme and results shown below in **Tables 8a** and **8b**.

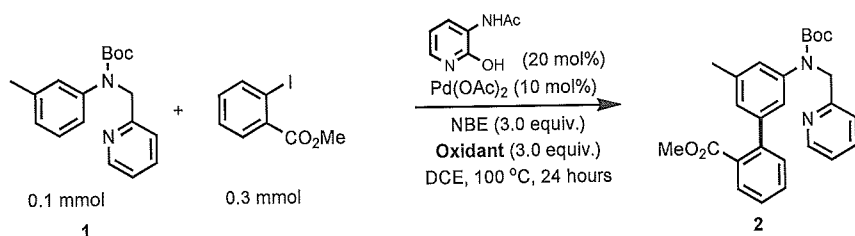
Table 8a

Entry	Solvent	BP (° C)	2 (%)	1 (%)	Entry	Solvent	BP (° C)	2 (%)	1 (%)
1	PhCH ₃	110	24	65	7	<i>t</i> -Amyl-OH	102	35	53
2	PhCF ₃	101	31	64	8	DCM	40	34	64
3	TBME	131	20	78	9	DCE	84	42	58
4	Dioxane	101	37	51	10	CHCl ₃	61	42	57
5	EA	77	30	67	11	Acetone	56	38	60
6	CH ₃ CN	82	36	47	12	DMF	153	14	85

The yields were determined by ¹H NMR.

Thus, use of each of the above-listed solvents provided product. However, DCE and chloroform (CHCl₃) provided the highest yield of product (**2**) and the lowest amount of residual starting material (**1**).

Table 8b



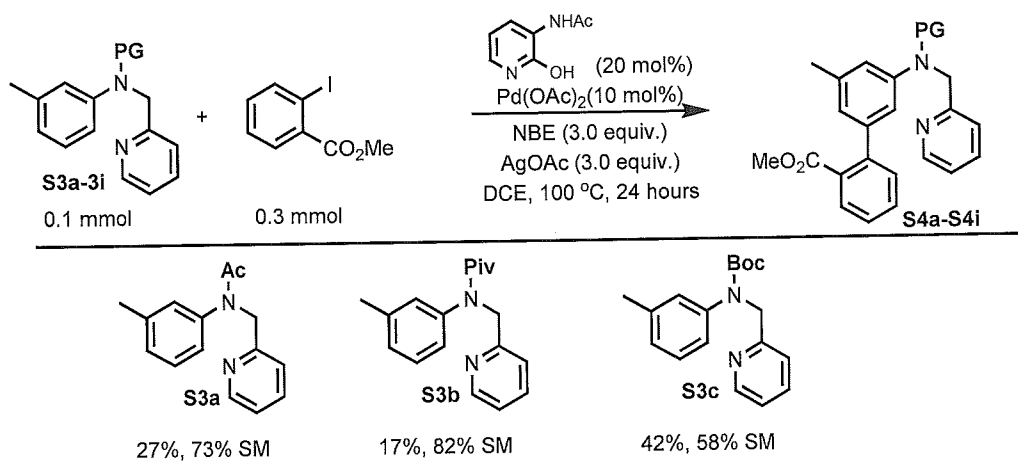
Entry	Oxidant	2 (%)	1 (%)	Entry	Oxidant	2 (%)	1 (%)
1	----	2	84	8	AgOPiv	10	87
2	AgOAc	42	58	9	AgOTs	<1	<1
3	Ag ₂ CO ₃	12	82	10	K ₂ S ₂ O ₈	<1	<1
4	Ag ₂ O	6	90	11	Na ₂ S ₂ O ₈	<1	<1
5	AgF	<1	<1	12	BQ	<1	44
6	AgNO ₃	4	88	13	PhI(OAc) ₂	2	64
7	AgOBz	17	76	14	Cu(OAc) ₂	<1	<1

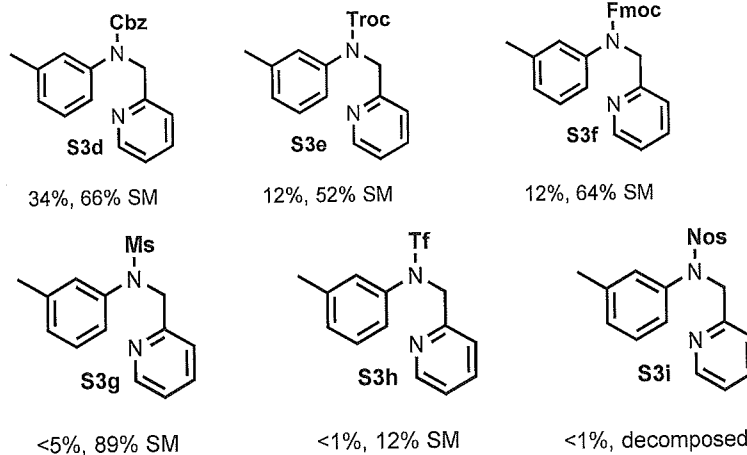
The yields were determined by ¹H NMR.

As is seen from the data above, silver acetate (AgOAc) provided the best yields of the several oxidants examined.

Several removable aniline-nitrogen protecting groups (PG) were studied for their effect if any on product yield. As is seen from the data in **Table 8c**, below, most were useful, with *t*-boc providing the greatest yield in the conditions examined. The protecting groups (PG) used are

Table 8c*





*The yields were determined by ^1H NMR; SM = starting material.

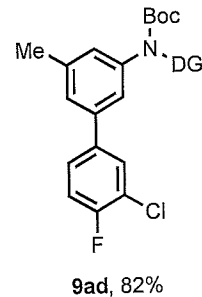
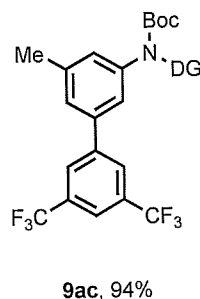
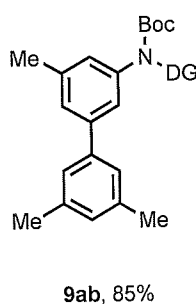
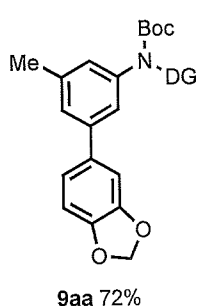
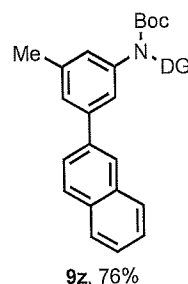
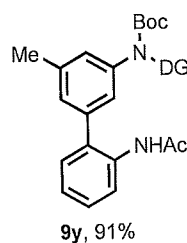
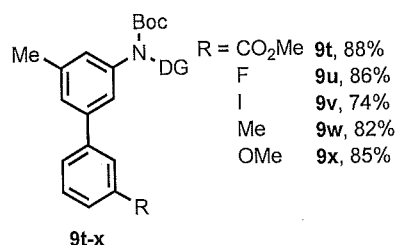
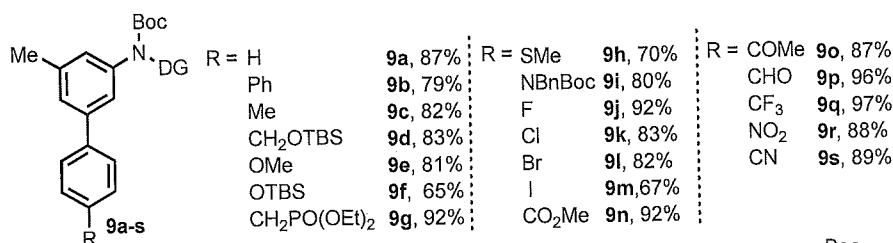
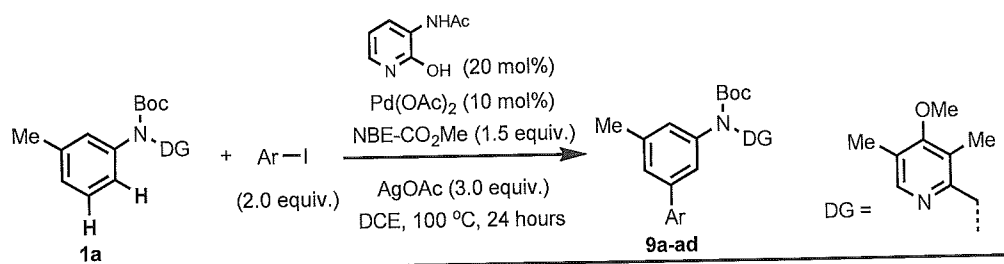
Ac = acetyl, Piv = pivaloyl, Boc = *t*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Troc = 2,2,2-trichloroethoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl, and Nos = nitrobenzenesulfonyl.

Having thoroughly examined the substrate scope of this reaction, focus was turned to evaluating the coupling partner scope using aniline **1a** as the model substrate. Although 3-aryl-5-methyl anilines are alternatively accessible via Suzuki-coupling of the commercially available 3-bromo-5-methylaniline, Compound **1a** was chosen as the model substrate to investigate the reactivity of a wide range of aryl iodides as it is relatively electron neutral when compared to alternatively substituted anilines.

Experimental results shown in **Table 9**, below, indicate that this reaction exhibited an exceptionally broad coupling partner scope when utilizing a modified norbornene.¹⁴ Electron donating and electron withdrawing groups at the *para*- and *meta*-positions of the aryl iodide coupling partner

were well tolerated, providing the desired products in good yields (**9a-y**).

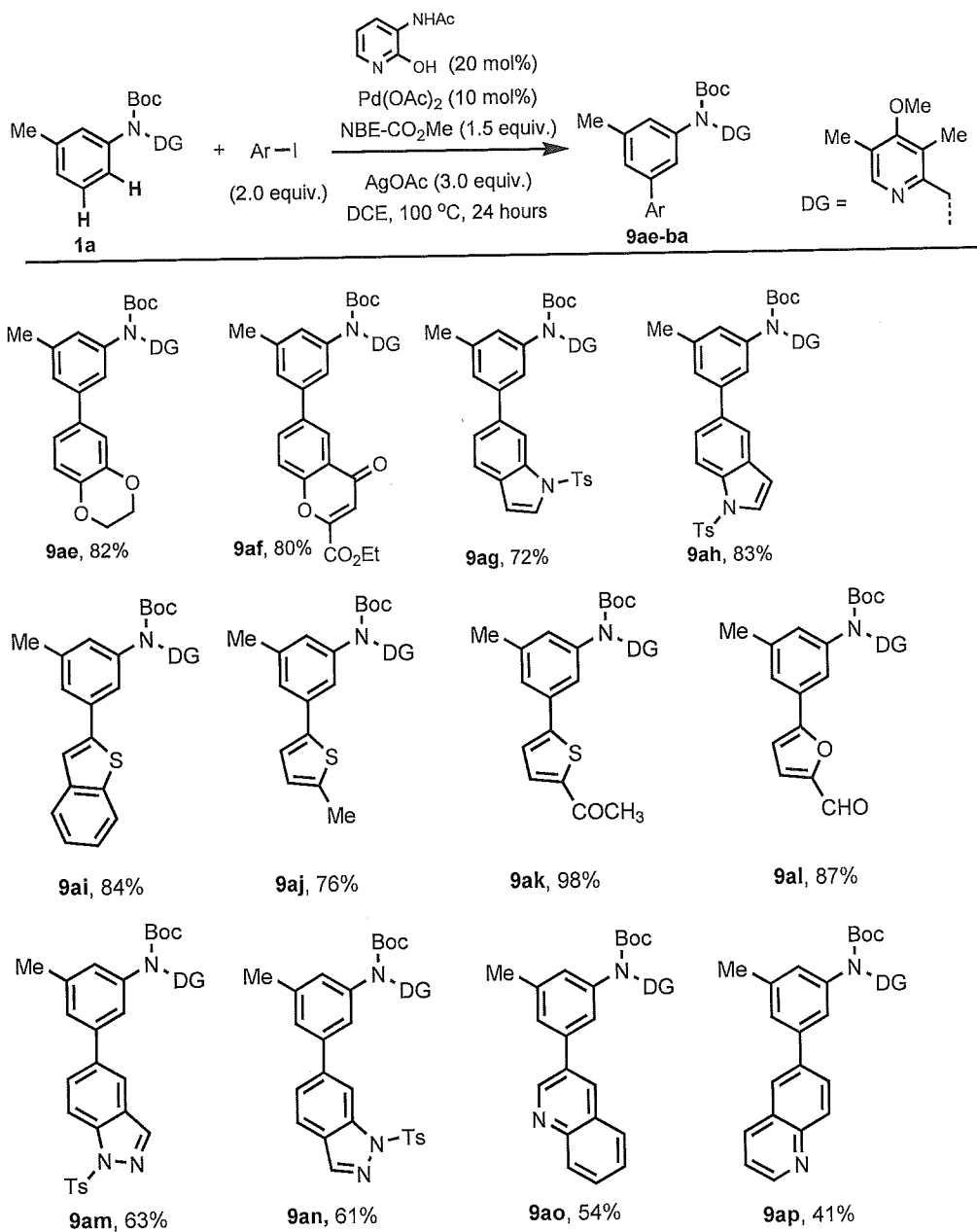
Table 9*

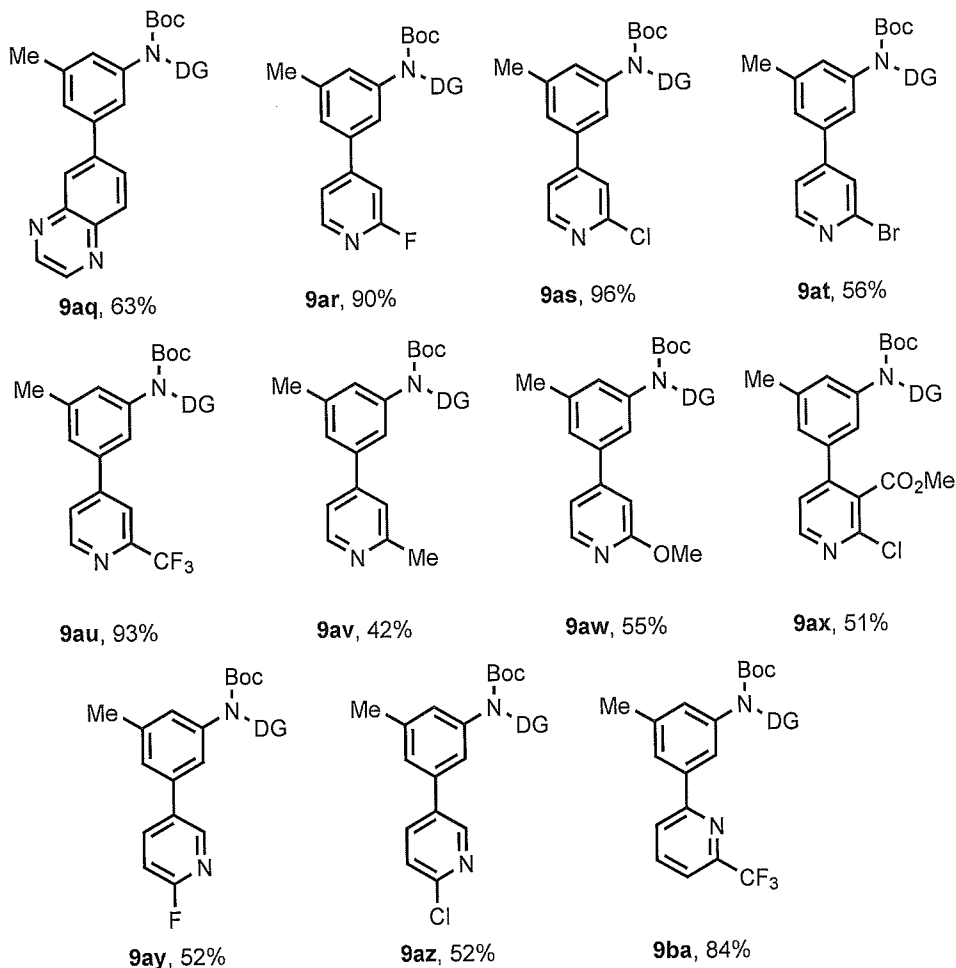


* In Tables 9-11: TBS = *tert*-butyldimethylsilyl; Ts = 4-toluenesulfonyl; NBE- CO_2Me = methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate. The values under each structure indicate isolated yields. Reaction conditions: Substrate (0.1 mmol), Ar-I (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol%), **L12** (20 mol%), NBE- CO_2Me (1.5 equiv.), AgOAc (3.0 equiv.), 1,2-dichloroethane (0.5 mL), 100 °C, 24 hours.

Interestingly, this reaction was not limited to simple aryl iodides and an array of

heterocyclic aryl iodides worked well in this reaction (**9ae-ba**). Indoles, thiophenes, furan, indazole, quinoline, quinazoline, and a range of pyridines were suitable coupling partners, showcasing the utility of this reaction for medicinal chemistry efforts where heterocyclic motifs are prevalent. These results are shown in **Table 10**, below.

Table 10

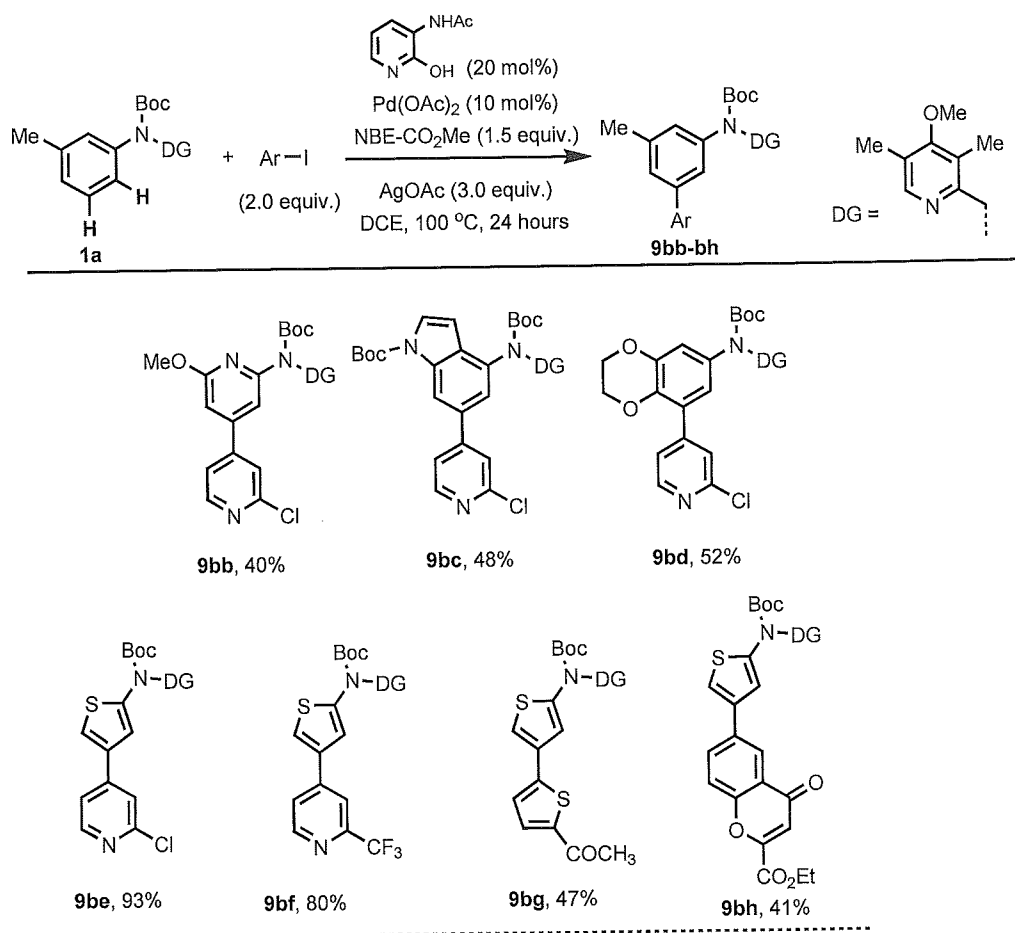


*For **9ap**, **9av**, **9ba**, **9bb** and **9bc**, Pd(OAc)₂ (20 mol%) and **L12** (40 mol%) were used.

To determine whether the broad coupling partner scope observed in this reaction was enabled by the ligand, the reaction was carried out under the optimized conditions with 2-chloro-4-iodopyridine in the absence of **L12** and found the yield to be 9% by ¹H NMR. This result highlights the importance of the MPAHP ligands for this transformation.

In order to fully investigate the compatibility of this reaction with heterocycles, the efficiency of coupling heterocyclic substrates with heterocyclic aryl iodides was examined. As can be

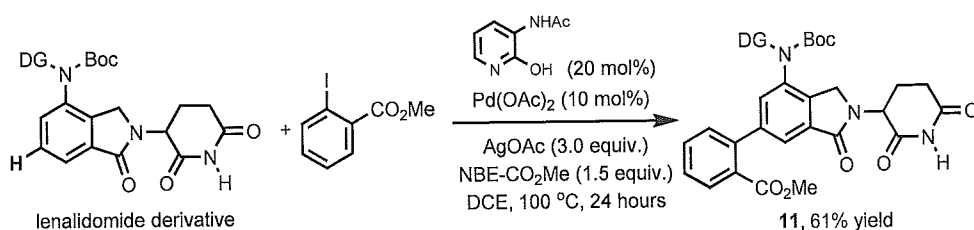
seen in **Table 11**, (compounds **9bb-9bh**), this ligand enables the coupling of heterocyclic coupling partners with heterocyclic substrates in good to excellent yields. Furthermore, the scalability of this reaction was demonstrated by performing the *meta*-C-H coupling of aniline substrate **1a** on gram-scale with 5 mol% Pd(OAc)₂ and 5 mol% **L12**, providing the desired product cleanly in 93% yield.

Table 11*

Given the efficiency of the *meta*-C-H coupling of aniline substrates on a preparative scale, the applicability of this methodology was sought to be demonstrated using medicinally relevant compounds. Recently, the drug thalidomide and its

derivatives pomalidomide and lenalidomide (IMiDs) have been repurposed for several clinical indications including multiple myeloma (MM) and myelodysplasia. Crystallographic evidence for IMiD binding to a key target, cereblon (CRBN),³¹ suggests that chemical modification of the solvent-exposed phthalimide part of the IMiDs could lead to molecules with altered specificity.

Efforts were therefore initiated to evaluate the feasibility of applying the ligand enabled, *meta*-C-H arylation of aniline derivatives to functionalize the solvent-exposed, *meta*-position of lenalidomide. This exemplifies a scenario where utilizing norbornene-mediated *meta*-C-H functionalization is advantageous as it allows elaboration of the parent drug molecule in relatively few steps. Gratifyingly, the *meta*-arylation of a lenalidomide derivative proceeded smoothly to provide the desired product (Compound **11**) in 61% isolated yield (below). The successful utilization of the

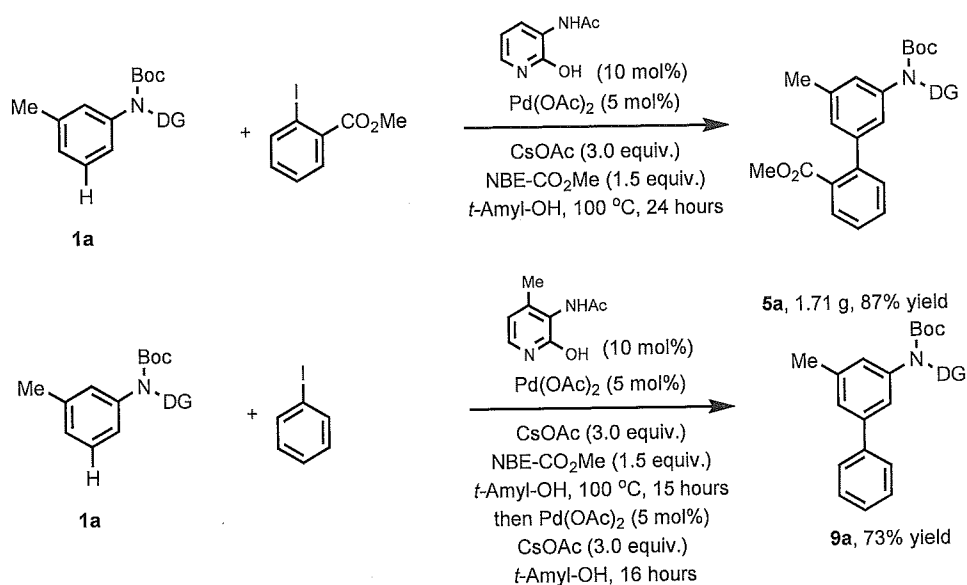


Boc = *tert*-butoxycarbonyl; NBE-CO₂Me = methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate;
Ac = Acetyl; DCE = 1,2-dichloroethane

norbornene mediated *meta*-C-H functionalization in this setting showcases the potential utility of this reaction in drug discovery.

Recognizing the robust nature of the MPAHP ligands, an improvement of the practicality of the

reaction conditions in collaboration with Bristol-Myers Squibb. A high throughput screen was undertaken to establish Ag-free conditions with process friendly solvents. Through this screen, it was found that the use of CsOAc in place of AgOAc in *t*-Amyl-OH could provide excellent yields on gram-scale reactions with *ortho*-substituted aryl iodides, and synthetically useful yields with simple aryl iodides when utilizing **L12** or **L17** respectively as are illustrated in the reaction schemes below. The



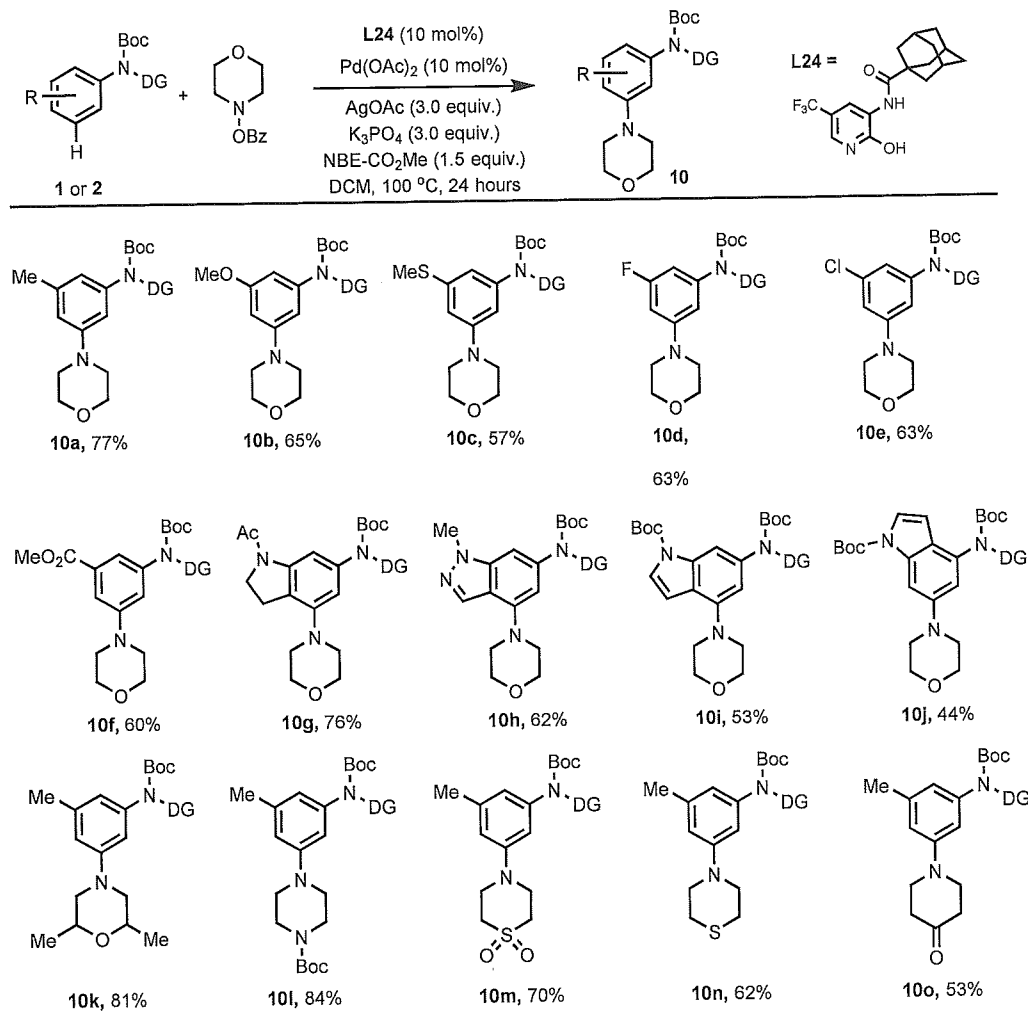
DCM = dichloromethane.

removal of silver from the Pd(II) catalyzed, norbornene mediated *meta*-C-H arylation reaction for the first time is crucial for adopting this method in synthesis, especially when reactions need to be performed beyond gram-scale.

The applicability of this ligand scaffold in promoting other transformations was attempted in other challenging *meta*-C-H amination reactions. After systematic optimization, the MPAHP ligand **L24**

was found to promote the norbornene mediated *meta*-amination of a variety of anilines with N-O benzoyl morpholine to provide Compounds **10a-j** in synthetically useful yields. These reactions are illustrated below in **Table 12**.

Table 12*

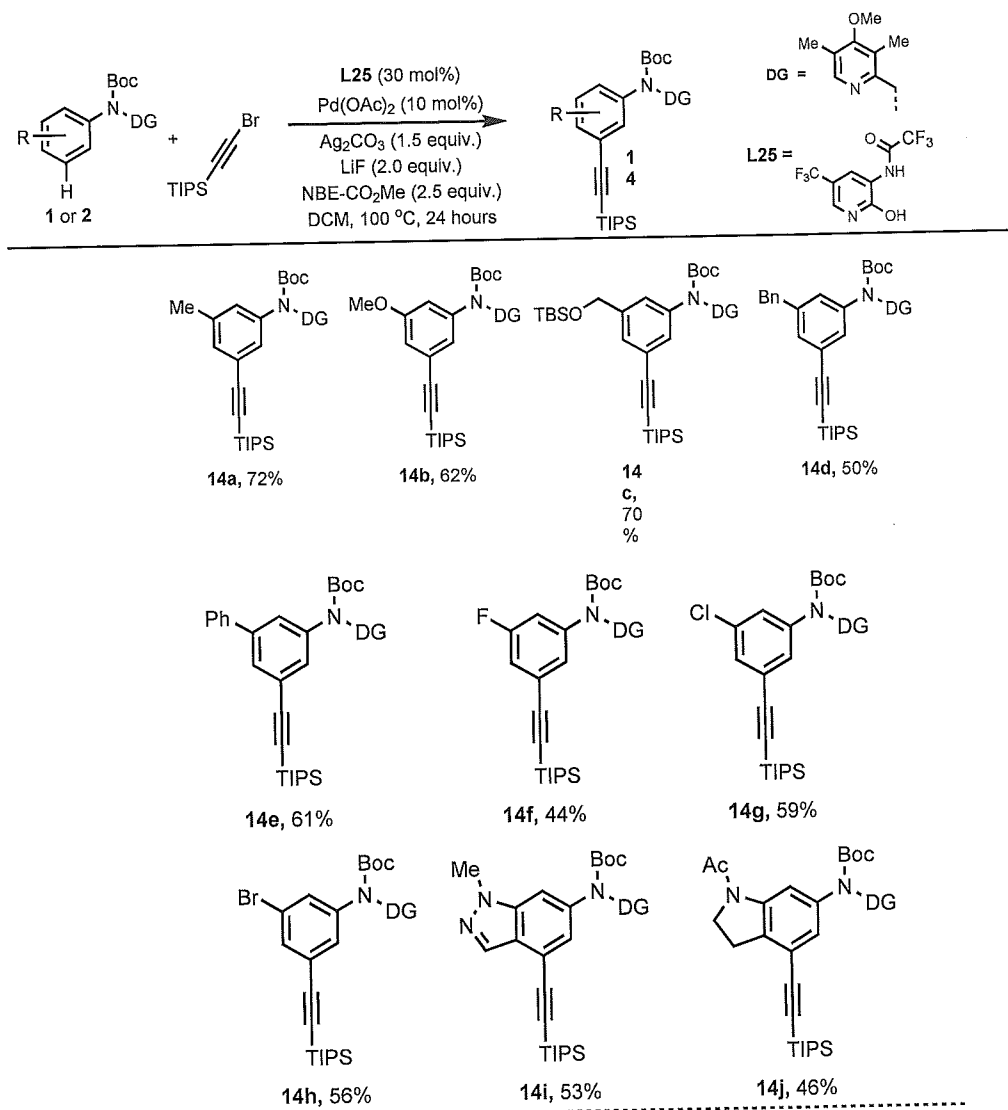


*Bz = benzoyl; DCM = dichloromethane; Boc = *tert*-butyloxycarbonyl; Bn = benzyl; NBE-CO₂Me = methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate. Reaction conditions: Compound **1** or **2** (0.1 mmol), aminating reagent (0.15 mmol), Pd(OAc)₂ (10 mol%), **L24** (10 mol%), NBE-CO₂Me (1.5 equiv.), AgOAc (2.0 equiv.), dichloromethane (1.0 mL), 100 °C, 24 hours. For Compounds **10f**, **10n** and **10o**, Pd(OAc)₂ (15 mol%), **L24** (15 mol%), AgOAc (3.0 equiv.) and NBE-CO₂Me (3.0 equiv.) were used.

Although linear amines do not work well in this transformation under the current conditions, a variety of 6-membered amines can be smoothly coupled to provide **10k-o**. These results are also shown in **Table 12**, above. This is believed to be the first report of a *meta*-C-H amination reaction in the literature.³²

Furthermore, due to the robust catalysis enabled by the MPAHP ligands, the possibility of utilizing alkynyl bromides as coupling partners to provide *meta*-alkynylated products was considered. It is important to note that this reaction has no precedent in the Catellani reaction, and it is believed that no *meta*-C-H alkynylation reactions have been reported. To our great delight, after a brief evaluation of MPAHP ligands and reaction conditions, *meta*-C-H alkynylation of a variety of aniline-derived substrates could be achieved, providing Compounds **14a-j** in good yields. This reaction scheme and results are shown in **Table 13**, below.

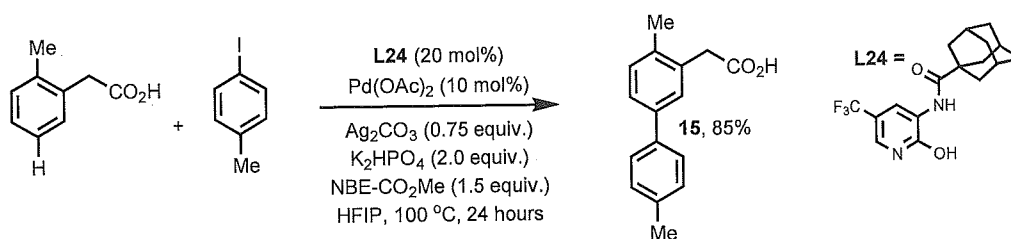
Table 13*



*TIPS = triisopropylsilyl; TBS = *tert*-butyldimethylsilyl;
 Reaction conditions: Compounds 1 or 2 (0.1 mmol), alkynylating reagent (0.2 mmol), Pd(OAc)₂ (10 mol%), L25 (30 mol%), NBE-CO₂Me (2.5 equiv.), Ag₂CO₃ (1.5 equiv.), LiF (2.0 equiv.), dichloromethane (1.0 mL), 100 °C, 24 hours.

Given that the original report^{12,14} of this norbornene-mediated *meta*-C-H arylation strategy required installation of a directing group with phenylacetic acid substrates, whether the MPAHP ligands could enable a *meta*-C-H arylation of phenylacetic acids using the free acid as the directing group was examined. Indeed, as can be seen

from the reaction scheme and results shown in the reaction scheme shown below, 2-methylphenylacetic acid could be arylated at the *meta*-position in the presence of MPAHP **L24** to provide Compound **15** in 85% isolated yield. Importantly, all three of the palladium-catalyzed transformations shown in the reaction schemes of **Tables 12** and **13**, and that below that was carried out in hexafluoroisopropanol (HFIP) are ligand-enabled and provide only trace product amounts in the absence of an MPAHP ligand.



A versatile ligand scaffold for Pd(II) catalyzed *meta*-C-H arylation of a wide range of arenes using norbornene as a transient mediator is disclosed. Heterocyclic substrates and coupling partners are well tolerated under the developed reaction conditions, which should enable rapid uptake of this ligand enabled methodology in drug discovery. The utility of this ligand is further demonstrated by enabling the development of both a challenging *meta*-C-H amination reaction and an unprecedented *meta*-C-H alkynylation reaction. In addition, in the case of phenylacetic acid substrates, installation of a directing group is omitted as the MPAHP ligand promotes the *meta*-C-H functionalization of this class of substrates using the native acid as the directing group.

Methods Summary

General procedure for the MPAHP-promoted norbornene-mediated meta-C-H activation of anilines. Substrate (0.1 mmol), Ar-I (0.2 mmol), Pd(OAc)₂ (2.2 mg, 10 mol%), **L12** (3.0 mg, 20 mol%), AgOAc (50.1 mg, 0.3 mmol), 2-norbornene (14.1 mg, 0.15 mmol) or NBE-CO₂Me (21.6 mg, 0.15 mmol) and 1,2-dichloroethane (0.5 mL) were added to a 2-dram vial. The vial was capped and closed tightly, then the reaction mixture was stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with dichloromethane as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired arylated product.

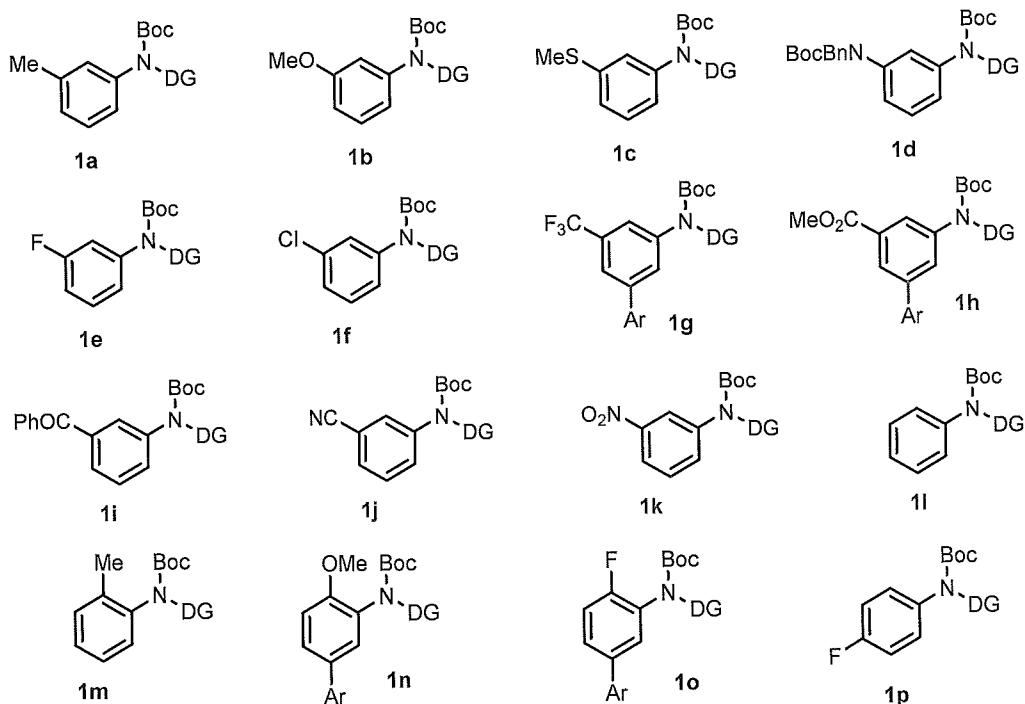
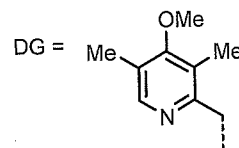
General Information

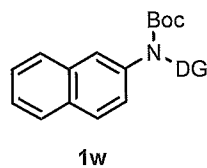
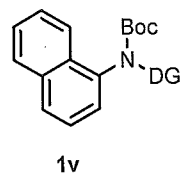
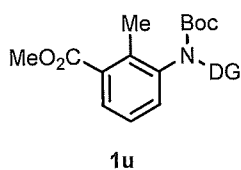
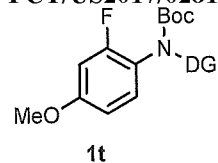
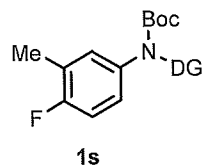
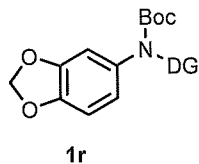
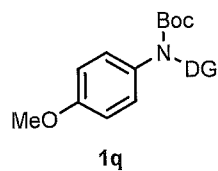
2-Norbornene and AgOAc were purchased from Sigma-Aldrich. NBE-CO₂Me (methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate) was synthesized following literature procedures. [Shen et al., *J. Am. Chem. Soc.* **137**:11574-11577 (2015).] Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. ¹H NMR was recorded on Bruker AMX-400 instrument (400 MHz) or Bruker DRX-600 instrument (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t =

triplet, q = quartet, p = pentet, sext = sextet, sep = septet m = multiplet, br = broad. Coupling constants, J , were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker AMX-400 instrument (100 MHz) or Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. ^{19}F NMR spectra were recorded on Bruker AMX-400 instrument (376 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to either the center line of a triplet at 77.0 ppm of chloroform- d or referenced to the center line of a septet at 39.52 ppm of DMSO- d_6 . High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

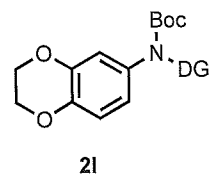
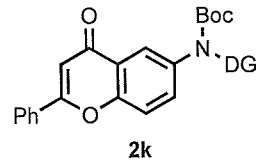
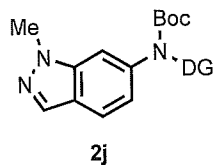
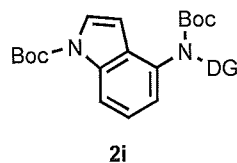
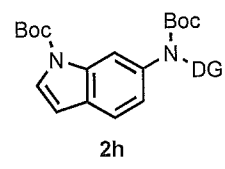
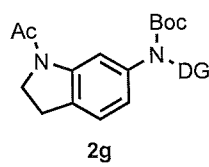
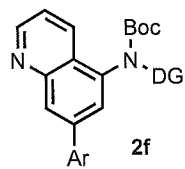
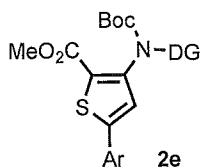
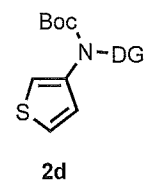
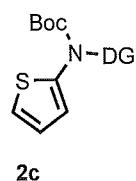
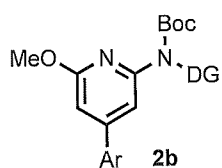
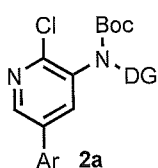
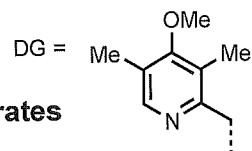
Substrate Molecules

Aniline substrates

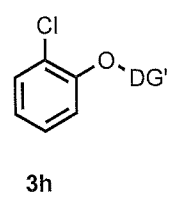
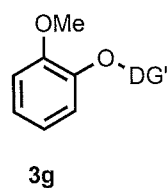
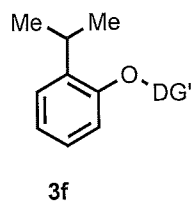
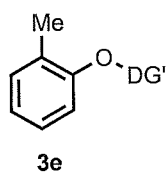
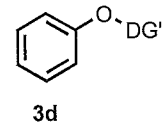
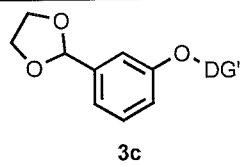
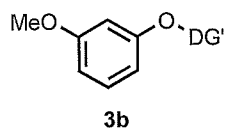
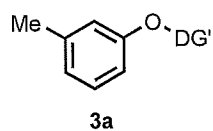
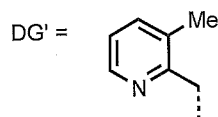


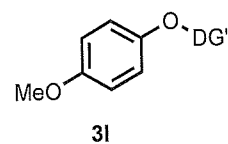
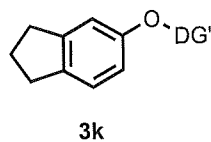
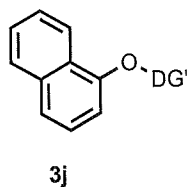
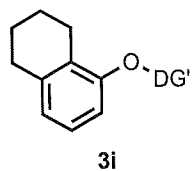


Heterocycle-containing aromatic amine substrates

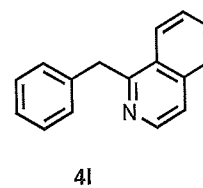
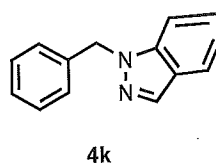
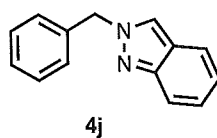
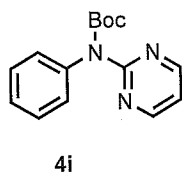
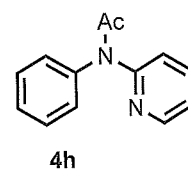
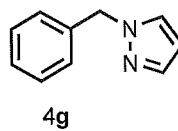
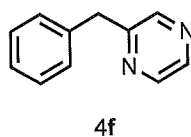
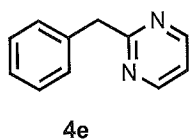
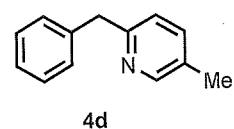
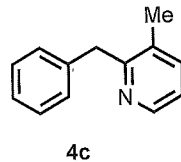
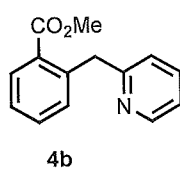
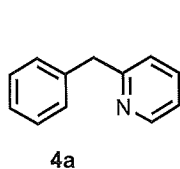


Phenol substrates

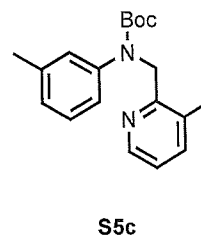
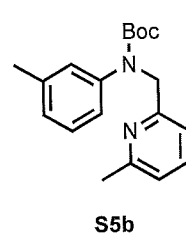
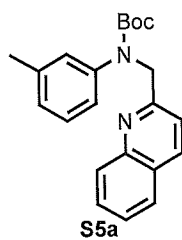
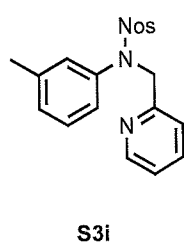
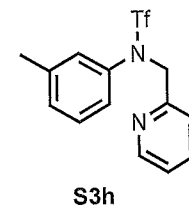
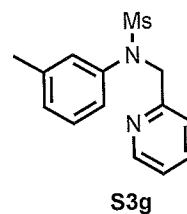
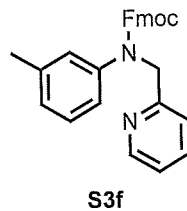
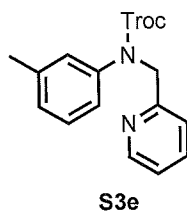
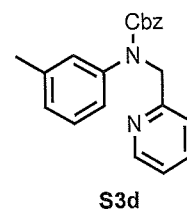
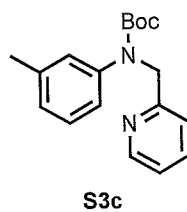
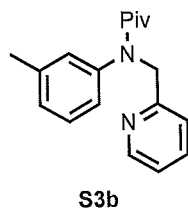
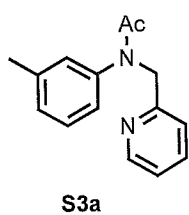


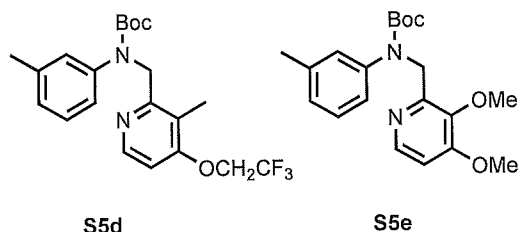


Other heterocycle substrates

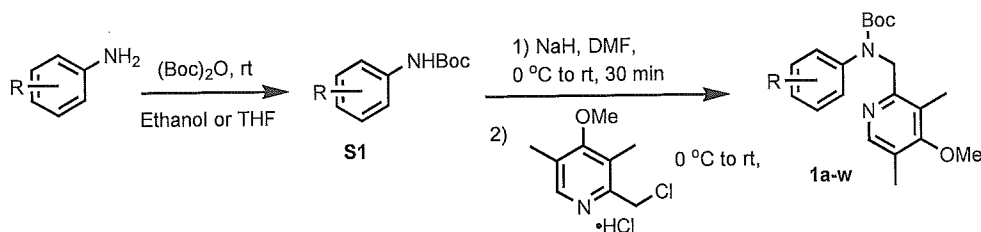


Other Substrates





Preparation of Aniline Substrates



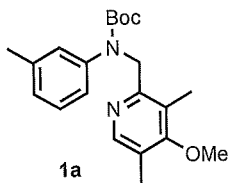
Boc-protected anilines (**S1**) were synthesized following literature procedures starting from the free anilines. Substrates **1a-w** were synthesized following the general procedure.

General procedure for synthesis of Boc-protected amines

S1: To a solution of anilines in ethanol was added (Boc)₂O (1.1 equiv.) at room temperature. After the reaction was completed, the solution was concentrated under vacuum to afford the Boc-protected amines in high yield. The Boc-protected amines were used for next step without further purification. [Vilaivan, *Tetrahedron Lett* **47**, 6739-6742 (2006).]

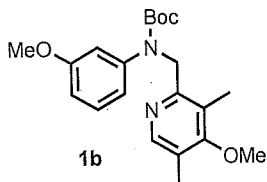
General procedure for synthesis of substrates 1a-w: To a solution of Boc-protected anilines **S1** (1.2 equiv.) in DMF was added NaH (3.0 equiv.) at 0 °C, and the resulting mixture was allowed to warm up to room temperature for 30 min. The mixture was cooled to 0 °C again, then 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (1.0 equiv.) was added into the mixture slowly. The resulting mixture was allowed to warm up to room temperature for another 12 hours. After the reaction completed, EtOAc was added to dilute the reaction mixture, then the organic phase was washed with water, brine and

dried over Na_2SO_4 . After concentrated by rotatory evaporation, the residue was purified by silica gel chromatography to afford the desired substrates **1a-w**.



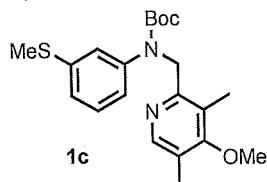
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(m-tolyl)carbamate (1a)

Colorless solid, mp = 73 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.10 (t, J = 7.7 Hz, 1H), 7.06 (s, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 4.90 (s, 2H), 3.72 (s, 3H), 2.27 (s, 3H), 2.21 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.62, 155.18, 154.78, 148.91, 142.70, 138.03, 128.05, 126.95, 126.29, 124.57, 123.68, 123.50, 80.14, 59.83, 53.54, 28.25, 21.34, 13.19, 10.40; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 357.2173, found: 357.2172.



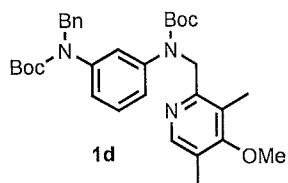
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(3-methoxyphenyl)carbamate (1b)

Colorless solid, mp = 65 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.13 (t, J = 8.2 Hz, 1H), 6.84 (d, J = 7.4 Hz, 2H), 6.70-6.63 (m, 1H), 4.90 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.62, 159.49, 155.04, 154.68, 148.97, 144.04, 128.84, 124.62, 123.67, 118.87, 112.47, 111.17, 80.29, 59.84, 55.23, 53.51, 28.27, 13.20, 10.39; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 373.2122, found: 373.2121.



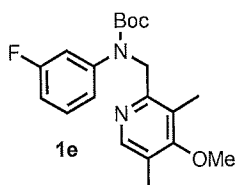
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(3-(methylthio)phenyl)carbamate (1c)

Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 7.18–7.11 (m, 2H), 7.07–6.97 (m, 2H), 4.89 (s, 2H), 3.72 (s, 3H), 2.40 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.62, 154.88, 154.56, 148.92, 143.30, 138.20, 128.52, 124.82, 124.65, 123.89, 123.65, 123.30, 80.37, 59.81, 53.31, 28.21, 15.89, 13.16, 10.36; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 389.1893, found: 389.1893.



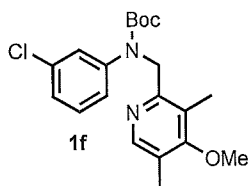
tert-Butyl (3-(benzyl(tert-butoxycarbonyl)-amino)phenyl)-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1d)

Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.31–7.02 (m, 8H), 6.88 (d, $J = 7.4$ Hz, 1H), 4.84 (s, 2H), 4.73 (s, 2H), 3.71 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H), 1.44–1.30 (m, 18H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.55, 154.78, 154.50, 154.46, 148.85, 143.15, 142.72, 138.49, 128.17, 128.02, 127.20, 126.84, 124.51, 124.17, 123.87, 123.73, 123.50, 80.29, 80.19, 59.73, 53.82, 53.27, 28.13, 28.11, 13.09, 10.25; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{32}\text{H}_{42}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 548.3119, found: 548.3120.



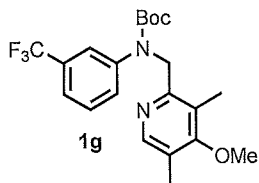
tert-Butyl (3-fluorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1e)

Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 7.18 (q, $J = 7.4$ Hz, 1H), 7.10–6.97 (m, 2H), 6.86–6.76 (m, 1H), 4.89 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.68, 162.38 (d, $J = 245.3$ Hz), 154.63, 154.37, 149.03, 144.52 (d, $J = 10.3$ Hz), 129.15 (d, $J = 9.6$ Hz), 124.76, 123.52, 121.78, 113.69 (d, $J = 23.4$ Hz), 112.25 (d, $J = 21.0$ Hz), 80.68, 59.86, 53.27, 28.17, 13.20, 10.33; ^{19}F NMR (376 MHz, CDCl_3) δ -113.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{26}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 361.1922, found: 361.1920.



tert-Butyl (3-chlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1f)

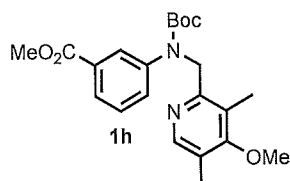
Colorless solid, mp = 68 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 7.29 (s, 1H), 7.21–7.12 (m, 2H), 7.12–7.04 (m, 1H), 4.88 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.68, 154.60, 154.35, 149.06, 144.17, 133.61, 129.15, 126.59, 125.52, 124.78, 124.51, 123.52, 80.72, 59.88, 53.23, 28.19, 13.22, 10.36; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{26}\text{ClN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 377.1626, found: 377.1628.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(3-(trifluoromethyl)phenyl)carbamate (1g)

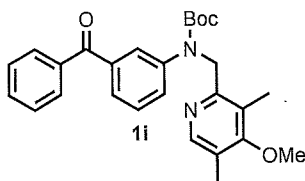
Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.54 (s, 1H), 7.47 (s, 1H), 7.39–7.31 (m, 2H), 4.92 (s,

2H), 3.73 (s, 3H), 2.21 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.75, 154.49, 154.30, 149.08, 143.44, 130.58 (q, $J = 32.2$ Hz), 129.39, 128.76, 124.89, 123.88 (d, $J = 272.3$ Hz); 123.59, 123.54, 121.95, 80.92, 59.86, 53.10, 28.16, 13.20, 10.38; ^{19}F NMR (376 MHz, CDCl_3) δ - 62.90; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 411.1890, found: 411.1890.



Methyl 3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)benzoate (1h)

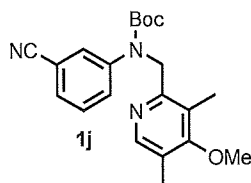
Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.92 (s, 1H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 7.9$ Hz, 1H), 4.93 (s, 2H), 3.87 (s, 3H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.64, 163.67, 154.63, 154.42, 148.94, 142.99, 131.04, 130.33, 128.26, 127.55, 126.54, 124.72, 123.66, 80.59, 59.79, 53.10, 52.01, 28.13, 13.13, 10.36; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 401.2071, found: 401.2072.



tert-Butyl (3-benzoylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1i)

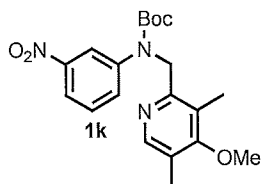
Light yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.75 (d, $J = 7.4$ Hz, 2H), 7.67 (s, 1H), 7.61-7.50 (m, 3H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.8$ Hz, 1H), 4.93 (s, 2H), 3.72 (s, 3H), 2.26-2.16 (m, 6H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 196.04, 163.69, 154.63, 154.51, 148.97, 142.97, 137.71, 137.35, 132.32, 130.55,

130.00, 128.21, 128.15, 127.87, 127.10, 124.75, 123.63,
80.66, 59.83, 53.16, 28.18, 13.18, 10.36; HRMS (ESI-TOF)
 m/z Calcd for $C_{27}H_{31}N_2O_4$ $[M+H]^+$: 447.2278, found: 447.2278.



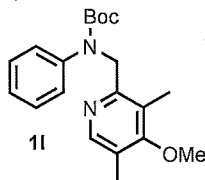
tert-Butyl ((3-cyanophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1j)

Colorless solid, 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.66–7.54 (m, 2H), 7.43–7.31 (m, 2H), 4.87 (s, 2H), 3.75 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.76, 154.14, 149.14, 144.04, 130.83, 129.57, 129.11, 128.74, 124.98, 123.37, 118.61, 112.31, 81.20, 59.92, 52.98, 28.12, 13.23, 10.32; HRMS (ESI-TOF) m/z Calcd for $C_{21}H_{26}N_3O_3$ $[M+H]^+$: 368.1969, found: 368.1969.



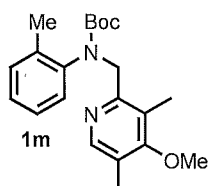
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-nitrophenyl)carbamate (1k)

Light yellow solid, 1H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, J = 2.2 Hz, 1H), 8.16 (s, 1H), 8.00–7.93 (m, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 4.93 (s, 2H), 3.75 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.81, 154.13, 154.07, 149.15, 148.12, 144.24, 132.19, 128.82, 125.02, 123.49, 121.22, 119.98, 81.36, 59.92, 52.91, 28.12, 13.22, 10.36; HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{26}N_3O_5$ $[M+H]^+$: 388.1867, found: 388.1865.



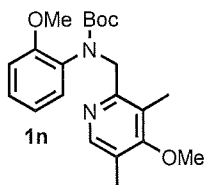
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(phenyl)carbamate (1l)

Light yellow solid, mp = 60 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.26–7.18 (m, 4H), 7.14–7.15 (m, 1H), 4.92 (s, 2H), 3.72 (s, 3H), 2.25–2.17 (m, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.63, 155.06, 154.74, 148.93, 142.74, 128.29, 126.46, 125.49, 124.63, 123.76, 80.23, 59.82, 53.45, 28.23, 13.19, 10.39; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 343.2016, found: 343.2015.



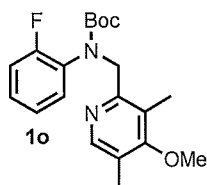
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(o-tolyl)carbamate (1m)

Light yellow liquid, rotameric mixture; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 7.25–6.87 (m, 4H), 5.13 (d, J = 14.8 Hz, 1H), 4.70–4.39 (m, 1H), 3.71 (s, 3H), 2.20 (s, 6H), 2.13 (s, 3H), 1.54–1.28 (m, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture, resonances for the minor rotamer are enclosed in parenthesis (): δ 163.68, 154.95 (155.19), 154.85 (154.37), 148.85, 140.63 (141.16), 135.87 (136.15), 130.22 (130.55), 128.28, 126.87, 126.06 (126.40), 124.97 (124.72), 124.87 (124.00), 79.71 (80.05), 59.71, 52.50 (53.38), 28.22, 17.49 (17.63), 13.18, 10.60; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 357.2173, found: 357.2172.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(2-methoxyphenyl)carbamate (1n)

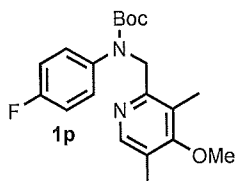
Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.12 (t, $J = 7.6$ Hz, 1H), 6.93–6.65 (m, 3H), 5.46–4.37 (m, 2H), 3.77 (brs, 3H), 3.72 (s, 3H), 2.25 (s, 3H), 2.18 (brs, 3H), 1.55–1.26 (m, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture, resonances for the minor rotamer the the minor rotamer are enclosed in parenthesis (): δ 163.68 (163.60), 155.45 (155.59), 155.32, 155.10 (154.83), 148.58, 130.61 (130.28), 129.42, 127.79 (128.02), 125.35 (124.59), 124.76 (124.49), 119.95 (120.39), 110.89 (111.68), 79.47 (80.09), 59.72, 55.14 (55.59), 52.42 (53.29), 28.17 (28.26), 13.16, 10.57; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 373.2122, found: 373.2121.



tert-Butyl (2-fluorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1o)

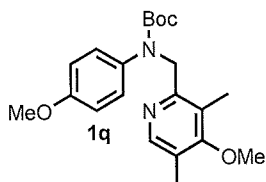
Colorless solid, mp = 59 °C, rotameric mixture, ratio of the rotamers = 75/25; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.40–7.06 (m, 2H), 7.05–6.89 (m, 2H), 4.93 (s, 2H), 3.72 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture, resonances for the minor rotamer the the minor rotamer are enclosed in parenthesis (): δ 163.79, 158.15 (d, $J = 248.9$ Hz), 154.68, 154.30, 148.72, 129.69 (d, $J = 12.0$ Hz), 129.28, 127.90 (d, $J = 7.8$ Hz), 125.12, 124.97, 123.79, 115.56 (d, $J = 21.3$ Hz), 80.48, 59.75, 52.69 (53.39), 28.07, 13.16, 10.49; ^{19}F NMR (376 MHz, CDCl_3) for major isomer: δ -

121.13; ^{19}F NMR (376 MHz, CDCl_3) for minor isomer: δ -
 120.82; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{26}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$:
 361.1922, found: 361.1922.



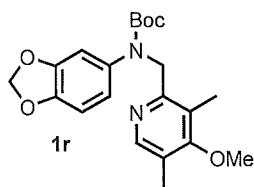
tert-Butyl (4-fluorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1p)

Light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.19 (s, 2H), 6.91 (t, $J = 8.6$ Hz, 2H), 4.88 (s, 2H), 3.72 (s, 3H), 2.21 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.72, 160.46 (d, $J = 244.4$ Hz), 154.82, 154.78, 148.96, 138.65, 128.43 (d, $J = 8.0$ Hz), 124.81, 123.93, 115.06 (d, $J = 22.8$ Hz), 80.39, 59.85, 53.50, 28.22, 13.20, 10.40; ^{19}F NMR (376 MHz, CDCl_3) δ -117.08; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{26}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 361.1922, found: 361.1923.



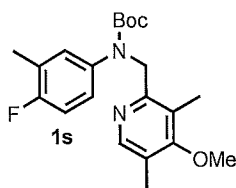
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(4-methoxyphenyl)carbamate (1q)

Red solid, ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.10 (brs, 2H), 6.74 (d, $J = 8.4$ Hz, 2H), 4.89 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 2.25-2.16 (m, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.67, 157.34, 155.15, 155.08, 148.88, 135.52, 127.99, 124.68, 124.09, 113.56, 80.04, 59.81, 55.31, 53.67, 28.28, 13.19, 10.43; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 373.2122, found: 373.2123.



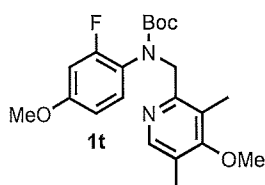
tert-Butyl benzo[d][1,3]dioxol-5-yl((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1r)

Colorless solid, mp = 87 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 6.77 (s, 1H), 6.65 (s, 2H), 5.90 (s, 2H), 4.84 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.24, 154.58, 154.53, 148.48, 146.76, 145.02, 136.32, 124.28, 123.48, 119.75, 108.27, 107.11, 100.71, 79.75, 59.40, 53.38, 27.82, 12.76, 9.98; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 387.1914, found: 387.1914.



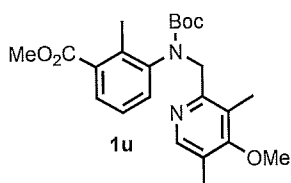
tert-Butyl (4-fluoro-3-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1s)

Colorless solid, mp = 78 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 6.83 (t, J = 9.0 Hz, 1H), 4.86 (s, 2H), 3.73 (s, 3H), 2.24–2.19 (m, 6H), 2.18 (d, J = 1.9 Hz, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.68, 159.05 (d, J = 243.2 Hz), 154.94, 154.81, 148.90, 138.26, 129.63 (d, J = 5.3 Hz), 125.69, 124.72, 124.59 (d, J = 18.6 Hz), 123.83, 114.59 (d, J = 23.3 Hz), 80.26, 59.81, 53.58, 28.22, 14.51, 13.18, 10.40; ^{19}F NMR (376 MHz, CDCl_3) δ -121.37; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{28}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 375.2078, found: 375.2079.



***tert*-butyl (2-fluoro-4-methoxyphenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1t)**

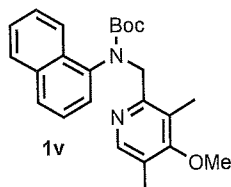
Red liquid, rotameric mixture, ratio of the rotamers = 75/25; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (brs, 1H), 7.18 (s, 0.25H), 7.00 (d, J = 9.1 Hz, 0.75H), 6.63-6.44 (m, 2H), 5.02-4.75 (m, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H), 1.52-1.31 (m, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture: δ 163.81, 159.63, 159.41, 159.20, 159.16, 159.03, 158.95, 158.01, 157.76, 154.96, 154.81, 154.66, 148.69, 130.50, 129.73, 125.28, 124.99, 124.42, 122.33, 122.24, 109.53, 108.98, 101.75, 101.59, 80.62, 80.22, 76.79, 59.73, 55.48, 53.61, 52.77, 28.10, 13.17, 10.52; ^{13}C NMR (150 MHz, CDCl_3) for major isomer: δ 163.81, 159.03, 158.95, 158.58 (d, J = 248.7 Hz), 154.74 (d, J = 22.2 Hz), 148.69, 129.73, 125.28, 124.99, 122.29 (d, J = 13.1 Hz), 108.98, 101.67 (d, J = 24.2 Hz), 80.22, 59.73, 55.48, 52.77, 28.10, 13.17, 10.52; ^{19}F NMR (376 MHz, CDCl_3) for major isomer: δ -119.19; ^{19}F NMR (376 MHz, CDCl_3) for minor isomer: δ -118.92; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{28}\text{FN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 391.2028, found: 391.2028.



Methyl 3-((*tert*-butoxycarbonyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-2-methylbenzoate (1u)

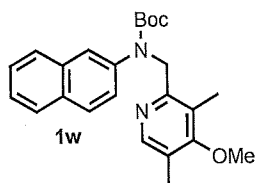
Colorless liquid, rotameric mixture, ratio of the rotamers = 70/30; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (brs, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.47 (s, 0.3H), 7.21 (d, J = 7.8 Hz, 0.7H), 7.16-7.00 (m, 1H), 5.16 (d, J = 14.9 Hz, 1H), 4.66-4.30 (m, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 2.50-2.30 (m, 3H), 2.20 (s, 6H), 1.52-1.28 (m, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture, resonances for the minor rotamer the the minor rotamer are enclosed in parenthesis (): δ 168.05, 163.75 (163.65), 154.70 (154.79), 154.48,

148.89, 141.94 (142.56), 137.93 (138.10), 132.50 (132.90),
130.91 (131.28), 129.15, 125.50 (125.79), 124.98, 124.86
(123.85), 80.07, 59.72, 52.44 (53.27), 51.85, 28.16,
15.07, 13.17, 10.61; HRMS (ESI-TOF) m/z Calcd for $C_{23}H_{31}N_2O_5$
[M+H]⁺: 415.2227, found: 415.2226.



**tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)-
methyl)(naphthalen-1-yl)carbamate (1v)**

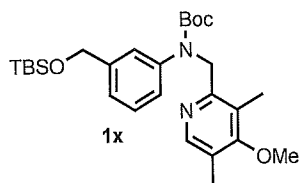
Colorless solid, rotameric mixture, ¹H NMR (400 MHz, CDCl₃)
δ 8.11 (s, 1H), 7.87 (s, 1H), 7.84-7.77 (m, 1H), 7.70 (d,
 J = 8.2 Hz, 1H), 7.52-7.39 (m, 2H), 7.38-7.18 (m, 2H),
5.37 (d, J = 15.2 Hz, 1H), 4.66 (d, J = 15.1 Hz, 1H), 3.66
(s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 1.70-1.05 (m, 9H); ¹³C
NMR (150 MHz, CDCl₃) rotameric mixture, resonances for the
minor rotamer are enclosed in parenthesis (): δ 163.63,
155.46, 154.99, 148.89, 138.66, 134.23, 130.76, 128.14,
127.27, 126.37, 125.99, 125.66, 125.32, 124.75, 124.66,
122.88, 79.93, 59.69, 53.00 (53.86), 28.06, 13.13, 10.54;
HRMS (ESI-TOF) m/z Calcd for $C_{24}H_{29}N_2O_3$ [M+H]⁺: 393.2173,
found: 393.2173.



**tert-butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)-
methyl)(naphthalen-2-yl)carbamate (1w)**

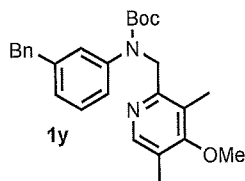
Colorless solid, mp = 81 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.14
(s, 1H), 7.78-7.72 (m, 1H), 7.72-7.67 (m, 2H), 7.65 (s,
1H), 7.44 (d, J = 8.6 Hz, 1H), 7.42-7.34 (m, 2H), 5.03 (s,
2H), 3.71 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H), 1.41 (s,
9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.66, 154.99, 154.78,

148.97, 140.41, 133.41, 131.37, 127.73, 127.70, 127.37, 126.03, 125.78, 125.36, 124.67, 123.75, 123.52, 80.43, 59.80, 53.63, 28.25, 13.17, 10.43; HRMS (ESI-TOF) m/z Calcd for $C_{24}H_{29}N_2O_3$ $[M+H]^+$: 393.2173, found: 393.2172.



tert-Butyl (3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1x)

Light yellow liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.23-7.15 (m, 2H), 7.12 (d, J = 7.9 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 4.91 (s, 2H), 4.66 (s, 2H), 3.72 (s, 3H), 2.24-2.16 (m, 6H), 1.39 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.60, 155.03, 154.79, 148.95, 142.79, 141.69, 128.05, 124.93, 124.55, 123.81, 123.61, 123.03, 80.17, 64.61, 64.59, 59.81, 53.46, 28.24, 25.88, 25.86, 18.32, 13.17, 10.34, -5.33; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{43}N_2O_4Si$ $[M+H]^+$: 487.2987, found: 487.2986.

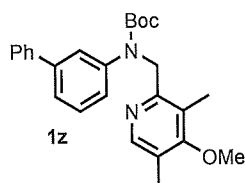


tert-Butyl (3-benzylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1y)

Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.28-7.20 (m, 2H), 7.20-6.99 (m, 6H), 6.91 (d, J = 7.1 Hz, 1H), 4.89 (s, 2H), 3.89 (s, 2H), 3.69 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.64, 155.04, 154.72, 148.88, 142.70, 141.02, 140.89, 128.85, 128.35, 128.29, 127.34, 126.19, 125.94, 124.60, 123.96, 123.82, 80.21, 59.79, 53.44, 41.62, 28.21, 13.20,

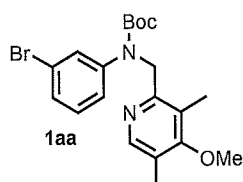
10.39; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{33}N_2O_3$ $[M+H]^+$:

433.2486, found: 433.2484.



tert-Butyl [1,1'-biphenyl]-3-yl((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1z)

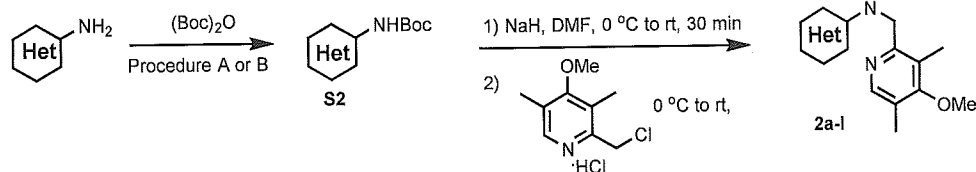
Light yellow liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.52-7.46 (m, 2H), 7.44 (s, 1H), 7.42-7.36 (m, 2H), 7.36-7.27 (m, 3H), 7.23 (d, $J = 8.3$ Hz, 1H), 4.97 (s, 2H), 3.71 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.68, 155.08, 154.72, 148.97, 143.09, 141.32, 140.87, 128.61, 127.19, 127.07, 125.43, 125.32, 124.70, 124.30, 123.82, 80.33, 59.81, 53.46, 28.28, 13.18, 10.43; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{31}N_2O_3$ $[M+H]^+$: 419.2329, found: 419.2327.



tert-Butyl (3-bromophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (1aa)

Colorless solid, 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.45 (s, 1H), 7.26-7.18 (m, 2H), 7.10 (t, $J = 8.0$ Hz, 1H), 4.87 (s, 2H), 3.74 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.68, 154.57, 154.33, 149.04, 149.03, 144.29, 129.46, 128.43, 125.00, 124.79, 123.53, 121.55, 80.74, 59.88, 53.21, 28.18, 13.21, 10.36; HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{26}BrN_2O_3$ $[M+H]^+$: 421.1121, found: 421.1121.

Preparation of Heterocyclic-Amine Substrates



S2a and **S2b** were synthesized following the *General Procedure A*; Aminothiophenes bearing Boc-protecting group **S2c-e** were commercial available; Boc-protected amines **S2f-1** were synthesized following the *General Procedure B*. Substrates **2a-1** were synthesized following the general procedure.

General procedure A for synthesis of Boc-protected amines

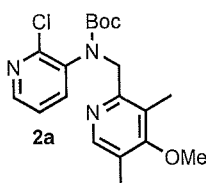
S2: To a solution of amine (5 mmol) in THF (20 mL) was added a solution of sodium bis(trimethylsilyl)amide (2.5 N in THF) slowly at -15 °C under nitrogen, and the resulting mixture was stirred for 30 min at the same temperature. Next, (Boc)₂O (1.1 equiv.) was added at the same temperature. The reaction mixture was allowed to warm up to room temperature. After the reaction was completed, the resulting mixture was diluted with EtOAc (50 mL), and the organic phase was washed with water (50 mL) and then brine (50 mL), dried over MgSO₄, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel gave **S2**. [Demont ert al., *Med. Chem.*, **58**:5649-5673 (2015).]

General procedure B for synthesis of Boc-protected amines

S2: To a solution of amine in ethanol was added (Boc)₂O (1.1 equiv.) at room temperature. After the reaction was completed, the solution was concentrated under vacuum to afford the Boc-protected amines in high yield. The Boc-protected amines were used for next step without further purification. [Vilaivan, *Tetrahedron Lett* **47**:6739-6742 (2005).]

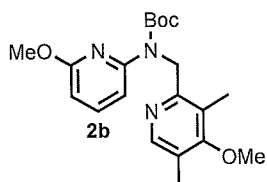
General procedure for synthesis of substrates 2a-1: To a solution of Boc-protected amine **S2** (1.2 equiv.) in DMF was added NaH (3.0 equiv.) at 0 °C, and the resulting mixture

was allowed to warm up to room temperature for 30 minutes. The mixture was cooled to 0 °C again, then 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (1.0 equiv.) was added into the mixture slowly. The resulting mixture was allowed to warm to room temperature for another 12 hours. After the reaction completed, EtOAc was added to dilute the reaction mixture, then the organic phase was washed with water, brine and dried over Na₂SO₄. After concentrated *in vacuo*, the residue was purified by flash chromatography on silica gel to afford **2**.



tert-Butyl (2-chloropyridin-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2a)

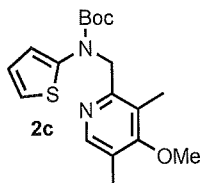
Colorless solid, rotameric mixture, ratio of the rotamers = 76/24; ¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 4.7 Hz, 1H), 8.13 (s, 0.24H), 8.07 (s, 0.76H), 7.92 (s, 0.24H), 7.66 (d, *J* = 7.7 Hz, 0.76H), 7.22-7.10 (m, 1H), 5.16 (d, *J* = 15.4 Hz, 1H), 4.72-4.38 (m, 1H), 3.73 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H), 1.50-1.29 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) for major isomer: δ 163.86, 154.04, 153.75, 150.49, 148.80, 147.43, 139.21, 136.43, 125.23, 125.07, 122.51, 81.02, 59.75, 51.62, 28.03, 13.17, 10.66; HRMS (ESI-TOF) *m/z* Calcd for C₁₉H₂₅ClN₃O₃ [M+H]⁺: 378.1579, found: 378.1579.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(6-methoxypyridin-2-yl)carbamate (2b)

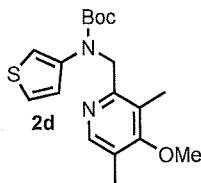
Light yellow liquid, ¹H NMR (400 MHz, CDCl₃) δ 8.12 (s, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H),

6.37 (d, $J = 7.9$ Hz, 1H), 5.20 (s, 2H), 3.72 (s, 3H), 3.62 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.32, 162.09, 155.91, 154.45, 152.20, 148.85, 139.43, 123.84, 122.42, 110.75, 104.67, 80.95, 59.82, 52.84, 49.28, 28.15, 13.13, 10.32; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 374.2074, found: 374.2073.



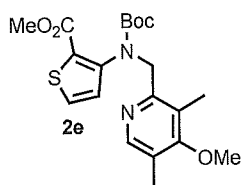
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(thiophen-2-yl)carbamate (2c)

Light yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 6.89 (d, $J = 5.5$ Hz, 1H), 6.73 (dd, $J = 5.6, 3.8$ Hz, 1H), 6.57 (d, $J = 3.6$ Hz, 1H), 4.96 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.71, 154.15, 154.00, 149.00, 145.12, 124.83, 124.21, 123.75, 120.38, 116.32, 81.52, 59.85, 53.87, 28.16, 13.19, 10.26; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 349.1580, found: 349.1579.



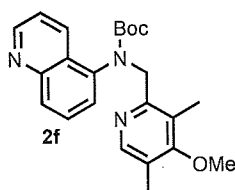
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(thiophen-3-yl)carbamate (2d)

Light yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 7.12-7.08 (m, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 4.90 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.67, 154.80, 154.25, 149.00, 141.18, 125.41, 124.68, 123.61, 123.18, 114.83, 80.65, 59.84, 53.33, 28.23, 13.18, 10.27; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 349.1580, found: 349.1581.



Methyl 3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)thiophene-2-carboxylate (2e)

Light yellow liquid, rotameric mixture, ratio of rotamers = 34/64, ^1H NMR (400 MHz, CDCl_3) δ 8.20–7.98 (m, 1H), 7.37–7.16 (m, 1H), 6.99 (s, 0.34H), 6.76 (s, 0.66H), 5.14–4.68 (m, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H), 1.50–1.28 (m, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture, resonances for the minor rotamer are enclosed in parenthesis (δ 163.74 (163.60), 161.44 (161.32), 154.71 (155.16), 154.07 (154.16), 148.67 (148.75), 144.92 (145.84), 128.91 (129.28), 128.51 (128.78), 124.97 (125.02), 124.78 (124.71), 123.92, 80.28 (80.62), 59.75, 52.49 (53.43), 51.83, 28.08, 13.15, 10.50; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 407.1635, found: 407.1635.

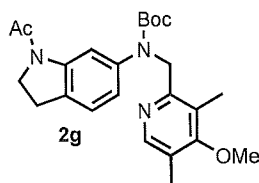


tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(quinolin-5-yl)carbamate (2f)

Red liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.88 (dd, J = 4.2, 1.6 Hz, 1H), 8.27 (s, 1H), 8.09 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.38 (dd, J = 8.5, 4.2 Hz, 2H), 5.21 (d, J = 15.3 Hz, 1H), 4.80 (d, J = 15.2 Hz, 1H), 3.67 (s, 3H), 2.17 (s, 6H), 1.25 (brs, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.73, 155.09, 154.54, 150.19, 148.97, 148.73, 138.85, 131.91, 128.89, 128.74, 126.24, 125.75, 124.95, 124.53, 120.89, 80.46, 59.75, 53.26, 28.07, 13.16,

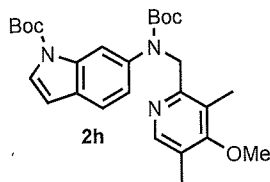
10.60; HRMS (ESI-TOF) m/z Calcd for $C_{23}H_{28}N_3O_3$ $[M+H]^+$:

394.2125, found: 394.2124.



tert-Butyl (1-acetyllindolin-6-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2g)

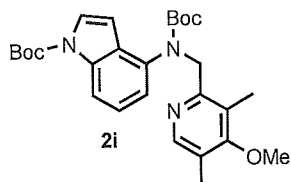
Light yellow solid, mp = 140 °C, rotameric mixture, ratio of rotamer = 22/78, 1H NMR (400 MHz, $CDCl_3$) δ 8.18-8.08 (m, 1.78H), 7.15 (s, 0.22H), 7.08 (d, J = 7.4 Hz, 0.22H), 7.00 (d, J = 8.0 Hz, 0.78H), 6.96-6.85 (m, 1H), 4.95-4.84 (m, 2H), 4.09 (t, J = 8.1 Hz, 0.44H), 4.02 (t, J = 8.4 Hz, 1.56H), 3.72 (s, 3H), 3.11 (t, J = 8.5 Hz, 1.56H), 2.98 (t, J = 8.5 Hz, 0.44H), 2.32-2.14 (m, 9H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) rotameric mixture, resonances for the minor rotamer are enclosed in parenthesis (δ 168.34 (168.19), 163.61 (163.68), 155.12 (154.97), 154.79, 148.78 (148.86), 142.93 (142.18), 142.08 (141.68), 128.43 (131.15), 125.15, 124.52 (124.79), 123.75 (123.89), 122.25 (121.66), 115.85 (113.80), 80.16 (80.38), 59.79, 53.55 (53.60), 49.18 (48.33), 28.21, 27.56 (26.39), 24.11 (24.31), 13.15, 10.44 (10.39); HRMS (ESI-TOF) m/z Calcd for $C_{24}H_{32}N_3O_4$ $[M+H]^+$: 426.2387, found: 426.2387.



tert-Butyl 6-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-1H-indole-1-carboxylate (2h)

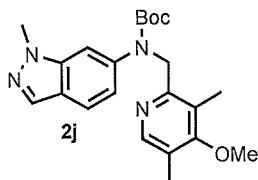
Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.95 (s, 1H), 7.53 (d, J = 3.7 Hz, 1H), 7.38 (d, J = 8.3

Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 1H), 6.47 (d, $J = 3.7$ Hz, 1H), 4.99 (s, 2H), 3.72 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H), 1.59 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.73, 154.75, 154.55, 149.01, 143.94, 139.80, 139.25, 124.81, 123.72, 123.58, 123.39, 120.34, 111.99, 84.65, 80.74, 59.85, 53.78, 28.20, 28.01, 13.19, 10.43; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{36}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 482.2649, found: 482.2650.



tert-Butyl 4-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-1H-indole-1-carboxylate (2i)

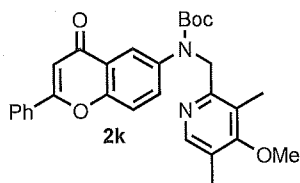
Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.52 (d, $J = 3.8$ Hz, 1H), 7.15 (t, $J = 8.0$ Hz, 1H), 7.01 (s, 1H), 6.52 (d, $J = 3.7$ Hz, 1H), 4.99 (s, 2H), 3.68 (s, 3H), 2.18 (s, 6H), 1.65 (s, 9H), 1.35 (brs, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.59, 154.98, 154.85, 149.65, 148.85, 135.80, 134.93, 128.51, 125.42, 124.68, 124.33, 124.16, 121.07, 113.58, 105.56, 83.62, 80.08, 59.70, 53.18, 28.16, 28.13, 13.14, 10.52; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{36}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 482.2649, found: 482.2649.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(1-methyl-1H-indazol-6-yl)carbamate (2j)

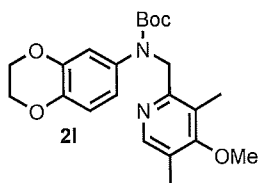
Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.87 (s, 1H), 7.55 (d, $J = 8.6$ Hz, 1H), 7.33 (s, 1H), 7.05 (d, $J = 8.6$ Hz, 1H), 4.99 (s, 2H), 3.98 (s, 3H), 3.73 (s,

3H), 2.24 (s, 3H), 2.21 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.70, 155.02, 154.81, 148.94, 141.45, 140.01, 132.47, 124.76, 123.84, 121.90, 120.82, 120.45, 106.53, 80.50, 59.84, 53.92, 35.50, 28.25, 13.21, 10.46; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{29}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 397.2234, found: 397.2234.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(4-oxo-2-phenyl-4H-chromen-6-yl)carbamate (2k)

Yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.99 (d, $J = 2.6$ Hz, 1H), 7.94-7.87 (m, 2H), 7.78 (d, $J = 9.1$ Hz, 1H), 7.57-7.49 (m, 3H), 7.47 (d, $J = 9.0$ Hz, 1H), 6.77 (s, 1H), 4.98 (s, 2H), 3.74 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.99, 163.75, 163.22, 154.50, 153.76, 149.03, 140.32, 133.36, 131.73, 131.53, 128.99, 126.22, 124.84, 123.84, 123.68, 121.85, 117.95, 107.19, 80.83, 59.89, 53.24, 28.18, 13.19, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 487.2227, found: 487.2226.



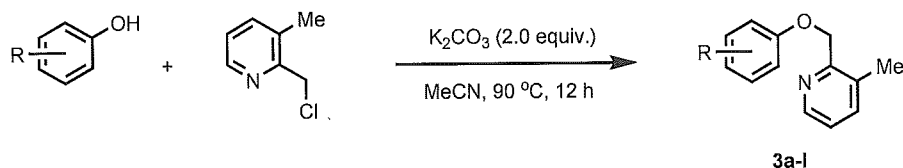
tert-Butyl (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2l)

Colorless solid, ^1H NMR (500 MHz, CDCl_3) δ 8.15 (s, 1H), 6.78 (s, 1H), 6.70 (s, 2H), 4.84 (s, 2H), 4.19 (s, 4H), 3.72 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.62, 155.05, 154.99, 148.92, 142.85, 141.48, 136.34, 124.59, 123.75, 120.17, 116.54, 115.81, 80.10, 64.24, 64.19, 59.82, 53.68, 28.25, 13.18,

10.37; HRMS (ESI-TOF) m/z Calcd for $C_{22}H_{29}N_2O_5$ $[M+H]^+$:

401.2071, found: 401.2071.

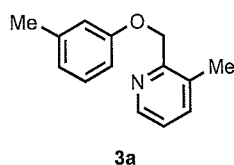
Preparation of Phenol Substrates



2-(Chloromethyl)-3-methylpyridine was synthesized following the literature. [Narendara et al., *Synthetic Commun*, **34**:1097-1103 (2004)]

General Procedure for Preparation of Phenol Substrates¹:

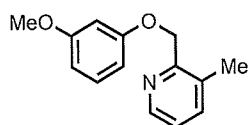
Phenol derivative (10 mmol) and K_2CO_3 (20 mmol) were added to a 100 mL round bottom flask equipped with a reflux condenser and diluted with 20 mL MeCN. Next, 2-(chloromethyl)-3-methylpyridine (12 mmol) was added to the mixture via syringe and the reaction mixture was stirred at 90 °C for 12 hours. After cooling to room temperature, the mixture was diluted with EtOAc and washed with 2 N NaOH three times. The resulting solution was dried over sodium sulfate, concentrated by rotatory evaporation and purified by silica gel chromatography to afford the desired phenol substrate Compounds **3a-l**.



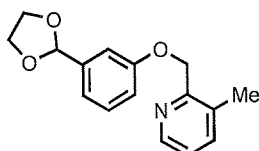
3-Methyl-2-((m-tolyl)oxy)methylpyridine (3a)

Light yellow liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.8 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.21-7.13 (m, 2H), 6.82-6.88 (m, 2H), 6.78 (d, J = 7.5 Hz, 1H), 5.20 (s, 2H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

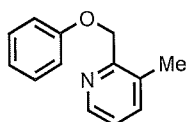
158.70, 154.40, 146.47, 139.42, 138.37, 133.26, 129.11, 123.35, 121.79, 115.69, 111.61, 70.73, 21.48, 18.14; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{15}NO$ $[M+H]^+$: 214.1226, found: 214.1228.

**3b****2-((3-Methoxyphenoxy)methyl)-3-methylpyridine (3b)**

Light yellow liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.7 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.23–7.10 (m, 2H), 6.66–6.59 (m, 2H), 6.52 (dd, J = 8.3, 2.4 Hz, 1H), 5.19 (s, 2H), 3.78 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.75, 159.96, 154.24, 146.57, 138.39, 133.21, 129.81, 123.41, 106.93, 106.75, 101.26, 70.83, 55.23, 18.14; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176, found: 230.1180.

**3c****2-((3-(1,3-Dioxolan-2-yl)phenoxy)methyl)-3-methylpyridine (3c)**

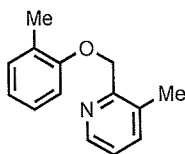
Clear liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.33–7.27 (m, 1H), 7.21–7.15 (m, 2H), 7.09 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 8.2, 2.7 Hz, 1H), 5.81 (s, 1H), 5.23 (s, 2H), 4.16–3.97 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.64, 154.04, 146.37, 139.42, 138.27, 133.16, 129.31, 123.32, 118.96, 115.54, 112.55, 103.32, 103.31, 70.71, 65.09, 18.01; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1281, found: 272.1284.



3d

3-Methyl-2-(phenoxymethyl)pyridine (3d)

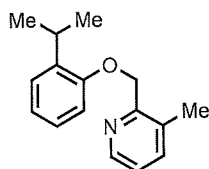
Clear liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 4.7$ Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.31–7.23 (m, 2H), 7.16 (dd, $J = 7.7, 4.8$ Hz, 1H), 7.06–7.00 (m, 2H), 6.94 (t, $J = 7.6$, 1H) 5.20 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.63, 154.26, 146.46, 138.30, 133.17, 129.32, 123.32, 120.88, 114.76, 70.73, 18.07; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}$ $[\text{M}+\text{H}]^+$: 200.1070, found: 200.1073.



3e

3-Methyl-2-((o-tolyl)oxy)methylpyridine (3e)

Light yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 4.9$ Hz, 1H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.19 (dd, $J = 7.7, 4.9$ Hz, 1H), 7.16–7.10 (m, 2H), 7.03 (d, $J = 8.1$ Hz, 1H), 6.86 (t, $J = 7.4$ Hz, 1H), 5.22 (s, 2H), 2.45 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.74, 154.66, 146.37, 138.37, 133.46, 130.62, 126.82, 126.75, 123.35, 120.54, 111.51, 71.16, 18.14, 16.23; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 214.1226, found: 214.1236.

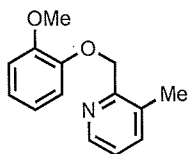


3f

2-((2-Isopropylphenoxy)methyl)-3-methylpyridine (3f)

Clear liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 4.4$, Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.24 – 7.16 (m, 2H), 7.14 (d, $J = 7.2$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 6.94 (t, $J = 7.4$ Hz, 1H), 5.22 (s, 2H) 3.34 (sep, $J = 6.9$ Hz,

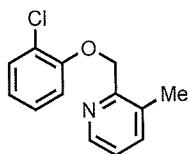
1H), 2.45 (s, 3H), 1.18 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.77, 154.74, 146.44, 138.35, 137.20, 133.43, 126.50, 126.05, 123.38, 120.86, 111.81, 71.31, 26.36, 22.90, 18.16; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}$ $[\text{M}+\text{H}]^+$: 242.1539, found: 242.1539.



3g

2-((2-Methoxyphenoxy)methyl)-3-methylpyridine (3g)

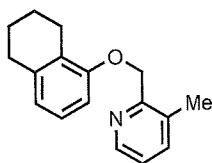
Yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 4.4$ Hz, 1H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.04 (dd, $J = 7.7, 4.8$ Hz, 1H), 6.98 (d, $J = 8.6$ Hz, 1H), 6.85–6.74 (m, 3H), 5.16 (s, 2H), 3.73 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.25, 149.65, 147.97, 146.22, 138.26, 133.36, 123.19, 121.41, 120.62, 114.42, 111.69, 71.86, 55.66, 18.02; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 230.1176, found: 230.1179.



3h

2-((2-Chlorophenoxy)methyl)-3-methylpyridine (3h)

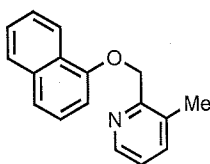
Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.43 (d, $J = 4.8$ Hz, 1H), 7.52 (d, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.23–7.14 (m, 3H), 6.92–6.84 (m, 1H), 5.31 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.98, 153.78, 146.24, 138.62, 133.90, 130.25, 127.65, 123.60, 122.95, 121.59, 114.23, 72.02, 18.22; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{13}\text{ClNO}$ $[\text{M}+\text{H}]^+$: 234.0680, found: 234.0682.



3i

3-Methyl-2-(((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)methyl)pyridine (3i)

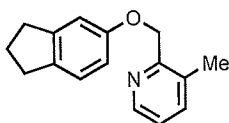
Orange solid, ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 4.7$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.19 (dd, $J = 7.6, 4.8$ Hz, 1H), 7.06 (t, $J = 7.9$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.71 (d, $J = 7.6$ Hz, 1H), 5.21 (s, 2H), 2.75 (t, $J = 5.1$ Hz, 2H), 2.66 (t, $J = 6.3$ Hz, 2H), 2.44 (s, 3H), 1.84–1.68 (m, $J = 3.3$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.34, 154.77, 146.34, 138.49, 138.35, 133.49, 126.13, 125.62, 123.32, 121.62, 108.20, 71.06, 29.61, 23.10, 22.79, 22.75, 18.20; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{20}\text{NO}$ $[\text{M}+\text{H}]^+$: 254.1539, found: 254.1537.



3j

3-Methyl-2-((naphthalen-1-yloxy)methyl)pyridine (3j)

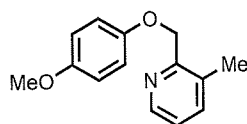
Orange liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, $J = 4.9$ Hz, 1H), 8.25 (d, $J = 8.2$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.50–7.42 (m, 3H), 7.38 (t, $J = 7.9$ Hz, 1H), 7.27–7.20 (m, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 5.42 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.40, 154.31, 146.40, 138.54, 134.49, 133.69, 127.43, 126.31, 125.85, 125.64, 125.14, 123.52, 122.00, 120.46, 105.40, 71.32, 18.27; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$: 250.1226, found: 250.1228.



3k

2-((2,3-Dihydro-1H-inden-5-yl)oxy)methyl)-3-methylpyridine (3k)

Yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 4.8$ Hz, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.18 (dd, $J = 7.7, 4.8$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 6.92 (s, 1H), 6.81 (dd, $J = 8.0, 2.2$ Hz, 1H), 5.18 (s, 2H), 2.92 – 2.79 (m, 4H), 2.43 (s, 3H), 2.06 (p, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.60, 154.53, 146.38, 145.64, 138.43, 136.52, 133.33, 124.66, 123.34, 112.78, 110.91, 71.05, 33.13, 31.95, 25.77, 18.16; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$: 240.1383, found: 240.1386.

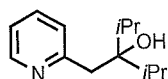


3l

2-((4-Methoxyphenoxy)methyl)-3-methylpyridine (3l)

Light yellow liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 4.8$ Hz, 1H), 7.50 (d, $J = 7.6$ Hz, 1H), 7.18 (dd, $J = 7.7, 4.8$ Hz, 1H), 6.96 (d, $J = 9.0$ Hz, 2H), 6.82 (d, $J = 9.0$ Hz, 2H), 5.16 (s, 2H), 3.76 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.53, 154.00, 152.87, 146.56, 138.37, 133.21, 123.36, 115.85, 114.58, 71.55, 55.68, 18.17; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 230.1176, found: 230.1179.

Preparation of Other Heterocyclic Substrates

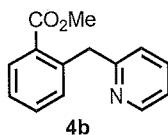


S7

2,4-Dimethyl-3-(2-pyridylmethyl)-3-pentanol (S7)

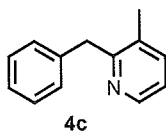
$n\text{-BuLi}$ (1.6 M in hexane, 13 mL, 20 mmol) was slowly added to a solution of 2-picoline (2.0 mL, 20 mmol) in tetrahydrofuran (20 mL) at -30°C and the reaction mixture was stirred for 30 minutes. Diisopropyl ketone (3.4 mL,

24 mmol) was then added, the reaction mixture was stirred for 2 hours at ambient temperature. Water (30 mL) was added, and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification (Hexane : EtOAc = 3 : 1) gave the pyridyl alcohol **S7** (3.5 g, 17 mmol) in 85% yield.

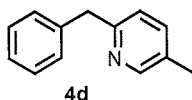


Methyl 2-(pyridin-2-ylmethyl)benzoate (4b) [Niwa et al., *Angew. Chem. Int. Ed.* **46**:2643-2645 (2007).]

Cesium carbonate (0.714 g, 2.0 mmol) was placed in a 50-mL two-necked reaction flask. Cesium carbonate was dried in vacuo with heating with a heat gun for 2 minutes. The flask was then filled with argon using standard Schlenk technique. Palladium trifluoroacetate (34 mg, 0.10 mmol), tricyclohexylphosphine (53 mg, 0.20 mmol), xylene (10 mL), pyridyl alcohol **S7** (0.414 g, 2.0 mmol), and methyl 2-iodobenzoate (576 mg, 2.2 mmol) were sequentially added at room temperature. The resulting mixture was heated at reflux for 10 hours. After the mixture was cooled to room temperature, water (30 mL) was added. The product was extracted with ethyl acetate (30 mL × 3). The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification (Hexane : EtOAc = 5 : 1) gave product Compound **4b** (272 mg, 1.2 mmol) in 60% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 4.6 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.54 (td, *J* = 7.7, 1.9 Hz, 1H), 7.50-7.42 (m, 1H), 7.36-7.28 (m, 2H), 7.13-7.02 (m, 2H), 4.56 (s, 2H), 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.93, 160.81, 149.15, 140.44, 136.28, 132.12, 131.98, 130.72, 129.96, 126.54, 122.96, 120.99, 51.91, 42.52; HRMS (ESI-TOF) *m/z* Calcd for C₁₄H₁₄NO₂ [M+H]⁺: 228.1019, found: 228.1019.

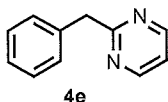
**2-Benzyl-3-methylpyridine (4c)**

Anhydrous cobalt(II) acetylacetonate (77 mg, 0.30 mmol) was placed in a 50 mL flask. Anhydrous dioxane (10 mL) was then added under argon. After the solution became red, benzylmagnesium chloride (2.0 M in THF, 4.5 mL, 9.0 mmol) was added at 0 °C. The mixture was stirred for about 5 minutes at 25 °C. Then, 2-bromo-3-methylpyridine (526 mg, 3.0 mmol) was added dropwise to the reaction mixture. After stirring for 2 hours at 25 °C, the reaction mixture was poured into water. The products were extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were dried over sodium sulfate and concentrated. Purification of the crude product by silica gel column chromatography (Hexane: EtOAc = 4 : 1) provided the corresponding product Compound **4c** (384 mg, 2.1 mmol) in 70% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 4.6 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.22–7.13 (m, 3H), 7.07 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.19 (s, 2H), 2.24 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.76, 146.74, 138.99, 137.96, 131.70, 128.61, 128.33, 126.04, 121.66, 42.21, 18.92; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₁₄N [M+H]⁺: 184.1121, found: 184.1121.

**2-Benzyl-5-methylpyridine (4d)** [Ohmiya et al., *Chem. Lett.*, **33**:1240–1241 (2004).]

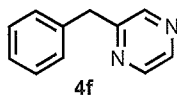
Anhydrous cobalt(II) acetylacetonate (77 mg, 0.30 mmol) was placed in a 50 mL flask. Anhydrous dioxane (10 mL) was then added under argon. After the solution became red, benzylmagnesium chloride (2 M in THF, 4.5 mL, 9.0 mmol) was added at 0 °C. The mixture was stirred for

about 5 minutes at 25 °C. Then, 2-bromo-5-methylpyridine (526 mg, 3.0 mmol) was added dropwise to the reaction mixture. After being stirred for 2 hours at 25 °C, the reaction mixture was poured into water. The products were extracted with ethyl acetate (30 mL× 3). The combined organic layers were dried over sodium sulfate and concentrated. Purification of the crude product by silica gel column chromatography (Hexane: EtOAc = 4 : 1) provided the corresponding product Compound **4d** (455 mg, 2.4 mmol) in 83% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.52 (s, 1H), 7.57-7.50 (m, 1H), 7.49-7.38 (m, 4H), 7.38-7.32 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 4.27 (s, 2H), 2.43 (s, 3H); ¹³C NMR (100 MHz, cdcl₃) δ 157.96, 149.60, 139.77, 137.09, 130.43, 128.98, 128.49, 126.22, 122.53, 44.18, 17.98; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₁₄N [M+H]⁺: 184.1121, found: 184.1121.



2-benzylpyrimidine (4e)

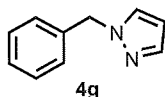
According to procedure for Compound **4c**, Compound **4e** was afforded in 83% yield using 2-(bromomethyl)pyrimidine. ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, *J* = 4.9 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 4.9 Hz, 1H), 4.30 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 170.03, 157.29, 138.19, 129.12, 128.52, 126.57, 118.63, 46.05; HRMS (ESI-TOF) *m/z* Calcd for C₁₁H₁₁N₂ [M+H]⁺: 171.0917, found: 171.0916.



2-Benzylpyrazine (4f)

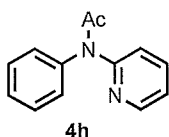
According to procedure for Compound **4c**, Compound **4f** was afforded in 70% yield using 2-(bromomethyl)pyrazine. ¹H NMR (400 MHz, CDCl₃) δ 8.50 (t, *J* = 2.0 Hz, 1H), 8.47 (s, 1H), 8.40 (d, *J* = 2.5 Hz, 1H), 7.36 - 7.20 (m, 5H), 4.17 (s, 2H); ¹³C NMR (100 MHz, cdcl₃) δ 156.44, 144.73, 144.04,

142.34, 138.08, 128.96, 128.72, 126.72, 41.94; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{11}N_2$ $[M+H]^+$: 171.0917, found: 171.0917.



1-Benzyl-1H-pyrazole (4g) [Kumpulainen et al., *Adv. Synth. Catal.* **356**:1555-1561 (2014).]

A round bottomed flask was charged with pyrazole (504 mg, 12.6 mmol), benzyl bromide (1.0 mL, 8.4 mmol), potassium carbonate (1.738 g, 12.6 mmol), potassium iodide (70 mg, 0.043 mmol) and dimethylformamide (10 mL). The mixture was heated to 80 °C for 13 hours. The reaction mixture was allowed to cool to room temperature and poured into a beaker containing water (20 mL) and ethyl acetate (50 mL). Next, the phases were separated and aqueous phase was extracted with ethyl acetate (50 mL). Combined organic extracts were dried with anhydrous sodium sulfate and solvents were evaporated. Purification by silica gel column chromatography (Hexane : EtOAc = 20 : 1) provided the corresponding product (796 mg, 5.0 mmol) in 60% yield. 1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 1.9 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.39-7.34 (m, 2H), 7.34-7.30 (m, 1H), 7.26-7.22 (m, 2H), 6.31 (t, J = 2.1 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.43, 136.59, 129.12, 128.69, 127.89, 127.52, 105.86, 55.82; HRMS (ESI-TOF) m/z Calcd for $C_{10}H_{11}N_2$ $[M+H]^+$: 159.0917, found: 159.0917.

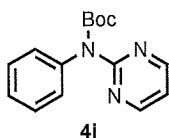


N-phenyl-N-(pyridin-2-yl)acetamide (4h) [Wang et al., *Tetrahedron Lett* **55**:7121-7123 (2014).]

A 10 mL flask equipped with a magnetic stir bar and a Teflon valve was charged with CuI (19 mg, 1 mol%), pyridin-2-amine (1.41 g, 15 mmol), and KO t Bu (2.12 g, 20 mmol).

The tube was evacuated and backfilled with argon. Under a counter flow of argon, 1,4-dioxane (25 mL) and bromobenzene (1.57 g, 10 mmol) were added via syringe and the tube was sealed. The reaction mixture was allowed to stir at 110 °C for 24 hours. The mixture was cooled to room temperature and 5.0 mL of brine was added. Subsequently, the mixture was extracted with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (hexanes : EtOAc = 8 : 1) to give the secondary amine as a colorless solid (1.35 g, 8.2 mmol) in 82% yield.

NaH (60% in mineral oil, 50 mg, 1.2 mmol) was added into the solution of secondary amine (170 mg, 10 mmol) in THF. The reaction mixture was stirred at room temperature for 30 minutes. Then acetyl chloride (110 mg, 1.5 mmol) was added and the reaction was monitored by TLC. Upon completion, the mixture was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with brine and dried over sodium sulfate and concentrated. The crude product was purified by column chromatography on silica gel (Hexanes : EtOAc = 20 : 1) to give the title product Compound **4h** (174 mg, 0.85 mmol) in 85% yield. ¹H NMR (600 MHz, CDCl₃) δ 8.43 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.71 (td, *J* = 7.8, 2.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.44–7.38 (m, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.32–7.27 (m, 2H), 7.13 (dd, *J* = 7.0, 5.1 Hz, 1H), 2.11 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.89, 155.18, 148.74, 141.96, 137.86, 129.38, 128.31, 127.54, 121.38, 121.13, 24.21; HRMS (ESI-TOF) *m/z* Calcd for C₁₃H₁₃N₂O [M+H]⁺: 213.1022, found: 213.1021.



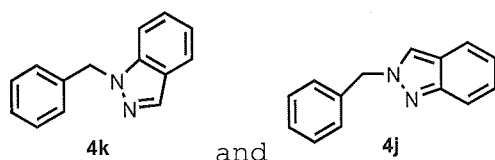
tert-Butyl phenyl(pyrimidin-2-yl)carbamate (4i) [Qian et

al., *Eur. J. Org. Chem.* 4837-4843 (2014).]

To an oven-dried flask containing aniline (1.39 g, 15.0 mmol) was added a solution of 2-chloro-pyrimidine (1.14 g, 10.0 mmol) and acetic acid (0.6 g, 10 mmol) in 1,4-dioxane (30.0 mL). The reaction mixture was stirred at 110 °C overnight. Upon completion, the mixture was extracted with CH₂Cl₂ (3×30 mL). The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by column chromatography on silica gel (hexanes : EtOAc = 5 : 1) to give the secondary amine as a colorless solid (1.28 g, 7.5 mmol) in 75% yield.

The secondary amine (513 mg, 3.0 mmol) was dissolved in anhydrous DMF (30 mL), and the solution was cooled to 0 °C in an ice/water bath. Sodium hydride (132 mg, 60% suspension in oil, 3.3 mmol) was added in portions. The suspension was stirred vigorously for an additional 20 minutes while maintaining the temperature below 5 °C and then (Boc)₂O (719 mg, 3.3 mmol) was added dropwise. After stirring for 30 minutes, the reaction mixture was brought to room temperature over a 1 hour period before water (5.0 mL) was added. The mixture was then diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was separated and extracted with water, 0.1 M HCl, sat. aqueous NaHCO₃ solution, and brine, then dried and concentrated. The resulting residue was then purified by silica gel chromatography (Hexanes : EtOAc = 10 : 1) to afford Compound **4i** (650 mg, 80%) as a clear, colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, *J* = 4.8 Hz, 2H), 7.44-7.35 (m, 2H), 7.32-7.26 (m, 1H), 7.25-7.20 (m, 2H), 7.04 (t, *J* = 4.8 Hz, 1H), 1.45 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 161.35, 158.21, 153.16, 141.25, 128.95, 127.69, 126.84, 117.14, 82.04, 28.05; HRMS (ESI-TOF) *m/z* Calcd for C₁₅H₁₈N₃O₂ [M+H]⁺: 272.1394, found: 272.1394.



1-Benzyl-1H-indazole and 2-Benzyl-2H-indazole

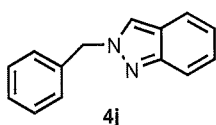
[Shumeiko et al., *Russ. J. Org. Chem.* **42**:294-295 (2006).]

A round-bottom flask was charged with indazole (1.18 g, 10.0 mmol), benzyl bromide (1.44 mL, 10.0 mmol), potassium hydroxide (0.56 g, 10.0 mmol), tetrabutylammonium chloride (189 mg, 0.5 mmol) and toluene (50 mL). The mixture was heated to 110 °C overnight (about 18 hours). The reaction mixture was allowed to cool to room temperature and poured into a beaker containing water (20 mL) and ethyl acetate (50 mL). Phases were separated and the aqueous phase was extracted with ethyl acetate (50 mL). Combined organic extracts were dried over anhydrous sodium sulfate and solvents were evaporated. The resulting residue was then purified by silica gel column chromatography (Hexanes:

EtOAc = 20:1 – 10:1) to provide the corresponding

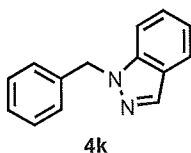
1-benzyl-1H-indazole **4k** (1.1 g, 5.5 mmol) in 55% yield and

2-benzyl-2H-indazole **4k'** (561 mg, 2.7 mmol) in 27% yield.

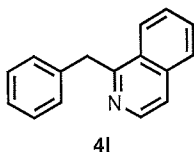


2-Benzyl-2H-indazole (4j)

¹H NMR (400 MHz, CDCl₃) δ 7.89-7.85 (m, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.38-7.30 (m, 3H), 7.30-7.23 (m, 3H), 7.06 (dd, *J* = 8.3, 6.7 Hz, 1H), 5.58 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 148.90, 135.73, 128.87, 128.32, 127.92, 125.91, 122.78, 122.06, 121.71, 120.09, 117.50, 57.47; HRMS (ESI-TOF) *m/z* Calcd for C₁₄H₁₃N₂ [M+H]⁺: 209.1073, found: 209.1074.

**1-Benzyl-1H-indazole (4k)**

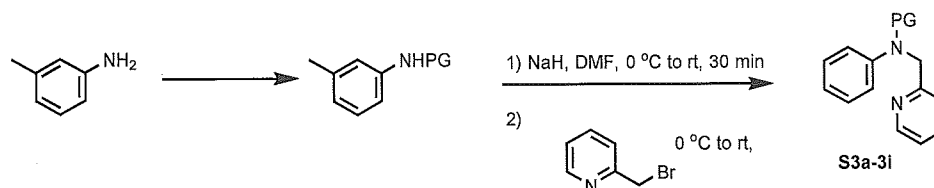
^1H NMR (600 MHz, CDCl_3) δ 8.04 (d, $J = 0.9$ Hz, 1H), 7.74 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.36–7.31 (m, 2H), 7.30–7.26 (m, 2H), 7.26–7.23 (m, 1H), 7.21–7.19 (m, 1H), 7.19–7.17 (m, 1H), 7.15–7.12 (m, 1H), 5.60 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 139.52, 136.86, 133.36, 128.69, 127.70, 127.14, 126.35, 124.34, 121.12, 120.61, 109.26, 52.95; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2$ $[\text{M}+\text{H}]^+$: 209.1073, found: 209.1074.

1-Benzylisoquinoline (4l)

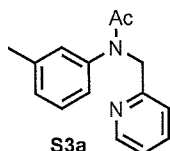
Anhydrous cobalt(II) acetylacetonate (77 mg, 0.30 mmol) was placed in a 50 mL flask. Anhydrous 1,4-dioxane (10 mL) was then added under argon. After the solution became red, benzylmagnesium chloride (2 M in THF solution, 4.5 mL, 9.0 mmol) was added at 0 °C. The mixture was stirred for about 5 minutes at 25 °C. Next, 2-chloroquinoline (491 mg, 3.0 mmol) was added dropwise to the reaction mixture. After being stirred for 2 hours at 25 °C, the reaction mixture was poured into water. The products were extracted with ethyl acetate (3 $\times$ 30 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification of the crude product by silica gel column chromatography (Hexanes: EtOAc = 4 : 1) provided the corresponding product Compound **4l** (328 mg, 1.5 mmol) in 50% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, $J = 8.5$ Hz, 1H), 7.99 (d, $J = 8.5$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.68 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.33–7.25 (m, 4H), 7.25–7.16 (m, 2H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.14, 147.74, 139.15,

136.42, 129.41, 129.15, 128.92, 128.56, 127.44, 126.70, 126.42, 125.91, 121.46, 45.50; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{14}N$ $[M+H]^+$: 220.1121, found: 220.1121.

Synthesis of Substrates Bearing Different Protecting Groups

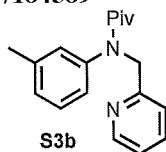


S3a-3i were synthesized following a similar procedure to make substrate **1**. The protected amines were prepared as previously described. [Pialat et al., *Org. Lett.* **15**:1764-1767 (2013); Brasche et al., *Org. Lett.* **10**:2207-2210 (2008); Wipf et al., *Org. Lett.* **10**:4383-4386 (2008); Imanishi et al., *Adv. Synth. Catal.* **354**:771-776 (2012); Gawande et al., *Green Chem.* **13**:3355-3359 (2011); Johnson et al., *J. Org. Chem.* **68**:5300-5309 (2003); and Le Pera et al., *Tetrahedron* **62**:100-6106 (2006).]

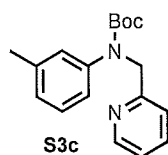


N-(Pyridin-2-ylmethyl)-N-(m-tolyl)acetamide (S3a)

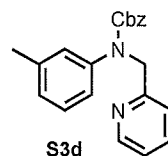
Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 4.9 Hz, 1H), 7.64 (td, J = 7.7, 1.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.14 (dd, J = 7.5, 5.0 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.92 (d, J = 7.9 Hz, 1H), 5.02 (s, 2H), 2.31 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.69, 157.40, 149.02, 143.16, 139.55, 136.44, 129.22, 128.59, 128.31, 124.85, 122.40, 122.03, 54.87, 22.57, 21.20; HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1335, found: 241.1335.

**N-(Pyridin-2-ylmethyl)-N-(m-tolyl)pivalamide (S3b)**

Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.46 (d, J = 4.8 Hz, 1H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.21 – 7.05 (m, 3H), 6.99 (s, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.95 (s, 2H), 2.30 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.81, 157.95, 148.84, 143.71, 138.86, 136.35, 130.05, 128.62, 128.59, 126.50, 122.23, 121.82, 58.48, 40.96, 29.46, 21.17; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 283.1805, found: 283.1805.

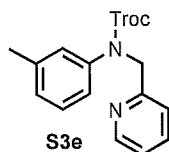
**tert-Butyl (pyridin-2-ylmethyl)(m-tolyl)carbamate (S3c)**

Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, J = 4.6 Hz, 1H), 7.66 (td, J = 7.7, 1.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.20–7.09 (m, 3H), 7.06 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 7.4 Hz, 1H), 4.96 (s, 2H), 2.30 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.73, 154.67, 149.09, 142.87, 138.39, 136.46, 128.35, 126.41, 126.36, 122.80, 121.79, 120.73, 80.59, 55.92, 28.17, 21.33; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 299.1754, found: 299.1754.

**Benzyl (pyridin-2-ylmethyl)(m-tolyl)carbamate (S3d)**

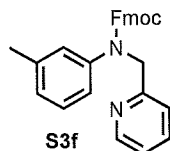
Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, J = 4.7 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.33–7.25 (m, 4H), 7.25–7.11 (m, 4H), 7.09 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 5.18 (s, 2H), 5.00 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 157.83, 155.60, 149.20,

142.14, 138.65, 136.52, 136.40, 128.57, 128.29, 127.80, 127.63, 127.18, 126.94, 123.26, 122.00, 121.25, 67.37, 56.10, 21.29; HRMS (ESI-TOF) m/z Calcd for $C_{21}H_{21}N_2O_2$ $[M+H]^+$: 333.1598, found: 333.1598.



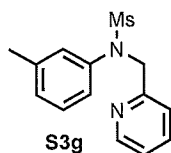
2,2,2-Trichloroethyl (pyridin-2-ylmethyl) (m-tolyl)-carbamate (S3e)

Colorless solid, 1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.8 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.25–7.06 (m, 4H), 7.03 (d, J = 7.5 Hz, 1H), 5.05 (s, 2H), 4.79 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.16, 154.02, 149.35, 142.16, 141.00, 138.78, 136.61, 128.65, 127.70, 126.36, 123.82, 122.24, 121.66, 95.39, 77.25, 77.04, 76.83, 75.20, 56.43, 21.30; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{16}Cl_3N_2O_2$ $[M+H]^+$: 373.0272, found: 373.0271.



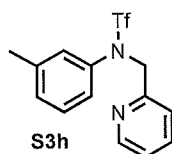
(9H-Fluoren-9-yl)methyl (pyridin-2-ylmethyl) (m-tolyl)-carbamate (S3f)

Light yellow solid, 1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.8 Hz, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.30–7.21 (m, 3H), 7.21–7.12 (m, 4H), 7.11–7.02 (d, J = 6.3 Hz, 2H), 6.99 (d, J = 6.9 Hz, 1H), 4.97 (s, 2H), 4.45 (d, J = 7.0 Hz, 2H), 4.10 (t, J = 7.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.65, 155.75, 149.23, 143.71, 141.89, 141.19, 138.84, 136.57, 128.73, 127.51, 126.86, 125.09, 124.26, 122.07, 121.54, 119.78, 67.60, 56.08, 47.11, 21.32; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{25}N_2O_2$ $[M+H]^+$: 421.1911, found: 421.1911.



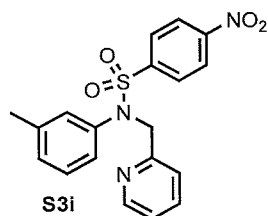
***N*-(Pyridin-2-ylmethyl)-*N*-(*m*-tolyl)methanesulfonamide (S3g)**

Light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 4.7 Hz, 1H), 7.64 (td, J = 7.7, 1.8 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.24–7.11 (m, 4H), 7.06 (d, J = 7.3 Hz, 1H), 5.01 (s, 2H), 3.04 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 156.70, 149.06, 139.37, 136.70, 129.07, 128.82, 128.75, 124.96, 122.46, 122.35, 56.53, 38.13, 21.28; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 277.1005, found: 277.1005.



1,1,1-Trifluoro-*N*-(pyridin-2-ylmethyl)-*N*-(*m*-tolyl)-methanesulfonamide (S3h)

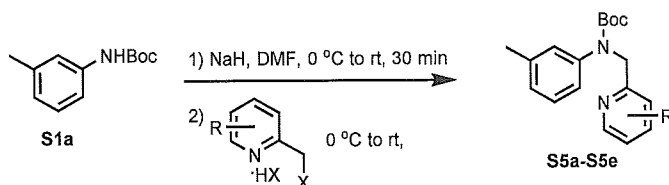
Yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, J = 4.8 Hz, 1H), 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.24–7.15 (m, 2H), 7.14–7.04 (m, 3H), 5.07 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 154.65, 149.38, 139.53, 136.84, 129.97, 129.42, 129.10, 125.91, 122.99, 122.61, 120.46 (q, J = 324.2 Hz), 58.52, 21.22; ^{19}F NMR (376 MHz, CDCl_3) δ -73.54; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 331.0723, found: 331.0723.



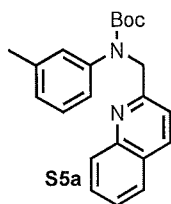
4-Nitro-*N*-(pyridin-2-ylmethyl)-*N*-(*m*-tolyl)benzenesulfonamide (S3i)

Light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, J = 4.7 Hz, 1H), 8.30 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.66 (td, J = 7.7, 1.7 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.17–7.09 (m, 2H), 7.06 (d, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.83 (d, J = 7.7 Hz, 1H), 4.93 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 155.77, 150.05, 149.06, 144.00, 139.35, 138.44, 136.76, 129.34, 129.22, 128.96, 125.09, 123.93, 122.62, 122.44, 56.87, 21.22; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 384.1013, found: 384.1013.

Synthesis of Substrates Bearing Different Directing Groups

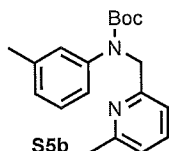


S5a-S5e were synthesized following a similar procedure to prepare substrate **1**.



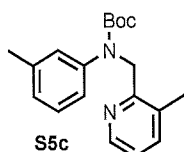
tert-Butyl (quinolin-2-ylmethyl) (m-tolyl)carbamate (**S5a**)

Light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.72–7.66 (m, 1H), 7.55–7.47 (m, 2H), 7.21–7.12 (m, 2H), 7.09 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 5.13 (s, 2H), 2.29 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.14, 154.91, 147.63, 142.84, 138.47, 136.63, 129.51, 128.97, 128.42, 127.53, 127.16, 126.62, 126.57, 126.09, 123.04, 118.88, 80.73, 56.48, 28.22, 21.37; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 349.1911, found: 349.1911.



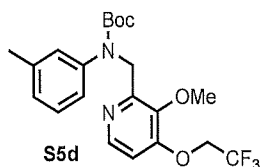
tert-Butyl ((quinolin-2-ylmethyl)(m-tolyl)carbamate (S5b)

Light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 7.55 (t, J = 7.7 Hz, 1H), 7.19–7.10 (m, 3H), 7.07 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 4.92 (s, 2H), 2.51 (s, 3H), 2.30 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 158.07, 157.70, 154.71, 142.95, 138.32, 136.68, 128.31, 126.36, 126.32, 122.76, 121.23, 117.34, 80.53, 55.96, 28.18, 24.34, 21.34; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 313.1911, found: 313.1911.



tert-Butyl ((3-methylpyridin-2-yl)methyl)(m-tolyl)-carbamate (S5c)

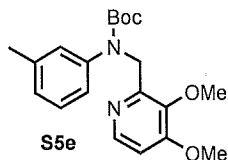
Light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.37 (d, J = 4.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.16 – 7.00 (m, 4H), 6.92 (d, J = 7.4 Hz, 1H), 4.93 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 155.32, 154.74, 146.51, 142.81, 138.05, 137.46, 130.61, 128.06, 126.85, 126.26, 123.39, 121.90, 80.10, 53.44, 28.16, 21.29, 18.00; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 313.1911, found: 313.1911.



tert-Butyl ((3-methoxy-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)(m-tolyl)carbamate (S5d)

Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, J = 5.6 Hz, 1H), 7.16–6.98 (m, 3H), 6.92 (d, J = 7.4 Hz, 1H), 6.59

(d, $J = 5.6$ Hz, 1H), 4.93 (s, 2H), 4.37 (q, $J = 7.9$ Hz, 2H), 2.27 (s, 3H), 2.20 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 161.13, 157.09, 154.73, 147.71, 142.75, 138.09, 128.08, 126.81, 126.30, 123.38, 122.98 (q, $J = 278.34$ Hz), 119.92, 105.10, 80.21, 65.31 (q, $J = 36.2$ Hz), 53.37, 28.18, 21.30, 9.64; ^{19}F NMR (376 MHz, CDCl_3) δ -74.21; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 411.1890, found: 411.1890.

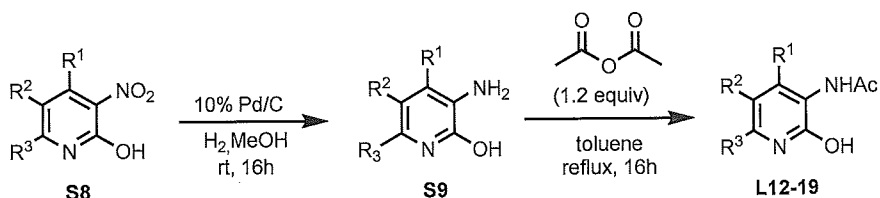


tert-Butyl ((3,4-dimethoxypyridin-2-yl)methyl) (m-tolyl)-carbamate (S5e)

Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.21 (d, $J = 5.5$ Hz, 1H), 7.19–7.03 (m, 3H), 6.91 (d, $J = 7.0$ Hz, 1H), 6.74 (d, $J = 5.5$ Hz, 1H), 4.97 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 2.28 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 157.99, 154.90, 151.47, 145.59, 143.22, 142.90, 138.01, 128.04, 126.85, 126.11, 123.41, 106.49, 79.97, 60.41, 55.54, 50.72, 28.24, 21.33; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 359.1965, found: 359.1964.

Synthesis of MPAHP Ligands

Ligands **L12-19** were synthesized from commercially available amines **S9**. In cases where the amines were not commercially available, the free amines **S9** were synthesized by the reduction of the nitro group.



Reduction: In a 100 mL round bottom flask, **S8** (10.0 mmol), 10% Pd/C (1.0 mmol) were added and the flask was sealed with a rubber stopper. Next, 50 mL methanol was added under nitrogen. The nitrogen was removed and the flask

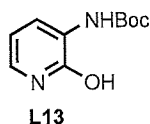
was back filled with hydrogen three times. Then a hydrogen balloon was left on the flask and the reaction mixture was stirred for 16 hours at room temperature. After the 16 hours, the reaction mixture was filtered through a pad of Celite® and the solvent was evaporated to obtain the pure amino product in quantitative yields.

Acetyl protection: In a 50 mL round bottom flask, **S9** (8.0 mmol), acetic anhydride (9.6 mmol) and 20 mL toluene were added and the reaction mixture was refluxed for 16 hours. The solvent was removed and the residue was washed with diethyl ether (5.0 mL) twice to remove impurities. The left over residue was recrystallized with methanol to obtain the product.



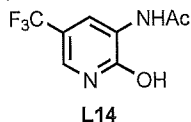
N-(2-Hydroxypyridin-3-yl)acetamide (L12)

Black solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.89 (s, 1H), 9.18 (s, 1H), 8.20 (dd, J = 7.4, 1.8 Hz, 1H), 7.06 (dd, J = 6.6, 1.9 Hz, 1H), 6.18 (t, J = 6.9 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 169.30, 157.25, 129.45, 127.53, 123.25, 105.20, 24.00; HRMS (ESI-TOF) m/z Calcd for $\text{C}_7\text{H}_9\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 153.0659, found: 153.0659.



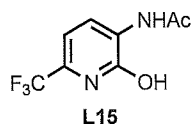
tert-Butyl (2-hydroxypyridin-3-yl)carbamate (L13)

Beige solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.91 (s, 1H), 7.79 (dd, J = 7.1, 2.0 Hz, 1H), 7.68 (s, 1H), 7.03 (dd, J = 6.6, 1.8 Hz, 1H), 6.21 (t, J = 6.9 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 157.01, 152.11, 129.01, 126.59, 120.66, 105.35, 80.01, 27.88; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 211.1077, found: 211.1077.



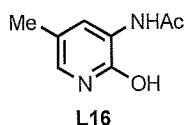
***N*-(2-Hydroxy-5-(trifluoromethyl)pyridin-3-yl)acetamide
(L14)**

Beige solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.51 (s, 1H), 9.55 (s, 1H), 8.41 (d, $J = 2.6$ Hz, 1H), 7.69–7.61 (m, 1H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 170.23, 157.16, 130.11, 127.64 (q, $J = 4.7$ Hz), 123.86 (q, $J = 269.5$ Hz), 116.81, 107.23 (q, $J = 34.1$ Hz), 24.00; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -60.60; HRMS (ESI-TOF) m/z Calcd for $\text{C}_8\text{H}_8\text{F}_3\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 221.0532, found: 221.0532.



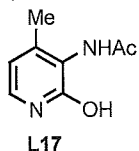
***N*-(2-Hydroxy-6-(trifluoromethyl)pyridin-3-yl)acetamide
(L15)**

Beige solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.54 (s, 1H), 8.46 (d, $J = 7.9$ Hz, 1H), 7.13 (d, $J = 7.9$ Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 169.98, 155.31, 132.92, 127.74, 124.99, 121.16 (q, $J = 272.7$ Hz), 110.60, 23.99; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -65.22; HRMS (ESI-TOF) m/z Calcd for $\text{C}_8\text{H}_8\text{F}_3\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 221.0532, found: 221.0532.

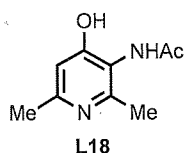


***N*-(2-Hydroxy-5-methylpyridin-3-yl)acetamide (L16)**

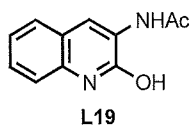
Colorless solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.68 (s, 1H), 9.15 (s, 1H), 8.11 (d, $J = 2.4$ Hz, 1H), 6.85 (dd, $J = 2.3$, 1.2 Hz, 1H), 2.10 (s, 3H), 2.01 (d, $J = 1.1$ Hz, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 169.27, 156.32, 128.89, 125.50, 124.50, 113.60, 24.03, 17.10; HRMS (ESI-TOF) m/z Calcd for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 167.0815, found: 167.0815.

**N-(2-Hydroxy-4-methylpyridin-3-yl)acetamide (L17)**

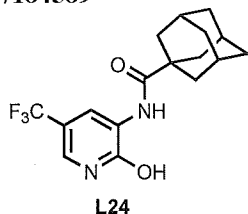
Colorless solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.60 (s, 1H), 9.08 (s, 1H), 7.16 (d, $J = 6.7$ Hz, 1H), 6.06 (d, $J = 6.7$ Hz, 1H), 1.99 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 167.97, 159.90, 145.60, 130.99, 125.64, 107.86, 22.75, 18.49; HRMS (ESI-TOF) m/z Calcd for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 167.0815, found: 167.0815.

**N-(4-Hydroxy-2,6-dimethylpyridin-3-yl)acetamide (L18)**

Colorless solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.12 (s, 1H), 8.84 (s, 1H), 5.91 (s, 1H), 2.17 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 174.23, 168.04, 145.41, 142.63, 122.97, 113.63, 22.77, 18.35, 16.19; HRMS (ESI-TOF) m/z Calcd for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 181.0972, found: 181.0972.

**N-(2-Hydroxyquinolin-3-yl)acetamide (L19)**

Beige solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.22 (s, 1H), 9.43 (s, 1H), 8.63 (s, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.43–7.35 (m, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.17 (t, $J = 7.5$ Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 169.70, 157.43, 134.32, 128.76, 128.10, 127.25, 122.41, 120.49, 119.72, 114.87, 24.11; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 203.0815, found: 203.0815.

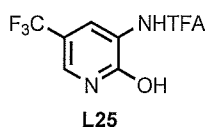


To a solution of amine (2.0 mmol) and 1-adamantanecarbonyl chloride (437.1 mg, 2.2 mmol) in DCM (10.0 mL) was added triethylamine (0.56 mL, 4.0 mmol) at 0 °C.

The mixture was allowed to warm to room temperature and stirred at room temperature. After the reaction was completed, the solvent was removed under vacuum and the resulting residue was then purified by silica gel chromatography to afford **L24** as a colorless solid.

(3r,5r,7r)-N-(2-Hydroxy-5-(trifluoromethyl)pyridin-3-yl)adamantane-1-carboxamide (L24)

Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 12.80 (brs, 1H), 8.76 (d, J = 2.4 Hz, 1H), 8.56 (s, 1H), 7.50 (s, 1H), 2.13 (s, 3H), 2.07–1.90 (m, 6H), 1.84–1.69 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.36, 159.30, 129.79, 125.78, 125.32, 125.28, 125.24, 125.20, 123.99, 122.20, 120.41, 119.15, 112.65, 112.41, 112.18, 111.95, 42.05, 39.10, 38.74, 36.43, 36.32, 28.00, 27.86; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 341.1471, found: 341.1474.

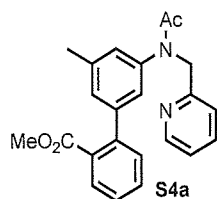


2,2,2-Trifluoro-N-(2-hydroxy-5-(trifluoromethyl)pyridin-3-yl)acetamide (L25)

Colorless solid, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.66 (brs, 2H), 8.12 (d, J = 2.6 Hz, 1H), 7.98–7.88 (m, 1H); ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 157.45, 155.22 (q, J = 37.5 Hz), 132.36 (q, J = 5.3 Hz), 126.82, 124.67 (q, J = 3.0 Hz), 123.52 (q, J = 269.6 Hz), 115.37 (q, J = 286.2 Hz), 106.75 (q, J = 34.5 Hz); HRMS (ESI-TOF) m/z Calcd for $\text{C}_8\text{H}_5\text{F}_6\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 275.0250, found: 275.0250.

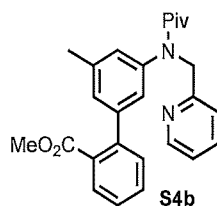
Condition Screening

Ligand screened



Methyl 3'-methyl-5'-(N-(pyridin-2-ylmethyl)acetamido)-[1,1'-biphenyl]-2-carboxylate (S4a)

Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.50 (d, J = 4.8 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 6.9 Hz, 2H), 7.26 (d, J = 6.9 Hz, 1H), 7.20–7.13 (m, 1H), 7.07 (s, 1H), 6.98 (s, 1H), 6.90 (s, 1H), 5.05 (s, 2H), 3.60 (s, 3H), 2.36 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.85, 168.42, 157.30, 148.81, 142.85, 142.64, 141.45, 139.37, 136.77, 131.33, 130.56, 130.50, 129.91, 128.59, 127.47, 127.03, 125.32, 122.39, 122.14, 54.85, 51.94, 22.64, 21.29; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 375.1703, found: 375.1703.

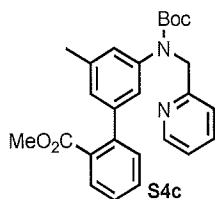


Methyl 3'-methyl-5'-(N-(pyridin-2-ylmethyl)pivalamido)-[1,1'-biphenyl]-2-carboxylate (S4b)

Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, J = 4.4 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.66 (td, J = 7.8, 1.8 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.43–7.37 (m, 2H), 7.21–7.11 (m, 2H), 7.04–6.98 (m, 2H), 6.92 (s, 1H), 4.98 (s, 2H), 3.56 (s, 3H), 2.34 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.91, 168.61, 157.94, 148.84, 143.60, 142.35, 141.50, 138.56, 136.59, 131.27, 130.63, 130.53, 129.88, 128.84, 128.73, 127.43, 126.57, 122.25, 121.94,

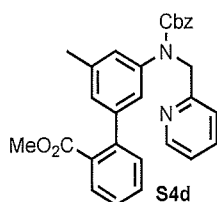
58.58, 51.89, 41.09, 29.60, 21.26; HRMS (ESI-TOF) m/z

Calcd for $C_{26}H_{29}N_2O_3$ $[M+H]^+$: 417.2173, found: 417.2172.



Methyl 3'-((tert-butoxycarbonyl)(pyridin-2-ylmethyl)-amino)-5'-methyl-[1,1'-biphenyl]-2-carboxylate (S4c)

Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.8 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.41-7.35 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.22-7.15 (m, 1H), 7.11 (s, 1H), 7.06 (s, 1H), 6.93 (s, 1H), 4.99 (s, 2H), 3.57 (s, 3H), 2.34 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.09, 158.62, 154.60, 148.87, 142.66, 141.80, 141.58, 138.13, 136.77, 131.10, 130.92, 130.55, 129.61, 127.14, 126.53, 125.36, 123.13, 121.90, 120.81, 80.68, 55.92, 51.89, 28.18, 21.38; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{29}N_2O_4$ $[M+H]^+$: 433.2122, found: 433.2122.

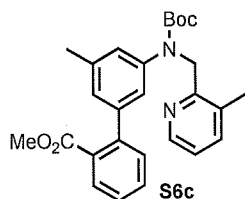


Methyl 3'-((benzyloxy)carbonyl)(pyridin-2-ylmethyl)-amino)-5'-methyl-[1,1'-biphenyl]-2-carboxylate (S4d)

Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.9 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.35-7.18 (m, 7H), 7.18-7.12 (m, 1H), 7.09 (s, 1H), 7.05 (s, 1H), 6.96 (s, 1H), 5.18 (s, 2H), 5.03 (s, 2H), 3.50 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.02, 157.82, 155.59, 149.25, 141.97, 141.81, 141.65, 138.36, 136.61, 136.35, 131.15, 131.13, 130.87, 130.56, 129.68, 128.32, 127.85, 127.68, 127.23, 127.19, 125.72,

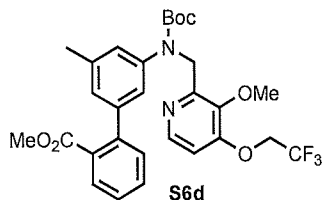
123.60, 122.05, 121.22, 67.47, 56.19, 51.87, 21.36; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{27}N_2O_4$ $[M+H]^+$: 467.1965, found: 467.1965.

Directing group



Methyl 3'-((tert-butoxycarbonyl)((3-methylpyridin-2-yl)-methyl)amino)-5'-methyl-[1,1'-biphenyl]-2-carboxylate (S6c)

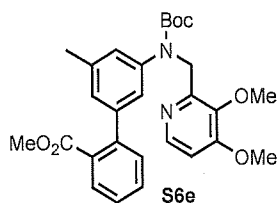
Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 4.4 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.1 Hz, 1H), 7.42-7.33 (m, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 7.10-7.03 (m, 2H), 6.89 (s, 1H), 4.93 (s, 2H), 3.57 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.26, 155.35, 154.68, 146.58, 142.78, 141.97, 141.19, 137.69, 137.45, 131.02, 130.93, 130.56, 129.53, 126.98, 126.33, 125.88, 123.55, 121.90, 80.12, 53.50, 51.81, 28.18, 21.34, 18.03; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{31}N_2O_4$ $[M+H]^+$: 447.2278, found: 447.2278.



Methyl 3'-((tert-butoxycarbonyl)((3-methoxy-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)amino)-5'-methyl-[1,1'-biphenyl]-2-carboxylate (S6d)

Colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 6.89 (s, 1H), 6.60 (d, J = 5.6 Hz, 1H), 4.94 (s, 2H), 4.37 (q, J = 7.9 Hz, 2H),

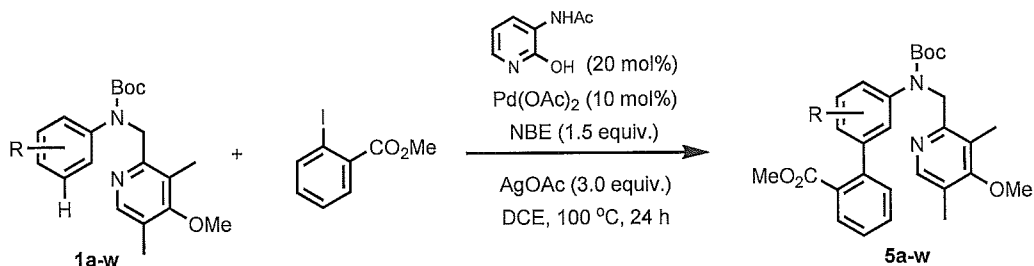
3.59 (s, 3H), 2.32 (s, 3H), 2.20 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.22, 161.11, 157.10, 154.67, 147.78, 142.73, 141.97, 141.18, 137.70, 131.04, 130.91, 130.55, 129.55, 127.00, 126.34, 125.83, 123.49, 122.99 (q, $J = 277.9$ Hz), 119.77, 105.10, 80.19, 65.33 (q, $J = 36.3$ Hz), 53.41, 51.81, 28.19, 21.34, 9.64; ^{19}F NMR (376 MHz, CDCl_3) δ -74.20; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{32}\text{F}_3\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 545.2258, found: 545.2258.



Methyl 3'-((tert-butoxycarbonyl)((3,4-dimethoxypyridin-2-yl)methyl)amino)-5'-methyl-[1,1'-biphenyl]-2-carboxylate (S6e)

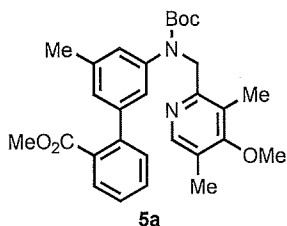
Colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.23 (d, $J = 5.5$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.40–7.28 (m, 2H), 7.14 (s, 1H), 7.11 (s, 1H), 6.89 (s, 1H), 6.75 (d, $J = 5.5$ Hz, 1H), 4.98 (s, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 2.32 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.31, 157.99, 154.82, 151.39, 145.57, 143.14, 142.81, 141.99, 141.15, 137.65, 131.01, 131.00, 130.94, 130.58, 129.52, 126.94, 126.21, 125.89, 123.52, 106.51, 80.00, 60.40, 55.55, 51.84, 50.86, 28.22, 21.35; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 493.2333, found: 493.2332.

Meta-Arylation of Anilines



General Procedure for meta-Arylation of Anilines:

Substrate **1** (0.1 mmol), Ar-I (0.2 mmol), Pd(OAc)₂ (2.2 mg, 10 mol%), **L12** (3.0 mg, 20 mol%), AgOAc (50.1 mg, 0.3 mmol), 2-Norbornene (14.1 mg, 0.15 mmol) or NBE-CO₂Me (21.6 mg, 0.15 mmol) and DCE (0.5 mL) were added to a 2 dram vial. The vial was capped and closed tightly. Then the reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulted solution was concentrated and purified by preparative TLC to afford the desired arylated product. (*In cases where mono:di ratios are possible, the selectivity was determined by ¹H NMR.*)

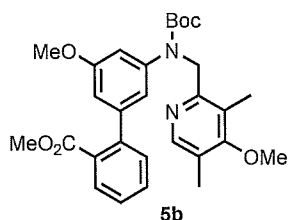


Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-methyl-[1,1'-biphenyl]-2-carboxylate (5a**)**

Substrate **1a** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5a** was obtained in 98% yield as a light yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 9.1 Hz, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 4.90 (s, 2H), 3.71 (s, 3H), 3.57 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 1.38 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 169.24, 163.59, 155.18, 154.67, 148.91, 142.61, 141.97, 141.13, 137.63, 131.00, 130.92, 130.54, 129.52, 126.97, 126.33, 125.93, 124.54, 123.64, 123.57, 80.09, 59.79, 53.54, 51.77, 28.22, 21.33, 13.16,

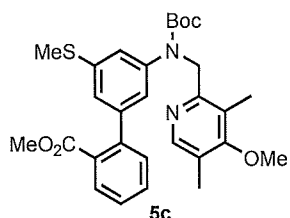
10.38; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_5$ $[M+H]^+$:

491.2540, found: 491.2540.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-methoxy-[1,1'-biphenyl]-2-carboxylate (5b)

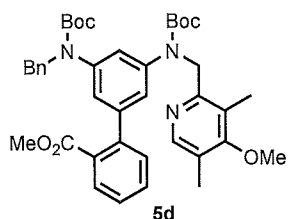
Substrate **1b** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5b** was obtained in 97% yield as a colorless liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.75 (dd, J = 7.7, 1.5 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.37 (td, J = 7.6, 1.4 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 6.86 (s, 1H), 6.83 (s, 1H), 6.62 (t, J = 1.9 Hz, 1H), 4.91 (s, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 3.59 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.10, 163.62, 159.09, 155.01, 154.56, 148.91, 143.74, 142.09, 141.80, 131.00, 130.45, 129.49, 127.15, 124.58, 123.60, 119.21, 111.54, 111.26, 80.23, 59.79, 55.31, 53.46, 51.85, 28.23, 13.14, 10.36; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_6$ $[M+H]^+$: 507.2490, found: 507.2490.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-(methylthio)-[1,1'-biphenyl]-2-carboxylate (5c)

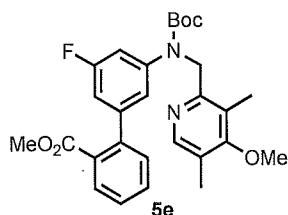
Substrate **1c** was arylated following the general *meta*-arylation procedure using 2-norbornene. After

purification by preparative thin-layer chromatography, Compound **5c** was obtained in 73% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.18 (s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 4.90 (s, 2H), 3.72 (s, 3H), 3.59 (s, 3H), 2.42 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.98, 163.62, 154.91, 154.50, 148.96, 143.14, 141.75, 141.41, 137.98, 131.14, 130.87, 130.50, 129.66, 127.31, 124.65, 123.64, 123.53, 80.36, 59.83, 53.37, 51.88, 28.23, 15.90, 13.17, 10.38; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 523.2261, found: 523.2261.



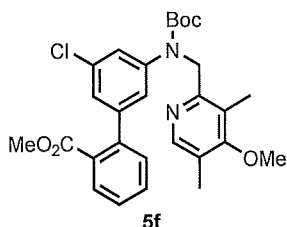
Methyl 3'-(benzyl(tert-butoxycarbonyl)amino)-5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl)amino)-[1,1'-biphenyl]-2-carboxylate (5d**)**

Substrate **1d** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5d** was obtained in 89% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.11 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.30-7.15 (m, 6H), 7.11 (s, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 4.84 (s, 2H), 4.78 (s, 2H), 3.70 (s, 3H), 3.49 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H), 1.37 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.82, 163.59, 154.82, 154.49, 154.47, 148.94, 142.97, 142.38, 141.48, 141.42, 138.51, 131.07, 130.84, 130.55, 129.65, 128.26, 127.27, 127.20, 126.91, 124.55, 124.08, 123.91, 123.46, 123.16, 80.41, 80.26, 59.80, 53.94, 53.38, 51.75, 28.21,

28.18, 13.15, 10.32; HRMS (ESI-TOF) m/z Calcd for $C_{40}H_{48}N_3O_7$ [M+H]⁺: 682.3487, found: 682.3486.

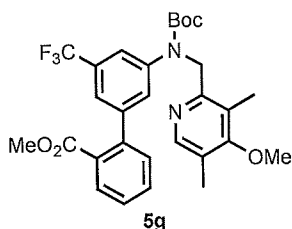
Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-fluoro-[1,1'-biphenyl]-2-carboxylate (5e)

Substrate **1e** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5e** was obtained in 94% yield as a colorless solid. mp = 97 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.80 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.50 (td, *J* = 7.6, 1.5 Hz, 1H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.11-7.00 (m, 2H), 6.83-6.75 (m, 1H), 4.89 (s, 2H), 3.73 (s, 3H), 3.62 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 168.59, 163.64, 161.86 (d, *J* = 244.6 Hz), 154.63, 154.28, 149.03, 144.18 (d, *J* = 10.2 Hz), 142.71 (d, *J* = 9.7 Hz), 140.98 (d, *J* = 1.8 Hz), 131.28, 130.65, 130.50, 129.83, 127.56, 124.72, 123.39, 122.00, 112.39 (d, *J* = 22.4 Hz), 80.65, 59.84, 53.29, 51.92, 28.17, 13.18, 10.32; ¹⁹F NMR (376 MHz, CDCl₃) δ -114.11; HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{32}FN_2O_5$ [M+H]⁺: 495.2290, found: 495.2289.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-chloro-[1,1'-biphenyl]-2-carboxylate (5f)

Substrate **1f** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5f** was obtained in 92% yield as a colorless solid. mp = 98 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.36-7.28 (m, 2H), 7.18 (s, 1H), 7.05 (s, 1H), 5.01 (s, 2H), 3.78 (s, 3H), 3.63 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H), 1.40 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 168.38, 165.08, 154.14, 153.64, 147.26, 143.18, 142.84, 140.70, 133.18, 131.43, 130.64, 130.42, 129.95, 127.68, 125.79, 125.55, 125.31, 124.82, 81.08, 60.11, 52.20, 51.92, 28.16, 28.13, 13.43, 10.58; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₂ClN₂O₅ [M+H]⁺: 511.1994, found: 511.1994.

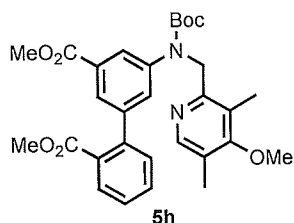


Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (5g**)**

Substrate **1g** was arylated following the general *meta*-arylation procedure using NBE-CO₂Me. After purification by preparative thin-layer chromatography, Compound **5g** was obtained in 94% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.48 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.35-7.28 (m, 2H), 4.93 (s, 2H), 3.72 (s, 3H), 3.59 (s, 3H), 2.21 (s, 6H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 168.40, 163.70, 154.52, 154.22, 149.07, 143.32, 142.18, 140.70, 131.48, 130.63, 130.57, 130.18 (q, *J* = 32.5 Hz), 130.12, 129.39, 127.81, 124.82, 123.85 (q, *J* = 272.8 Hz), 123.47, 122.18, 122.07 (q, *J* = 3.8 Hz), 80.87, 59.84, 53.13, 51.85, 28.15, 13.18, 10.36; ¹⁹F NMR

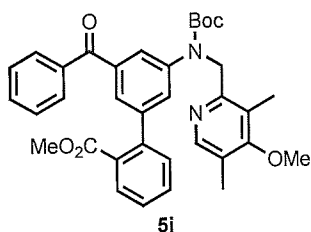
(376 MHz, CDCl₃) δ -62.70; HRMS (ESI-TOF) m/z Calcd for

C₂₉H₃₂F₃N₂O₅ [M+H]⁺: 545.2258, found: 545.2259.



Dimethyl 5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-[1,1'-biphenyl]-2,3'-dicarboxylate (5h)

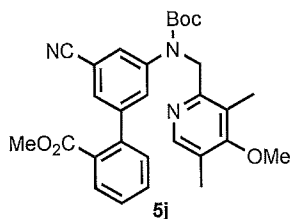
Substrate **1h** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5h** was obtained in 94% yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 7.95 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.75 (s, 1H), 7.56–7.45 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 4.93 (s, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 3.58 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 168.41, 166.57, 163.67, 154.70, 154.38, 149.00, 142.92, 141.68, 141.21, 131.37, 130.99, 130.71, 130.43, 130.01, 127.54, 126.56, 126.36, 124.71, 123.54, 80.60, 59.81, 53.18, 52.10, 51.83, 28.16, 13.16, 10.38; HRMS (ESI-TOF) m/z Calcd for C₃₀H₃₅N₂O₇ [M+H]⁺: 535.2439, found: 535.2439.



Methyl 3'-benzoyl-5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-[1,1'-biphenyl]-2-carboxylate (5i)

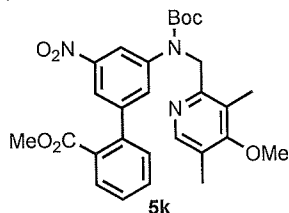
Substrate **1i** was arylated following the general *meta*-arylation procedure using 2-norbornene. After

purification by preparative thin-layer chromatography, Compound **5i** was obtained in 93% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.70 (s, 1H), 7.61–7.37 (m, 7H), 7.33 (d, J = 7.6 Hz, 1H), 4.95 (s, 2H), 3.71 (s, 3H), 3.63 (s, 3H), 2.21 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 195.85, 168.29, 163.68, 154.67, 154.43, 148.98, 142.87, 141.50, 141.26, 137.35, 137.33, 132.36, 131.42, 130.82, 130.48, 130.41, 130.05, 130.02, 128.18, 127.56, 127.13, 126.67, 124.71, 123.52, 80.63, 59.83, 53.20, 51.89, 28.19, 13.18, 10.37; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{35}\text{H}_{37}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 581.2646, found: 581.2646.



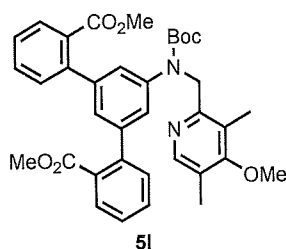
Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-cyano-[1,1'-biphenyl]-2-carboxylate (5j)

Substrate **1j** was arylated following the general *meta*-arylation procedure using NBE- CO_2Me . After purification by preparative thin-layer chromatography, Compound **5j** was obtained in 93% yield as a colorless solid. mp = 106 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.62 (s, 1H), 7.60–7.50 (m, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.33 (s, 1H), 7.28 (d, J = 9.0 Hz, 1H), 4.88 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.80, 163.70, 154.19, 154.05, 149.12, 143.79, 142.73, 140.27, 131.68, 130.88, 130.67, 130.31, 130.10, 128.52, 128.08, 124.90, 123.22, 118.55, 111.81, 81.11, 59.88, 53.00, 51.99, 28.10, 13.20, 10.28; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 502.2336, found: 502.2336.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-nitro-[1,1'-biphenyl]-2-carboxylate (5k)

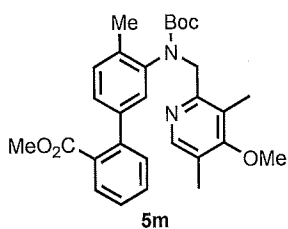
Substrate **1k** was arylated following the general *meta*-arylation procedure using NBE-CO₂Me. After purification by preparative thin-layer chromatography, Compound **5k** was obtained in 89% yield as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (q, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 7.96-7.88 (m, 2H), 7.67 (s, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 4.93 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 2.23 (s, 6H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 167.74, 163.75, 154.21, 154.02, 149.15, 147.71, 143.89, 142.56, 140.27, 132.22, 131.76, 130.75, 130.40, 130.08, 128.19, 124.93, 123.33, 119.80, 81.27, 59.90, 52.96, 52.02, 28.11, 13.22, 10.34; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₂N₃O₇ [M+H]⁺: 522.2235, found: 522.2235.



Dimethyl 5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (5l)

Substrate **1l** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ¹H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* < 20:1). After purification by preparative thin-layer chromatography, Compound **5l** was

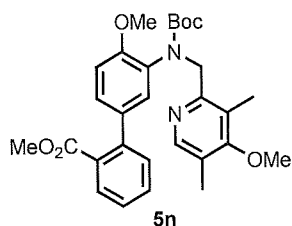
obtained in 92% yield as a light yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.78 (dd, $J = 7.7, 1.4$ Hz, 2H), 7.49 (td, $J = 7.5, 1.5$ Hz, 2H), 7.38 (td, $J = 7.6, 1.3$ Hz, 2H), 7.34 (s, 1H), 7.32 (s, 1H), 7.29–7.21 (m, 2H), 7.01 (t, $J = 1.7$ Hz, 1H), 4.93 (s, 2H), 3.70 (s, 3H), 3.61 (s, 6H), 2.21 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.99, 163.58, 155.04, 154.55, 148.94, 142.56, 141.68, 141.13, 131.09, 130.93, 130.64, 129.68, 127.17, 125.60, 125.36, 124.58, 123.52, 80.18, 59.79, 53.50, 51.84, 28.21, 13.15, 10.37; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{36}\text{H}_{39}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 611.2752, found: 611.2754.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4'-methyl-[1,1'-biphenyl]-2-carboxylate (5m)

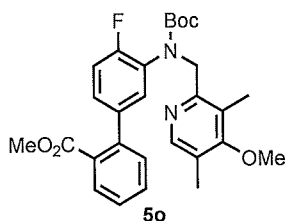
Substrate **1m** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5m** was obtained in 81% yield as a colorless liquid. Rotameric mixture, ratio of the rotamers = 70/30; ^1H NMR (400 MHz, CDCl_3) δ 8.11 (s, 1H), 7.73 (d, $J = 7.7$ Hz, 1H), 7.44 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.6$ Hz, 1H), 7.31–6.98 (m, 3.3H), 6.86 (s, 0.7H), 5.26 (d, $J = 14.9$ Hz, 0.7H), 5.18–5.04 (m, 0.3H), 4.51 (d, $J = 14.7$ Hz, 1H), 3.66 (s, 3H), 3.55 (s, 3H), 2.33–2.12 (m, 9H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture, resonances for the minor rotamer are enclosed in parenthesis (): δ 169.20 (169.50), 163.76 (163.54), 155.07 (155.34), 154.75 (154.09), 148.88, 141.49 (141.25), 140.41, 139.11, 134.90 (135.29), 130.95, 130.86, 130.47, 130.27, 129.89, 129.59, 128.31, 126.87, 124.95 (124.65), 123.71, 79.77 (79.90), 59.69, 52.52 (53.54), 51.72

(51.84), 28.22, 17.31 (17.52), 13.13, 10.61; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_5$ $[M+H]^+$: 491.2540, found: 491.2540.



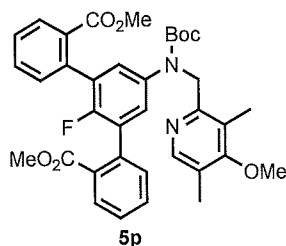
Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (5n)

Substrate **1n** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5n** was obtained in 84% yield as a colorless liquid. Rotameric mixture, ratio of the rotamers = 75/25; 1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.26-6.76 (m, 4H), 5.33 (s, 0.75H), 4.91-4.30 (m, 1.25H), 3.83 (s, 3H), 3.67 (s, 3H), 3.55 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H), 1.49-1.30 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) rotameric mixture: δ 169.56, 169.35, 163.76, 163.59, 155.70, 155.53, 155.24, 154.82, 154.49, 148.62, 141.28, 133.15, 132.99, 130.88, 130.85, 130.63, 130.45, 130.38, 129.53, 127.78, 127.71, 126.68, 126.62, 125.28, 124.84, 124.56, 124.19, 111.22, 110.42, 79.98, 79.51, 59.70, 55.72, 55.31, 53.50, 52.50, 51.86, 51.70, 28.19, 13.11, 10.58; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_6$ $[M+H]^+$: 507.2490, found: 507.2491.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4'-fluoro-[1,1'-biphenyl]-2-carboxylate (5o)

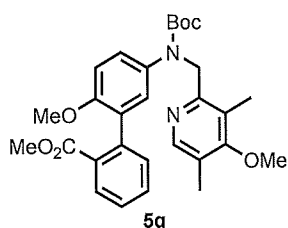
Substrate **1o** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5o** was obtained in 90% yield as a colorless liquid. Rotameric mixture, ratio of the rotamers = 75/25; ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.77 (dd, J = 7.7, 1.4 Hz, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 7.37 (t, J = 7.3 Hz, 1H), 7.25-6.91 (m, 4H), 4.94 (s, 2H), 3.70 (s, 3H), 3.56 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.85, 163.77, 157.50 (d, J = 249.6 Hz), 154.68, 154.23, 148.77, 140.84, 137.07 (d, J = 3.7 Hz), 131.16, 130.73, 130.55, 129.80, 129.50, 129.36, 129.28, 127.78 (d, J = 7.8 Hz), 127.24, 124.96, 115.06 (d, J = 21.6 Hz), 80.50, 59.74, 52.70, 51.74, 28.07, 13.14, 10.48; ^{19}F NMR (376 MHz, CDCl_3) for major isomer: δ -123.17; ^{19}F NMR (376 MHz, CDCl_3) for minor isomer: δ -122.57; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{32}\text{FN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 495.2290, found: 495.2291.



Dimethyl 5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-2'-fluoro-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (5p)

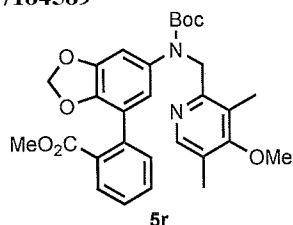
Substrate **1p** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of the crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* < 20:1). After purification by preparative thin-layer chromatography, Compound **5p** was obtained in 90% yield as a light yellow

solid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.91 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.18 (s, 2H), 4.95 (s, 2H), 3.70 (s, 3H), 3.64 (s, 6H), 2.21 (s, 6H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.79, 163.69, 154.99, 154.58, 153.56 (d, J = 244.3 Hz), 148.91, 138.04, 136.02, 131.52, 131.42, 130.96, 130.01, 128.54 (d, J = 18.4 Hz), 127.98, 127.80, 124.74, 123.92, 80.29, 59.78, 53.54, 51.87, 28.24, 13.16, 10.44; ^{19}F NMR (376 MHz, CDCl_3) δ -123.88; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{36}\text{H}_{38}\text{FN}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 629.2658, found: 629.2657.



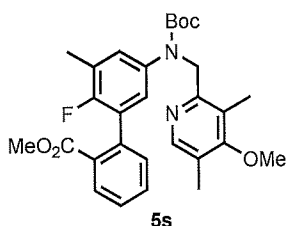
Methyl 5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-2'-methoxy-[1,1'-biphenyl]-2-carboxylate (5q)

Substrate **1q** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* > 20:1). After purification by preparative thin-layer chromatography, Compound **5q** was obtained in 64% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.16 (brs, 2H), 7.01 (s, 1H), 6.73 (d, J = 8.7 Hz, 1H), 4.93 (brs, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 3.56 (s, 3H), 2.30-2.10 (m, 6H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.60, 163.75, 155.29, 154.99, 153.89, 148.84, 138.17, 135.35, 131.60, 131.49, 131.20, 130.30, 129.32, 128.85, 127.12, 126.88, 124.74, 124.39, 109.71, 80.03, 59.79, 55.35, 53.66, 51.48, 28.30, 13.17, 10.51; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 507.2490, found: 507.2491.



Methyl 2-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)benzo[d][1,3]dioxol-4-yl)benzoate (5r)

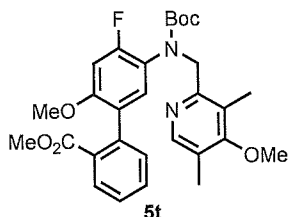
Substrate **1r** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5r** was obtained in 83% yield as a light yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 6.81 (s, 1H), 6.68 (s, 1H), 5.87 (s, 2H), 4.88 (s, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.36, 163.70, 155.02, 154.92, 148.85, 146.61, 142.64, 136.74, 135.93, 131.57, 130.88, 130.76, 130.06, 127.66, 124.71, 123.99, 121.88, 120.87, 107.96, 101.15, 80.15, 59.79, 53.76, 51.89, 28.24, 13.16, 10.41; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 521.2282, found: 521.2283.



Methyl 5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-2'-fluoro-3'-methyl-[1,1'-biphenyl]-2-carboxylate (5s)

Substrate **1s** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5s** was obtained in 94% yield as a light yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.92 (d, J

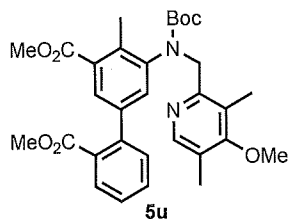
= 7.7 Hz, 1H), 7.52 (td, J = 7.6, 1.4 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.10 (s, 1H), 6.96 (s, 1H), 4.90 (s, 2H), 3.71 (s, 3H), 3.63 (s, 3H), 2.21 (d, J = 2.3 Hz, 9H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.87, 163.69, 155.58 (d, J = 243.2 Hz), 155.03, 154.69, 148.85, 137.86, 136.35, 131.58, 131.32, 130.77, 129.96, 128.67 (d, J = 5.1 Hz), 128.35 (d, J = 18.1 Hz), 127.66, 126.39, 124.71, 124.08 (d, J = 19.5 Hz), 123.89, 80.20, 59.78, 53.57, 51.74, 28.22, 14.66 (d, J = 4.0 Hz), 13.15, 10.41; ^{19}F NMR (376 MHz, CDCl_3) δ -124.82; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{34}\text{FN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 509.2446, found: 509.2447.



Methyl 5'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4'-fluoro-2'-methoxy-[1,1'-biphenyl]-2-carboxylate (5t)

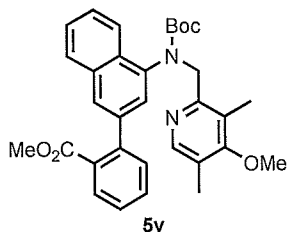
Substrate **1t** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5t** was obtained in 92% yield as a colorless solid. Rotameric mixture, ratio of the rotamers = 76/24; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.14 (s, 0.48H), 6.99 (s, 0.76H), 6.83 (s, 0.76H), 6.54 (d, J = 11.7 Hz, 1H), 5.30-4.60 (m, 2H), 3.68 (s, 3H), 3.64 (s, 3H), 3.56 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture: δ 168.42, 163.89, 163.80, 158.89, 157.23, 155.41, 155.35, 155.02, 154.66, 154.29, 148.71, 137.20, 131.49, 131.12, 130.76, 130.71, 130.56, 129.44, 127.23, 125.97, 125.40, 125.07, 124.87, 124.36, 121.96, 121.54, 121.46, 99.03, 98.88, 98.52, 98.35, 80.59, 59.71, 55.55, 53.83,

52.66, 51.41, 28.12, 13.14, 10.57; ^{19}F NMR (376 MHz, CDCl_3) for major isomer: δ -119.67; ^{19}F NMR (376 MHz, CDCl_3) for minor isomer: δ -118.80; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{34}\text{FN}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 525.2395, found: 525.2395.



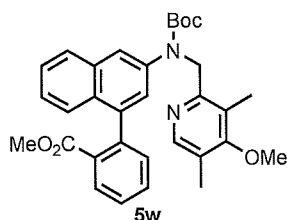
Dimethyl 5'-((tert-butoxycarbonyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4'-methyl-[1,1'-biphenyl]-2,3'-dicarboxylate (5u)

Substrate **1u** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5u** was obtained in 92% yield as a colorless liquid. Rotameric mixture, ratio of the rotamers = 74/26; ^1H NMR (400 MHz, CDCl_3) δ 8.22-8.05 (m, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.70 (s, 0.74H), 7.59 (d, J = 3.7 Hz, 0.26H), 7.47 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.34-7.04 (m, 2H), 5.35-5.05 (m, 1H), 4.54-4.30 (m, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 3.55 (s, 3H), 2.57-2.38 (m, 3H), 2.27-2.15 (m, 6H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture: δ 169.05, 168.64, 167.81, 163.78, 163.55, 155.01, 154.64, 154.30, 148.94, 142.67, 141.82, 140.66, 138.61, 137.22, 136.92, 132.94, 132.41, 131.20, 130.57, 130.50, 129.93, 129.13, 127.38, 124.99, 124.77, 124.67, 123.49, 80.13, 59.70, 53.43, 52.55, 51.92, 51.75, 28.17, 15.00, 13.12, 10.61; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 549.2595, found: 549.2596.



Methyl 2-(4-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)naphthalen-2-yl)benzoate (5v)

Substrate **1v** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **5v** was obtained in 92% yield as a colorless solid. Rotameric mixture, ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.92 (s, 1H), 7.87-7.77 (m, 2H), 7.66 (s, 1H), 7.56-7.44 (m, 3H), 7.40 (t, $J = 7.5$ Hz, 1H), 7.34-7.18 (m, 2H), 5.56-5.18 (m, 1H), 4.61 (d, $J = 15.2$ Hz, 1H), 3.63 (s, 3H), 3.46 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 1.56-1.14 (m, 9H); ^{13}C NMR (150 MHz, CDCl_3) rotameric mixture: δ 169.07, 163.64, 155.33, 155.03, 148.96, 141.59, 138.49, 138.37, 134.01, 131.13, 131.01, 130.80, 129.82, 128.36, 127.66, 127.20, 126.76, 126.17, 126.07, 124.76, 124.46, 123.31, 122.91, 79.96, 59.67, 53.15, 51.75, 50.06, 28.07, 13.10, 10.52; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 527.2540, found: 527.2541.

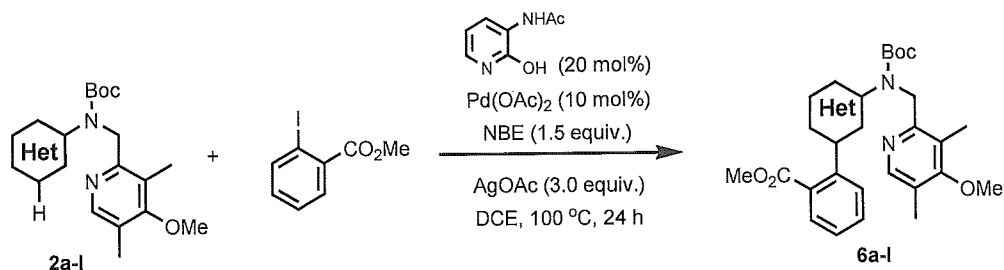


Methyl 2-(3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)naphthalene-1-yl)benzoate (5w)

Substrate **1w** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography Compound **5w** was obtained in 92% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 8.00 (d, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.66 (s, 1H), 7.58 (t, $J = 7.3$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.41-7.22 (m, 5H), 5.06 (s, 2H), 3.70 (s, 3H), 3.23 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz,

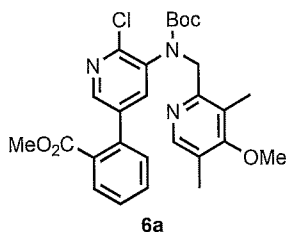
CDCl₃) δ 167.79, 163.68, 155.11, 154.65, 148.94, 140.85, 139.61, 139.57, 133.26, 131.79, 131.61, 131.43, 130.13, 130.00, 128.09, 127.57, 126.09, 125.60, 125.52, 125.10, 124.67, 123.85, 122.79, 80.40, 59.81, 53.70, 51.56, 28.27, 13.17, 10.48; HRMS (ESI-TOF) m/z Calcd for C₃₂H₃₅N₂O₅ [M+H]⁺: 527.2540, found: 527.2538.

Meta-Arylation of Heterocycle-Containing Aromatic Amines



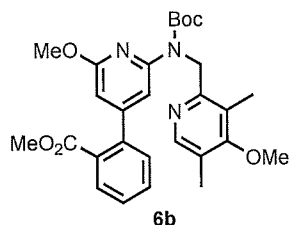
General Procedures for meta-Arylation of Heterocycle-Containing Aromatic Amines:

Substrate **2** (0.1 mmol), Ar-I (0.2 mmol), Pd(OAc)₂ (2.2 mg, 10 mol%), **112** (3.0 mg, 20 mol%), AgOAc (50.1 mg, 0.3 mmol), 2-Norbornene (14.1 mg, 0.15 mmol) or NBE-CO₂Me (21.6 mg, 0.15 mmol) and DCE (0.5 mL) were added to a 2-dram vial. The vial was capped and closed tightly. Then the reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resultant solution was concentrated and purified by preparative TLC plate to afford the desired arylated product.



Methyl 2-((5-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-6-chloropyridin-3-yl)benzoate (**6a**)

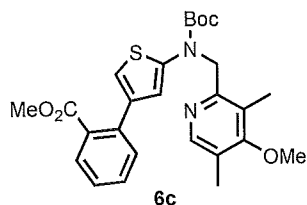
Substrate **2a** was arylated following the general *meta*-arylation procedure using NBE-CO₂Me. After purification by preparative thin-layer chromatography, Compound **6a** was obtained in 53% yield as a colorless liquid. Rotameric mixture, ratio of the rotamers = 77/23; ¹H NMR (400 MHz, CDCl₃) δ 8.25-8.12 (m, 1H), 8.10 (s, 0.77H), 7.99 (s, 0.23H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.65 (s, 0.77H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.27 (s, 0.46H), 7.17 (d, *J* = 7.6 Hz, 0.77H), 5.24 (d, *J* = 15.5 Hz, 1H), 4.56 (d, *J* = 15.5 Hz, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 2.33-2.23 (m, 3H), 2.20 (s, 3H), 1.40 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) rotameric mixture: δ 167.98, 167.68, 163.94, 163.69, 154.64, 154.12, 153.79, 149.03, 148.91, 148.78, 146.47, 140.22, 138.99, 137.15, 136.54, 136.33, 135.68, 131.78, 130.84, 130.60, 130.46, 130.29, 128.36, 128.26, 125.26, 124.97, 124.86, 123.59, 81.08, 59.79, 52.51, 51.91, 51.67, 28.09, 13.18, 10.67, 10.50; HRMS (ESI-TOF) *m/z* Calcd for C₂₇H₃₁ClN₃O₅ [M+H]⁺: 512.1947, found: 512.1946.



Methyl 2-(2-((*tert*-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-6-methoxypyridin-4-yl)benzoate (6b**)**

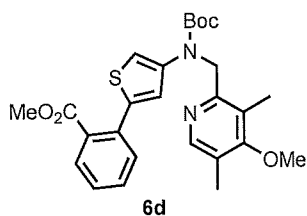
Substrate **2b** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6b** was obtained in 72% yield as a colorless liquid. Only 4% NMR yield was obtained in the absence of **L12**. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46-7.39 (m, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 6.32 (s, 1H), 5.24 (s, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 2.26 (s, 3H), 2.21

(s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.27, 163.33, 161.85, 156.03, 154.28, 153.00, 151.84, 148.82, 140.63, 131.35, 130.42, 130.26, 129.83, 127.90, 123.82, 122.36, 110.87, 104.23, 80.92, 59.83, 53.00, 52.05, 49.35, 28.13, 13.14, 10.34; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{34}\text{N}_3\text{O}_6$ $[\text{M}+\text{H}]^+$: 508.2442, found: 508.2442.



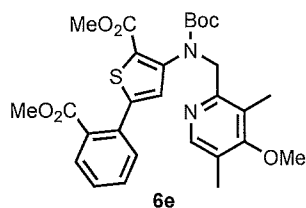
Methyl 2-(5-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-thiophen-3-yl)benzoate (6c)

Substrate **2c** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6c** was obtained in 79% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.56-7.39 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 6.97 (s, 1H), 6.80 (s, 1H), 5.48 (s, 2H), 3.96 (s, 3H), 3.73 (s, 3H), 2.35 (s, 6H), 1.50 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.58, 168.72, 153.40, 150.44, 141.74, 138.94, 136.46, 131.35, 130.71, 130.40, 129.44, 128.83, 128.72, 128.13, 127.24, 123.99, 118.73, 82.96, 60.92, 52.06, 49.86, 28.09, 14.16, 11.10; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 483.1948, found: 483.1949.



Methyl 2-(4-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-thiophen-2-yl)benzoate (6d)

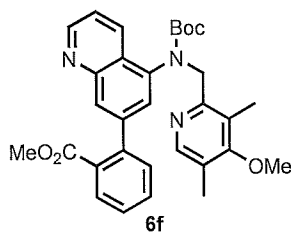
Substrate **2d** was arylated following the general *meta*-arylation procedure using NBE-CO₂Me. After purification by preparative thin-layer chromatography, Compound **6d** was obtained in 56% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.49–7.39 (m, 2H), 7.39–7.32 (m, 1H), 7.07 (s, 1H), 6.96 (s, 1H), 4.91 (s, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 2.26–2.19 (m, 6H), 1.44 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 169.04, 163.69, 154.77, 154.18, 149.05, 140.87, 139.46, 134.13, 131.51, 130.88, 129.27, 127.64, 124.68, 123.50, 115.39, 80.72, 59.86, 53.21, 52.13, 28.25, 13.20, 10.29; HRMS (ESI-TOF) *m/z* Calcd for C₂₆H₃₁N₂O₅S [M+H]⁺: 483.1948, found: 483.1948.



Methyl 3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5-(2-(methoxycarbonyl)phenyl)thiophene-2-carboxylate (6e)

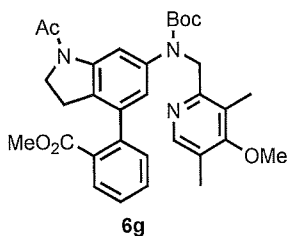
Substrate **2e** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6e** was obtained in 65% yield as a colorless liquid. Rotameric mixture, ratio of the rotamers = 65/35; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.45–7.29 (m, 2H), 7.06 (s, 0.35H), 6.80 (s, 0.65H), 5.20–4.60 (m, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) rotameric mixture: δ 168.16, 167.85, 163.31, 163.14, 161.03, 160.90, 154.89, 154.29, 153.70, 132.81, 131.11, 131.03, 130.72, 130.38, 129.28, 128.41, 128.18, 128.10, 127.77, 124.49, 124.38, 124.28, 124.12, 124.05, 123.05, 79.91, 59.37, 53.02, 52.14, 51.79, 51.68, 51.47, 27.72, 12.74, 10.07;

HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{33}N_2O_7S$ $[M+H]^+$: 541.2003,
found: 541.2003.



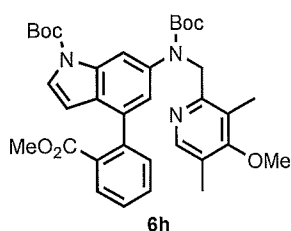
Methyl 2-(5-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-quinolin-7-yl)benzoate (6f)

Substrate **2f** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6f** was obtained in 76% yield as a red liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.91 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.34 (d, $J = 8.4$ Hz, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.3$ Hz, 1H), 7.51–7.30 (m, 4H), 5.24 (d, $J = 15.5$ Hz, 1H), 4.76 (d, $J = 15.3$ Hz, 1H), 3.65 (s, 3H), 3.52 (s, 3H), 2.28–2.10 (m, 6H), 1.54–1.10 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.50, 163.67, 154.97, 154.56, 150.52, 148.99, 148.57, 142.19, 141.25, 138.52, 132.00, 131.46, 130.91, 130.66, 130.17, 127.65, 127.48, 126.97, 125.23, 124.87, 124.23, 120.86, 80.44, 59.72, 53.40, 51.82, 28.08, 13.12, 10.51; HRMS (ESI-TOF) m/z Calcd for $C_{31}H_{34}N_3O_5$ $[M+H]^+$: 528.2493, found: 528.2493.



Methyl 2-(1-acetyl-6-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-amino)-indolin-4-yl)benzoate (6g)

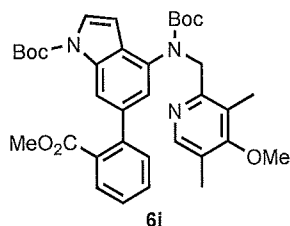
Substrate **2g** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6g** was obtained in 89% yield as a light yellow solid. Rotameric mixture, ratio of the rotamers = 78/22; mp = 79 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.08 (m, 1.78H), 7.96-7.84 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.26-7.09 (m, 1.22H), 6.74 (s, 1H), 5.00-4.80 (m, 2H), 4.12-3.90 (m, 2H), 3.70 (s, 2H), 3.66-3.52 (m, 3H), 2.82 (t, *J* = 8.4 Hz, 1.56H), 2.69 (t, *J* = 8.4 Hz, 0.44H), 2.38-2.08 (m, 9H), 1.40 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) resonances for the minor rotamer are enclosed in parenthesis (): δ 168.46 (168.29), 167.88 (167.52), 163.60 (163.66), 155.15 (155.03), 154.68, 148.74 (148.82), 142.41, 142.00 (141.16), 140.54 (140.45), 137.49 (138.91), 131.49 (131.67), 130.52 (130.47), 130.13 (129.85), 129.97 (129.28), 127.41 (127.61), 126.70, 124.50 (124.75), 123.90, 122.52 (121.91), 114.62 (112.46), 80.12 (80.33), 59.74 (59.79), 53.54, 51.87 (51.92), 49.12 (48.19), 28.21, 26.81 (25.60), 24.14 (24.36), 13.12, 10.45 (10.37); HRMS (ESI-TOF) *m/z* Calcd for C₃₂H₃₈N₃O₆ [M+H]⁺: 560.2755, found: 560.2755.



***tert*-Butyl 6-((*tert*-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4-(2-(methoxycarbonyl)-phenyl)-1H-indole-1-carboxylate (**6h**)**

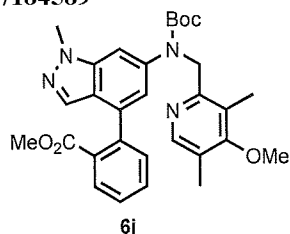
Substrate **2h** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6h** was obtained in 66% yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.57-7.47 (m, 2H), 7.43 (t,

$J = 7.6$ Hz, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 7.03 (s, 1H), 6.22 (d, $J = 3.7$ Hz, 1H), 5.01 (s, 2H), 3.71 (s, 3H), 3.42 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 1.60 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.58, 163.70, 155.30, 154.94, 149.55, 148.84, 140.23, 139.22, 134.48, 133.59, 131.39, 131.32, 131.14, 129.92, 127.36, 127.32, 126.33, 124.64, 124.05, 122.40, 112.86, 105.68, 83.59, 80.08, 59.76, 54.11, 51.88, 28.27, 28.04, 13.12, 10.50; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{35}\text{H}_{42}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$: 616.3017, found: 616.3018.



***tert*-Butyl 4-((*tert*-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-6-(2-(methoxycarbonyl)-phenyl)-1H-indole-1-carboxylate (6i)**

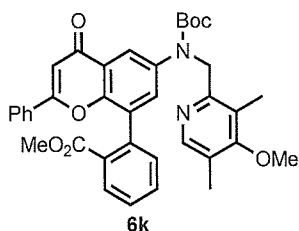
Substrate **2i** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6i** as obtained in 51% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 8.01 (s, 1H), 7.75 (d, $J = 7.7$ Hz, 1H), 7.56 (d, $J = 3.7$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.41-7.28 (m, 2H), 7.02 (brs, 1H), 6.58 (d, $J = 3.7$ Hz, 1H), 4.97 (brs, 2H), 3.66 (s, 3H), 3.54 (s, 3H), 2.18 (s, 6H), 1.64 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.41, 163.58, 155.02, 154.78, 149.61, 148.93, 142.31, 137.48, 135.73, 134.72, 131.18, 130.97, 130.92, 129.65, 127.71, 126.83, 125.87, 124.67, 124.15, 121.93, 113.59, 105.71, 83.78, 80.07, 59.72, 53.36, 51.76, 28.20, 28.13, 13.15, 10.50; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{35}\text{H}_{42}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$: 616.3017, found: 616.3018.



Methyl 2-(6-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-1-methyl-1H-indazol-4-yl)benzoate (6j)

Substrate **2j** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6j** as obtained in 90% yield as a colorless solid.

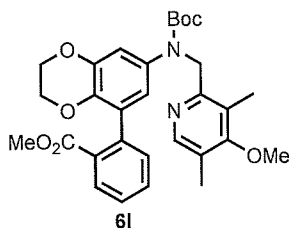
mp = 79 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.63 (s, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.35 (s, 1H), 6.98 (s, 1H), 5.00 (s, 2H), 4.00 (s, 3H), 3.71 (s, 3H), 3.44 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.40 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 168.39, 163.70, 155.05, 154.71, 148.89, 141.40, 139.77, 139.61, 134.29, 131.56, 131.45, 131.09, 131.02, 130.00, 127.64, 124.73, 123.79, 121.46, 120.66, 105.64, 80.43, 59.80, 53.89, 51.89, 35.65, 28.23, 13.17, 10.45; HRMS (ESI-TOF) *m/z* Calcd for C₃₀H₃₅N₄O₅ [M+H]⁺: 531.2602, found: 531.2604.



Methyl 2-(6-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4-oxo-2-phenyl-4H-chromen-8-yl)benzoate (6k)

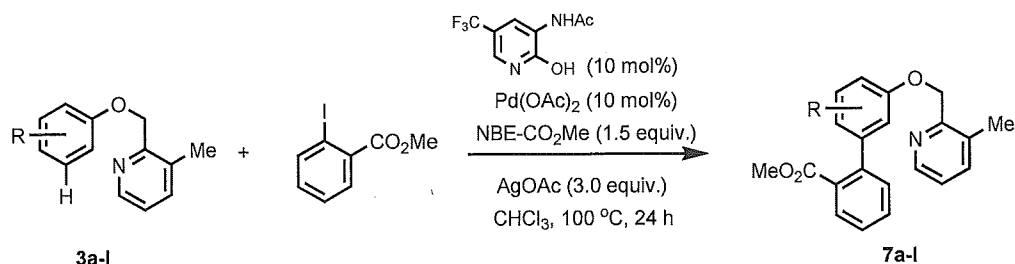
Substrate **2k** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **6k** was obtained in 87% yield as a colorless

solid. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 8.11 (d, $J = 7.7$ Hz, 1H), 8.01 (d, $J = 2.6$ Hz, 1H), 7.78–7.62 (m, 2H), 7.61–7.49 (m, 3H), 7.48–7.33 (m, 4H), 6.77 (s, 1H), 5.02 (q, $J = 15.1, 14.2$ Hz, 2H), 3.74 (s, 3H), 3.40 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 178.08, 167.21, 163.75, 162.67, 154.60, 154.40, 150.81, 149.03, 139.91, 136.59, 134.50, 133.25, 132.19, 131.89, 131.69, 131.39, 131.27, 130.74, 130.52, 130.27, 128.83, 128.39, 126.00, 124.81, 123.70, 123.49, 120.74, 106.72, 80.78, 59.88, 53.26, 51.70, 28.20, 13.19, 10.44; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{37}\text{H}_{37}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 621.2595, found: 621.2596.

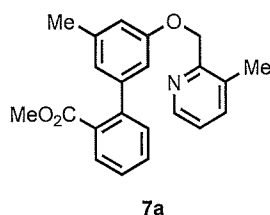


Methyl 2-(7-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)benzoate (61)

Substrate **21** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **61** was obtained in 91% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.36 (s, 1H), 7.21 (d, $J = 6.4$ Hz, 1H), 6.81 (s, 1H), 6.67 (s, 1H), 4.89 (s, 2H), 4.15 (dd, $J = 5.6, 2.8$ Hz, 2H), 4.09 (dd, $J = 5.7, 2.8$ Hz, 2H), 3.71 (s, 3H), 3.64 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.41, 163.63, 155.14, 154.84, 148.86, 142.40, 138.20, 137.39, 135.73, 131.50, 131.39, 131.22, 129.88, 129.41, 127.28, 124.60, 123.90, 120.95, 115.08, 80.03, 64.11, 64.02, 59.77, 53.66, 51.62, 28.25, 13.14, 10.39; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{30}\text{H}_{35}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 535.2439, found: 535.2438.

Meta-Arylation of Phenols

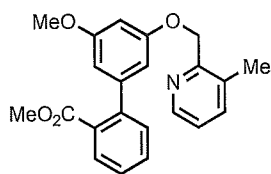
General Procedure for meta-Arylation of Phenols: Substrate **3** (0.2 mmol), Ar-I (0.6 mmol), Pd(OAc)₂ (4.5 mg, 10 mol%), **L14** (4.4 mg, 10 mol%), AgOAc (100.0 mg, 0.6 mmol), NBE-CO₂Me (45.6 mg, 0.3 mmol) and CHCl₃ (1.0 mL) were added to a 50 mL schlenk tube. The tube was capped and closed tightly. The reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with EtOAc as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC plate to afford the desired arylated product. (In cases where mono:di ratios are possible, the selectivity was determined by ¹H NMR.)



Methyl 3'-(3-methyl-5-methoxyphenyl)-[1,1'-biphenyl]-2-carboxylate (7a)

Substrate **3a** was arylated following the general meta-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7a** was obtained in 87% yield as a light yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, *J* = 4.4 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.54–7.45 (m, 1H), 7.41–7.34 (m, 2H), 7.19 (dd, *J* = 7.7, 4.8 Hz, 2H), 6.86 (s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 5.20 (s, 2H), 3.63 (s, 3H), 2.43 (s, 3H),

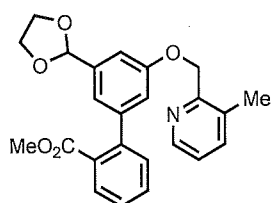
2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.26, 158.48, 154.32, 146.55, 142.35, 142.13, 139.01, 138.34, 133.22, 131.04, 131.02, 130.46, 129.49, 127.06, 123.38, 122.02, 114.56, 111.92, 70.81, 51.92, 21.53, 18.16; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 348.1594, found: 348.1598.



7b

Methyl 3'-(3-methoxy-5'-((3-methylpyridin-2-yl)methoxy))-[1,1'-biphenyl]-2-carboxylate (7b)

Substrate **3b** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7b** was obtained in 91% yield as a light yellow liquid ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, J = 4.7 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.54–7.46 (m, 2H), 7.42–7.35 (m, 2H), 7.19 (dd, J = 7.7, 4.8 Hz, 1H), 6.26–6.58 (m, 2H), 6.48 (s, 1H), 5.19 (s, 2H), 3.79 (s, 3H), 3.64 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.18, 160.32, 159.56, 154.14, 146.61, 143.23, 142.00, 138.36, 133.17, 131.09, 131.05, 130.34, 129.47, 127.24, 123.42, 107.40, 107.03, 100.18, 70.86, 55.33, 51.99, 18.14; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 364.1543, found: 364.1552.

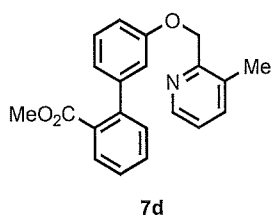


7c

Methyl 3'-(1,3-dioxolan-2-yl)-5'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (7c)

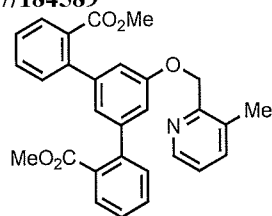
Substrate **3c** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7c** was

obtained in 53% yield as a clear liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 4.8$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.55–7.46 (m, 2H), 7.43–7.34 (m, 2H), 7.19 (dd, $J = 7.7$, 4.8 Hz, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 7.01 (t, $J = 1.9$ Hz, 1H); 5.82 (s, 1H), 5.23 (s, 2H), 4.16–3.95 (m, 4H), 3.61 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.21, 158.58, 154.15, 146.61, 142.68, 141.68, 139.35, 138.39, 133.30, 131.15, 131.06, 130.54, 129.68, 127.31, 123.48, 119.50, 115.78, 111.57, 103.46, 71.00, 65.27, 51.98, 18.20; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 406.1649, found: 406.1656.



Methyl 3'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (7d)

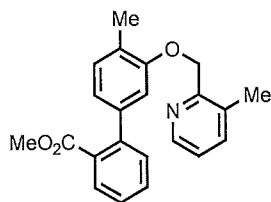
Substrate **3d** was arylated following the general *meta*-arylation procedure for phenols. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 1:1). After purification by preparative thin-layer chromatography, Compound **7d** was obtained in 38% yield as a clear liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 4.3$ Hz, 1H), 7.81–7.77 (m, 1H), 7.54–7.49 (m, 2H), 7.40 (td, $J = 7.6$, 1.3 Hz, 1H), 7.38–7.35 (m, 1H), 7.30 (t, $J = 7.9$ Hz, 1H), 7.19 (dd, $J = 7.7$, 4.8 Hz, 1H), 7.03 (ddd, $J = 8.3$, 2.6, 0.9 Hz, 1H), 7.00 (s, 1H), 6.90 (ddd, $J = 7.5$, 1.7, 0.9 Hz, 1H), 5.22 (s, 2H), 3.62 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.15, 158.53, 154.28, 146.61, 142.68, 142.10, 138.40, 133.27, 131.15, 130.99, 130.55, 129.64, 128.99, 127.20, 123.44, 121.24, 114.99, 113.63, 70.89, 51.95, 18.20; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 334.1438, found: 334.1443.



7d'

Dimethyl 5'-((3-methylpyridin-2-yl)methoxy)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (7d')

Substrate **3d** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7d'** was obtained in 40% yield as a clear liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, *J* = 4.9 Hz, 1H), 7.81–7.76 (m, 2H), 7.55–7.48 (m, 3H), 7.43–7.37 (m, 4H), 7.20 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.99 (s, 2H), 6.86 (s, 1H), 5.23 (s, 2H), 3.65 (s, 6H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.09, 158.22, 154.11, 146.58, 142.40, 141.86, 138.43, 133.25, 131.13, 131.05, 130.58, 129.67, 127.27, 123.47, 121.51, 113.81, 70.88, 51.98, 18.19; HRMS (ESI-TOF) *m/z* Calcd for C₂₉H₂₆NO₅ [M+H]⁺: 468.1805, found: 468.1809.

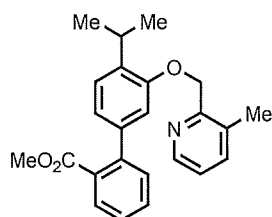


7e

Methyl 4'-methyl-3'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (7e)

Substrate **3e** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7e** was obtained in 85% yield as a light yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, *J* = 4.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.55–7.47 (m, 2H), 7.42–7.33 (m, 2H), 7.20 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 5.21 (s, 2H), 3.64 (d, *J* = 0.7 Hz, 3H), 2.45 (s, 3H), 2.25 (s, 3H); ¹³C NMR (100

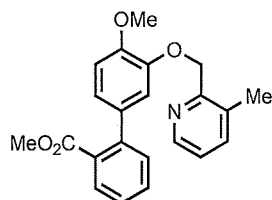
MHz, CDCl₃) δ 169.32, 156.53, 154.54, 146.49, 142.29, 139.95, 138.32, 133.39, 131.09, 131.00, 130.62, 130.27, 129.54, 126.94, 125.90, 123.39, 120.64, 111.72, 71.19, 51.97, 18.16, 16.08; HRMS (ESI-TOF) m/z Calcd for C₂₂H₂₂NO₃ [M+H]⁺: 348.1594, found: 348.1597.



7f

Methyl 4'-isopropyl-3'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (7f)

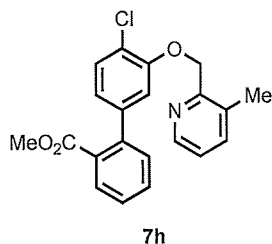
Substrate **3f** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7f** was obtained in 89% yield as clear liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, J = 4.6 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.56–7.46 (m, 2H), 7.42–7.35 (m, 2H), 7.26–7.16 (m, 2H), 7.04 (s, 1H), 6.89 (d, J = 7.8 Hz, 1H), 5.20 (s, 2H), 3.63 (s, 3H), 3.34 (hept, J = 7.0 Hz, 1H), 2.45 (s, 3H), 1.20 (d, J = 6.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.43, 155.58, 154.58, 146.52, 142.18, 139.50, 138.28, 136.18, 133.32, 131.09, 131.03, 130.59, 129.49, 126.90, 125.70, 123.39, 120.94, 111.96, 71.28, 51.93, 26.36, 22.84, 18.14; HRMS (ESI-TOF) m/z Calcd for C₂₄H₂₆NO₃ [M+H]⁺: 376.1907, found: 376.1907.



7g

Methyl 4'-methoxy-3'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (7g)

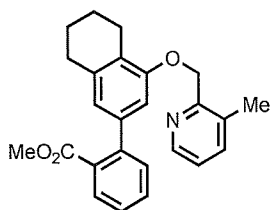
Substrate **3g** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7g** was obtained in 54% yield as a light yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.42 (d, J = 4.9 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.53–7.47 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.17 (dd, J = 7.7, 4.8 Hz, 1H), 7.07 (d, J = 1.2 Hz, 1H), 6.94–6.84 (m, 2H), 5.25 (s, 2H), 3.88 (s, 3H), 3.63 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.39, 154.26, 149.19, 147.74, 146.49, 141.84, 138.36, 133.85, 133.43, 131.08, 130.96, 130.63, 129.58, 126.81, 123.35, 121.44, 114.84, 111.27, 72.02, 55.89, 51.96, 18.20; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 364.1543, found: 364.1547.



Methyl 4'-chloro-3'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (7h)

Substrate **3h** was arylated following a slightly modified *meta*-arylation procedure for phenols. For this substrate, **L12** was used in place of **L14** and the reaction was run for 36 hours. After purification by preparative thin-layer chromatography, Compound **7h** was obtained in 81% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.42 (d, J = 4.7 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.56–7.49 (m, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.20 (dd, J = 7.7, 4.8 Hz, 1H), 7.14 (d, J = 1.9 Hz, 1H), 6.82 (dd, J = 8.1, 1.9 Hz, 1H), 5.29 (s, 2H), 3.62 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.71, 153.72, 153.63, 146.40, 141.40, 141.18, 138.50, 133.78, 131.33, 130.65, 130.56, 129.89, 129.65, 127.48, 123.60, 122.11, 121.68, 114.38, 72.13, 51.98, 18.23; HRMS

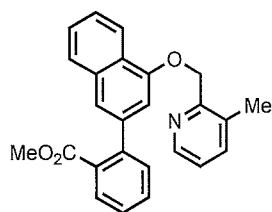
(ESI-TOF) m/z Calcd for $C_{21}H_{19}ClNO_3$ $[M+H]^+$: 368.1048, found: 368.1053.



7i

Methyl 2-(4-((3-methylpyridin-2-yl)methoxy)-5,6,7,8-tetrahydronaphthalen-2-yl)benzoate (7i)

Substrate **3i** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7i** was obtained in 90% yield as a light yellow liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 4.7 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.54–7.46 m, 2H), 7.41–7.33 (m, 2H), 7.18 (dd, J = 7.6, 4.8 Hz, 1H), 6.82 (s, 1H), 6.68 (s, 1H), 5.17 (s, 2H), 3.66 (s, 3H), 2.78–2.74 (m, 2H), 2.71–2.65 (m, 2H), 2.43 (s, 3H), 1.82–1.72 m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.50, 156.15, 154.63, 146.45, 142.35, 138.65, 138.27, 138.14, 133.37, 131.08, 130.98, 130.58, 129.38, 126.80, 125.29, 123.33, 121.58, 108.53, 71.05, 51.99, 29.67, 23.04, 22.79, 22.70, 18.19; HRMS (ESI-TOF) m/z Calcd for $C_{25}H_{26}NO_3$ $[M+H]^+$: 388.1907, found: 388.1910.

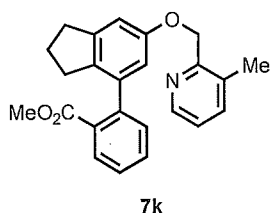


7j

Methyl 2-(4-((3-methylpyridin-2-yl)methoxy)naphthalen-2-yl)benzoate (7j)

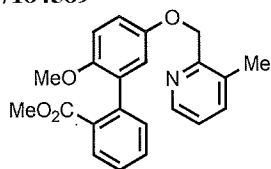
Substrate **3j** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7j** was obtained in 87% yield as a yellow liquid. 1H NMR (400 MHz,

CDCl₃) δ 8.47 (d, J = 4.8, 1.5 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.84 (dd, J = 7.6 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.59–7.52 (m, 2H), 7.51–7.40 (m, 4H), 7.39 (s, 1H), 7.23 (dd, J = 7.7, 4.9 Hz, 1H), 7.02 (d, J = 1.4 Hz, 1H), 5.38 (s, 2H), 3.55 (s, 3H), 2.47 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.27, 154.25, 154.04, 146.57, 142.43, 139.06, 138.40, 134.23, 133.52, 131.19, 131.15, 130.84, 129.71, 127.66, 127.22, 126.70, 125.25, 124.76, 123.52, 121.98, 119.70, 106.67, 71.33, 51.97, 18.23; HRMS (ESI-TOF) m/z Calcd for C₂₅H₂₂NO₃ [M+H]⁺: 384.1594, found: 384.1598.



Methyl 2-(6-((3-methylpyridin-2-yl)methoxy)-2,3-dihydro-1H-inden-4-yl)benzoate (7k)

Substrate **3k** was arylated following the general *meta*-arylation procedure for phenols. After purification by preparative thin-layer chromatography, Compound **7k** was obtained in 42% yield as a clear liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, J = 4.9 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.54–7.48 (m, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.31–7.23 (m, 1H), 7.18 (dd, J = 7.7, 4.8 Hz, 1H), 6.92 (s, 1H), 6.69 (d, J = 2.3 Hz, 1H), 5.18 (s, 2H), 3.62 (s, 3H), 2.93 (t, J = 7.4 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 2.43 (s, 3H), 2.06 – 1.94 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.28, 157.49, 154.57, 146.50, 145.21, 142.14, 138.50, 138.34, 134.70, 133.27, 131.35, 130.67, 130.38, 129.80, 127.03, 123.32, 113.01, 109.93, 71.11, 51.94, 33.41, 31.11, 25.59, 18.21; HRMS (ESI-TOF) m/z Calcd for C₂₄H₂₄NO₃ [M+H]⁺: 374.1757, found: 374.1757.

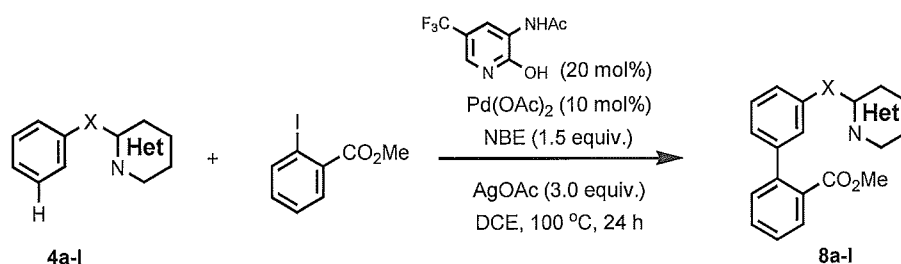


71

Methyl 2'-methoxy-5'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (71)

Substrate **31** was arylated following the general *meta*-arylation procedure for phenols. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 20>1). After purification by preparative thin-layer chromatography, Compound **71** was obtained in 58% yield as a light yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, J = 4.3 Hz, 1H), 7.85 (dd, J = 7.7, 1.4 Hz, 1H), 7.57–7.49 (m, 2H), 7.39 (td, J = 7.6, 1.2 Hz, 1H), 7.31 (dd, J = 7.6, 1.3 Hz, 1H), 7.19 (dd, J = 7.6, 4.8 Hz, 1H), 7.02–6.96 (m, 2H), 6.80 (d, J = 8.5 Hz, 1H), 5.19 (s, 2H), 3.63–3.68 (m, 6H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.52, 154.52, 152.76, 150.57, 146.55, 138.40, 138.36, 133.23, 131.62, 131.51, 131.37, 131.20, 129.30, 127.18, 123.36, 117.34, 114.11, 111.00, 71.48, 55.73, 51.68, 18.21; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 364.1543, found: 364.1543.

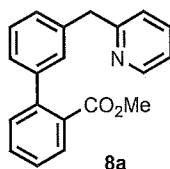
Meta-Arylation of Other Heterocyclic Substrates



General Procedure for meta-Arylation of Other Heterocycle

Substrates: Substrate **4** (0.1 mmol), methyl 2-iodobenzoate (43.0 μL , 0.3 mmol), $\text{Pd}(\text{OAc})_2$ (2.2 mg, 10 mol%), **L14** (4.4 mg, 20 mol%), AgOAc (50.1 mg, 0.3 mmol), 2-Norbornene (14.1 mg, 0.15 mmol) and CHCl_3 (1.0 mL) were added to a 2-dram vial. The vial was capped and closed tightly. Then

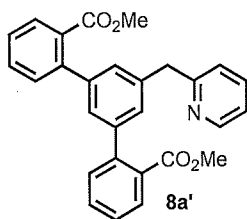
the reaction mixture was then stirred at 90 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resultant solution was concentrated and purified by preparative TLC to afford the desired arylated product. (In cases where *mono:di* ratios are possible, the selectivity was determined by ^1H NMR.)



Methyl 3'-(pyridin-2-ylmethyl)-[1,1'-biphenyl]-2-carboxylate (8a)

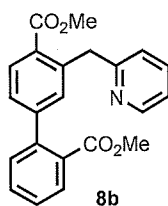
Substrate **4a** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 2:1). After purification by preparative thin-layer chromatography, Compounds **8a** and **8a'** were obtained in 92% total yield.

^1H NMR (400 MHz, CDCl_3) δ 8.58–8.53 (m, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.58 (td, J = 7.7, 1.8 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.42–7.31 (m, 3H), 7.30–7.24 (m, 1H), 7.23–7.16 (m, 2H), 7.16–7.08 (m, 2H), 4.19 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.11, 160.85, 149.30, 142.23, 141.50, 139.17, 136.53, 131.15, 130.88, 130.64, 129.66, 129.10, 128.30, 128.04, 127.09, 126.38, 123.11, 121.25, 51.84, 44.62; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{20}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 304.1332, found: 304.1332.



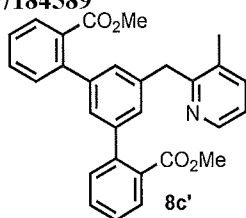
**Dimethyl 5'-(pyridin-2-ylmethyl)-[1,1':3',1''-terphenyl]-
2,2''-dicarboxylate (8a')**

^1H NMR (400 MHz, CDCl_3) δ 8.55 (d, $J = 3.6$ Hz, 1H), 7.82-7.76 (m, 2H), 7.60 (td, $J = 7.7, 1.8$ Hz, 1H), 7.54-7.47 (m, 2H), 7.43-7.36 (m, 4H), 7.20 (s, 2H), 7.19-7.15 (m, 2H), 7.12 (dd, $J = 7.5, 5.0$ Hz, 1H), 4.23 (s, 2H), 3.58 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.10, 160.77, 149.30, 141.94, 141.44, 138.84, 136.54, 131.15, 131.02, 130.67, 129.70, 128.12, 127.19, 126.46, 123.13, 121.30, 51.87, 44.56; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{24}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 438.1700, found: 438.1698.



**Dimethyl 5'-(pyridin-2-ylmethyl)-[1,1':3',1''-terphenyl]-
2,2''-dicarboxylate (8b)**

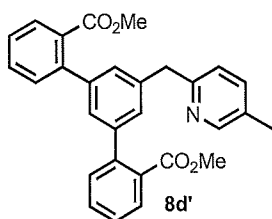
Substrate **4b** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **8b** was obtained in 92% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.55-8.49 (m, 1H), 8.00 (d, $J = 7.9$ Hz, 1H), 7.84 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.59-7.48 (m, 2H), 7.42 (td, $J = 7.6, 1.3$ Hz, 1H), 7.35 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.30-7.24 (m, 2H), 7.12-7.04 (m, 2H), 4.61 (s, 2H), 3.83 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.53, 167.72, 160.74, 149.08, 145.28, 141.29, 140.29, 136.36, 132.08, 131.38, 130.72, 130.56, 130.54, 129.98, 128.63, 127.70, 126.57, 122.88, 121.04, 51.96, 51.95, 42.53; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 362.1387, found: 362.1387.



Dimethyl 5'-((3-methylpyridin-2-yl)methyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8c')

Substrate **4c** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **8c'** was obtained in 55% total yield as a sole product.

¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 4.5 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.41–7.34 (m, 4H), 7.14–7.06 (m, 4H), 4.26 (s, 2H), 3.57 (s, 6H), 2.29 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 169.11, 158.50, 146.81, 142.01, 141.26, 138.57, 138.06, 131.84, 131.12, 131.03, 130.69, 129.66, 127.59, 127.14, 126.23, 121.85, 51.85, 42.24, 19.06; HRMS (ESI-TOF) *m/z* Calcd for C₂₉H₂₆NO₄ [M+H]⁺: 452.1856, found: 452.1856.

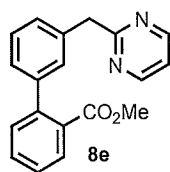


Dimethyl 5'-((5-methylpyridin-2-yl)methyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8d')

Substrate **4d** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **8d'** was obtained in 60% yield as a sole product.

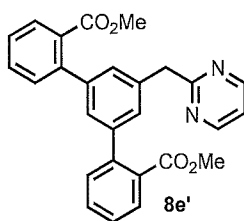
¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 2.2 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.50 (td, *J* = 7.5, 1.4 Hz, 2H), 7.43–7.35 (m, 5H), 7.18 (d, *J* = 1.6 Hz, 2H), 7.14 (t, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 4.18 (s, 2H), 3.59 (s, 6H),

2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.13, 157.76, 149.61, 141.99, 141.38, 139.18, 137.13, 131.13, 131.02, 130.69, 130.55, 129.69, 128.07, 127.17, 126.38, 122.61, 51.87, 44.07, 18.01; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{26}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 452.1856, found: 452.1855.



Methyl 3'-(pyrimidin-2-ylmethyl)-[1,1'-biphenyl]-2-carboxylate (8e)

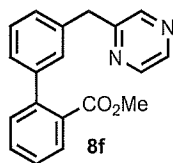
Substrate **4e** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 4:1). After purification by preparative thin-layer chromatography, Compounds **8e** and **8e'** were obtained in 64% total yield. ^1H NMR (600 MHz, CDCl_3) δ 8.68 (d, J = 4.9 Hz, 2H), 7.78 (ddd, J = 7.7, 1.4, 0.6 Hz, 1H), 7.50 (td, J = 7.6, 1.4 Hz, 1H); 7.41-7.32 (m, 4H), 7.31-7.29 (m, 1H), 7.18 (dt, J = 6.9, 1.8 Hz, 1H), 7.13 (t, J = 4.9 Hz, 1H), 4.33 (s, 2H), 3.57 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.89, 169.20, 157.29, 142.20, 141.40, 137.99, 131.13, 130.93, 130.69, 129.65, 129.10, 128.20, 128.05, 127.08, 126.59, 118.69, 51.87, 45.99; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 305.1285, found: 305.1284.



Dimethyl 5'-(pyrimidin-2-ylmethyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8e')

^1H NMR (400 MHz, CDCl_3) δ 8.69 (d, J = 4.9 Hz, 2H), 7.79 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.42-7.36 (m, 4H), 7.28 (s, 2H), 7.26 (s, 1H), 7.17-7.12 (m, 1H),

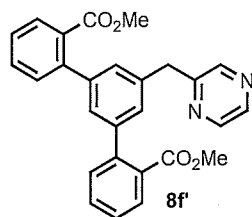
4.36 (s, 2H), 3.59 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.75, 169.22, 157.29, 141.93, 141.28, 137.74, 131.14, 131.05, 130.72, 129.69, 128.06, 127.17, 126.63, 118.77, 51.89, 45.86; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 439.1652, found: 439.1652.



Methyl 3'-(pyrazin-2-ylmethyl)-[1,1'-biphenyl]-2-carboxylate (8f)

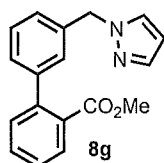
Substrate **4f** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 2:1). After purification by preparative thin-layer chromatography, Compounds **8f** and **8f'** were obtained in 84% total yield.

^1H NMR (400 MHz, CDCl_3) δ 8.51 (d, J = 2.0 Hz, 1H), 8.48 (s, 1H), 8.42 (d, J = 2.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.24-7.18 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 4.21 (s, 2H), 3.59 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.97, 156.41, 144.78, 144.08, 142.41, 142.09, 141.83, 137.81, 131.23, 130.79, 130.66, 129.76, 129.02, 128.48, 127.92, 127.23, 126.83, 51.92, 41.96; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 305.1285, found: 305.1285.



Dimethyl 5'-(pyrazin-2-ylmethyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8f')

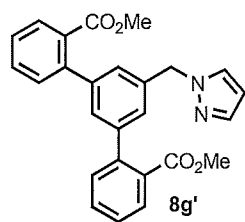
^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, $J = 1.6$ Hz, 1H), 8.49 (s, 1H), 8.43 (d, $J = 2.6$ Hz, 1H), 7.81 (d, $J = 7.7$ Hz, 2H), 7.54–7.48 (m, 2H), 7.44–7.36 (m, 4H), 7.20 (s, 2H), 7.17 (s, 1H), 4.25 (s, 2H), 3.61 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.97, 156.39, 144.81, 144.07, 142.45, 141.82, 141.76, 137.46, 131.24, 130.94, 130.70, 129.82, 128.01, 127.34, 126.91, 51.97, 41.95; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 439.1652, found: 439.1652.



Methyl 3'-((1H-pyrazol-1-yl)methyl)-[1,1'-biphenyl]-2-carboxylate (8g)

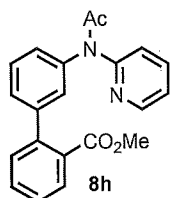
Substrate **4g** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 1:2). After purification by preparative thin-layer chromatography, Compounds **8g** and **8g'** were obtained in 84% total yield.

^1H NMR (400 MHz, CDCl_3) δ 8.69 (d, $J = 4.9$ Hz, 2H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.54–7.47 (m, 1H), 7.42–7.28 (m, 5H), 7.22 – 7.16 (m, 1H), 7.14 (t, $J = 4.9$ Hz, 1H), 4.33 (s, 2H), 3.57 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.89, 169.22, 157.30, 142.20, 141.41, 137.99, 131.14, 130.92, 130.70, 129.66, 129.10, 128.21, 128.05, 127.08, 126.60, 118.70, 51.88, 45.98; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 293.1285, found: 293.1285.



Dimethyl 5'-((1H-pyrazol-1-yl)methyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8g')

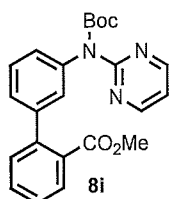
^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 7.7 Hz, 2H), 7.57–7.48 (m, 3H), 7.45–7.35 (m, 5H), 7.22 (s, 1H), 7.15 (s, 2H), 6.29 (t, J = 2.2 Hz, 1H), 5.39 (s, 2H), 3.62 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.80, 141.77, 141.64, 139.57, 136.00, 131.30, 130.82, 130.72, 129.88, 129.26, 128.10, 127.43, 126.71, 106.00, 55.79, 51.99; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 427.1652, found: 427.1652.



Methyl 3'-(*N*-(pyridin-2-yl)acetamido)-[1,1'-biphenyl]-2-carboxylate (8h)

Substrate **4h** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **8h** was obtained in 60% yield as a sole product.

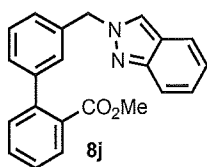
^1H NMR (400 MHz, CDCl_3) δ 8.47–8.40 (m, 1H), 7.83 (dd, J = 7.7, 1.4 Hz, 1H), 7.72 (td, J = 7.8, 2.0 Hz, 1H), 7.57–7.35 (m, 5H), 7.35–7.28 (m, 2H), 7.22 (t, J = 2.0 Hz, 1H), 7.17–7.10 (m, 1H), 3.59 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.03, 168.60, 155.16, 148.74, 142.68, 141.62, 141.37, 137.92, 131.38, 130.72, 130.60, 129.95, 129.14, 128.61, 127.52, 127.23, 121.43, 121.16, 51.97, 24.29; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 347.1390, found: 347.1389.



Methyl 3'-((*tert*-butoxycarbonyl)(pyrimidin-2-yl)amino)-[1,1'-biphenyl]-2-carboxylate (8i)

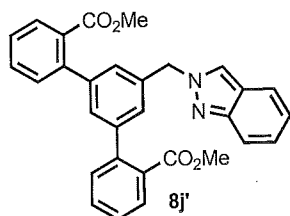
Substrate **4i** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification

by preparative thin-layer chromatography, **8i** was obtained in 50% yield as a sole product. ^1H NMR (400 MHz, CDCl_3) δ 8.66 (d, J = 4.8 Hz, 2H), 7.82–7.77 (m, 1H), 7.51 (td, J = 7.6, 1.4 Hz, 1H), 7.45–7.34 (m, 3H), 7.26–7.21 (m, 2H), 7.15 (t, J = 2.0 Hz, 1H), 7.05 (t, J = 4.8 Hz, 1H), 3.61 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.03, 161.28, 158.23, 153.14, 142.15, 141.49, 141.01, 131.21, 130.97, 130.62, 130.05, 129.77, 128.53, 127.61, 127.34, 126.79, 126.56, 117.27, 82.07, 51.95, 28.07; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 406.1761, found: 406.1761.



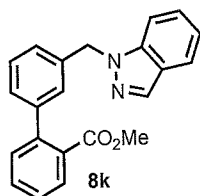
Methyl 3'-((2H-indazol-2-yl)methyl)-[1,1'-biphenyl]-2-carboxylate (8j)

Substrate **4j** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ^1H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 3:1). After purification by preparative thin-layer chromatography, Compounds **8j** and **8j'** were obtained in 74% total yield. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (d, J = 0.9 Hz, 1H), 7.82–7.76 (m, 1H), 7.78–7.70 (m, 1H), 7.49 (td, J = 7.5, 1.4 Hz, 1H), 7.43–7.27 (m, 5H), 7.24–7.10 (m, 4H), 5.64 (s, 2H), 3.47 (d, J = 0.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.82, 141.96, 141.83, 139.52, 136.68, 133.39, 131.24, 130.75, 130.68, 129.79, 128.43, 127.80, 127.28, 127.22, 126.38, 126.12, 124.38, 121.14, 120.64, 109.29, 52.96, 51.80; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 343.1441, found: 343.1442.



Dimethyl 5'-((2H-indazol-2-yl)methyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8j')

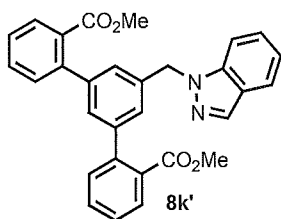
¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.43-7.31 (m, 6H), 7.15 (d, *J* = 11.4 Hz, 4H), 5.66 (s, 2H), 3.49 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 168.82, 141.73, 141.66, 139.49, 136.42, 133.40, 131.23, 130.88, 130.72, 129.83, 127.90, 127.37, 126.38, 126.25, 124.42, 121.16, 120.67, 109.33, 52.97, 51.82; HRMS (ESI-TOF) *m/z* Calcd for C₃₀H₂₅N₂O₄ [M+H]⁺: 477.1809, found: 477.1810.



Methyl 3'-((1H-indazol-1-yl)methyl)-[1,1'-biphenyl]-2-carboxylate (8k)

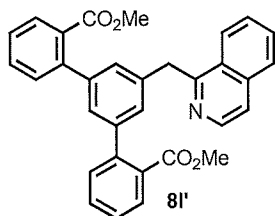
Substrate **4k** was arylated following the general *meta*-arylation procedure using 2-norbornene. Analysis of crude reaction mixture by ¹H NMR showed the selectivity of *mono*- and *di*- products (*mono:di* = 3:1). After purification by preparative thin-layer chromatography, **8k** and **8k'** was obtained in 50% total yield.

¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41-7.26 (m, 5H), 7.24-7.10 (m, 4H), 5.63 (s, 2H), 3.47 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.81, 141.94, 141.81, 139.51, 136.68, 133.38, 131.23, 130.74, 130.67, 129.78, 128.43, 127.79, 127.26, 127.21, 126.37, 126.11, 124.37, 121.13, 120.63, 109.28, 52.94, 51.79; HRMS (ESI-TOF) *m/z* Calcd for C₂₂H₁₉N₂O₂ [M+H]⁺: 343.1441, found: 343.1440.



Dimethyl 5'-((1H-indazol-1-yl)methyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8k')

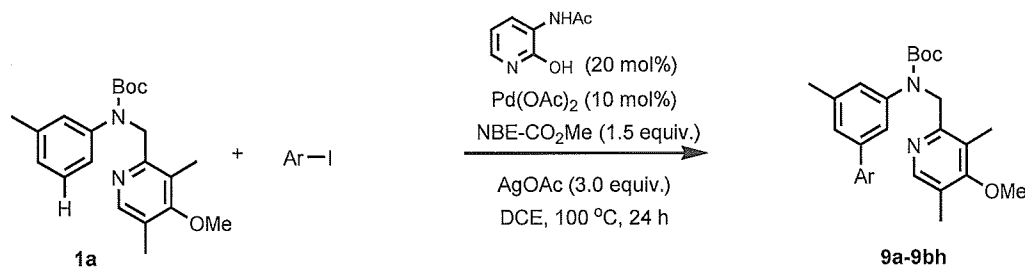
^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.79 (d, J = 7.9 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 7.44–7.31 (m, 6H), 7.20–7.10 (m, 4H), 5.66 (s, 2H), 3.49 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.81, 141.73, 141.66, 139.49, 136.42, 133.40, 131.23, 130.88, 130.72, 129.83, 127.90, 127.37, 126.38, 126.25, 124.42, 121.16, 120.67, 109.33, 52.97, 51.82; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 477.1809, found: 477.1808.



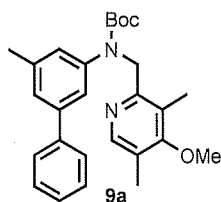
Dimethyl 5'-(isoquinolin-1-ylmethyl)-[1,1':3',1''-terphenyl]-2,2''-dicarboxylate (8l')

Substrate **41** was arylated following the general *meta*-arylation procedure using 2-norbornene. After purification by preparative thin-layer chromatography, Compound **81'** was obtained in 78% yield as a sole product.

^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 5.7 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.7 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.60–7.53 (m, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.41–7.32 (m, 4H), 7.22 (s, 2H), 7.10 (s, 1H), 4.73 (s, 2H), 3.41 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.07, 159.85, 142.02, 141.89, 141.41, 139.00, 136.61, 131.11, 131.03, 130.67, 129.86, 129.66, 127.57, 127.36, 127.23, 127.17, 127.14, 126.37, 125.90,

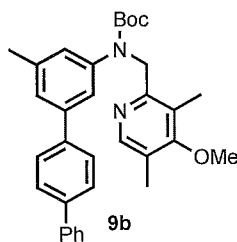
119.90, 51.70, 42.12; HRMS (ESI-TOF) m/z Calcd for $C_{32}H_{26}NO_4$ [M+H]⁺: 488.1856, found: 488.1857.**Scope of Aryl Iodides****General Procedure for meta-Arylation of Anilines:**

Substrate **1a** (0.1 mmol), Ar-I (0.2 mmol), Pd(OAc)₂ (2.2 mg, 10 mol%), Ligand (3.0 mg, 20 mol%), AgOAc (50.1 mg, 0.3 mmol), NBE-CO₂Me (21.6 mg, 0.15 mmol) and DCE (0.5 mL) were added to a 2-dram vial. The vial was capped and closed tightly. The reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC plate to afford the desired arylated product.

**tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-methyl-[1,1'-biphenyl]-3-yl)carbamate (9a)**

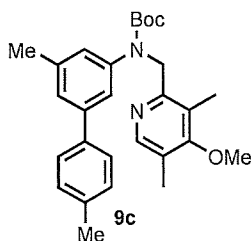
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9a** was obtained in 87% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.23 (s, 1H), 7.14 (s, 1H), 7.07 (s, 1H), 4.94 (s, 2H), 3.71 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.64,

155.20, 154.75, 148.96, 143.04, 141.14, 141.05, 138.35, 128.55, 127.08, 125.85, 125.23, 124.64, 123.74, 122.61, 80.25, 59.82, 53.55, 28.30, 21.46, 13.19, 10.44; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{33}N_2O_3$ $[M+H]^+$: 433.2486, found: 433.2487.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-methyl-[1,1':4',1''-terphenyl]-3-yl)carbamate (9b)

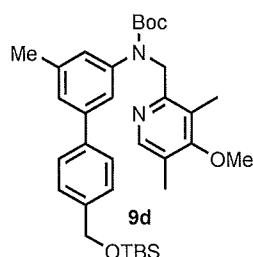
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9b** was obtained in 79% yield as a colorless solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.62 (d, $J = 8.0$ Hz, 4H), 7.56 (d, $J = 8.1$ Hz, 2H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.34 (t, $J = 7.3$ Hz, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.09 (s, 1H), 4.95 (s, 2H), 3.72 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.65, 155.20, 154.75, 148.97, 143.13, 140.67, 140.60, 139.94, 138.41, 137.83, 128.74, 127.41, 127.29, 127.25, 126.97, 125.97, 125.09, 124.65, 123.73, 122.48, 80.26, 59.82, 53.54, 28.30, 21.48, 13.19, 10.44; HRMS (ESI-TOF) m/z Calcd for $C_{33}H_{37}N_2O_3$ $[M+H]^+$: 509.2799, found: 509.2799.



tert-Butyl (4',5-dimethyl-[1,1'-biphenyl]-3-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9c)

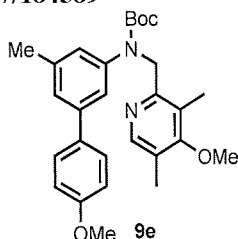
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9c** was obtained in 82% yield as a

colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.23–7.21 (m, 3H), 7.13 (s, 1H), 7.04 (s, 1H), 4.93 (s, 2H), 3.71 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 2.21 (s, 6H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.63, 155.21, 154.77, 148.94, 142.99, 141.04, 138.26, 138.15, 136.82, 129.26, 129.24, 126.89, 125.60, 125.04, 124.61, 123.73, 122.40, 80.20, 59.81, 53.55, 28.29, 28.26, 21.45, 21.05, 13.17, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 447.2642, found: 447.2643.



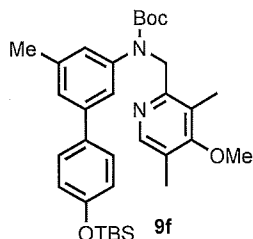
tert-Butyl (4'-(((tert-butyldimethylsilyl)oxy)methyl)-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9d)

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9d** was obtained in 83% yield as a light yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.21 (s, 1H), 7.14 (s, 1H), 7.05 (s, 1H), 4.94 (s, 2H), 4.76 (s, 2H), 3.71 (s, 3H), 2.33 (s, 3H), 2.21 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.65, 155.19, 154.76, 148.95, 142.98, 140.98, 140.34, 139.66, 138.30, 126.89, 126.29, 125.75, 125.15, 124.64, 123.77, 122.51, 80.23, 64.73, 59.81, 53.54, 28.29, 25.95, 21.46, 18.42, 13.18, 10.44, -5.24; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{34}\text{H}_{49}\text{N}_2\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 577.3456, found: 577.3456.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(4'-methoxy-5-methyl-[1,1'-biphenyl]-3-yl)carbamate (9e)

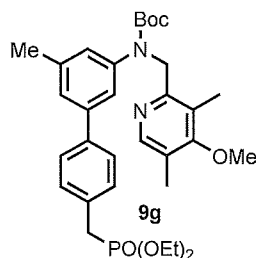
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9e** was obtained in 81% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.19 (s, 1H), 7.10 (s, 1H), 7.02 (s, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 4.93 (s, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 2.32 (s, 3H), 2.21 (s, 6H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.63, 158.98, 155.22, 154.77, 148.94, 143.01, 140.72, 138.27, 133.59, 128.06, 125.28, 124.82, 124.62, 123.74, 122.17, 113.98, 80.20, 59.82, 55.29, 53.55, 28.30, 21.46, 13.19, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₅N₂O₄ [M+H]⁺: 463.2591, found: 463.2591.



tert-Butyl (4'-((tert-butyldimethylsilyl)oxy)-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9f)

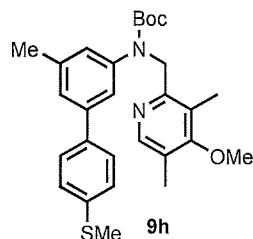
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9f** was obtained in 65% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.18 (s, 1H), 7.10 (s, 1H), 7.01 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 2H), 4.94 (s, 2H), 3.71 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H), 0.99 (s, 9H), 0.21 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 163.66, 155.23, 155.11, 154.77, 148.92, 142.91, 140.82,

138.24, 134.12, 128.00, 125.30, 124.88, 124.64, 123.82, 122.24, 120.14, 80.19, 59.81, 53.55, 28.30, 25.68, 21.45, 18.21, 13.18, 10.45, -4.40; HRMS (ESI-TOF) m/z Calcd for $C_{33}H_{47}N_2O_4Si$ $[M+H]^+$: 563.3300, found: 563.3300.



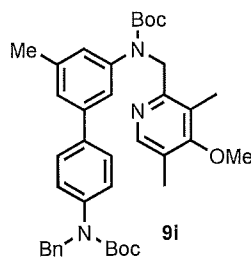
tert-Butyl (4'-((diethoxyphosphoryl)methyl)-5-methyl-[1,1'-biphenyl]-3-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) carbamate (9g)

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9g** was obtained in 92% yield as a colorless liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.43 (d, J = 7.9 Hz, 2H), 7.31 (dd, J = 8.3, 2.5 Hz, 2H), 7.23 (s, 1H), 7.13 (s, 1H), 7.06 (s, 1H), 4.94 (s, 2H), 4.12 - 3.94 (m, 4H), 3.72 (s, 3H), 3.17 (d, J = 21.6 Hz, 2H), 2.33 (s, 3H), 2.24-2.19 (m, 6H), 1.41 (s, 9H), 1.26 (t, J = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.63, 155.14, 154.72, 148.92, 143.06, 140.62, 139.56 (d, J = 4.1 Hz), 138.35, 130.43 (d, J = 9.0 Hz), 129.95 (d, J = 6.6 Hz), 127.15 (d, J = 3.3 Hz), 125.84, 125.03, 124.63, 123.71, 122.39, 80.25, 62.12 (d, J = 7.1 Hz), 59.81, 53.50, 33.36 (d, J = 138.4 Hz), 28.26, 21.43, 16.35 (d, J = 6.2 Hz), 13.17, 10.41; HRMS (ESI-TOF) m/z Calcd for $C_{32}H_{44}N_2O_6P$ $[M+H]^+$: 583.2932, found: 583.2931.



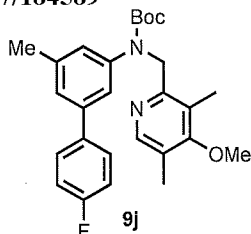
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-methyl-4'-(methylthio)-[1,1'-biphenyl]-3-yl) carbamate (9h)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9h** was obtained in 70% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 7.22 (s, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.93 (s, 2H), 3.72 (s, 3H), 2.50 (s, 3H), 2.33 (s, 3H), 2.21 (s, 6H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.65, 155.18, 154.74, 148.96, 143.14, 140.44, 138.42, 137.90, 137.33, 127.41, 126.80, 125.81, 124.87, 124.64, 123.72, 122.26, 80.27, 59.84, 53.54, 28.30, 21.47, 15.92, 13.20, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₅N₂O₃S [M+H]⁺: 479.2363, found: 479.2362.



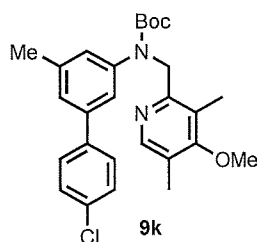
***tert*-Butyl (4'-(benzyl(tert-butoxycarbonyl)amino)-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9i)**

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9i** was obtained in 80% yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.33–7.27 (m, 2H), 7.27–7.14 (m, 6H), 7.10 (s, 1H), 7.05 (s, 1H), 4.92 (s, 2H), 4.85 (s, 2H), 3.70 (s, 3H), 2.31 (s, 3H), 2.24–2.16 (m, 6H), 1.43 (s, 9H), 1.40 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.63, 155.14, 154.74, 154.71, 148.94, 143.06, 141.90, 140.43, 138.61, 138.38, 138.33, 128.36, 127.29, 127.21, 127.02, 126.38, 125.79, 125.00, 124.61, 123.68, 122.39, 80.61, 80.24, 59.81, 53.89, 53.50, 28.26, 21.43, 13.17, 10.41; HRMS (ESI-TOF) *m/z* Calcd for C₃₉H₄₈N₃O₅ [M+H]⁺: 638.3588, found: 638.3588.



tert-Butyl (4'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9j)

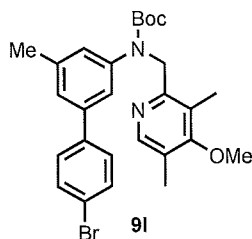
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9j** was obtained in 92% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.47 – 7.39 (m, 2H), 7.21 (s, 1H), 7.12 – 7.02 (m, 4H), 4.93 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.65, 162.31 (d, *J* = 246.4 Hz), 155.17, 154.69, 148.93, 143.13, 140.15, 138.45, 137.13, 128.59 (d, *J* = 8.3 Hz), 125.82, 125.05, 124.65, 123.71, 122.45, 115.38 (d, *J* = 21.1 Hz), 80.29, 59.82, 53.51, 28.27, 21.43, 13.18, 10.42; ¹⁹F NMR (376 MHz, CDCl₃) δ -116.22; HRMS (ESI-TOF) *m/z* Calcd for C₂₇H₃₂FN₂O₃ [M+H]⁺: 451.2391, found: 451.2391.



tert-Butyl (4'-chloro-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9k)

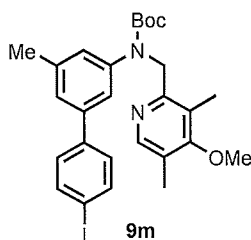
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9k** was obtained in 83% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.22 (s, 1H), 7.10 (s, 1H), 7.08 (s, 1H), 4.93 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.66, 155.13, 154.67, 148.94, 143.20, 139.89, 139.48, 138.55, 133.14, 128.69,

128.30, 126.14, 124.98, 124.68, 123.71, 122.39, 80.33,
59.83, 53.49, 28.27, 21.44, 13.19, 10.42. HRMS (ESI-TOF)
 m/z Calcd for $C_{27}H_{32}ClN_2O_3$ $[M+H]^+$: 467.2096, found: 467.2096.



tert-Butyl (4'-bromo-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9l)

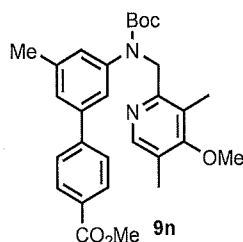
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9l** was obtained in 82% yield as a colorless solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.50 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 2H), 7.22 (s, 1H), 7.12-7.05 (m, 2H), 4.93 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.25-2.18 (m, 6H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.66, 155.13, 154.67, 148.94, 143.24, 139.95, 139.90, 138.57, 131.64, 128.66, 126.20, 124.92, 124.67, 123.69, 122.35, 121.31, 80.33, 59.83, 53.49, 28.27, 21.43, 13.20, 10.42; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}BrN_2O_3$ $[M+H]^+$: 511.1591, found: 511.1592.



tert-Butyl (4'-iodo-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9m)

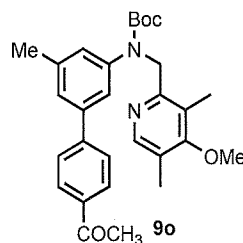
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9m** was obtained in 67% yield as a colorless solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.25-7.17 (m, 3H), 7.09 (s, 2H), 4.93 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.21 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.66, 155.12,

154.67, 148.95, 143.25, 140.56, 139.96, 138.59, 137.63, 128.94, 126.26, 124.87, 124.68, 123.71, 122.30, 92.81, 80.34, 59.84, 53.49, 28.27, 21.44, 13.20, 10.43; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}IN_2O_3$ $[M+H]^+$: 559.1452, found: 559.1451.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-methyl-[1,1'-biphenyl]-4-carboxylate (9n)

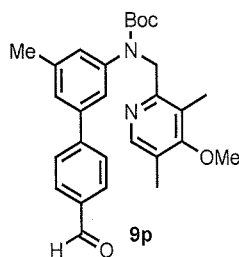
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9n** was obtained in 92% yield as a colorless liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.29 (s, 1H), 7.18 (s, 1H), 7.12 (s, 1H), 4.94 (s, 2H), 3.93 (s, 3H), 3.72 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.96, 163.70, 155.08, 154.65, 148.92, 145.47, 143.22, 139.92, 138.63, 129.90, 128.69, 126.96, 126.73, 125.26, 124.73, 123.76, 122.71, 80.38, 59.83, 53.45, 52.06, 28.26, 21.43, 13.19, 10.43; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_5$ $[M+H]^+$: 491.2540, found: 491.2541.



tert-Butyl (4'-acetyl-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9o)

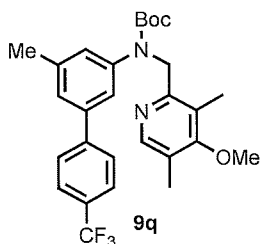
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9o** was obtained in 87% yield as a

colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.98 (d, $J = 8.2$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H), 7.31 (s, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 4.94 (s, 2H), 3.72 (s, 3H), 2.62 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 197.71, 163.67, 155.08, 154.65, 148.95, 145.64, 143.31, 139.79, 138.66, 135.69, 128.72, 127.14, 126.79, 125.22, 124.70, 123.69, 122.68, 80.39, 59.83, 53.47, 28.26, 26.61, 21.44, 13.19, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 475.2591, found: 475.2591.



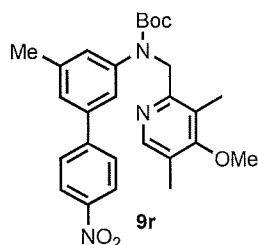
tert-Butyl (4'-formyl-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9p)

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9p** was obtained in 96% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 10.03 (s, 1H), 8.18 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.64 (d, $J = 8.1$ Hz, 2H), 7.33 (s, 1H), 7.19 (s, 1H), 7.15 (s, 1H), 4.94 (s, 2H), 3.73 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.90, 163.69, 155.08, 154.63, 148.96, 147.08, 143.38, 139.65, 138.77, 135.05, 130.10, 127.62, 127.02, 125.31, 124.74, 123.71, 122.79, 80.44, 59.85, 53.47, 28.26, 21.45, 13.21, 10.44; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 461.2435, found: 461.2436.



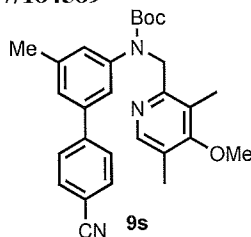
***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl) carbamate (9q)**

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9q** was obtained in 97% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.29 (s, 1H), 7.19–7.09 (m, 2H), 4.94 (s, 2H), 3.72 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.68, 155.10, 154.65, 148.96, 144.57, 143.36, 139.68, 138.71, 129.14 (q, *J* = 32.6 Hz), 127.34, 126.70, 125.50 (q, *J* = 3.4 Hz), 125.22, 124.71, 124.21 (q, *J* = 271.8 Hz); 123.69, 122.69, 80.41, 59.84, 53.47, 28.26, 21.43, 13.20, 10.42; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.62; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₂F₃N₂O₃ [M+H]⁺: 501.2360, found: 501.2360.



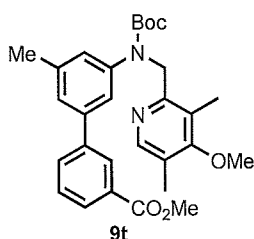
***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-methyl-4'-nitro-[1,1'-biphenyl]-3-yl) carbamate (9r)**

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9r** was obtained in 88% yield as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 8.6 Hz, 2H), 8.18 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.36 (s, 1H), 7.22–7.15 (m, 2H), 4.94 (s, 2H), 3.74 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 2.23 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.70, 155.02, 154.57, 148.96, 147.50, 146.91, 143.57, 138.96, 138.69, 127.72, 127.37, 125.24, 124.77, 123.92, 123.67, 122.76, 80.53, 59.87, 53.41, 28.24, 21.44, 13.22, 10.42; HRMS (ESI-TOF) *m/z* Calcd for C₂₇H₃₂N₃O₅ [M+H]⁺: 478.2336, found: 478.2336.



tert-Butyl (4'-cyano-5-methyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9s)

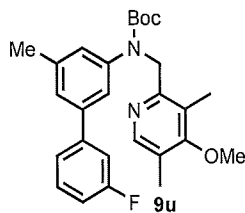
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9s** was obtained in 89% yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.31 (s, 1H), 7.19-7.12 (m, 2H), 4.93 (s, 2H), 3.73 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.40 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.70, 155.02, 154.57, 148.93, 145.53, 143.47, 139.11, 138.89, 132.41, 127.67, 127.12, 125.12, 124.76, 123.70, 122.61, 118.94, 110.68, 80.49, 59.86, 53.39, 28.24, 21.43, 13.21, 10.42; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₂N₃O₃ [M+H]⁺: 458.2438, found: 458.2438.



Methyl 3'-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5'-methyl-[1,1'-biphenyl]-3-carboxylate (9t)

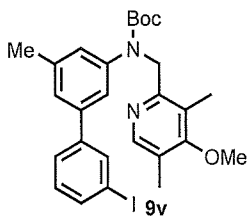
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9t** was obtained in 88% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 2H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.29 (s, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 4.95 (s, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.42 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 167.01, 163.68, 155.10, 154.69, 148.95, 143.19, 141.30, 140.03, 138.60, 131.50, 130.48, 128.66,

128.20, 126.24, 125.18, 124.69, 123.75, 122.64, 80.37, 59.83, 53.47, 52.13, 28.28, 21.44, 13.19, 10.44; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_5$ $[M+H]^+$: 491.2540, found: 491.2541.



tert-Butyl (3'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9u)

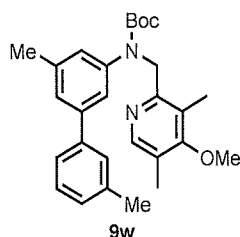
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9u** was obtained in 86% yield as a colorless liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.38–7.28 (m, 1H), 7.25 (d, $J = 6.2$ Hz, 1H), 7.20 (s, 1H), 7.18–7.07 (m, 3H), 6.98 (td, $J = 7.7, 2.1$ Hz, 1H), 4.94 (s, 2H), 3.72 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.69, 163.01 (d, $J = 245.4$ Hz), 155.15, 154.68, 148.97, 143.33 (d, $J = 7.6$ Hz), 143.15, 139.86, 138.57, 129.98 (d, $J = 8.6$ Hz), 126.47, 125.14, 124.73, 123.79, 122.68 (d, $J = 2.6$ Hz), 122.60, 113.95 (d, $J = 10.8$ Hz), 113.81 (d, $J = 9.9$ Hz), 80.34, 59.82, 53.52, 28.27, 21.43, 13.18, 10.44; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.61; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{32}FN_2O_3$ $[M+H]^+$: 451.2391, found: 451.2391.



tert-Butyl (3'-iodo-5-methyl-[1,1'-biphenyl]-3-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9v)

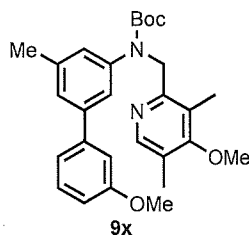
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9v** was obtained in 74% yield as a light

yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.80 (d, $J = 1.7$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.43 (d, $J = 7.8$ Hz, 1H), 7.17 (s, 1H), 7.14–7.06 (m, 3H), 4.93 (s, 2H), 3.73 (s, 3H), 2.33 (s, 3H), 2.22 (s, 6H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.70, 155.11, 154.67, 148.97, 143.29, 143.12, 139.53, 138.60, 136.08, 135.97, 130.22, 126.44, 126.34, 125.14, 124.73, 123.81, 122.59, 94.57, 80.37, 77.21, 59.88, 53.51, 28.29, 21.43, 13.25, 10.46; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{32}\text{IN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 559.1452, found: 559.1453.



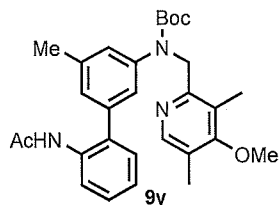
***tert*-Butyl (3',5-dimethyl-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9w)**

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9w** was obtained in 82% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.31–7.23 (m, 3H), 7.20 (s, 1H), 7.16–7.09 (m, 2H), 7.05 (s, 1H), 4.94 (s, 2H), 3.71 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 2.25–2.19 (m, 6H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.66, 155.23, 154.77, 148.94, 142.95, 141.26, 141.02, 138.28, 138.06, 128.44, 127.88, 127.83, 125.79, 125.27, 124.62, 124.17, 123.79, 122.67, 80.21, 59.81, 53.56, 28.30, 21.49, 21.45, 13.18, 10.44; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 447.2642, found: 447.2643.



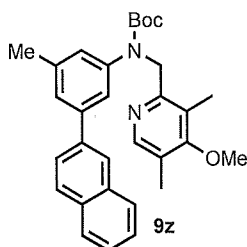
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3'-methoxy-5-methyl-[1,1'-biphenyl]-3-yl)-carbamate (9x)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9x** was obtained in 85% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.21 (s, 1H), 7.14 (s, 1H), 7.11-7.02 (m, 2H), 6.99 (t, *J* = 2.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.94 (s, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.66, 159.76, 155.18, 154.75, 148.95, 143.01, 142.59, 141.01, 138.34, 129.52, 126.05, 125.26, 124.66, 123.77, 122.67, 119.61, 112.80, 112.54, 80.25, 59.82, 55.24, 53.54, 28.30, 21.45, 13.18, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₅N₂O₄ [M+H]⁺: 463.2591, found: 463.2591.



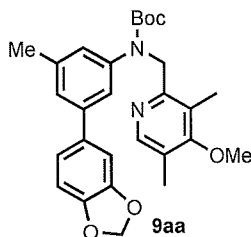
tert-Butyl (2'-acetamido-5-methyl-[1,1'-biphenyl]-3-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) carbamate (9y)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9y** was obtained in 91% yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 8.3 Hz, 1H), 8.16 (s, 1H), 7.64 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.25-7.17 (m, 2H), 7.14-7.07 (m, 2H), 6.94 (s, 1H), 4.89 (s, 2H), 3.74 (s, 3H), 2.33 (s, 3H), 2.23 (s, 6H), 2.11 (s, 3H), 1.35 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 169.01, 163.66, 155.11, 154.76, 148.93, 143.31, 139.42, 137.74, 135.06, 131.34, 129.69, 128.20, 127.12, 125.19, 124.70, 124.64, 123.33, 121.30, 80.44, 59.88, 53.27, 28.12, 24.53, 21.43, 13.20, 10.38; HRMS (ESI-TOF) *m/z* Calcd for C₂₉H₃₆N₃O₄ [M+H]⁺: 490.2700, found: 490.2700.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(naphthalen-2-yl)phenyl) carbamate (9z)

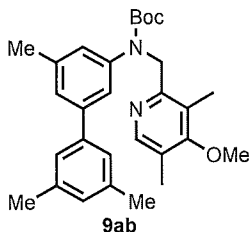
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9z** was obtained in 76% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 7.92 (s, 1H), 7.89-7.81 (m, 3H), 7.63 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.52-7.42 (m, 2H), 7.36 (s, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 4.97 (s, 2H), 3.71 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.43 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ 163.68, 155.22, 154.77, 148.98, 143.14, 141.03, 138.48, 138.38, 133.54, 132.52, 128.17, 128.10, 127.56, 126.16, 125.98, 125.78, 125.67, 125.58, 125.48, 124.67, 123.79, 122.90, 80.29, 59.83, 53.57, 28.31, 21.50, 13.21, 10.47; HRMS (ESI-TOF) *m/z* Calcd for C₃₁H₃₅N₂O₃ [M+H]⁺: 483.2642, found: 483.2642.



tert-Butyl (3-(benzo[d][1,3]dioxol-5-yl)-5-methylphenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) carbamate (9aa)

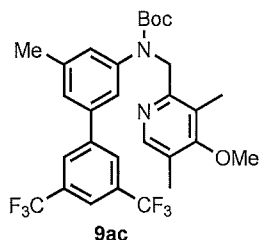
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9aa** was obtained in 72% yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.13 (s, 1H), 7.06 (s, 1H), 7.03 (s, 1H), 6.97-6.90 (m, 2H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.97 (s, 2H), 4.93 (s, 2H), 3.72 (s, 3H), 2.32 (s, 3H), 2.22 (s, 6H), 1.41 (s, 9H); ¹³C

NMR (150 MHz, CDCl₃) δ 163.66, 155.21, 154.72, 148.95, 147.88, 146.88, 142.98, 140.83, 138.33, 135.44, 125.59, 124.99, 124.68, 123.79, 122.37, 120.51, 108.37, 107.62, 101.03, 80.24, 59.82, 53.54, 28.29, 21.44, 13.18, 10.43; HRMS (ESI-TOF) m/z Calcd for C₂₈H₃₃N₂O₅ [M+H]⁺: 477.2384, found: 477.2384.



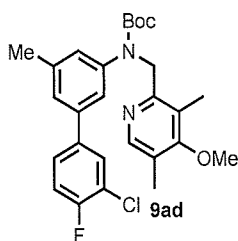
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3',5,5'-trimethyl-[1,1'-biphenyl]-3-yl)-carbamate (9ab)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ab** was obtained in 85% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 7.08 (s, 2H), 7.04 (s, 1H), 6.94 (s, 1H), 4.94 (s, 2H), 3.71 (s, 3H), 2.34 (s, 6H), 2.32 (s, 3H), 2.21 (s, 6H), 1.42 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.66, 155.26, 154.79, 148.94, 142.85, 141.36, 141.04, 138.22, 137.98, 128.72, 125.74, 125.32, 125.01, 124.61, 123.83, 122.72, 80.19, 59.82, 53.58, 28.30, 21.44, 21.35, 13.19, 10.46; HRMS (ESI-TOF) m/z Calcd for C₂₉H₃₇N₂O₃ [M+H]⁺: 461.2799, found: 461.2799.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-carbamate (9ac)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ac** was obtained in 94% yield as a light yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.89 (s, 2H), 7.81 (s, 1H), 7.28 (s, 1H), 7.19 (s, 1H), 7.15 (s, 1H), 4.95 (s, 2H), 3.73 (s, 3H), 2.37 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.42 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.80, 154.97, 154.60, 148.96, 143.61, 143.15, 139.22, 138.13, 131.87 (q, *J* = 33.3 Hz), 127.42, 127.18, 125.12, 124.92, 123.84, 123.29 (q, *J* = 273.3 Hz), 122.81, 120.72, 80.64, 59.85, 53.43, 28.26, 21.43, 13.17, 10.46; ¹⁹F NMR (376 MHz, CDCl₃) δ -63.09; HRMS (ESI-TOF) *m/z* Calcd for C₂₉H₃₁F₆N₂O₃ [M+H]⁺: 569.2233, found: 569.2233.

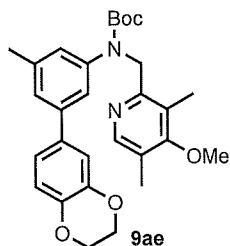


tert-Butyl (3'-chloro-4'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-carbamate (9ad)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ad** was obtained in 82% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.46 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.32 (ddd, *J* = 8.6, 4.6, 2.3 Hz, 1H), 7.20-7.11 (m, 2H), 7.10 (s, 1H), 7.07 (s, 1H), 4.93 (s, 2H), 3.73 (s, 3H), 2.33 (s, 3H), 2.26-2.19 (m, 6H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.72, 157.48 (d, *J* = 248.7 Hz), 155.12, 154.63, 148.96, 143.22, 138.91, 138.71, 138.32 (d, *J* = 4.1 Hz), 129.14, 126.70 (d, *J* = 6.9 Hz), 126.40, 125.01, 124.77, 123.80, 122.47, 120.97 (d, *J* = 17.8 Hz), 116.60 (d, *J* = 21.2 Hz), 80.41, 59.86, 53.49, 28.27, 21.42, 13.21, 10.45; ¹⁹F NMR (376 MHz, CDCl₃) δ -118.58; HRMS

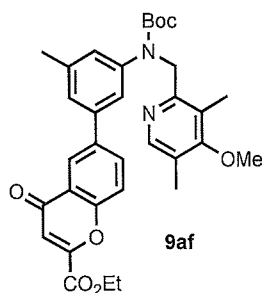
(ESI-TOF) m/z Calcd for $C_{27}H_{31}ClFN_2O_3$ $[M+H]^+$: 485.2002,

found: 485.2002.



tert-Butyl (3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9ae)

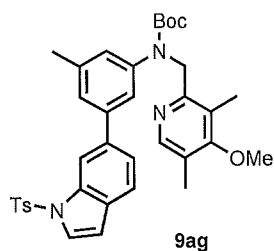
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9ae** was obtained in 82% yield as a colorless solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.12 (s, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.98-6.93 (m, 2H), 6.86 (d, J = 8.7 Hz, 1H), 4.93 (s, 2H), 4.26 (s, 4H), 3.72 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.69, 155.18, 154.74, 148.91, 143.48, 142.99, 142.88, 140.49, 138.26, 134.63, 125.54, 124.90, 124.69, 123.85, 122.27, 120.07, 117.30, 115.77, 80.20, 64.40, 64.36, 59.80, 53.49, 28.29, 21.43, 13.16, 10.43; HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{35}N_2O_5$ $[M+H]^+$: 491.2540, found: 491.2540.



Ethyl 6-(3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5-methylphenyl)-4-oxo-4H-chromene-2-carboxylate (9af)

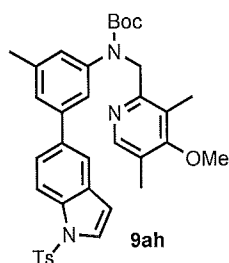
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9af** was obtained in 80% yield as a light yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 2.3

Hz, 1H), 8.19 (s, 1H), 7.89 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.64 (d, $J = 8.8$ Hz, 1H), 7.34 (s, 1H), 7.23 (s, 1H), 7.17–7.10 (m, 2H), 4.95 (s, 2H), 4.48 (q, $J = 7.1$ Hz, 2H), 3.73 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 1.45 (t, $J = 7.1$ Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 178.40, 163.69, 160.49, 155.23, 155.07, 154.62, 152.12, 148.96, 143.36, 138.95, 138.88, 138.83, 133.64, 126.70, 125.27, 124.76, 124.40, 123.75, 123.30, 122.62, 119.08, 114.64, 80.41, 62.98, 59.85, 53.44, 28.25, 21.40, 14.06, 13.19, 10.45; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{33}\text{H}_{37}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$: 573.2595, found: 573.2593.



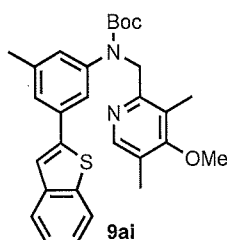
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(1-tosyl-1H-indol-6-yl)phenyl)carbamate (9ag)

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9ag** was obtained in 72% yield as a colorless solid. mp = 100 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H), 8.12 (s, 1H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 3.7$ Hz, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.35 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.32 (s, 1H), 7.22–7.16 (m, 3H), 7.11 (s, 1H), 6.63 (d, $J = 3.6$ Hz, 1H), 4.98 (s, 2H), 3.71 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.66, 155.08, 154.79, 149.03, 144.88, 143.13, 141.30, 138.39, 138.00, 135.32, 135.21, 129.86, 129.81, 126.76, 126.69, 125.78, 125.46, 124.70, 123.64, 122.98, 122.80, 121.26, 111.92, 108.82, 80.33, 59.83, 53.48, 28.30, 21.51, 13.20, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{36}\text{H}_{40}\text{N}_3\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 626.2683, found: 626.2683.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(1-tosyl-1H-indol-5-yl)phenyl)carbamate (9ah)

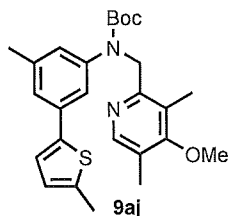
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ah** was obtained in 83% yield as a colorless solid. mp = 92 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.60 (s, 1H), 7.55 (d, *J* = 3.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.27-7.19 (m, 3H), 7.13 (s, 1H), 7.05 (s, 1H), 6.65 (d, *J* = 3.7 Hz, 1H), 4.94 (s, 2H), 3.71 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H), 2.25-2.17 (m, 6H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.64, 155.20, 154.71, 148.92, 144.92, 143.02, 141.16, 138.35, 136.63, 135.21, 134.11, 131.12, 129.86, 126.80, 126.74, 125.59, 125.39, 124.62, 124.14, 123.74, 122.76, 119.72, 113.51, 109.27, 80.23, 59.81, 53.53, 28.27, 21.52, 21.44, 13.18, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C₃₆H₄₀N₃O₅S [M+H]⁺: 626.2683, found: 626.2684.



tert-Butyl (3-(benzo[b]thiophen-2-yl)-5-methylphenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9ai)

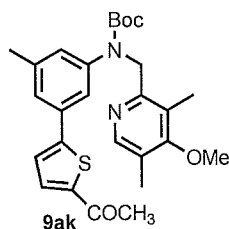
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ai** was obtained in 84% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.43 (s, 1H), 7.39 (s, 1H), 7.36-7.25 (m, 3H), 7.07 (s, 1H), 4.94 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H),

2.21 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.69, 154.99, 154.63, 149.01, 144.10, 143.25, 140.57, 139.35, 138.68, 134.09, 126.83, 124.71, 124.39, 124.38, 124.17, 123.73, 123.44, 122.15, 122.08, 119.34, 80.46, 59.84, 53.35, 28.29, 21.38, 13.20, 10.44; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 489.2206, found: 489.2206.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-(5-methylthiophen-2-yl)phenyl)carbamate (9aj)

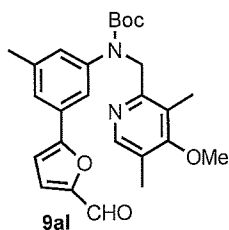
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9aj** was obtained in 76% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.20 (s, 1H), 7.10 (s, 1H), 6.98 (d, $J = 3.5$ Hz, 1H), 6.96 (s, 1H), 6.67 (d, $J = 3.5$ Hz, 1H), 4.91 (s, 2H), 3.71 (s, 3H), 2.47 (s, 3H), 2.28 (s, 3H), 2.21 (s, 6H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.64, 155.06, 154.68, 148.97, 143.09, 141.82, 139.17, 138.44, 134.49, 125.98, 125.57, 124.62, 123.71, 123.48, 122.74, 121.10, 80.29, 59.82, 53.38, 28.28, 21.36, 15.40, 13.18, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 453.2206, found: 453.2206.



tert-Butyl (3-(5-acetylthiophen-2-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9ak)

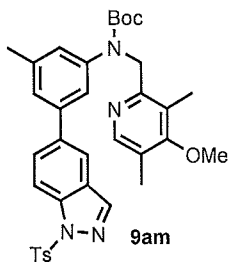
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9ak** was obtained in 98% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H),

7.61 (d, $J = 3.9$ Hz, 1H), 7.34 (s, 1H), 7.25–7.18 (m, 2H), 7.12 (s, 1H), 4.91 (s, 2H), 3.74 (s, 3H), 2.54 (s, 3H), 2.32 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 190.49, 163.69, 154.88, 154.50, 152.73, 148.99, 143.48, 142.79, 138.92, 133.32, 133.15, 127.62, 124.78, 124.08, 123.80, 123.65, 121.75, 80.52, 59.85, 53.30, 28.22, 26.47, 21.32, 13.19, 10.40; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 481.2156, found: 481.2156.



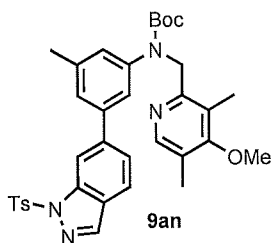
***tert*-Butyl (3-(5-formylfuran-2-yl)-5-methylphenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9al)**

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9al** was obtained in 87% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 9.61 (s, 1H), 8.17 (s, 1H), 7.52 (s, 1H), 7.42 (s, 1H), 7.28 (d, $J = 3.8$ Hz, 1H), 7.14 (s, 1H), 6.74 (d, $J = 3.7$ Hz, 1H), 4.92 (s, 2H), 3.74 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.11, 163.71, 159.35, 154.89, 154.52, 151.84, 148.94, 143.46, 139.00, 128.93, 128.53, 124.76, 123.70, 123.52, 123.15, 120.87, 107.72, 80.54, 59.87, 53.29, 28.22, 21.30, 13.19, 10.44; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 451.2227, found: 451.2227.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(1-tosyl-1H-indazol-5-yl)phenyl)carbamate (9am)**

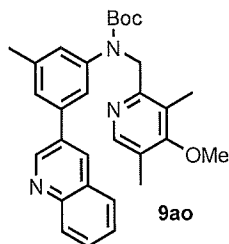
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9am** was obtained in 63% yield as a light yellow solid. mp = 137 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.24-8.15 (m, 3H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.75 (s, 1H), 7.69 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.29 (s, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.14 (s, 1H), 7.10 (s, 1H), 4.94 (s, 2H), 3.72 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 163.67, 155.15, 154.65, 148.93, 145.37, 143.29, 141.55, 140.24, 139.58, 138.64, 137.76, 134.50, 129.83, 129.12, 127.50, 126.43, 126.02, 125.35, 124.68, 123.69, 122.78, 119.28, 113.20, 80.36, 59.84, 53.49, 28.26, 21.60, 21.45, 13.21, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C₃₅H₃₉N₄O₅S [M+H]⁺: 627.2636, found: 627.2635.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(1-tosyl-1H-indazol-6-yl)phenyl)carbamate (9an)**

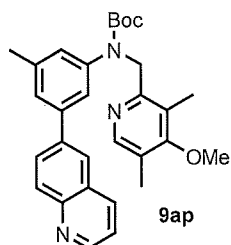
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9an** was obtained in 61% yield as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.41 (s, 1H), 7.26-7.20 (m, 3H), 7.17 (s, 1H), 4.97 (s, 2H), 3.73 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H), 1.44 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.69, 155.02, 154.75, 149.04, 145.32, 143.40, 142.70, 141.11, 140.91, 140.40, 138.71, 134.55, 129.83, 127.51, 126.63, 125.66, 124.85, 124.74, 124.23, 123.62, 123.12, 121.24, 111.17, 80.46, 59.86, 53.47, 28.28, 21.59, 21.48, 13.21,

10.43; HRMS (ESI-TOF) m/z Calcd for $C_{35}H_{39}N_4O_5S$ $[M+H]^+$:
627.2636, found: 627.2636.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(quinolin-3-yl)phenyl)carbamate (9ao)

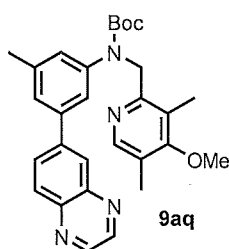
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9ao** was obtained in 54% yield as a colorless solid. 1H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, $J = 2.2$ Hz, 1H), 8.21 (d, $J = 2.2$ Hz, 1H), 8.20 (s, 1H), 8.11 (d, $J = 8.5$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.70 (t, $J = 7.7$ Hz, 1H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.43 (s, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 4.96 (s, 2H), 3.73 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.69, 155.04, 154.67, 149.94, 149.02, 147.26, 143.64, 138.96, 137.79, 133.70, 133.14, 129.25, 129.16, 127.94, 126.89, 126.62, 125.32, 124.74, 123.63, 122.75, 80.48, 59.86, 53.49, 28.29, 21.50, 13.22, 10.43; HRMS (ESI-TOF) m/z Calcd for $C_{30}H_{34}N_3O_3$ $[M+H]^+$: 484.2595, found: 484.2593.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(quinolin-6-yl)phenyl)carbamate (9ap)

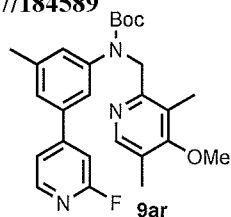
Following the general *meta*-arylation procedure using 20 mol% of $Pd(OAc)_2$ and 40 mol% of **L12**, Compound **9ap** was obtained in 41% yield as a light yellow liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, $J = 4.3, 1.7$ Hz, 1H), 8.22-

8.16 (m, 2H), 8.12 (d, $J = 8.7$ Hz, 1H), 7.91 (d, $J = 2.0$ Hz, 1H), 7.87 (dd, $J = 8.7, 2.1$ Hz, 1H), 7.41 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 7.13 (s, 1H), 4.97 (s, 2H), 3.73 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.72, 155.18, 154.72, 150.25, 148.98, 147.60, 143.29, 140.25, 139.18, 138.68, 136.20, 129.65, 129.25, 128.36, 126.37, 125.51, 125.39, 124.73, 123.81, 122.94, 121.39, 80.40, 59.86, 53.54, 28.31, 21.50, 13.22, 10.47; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{30}\text{H}_{34}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 484.2595, found: 484.2592.



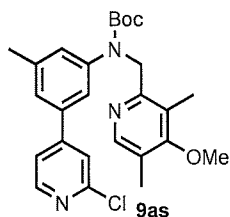
***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(quinoxalin-6-yl)phenyl)carbamate (9aq)**

Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9aq** was obtained in 63% yield as a yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.85 (d, $J = 1.8$ Hz, 1H), 8.82 (d, $J = 1.8$ Hz, 1H), 8.19 (s, 2H), 8.13 (d, $J = 8.7$ Hz, 1H), 7.96 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.44 (s, 1H), 7.32 (s, 1H), 7.19 (s, 1H), 4.97 (s, 2H), 3.74 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.71, 155.09, 154.66, 149.01, 145.30, 144.62, 143.47, 143.17, 142.77, 142.29, 139.51, 138.86, 129.87, 129.58, 126.94, 126.75, 125.58, 124.78, 123.75, 122.97, 80.44, 59.86, 53.49, 28.28, 21.49; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{29}\text{H}_{33}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 485.2547, found: 485.2547.



tert-Butyl (3-(2-fluoropyridin-4-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9ar)

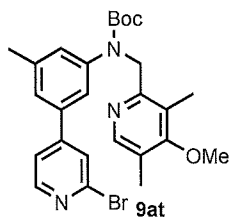
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ar** was obtained in 90% yield as a light yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 5.3 Hz, 1H), 8.18 (s, 1H), 7.33 (s, 1H), 7.30 (d, *J* = 5.2 Hz, 1H), 7.21 (s, 1H), 7.18 (s, 1H), 7.00 (s, 1H), 4.93 (s, 2H), 3.74 (s, 3H), 2.36 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 164.36 (d, *J* = 237.8 Hz), 163.74, 154.94, 154.52, 153.98, 153.93, 148.96, 147.74 (d, *J* = 15.4 Hz), 143.61, 139.11, 136.99, 128.18, 124.87, 123.74, 122.46, 119.49 (d, *J* = 3.9 Hz), 107.00 (d, *J* = 38.3 Hz), 80.59, 59.86, 53.35, 28.23, 21.40, 13.20, 10.42; ¹⁹F NMR (376 MHz, CDCl₃) δ -68.68; HRMS (ESI-TOF) *m/z* Calcd for C₂₆H₃₁FN₃O₃ [M+H]⁺: 452.2344, found: 452.2344.



tert-Butyl (3-(2-chloropyridin-4-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9as)

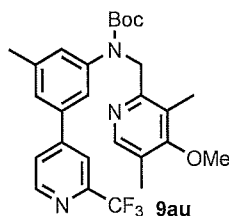
Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9as** was obtained in 96% yield as a colorless liquid. Only 9% NMR yield was obtained in the absence of **L12**. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 5.2 Hz, 1H), 8.18 (s, 1H), 7.41 (s, 1H), 7.33 (dd, *J* = 5.2, 1.5 Hz, 1H), 7.30 (s, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 4.93 (s, 2H), 3.74 (s, 3H), 2.36 (s, 3H), 2.24 (s, 6H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.74, 154.94,

154.50, 151.97, 151.44, 149.79, 148.96, 143.62, 139.16, 136.76, 128.20, 124.87, 124.84, 123.74, 122.47, 121.97, 120.46, 80.59, 59.87, 53.36, 28.22, 21.39, 13.21, 10.42; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{31}ClN_3O_3$ $[M+H]^+$: 468.2048, found: 468.2048.



tert-Butyl (3-(2-bromopyridin-4-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9at)

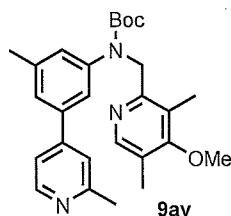
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9at** was obtained in 56% yield as a light yellow liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, $J = 5.2$ Hz, 1H), 8.18 (s, 1H), 7.57 (s, 1H), 7.36 (dd, $J = 5.2$, 1.5 Hz, 1H), 7.29 (s, 1H), 7.20 (s, 1H), 7.15 (s, 1H), 4.93 (s, 2H), 3.74 (s, 3H), 2.36 (s, 3H), 2.23 (s, 6H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.77, 154.92, 154.51, 151.18, 150.19, 148.95, 143.60, 142.70, 139.17, 136.64, 128.22, 125.78, 124.90, 124.88, 123.78, 122.49, 120.84, 80.62, 59.89, 53.34, 28.24, 21.40, 13.24, 10.44; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{31}BrN_3O_3$ $[M+H]^+$: 512.1543, found: 512.1540.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-(2-(trifluoromethyl)pyridin-4-yl)-phenyl)-carbamate (9au)

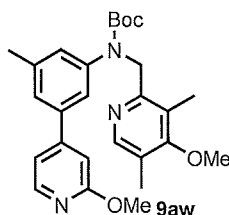
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9au** was obtained in 93% yield as a light yellow liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, $J = 5.1$

Hz, 1H), 8.18 (s, 1H), 7.77 (s, 1H), 7.60 (d, $J = 3.5$ Hz, 1H), 7.39 (s, 1H), 7.24 (s, 1H), 7.21 (s, 1H), 4.94 (s, 2H), 3.74 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.76, 154.90, 154.52, 150.27, 150.10, 148.96, 149.49 (q, $J = 33.2$ Hz), 143.80, 139.32, 136.79, 128.33, 124.88, 124.86, 124.10, 123.73, 122.54, 121.61 (q, $J = 274.4$ Hz), 118.40 (q, $J = 3.0$ Hz), 80.67, 59.86, 53.34, 28.23, 21.41, 13.18, 10.42; ^{19}F NMR (376 MHz, CDCl_3) δ -68.23; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{31}\text{F}_3\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 502.2312, found: 502.2312.



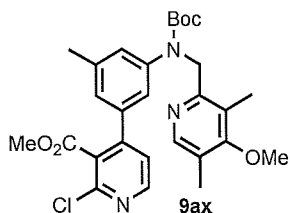
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-(2-methylpyridin-4-yl)phenyl)carbamate (9av)

Following the general *meta*-arylation procedure using 20 mol% of $\text{Pd}(\text{OAc})_2$ and 40 mol% of **L12**, Compound **9av** was obtained in 42% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, $J = 5.2$ Hz, 1H), 8.18 (s, 1H), 7.31 (s, 1H), 7.26 (s, 1H), 7.20 (d, $J = 5.2$ Hz, 1H), 7.17 (s, 1H), 7.16 (s, 1H), 4.93 (s, 2H), 3.73 (s, 3H), 2.59 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.69, 158.62, 155.06, 154.60, 149.38, 148.95, 148.54, 143.40, 138.81, 138.38, 127.42, 124.93, 124.73, 123.72, 122.47, 121.15, 118.82, 80.44, 59.84, 53.44, 28.26, 24.52, 21.42, 13.20, 10.43; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{34}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 448.2595, found: 448.2596.



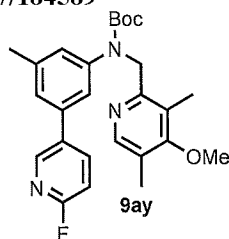
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-(2-methoxypyridin-4-yl)-5-methylphenyl) carbamate (9aw)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9aw** was obtained in 55% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 8.15 (d, *J* = 5.4 Hz, 1H), 7.26 (s, 1H), 7.16 (s, 2H), 7.00 (dd, *J* = 5.4, 1.5 Hz, 1H), 6.81 (s, 1H), 4.93 (s, 2H), 3.96 (s, 3H), 3.73 (s, 3H), 2.34 (s, 3H), 2.22 (s, 6H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 164.75, 163.73, 155.03, 154.61, 151.08, 148.97, 147.00, 143.32, 138.77, 138.21, 127.54, 124.94, 124.80, 123.77, 122.46, 115.38, 108.37, 80.46, 59.84, 53.46, 53.43, 28.26, 21.42, 13.20, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C²⁷H³⁴N³O⁴ [M+H]⁺: 464.2544, found: 464.2544.



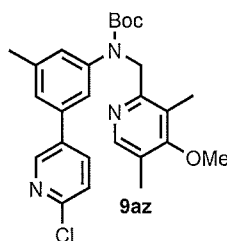
Methyl 4-(3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5-methyl-phenyl)-2-chloronicotinate (9ax)

Following the general *meta*-arylation procedure using NBE-CO₂Me, Compound **9ax** was obtained in 51% yield as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 5.1 Hz, 1H), 8.18 (s, 1H), 7.24–7.19 (m, 2H), 7.17 (s, 1H), 6.96 (s, 1H), 4.88 (s, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 2.32 (s, 3H), 2.225 (s, 3H), 2.217 (s, 3H), 1.37 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 166.19, 163.68, 154.86, 154.45, 150.21, 149.72, 148.97, 147.93, 143.57, 138.86, 136.58, 128.83, 127.89, 125.55, 124.74, 123.48, 123.09, 123.05, 80.52, 59.88, 53.32, 52.70, 28.18, 21.36, 13.22, 10.37; HRMS (ESI-TOF) *m/z* Calcd for C₂₈H₃₃ClN₃O₅ [M+H]⁺: 526.2103, found: 526.2103.



tert-Butyl (3-(6-fluoropyridin-3-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9ay)

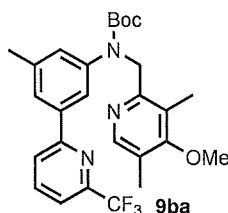
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9ay** was obtained in 52% yield as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, J = 2.6 Hz, 1H), 8.17 (s, 1H), 7.88 (td, J = 8.0, 2.6 Hz, 1H), 7.26 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 6.95 (dd, J = 8.5, 3.0 Hz, 1H), 4.93 (s, 2H), 3.73 (s, 3H), 2.35 (s, 3H), 2.26–2.20 (m, 6H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.70, 162.98 (d, J = 238.4 Hz), 155.02, 154.60, 148.97, 145.74 (d, J = 14.9 Hz), 143.59, 139.68 (d, J = 7.8 Hz), 138.95, 136.60, 134.70 (d, J = 4.6 Hz), 126.67, 124.93, 124.75, 123.64, 122.41, 109.22 (d, J = 37.5 Hz), 80.48, 59.85, 53.44, 28.25, 21.42, 13.20, 10.41; ^{19}F NMR (376 MHz, CDCl_3) δ -71.02; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{26}\text{H}_{31}\text{FN}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 452.2344, found: 452.2344.



tert-Butyl (3-(6-chloropyridin-3-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9az)

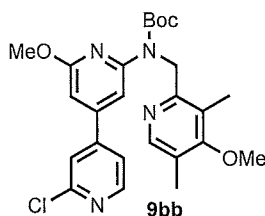
Following the general *meta*-arylation procedure using NBE- CO_2Me , Compound **9az** was obtained in 52% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 2.5 Hz, 1H), 8.17 (s, 1H), 7.75 (dd, J = 8.2, 2.6 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 7.09 (s, 1H), 4.92 (s, 2H), 3.73 (s, 3H), 2.35 (s, 3H), 2.22 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.70,

154.96, 154.59, 150.12, 148.98, 147.93, 143.68, 139.05, 137.15, 136.39, 135.51, 126.93, 124.87, 124.77, 124.04, 123.64, 122.34, 80.54, 59.87, 53.41, 28.24, 21.43, 13.21, 10.40; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{31}ClN_3O_3$ $[M+H]^+$: 468.2048, found: 468.2048.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-(3-methyl-5-(6-(trifluoromethyl)pyridin-2-yl)-phenyl)carbamate (9ba)

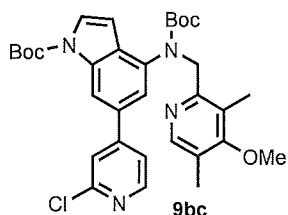
Following the general *meta*-arylation procedure using 20 mol% of $Pd(OAc)_2$ and 40 mol% of **L12**, Compound **9ba** was obtained in 84% yield as a red liquid. 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.86 (t, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.74 (s, 1H), 7.62 (s, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.18 (s, 1H), 4.97 (s, 2H), 3.71 (s, 3H), 2.36 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.77, 157.56, 154.95, 154.71, 148.86, 147.93 (q, $J = 34.2$ Hz), 143.17, 138.72, 137.86, 137.73, 128.28, 124.93, 124.76, 123.89, 122.84, 122.68, 121.51 (q, $J = 274.5$ Hz), 118.35 (q, $J = 2.8$ Hz), 80.50, 59.82, 53.25, 28.23, 21.45, 13.16, 10.44; HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{31}F_3N_3O_3$ $[M+H]^+$: 502.2312, found: 502.2312.



tert-Butyl (2'-chloro-6-methoxy-[4,4'-bipyridin]-2-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9bb)

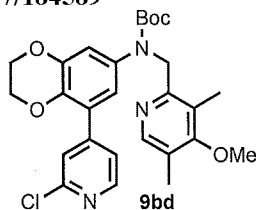
Substrate **2b** was arylated following the general *meta*-arylation procedure using 20 mol% of $Pd(OAc)_2$ and 40 mol%

of **L12**. After purification by preparative thin-layer chromatography, Compound **9bb** was obtained in 40% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, J = 5.2 Hz, 1H), 8.12 (s, 1H), 7.78 (s, 1H), 7.55 (s, 1H), 7.44 (dd, J = 5.2, 1.5 Hz, 1H), 6.55 (s, 1H), 5.26 (s, 2H), 3.74 (s, 3H), 3.65 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.38, 162.79, 155.60, 154.34, 153.17, 152.24, 150.12, 149.73, 148.92, 148.15, 123.97, 122.26, 122.23, 120.60, 108.40, 102.43, 81.45, 59.88, 53.22, 48.92, 28.16, 13.17, 10.34; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{25}\text{H}_{30}\text{ClN}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 485.1950, found: 485.1950.



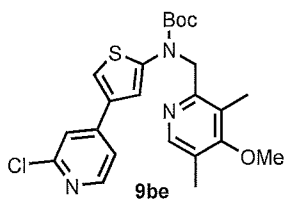
tert-Butyl 4-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-6-(2-chloro-pyridin-4-yl)-1H-indole-1-carboxylate (9bc)

Substrate **2i** was arylated following the general *meta*-arylation procedure using 20 mol% of $\text{Pd}(\text{OAc})_2$ and 40 mol% of **L12**. After purification by preparative thin-layer chromatography, Compound **9bc** was obtained in 48% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.41-8.31 (m, 2H), 8.13 (s, 1H), 7.61 (d, J = 3.7 Hz, 1H), 7.42 (s, 1H), 7.39 (d, J = 5.2 Hz, 1H), 7.21 (s, 1H), 6.58 (d, J = 3.7 Hz, 1H), 5.02 (s, 2H), 3.71 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.68 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.83, 154.94, 154.56, 152.00, 151.86, 149.75, 149.35, 148.90, 136.46, 135.52, 132.83, 129.57, 127.15, 125.08, 124.60, 121.95, 120.53, 112.49, 105.52, 84.22, 80.54, 59.82, 53.19, 28.18, 28.12, 13.21, 10.62; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{32}\text{H}_{38}\text{ClN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 593.2525, found: 593.2522.



tert-Butyl (8-(2-chloropyridin-4-yl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9bd)

Substrate **21** was arylated following the general *meta*-arylation procedure. After purification by preparative thin-layer chromatography, Compound **9bd** was obtained in 52% yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 8.35 (d, $J = 5.2$ Hz, 1H), 8.17 (s, 1H), 7.39 (s, 1H), 7.32 (d, $J = 5.2$ Hz, 1H), 6.92 (s, 1H), 6.78 (s, 1H), 4.86 (s, 2H), 4.24 (s, 4H), 3.74 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.78, 154.92, 154.72, 151.27, 149.10, 148.92, 148.27, 143.53, 138.83, 136.28, 125.60, 124.89, 124.36, 123.90, 122.86, 121.00, 117.09, 80.50, 64.34, 63.99, 59.88, 53.56, 28.25, 13.23, 10.43; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{31}\text{ClN}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 512.1947, found: 512.1948.



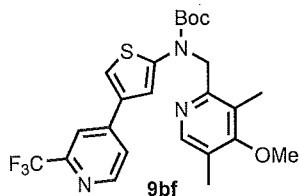
tert-Butyl (4-(2-chloropyridin-4-yl)thiophen-2-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9be)

Substrate **2c** was arylated following the general *meta*-arylation procedure. After purification by preparative thin-layer chromatography, Compound **9be** was obtained in 93% yield as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, $J = 5.2$ Hz, 1H), 8.20 (s, 1H), 7.36 (s, 1H), 7.29-7.22 (m, 2H), 6.92 (s, 1H), 5.03 (s, 2H), 3.75 (s, 3H), 2.23 (s, 6H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.86, 153.64, 153.46, 152.08, 149.83, 149.05, 146.81, 145.94, 134.60, 125.14, 123.73, 120.55, 119.14, 118.02, 112.98,

82.30, 59.91, 53.42, 28.12, 13.23, 10.29; HRMS (ESI-TOF)

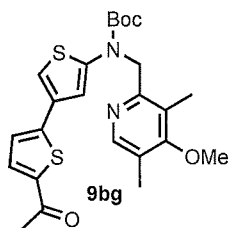
m/z Calcd for $C_{23}H_{27}ClN_3O_3S$ $[M+H]^+$: 460.1456, found:

460.1456.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (4-(2-(trifluoromethyl)pyridin-4-yl)thiophen-2-yl)carbamate (9bf)

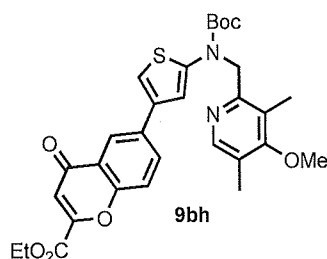
Substrate **2c** was arylated following the general *meta*-arylation procedure. After purification by preparative thin-layer chromatography, Compound **9bf** was obtained in 80% yield as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 5.2 Hz, 1H), 8.21 (s, 1H), 7.70 (s, 1H), 7.52 (d, J = 5.0 Hz, 1H), 7.31 (s, 1H), 6.99 (s, 1H), 5.05 (s, 2H), 3.75 (s, 3H), 2.27-2.20 (m, 6H), 1.49 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.92, 153.69, 153.46, 150.38, 149.08, 148.72 (q, J = 34.7 Hz), 147.03, 144.65, 134.71, 125.22, 123.81, 122.65, 121.60 (q, J = 274.3 Hz), 118.52, 117.08 (d, J = 3.4 Hz), 112.86, 82.42, 59.93, 53.44, 28.15, 13.24, 10.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.37; HRMS (ESI-TOF) m/z Calcd for $C_{24}H_{27}F_3N_3O_3S$ $[M+H]^+$: 494.1720, found: 494.1718.



tert-Butyl (5-acetyl-[2,3'-bithiophen]-5'-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (9bg)

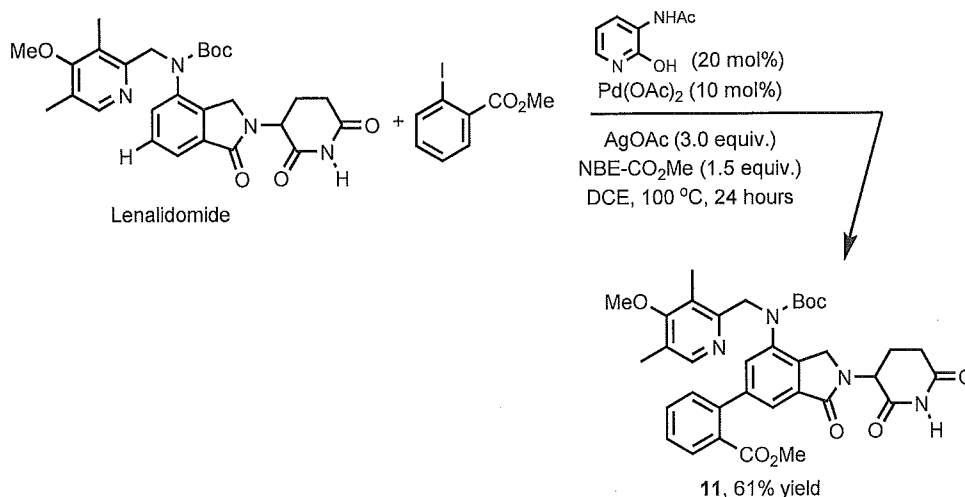
Substrate **2c** was arylated following the general *meta*-arylation procedure. After purification by preparative thin-layer chromatography, Compound **9bg** was obtained in

47% yield as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.56 (d, $J = 3.9$ Hz, 1H), 7.11 (s, 1H), 7.07 (d, $J = 3.9$ Hz, 1H), 6.83 (s, 1H), 5.00 (s, 2H), 3.75 (s, 3H), 2.52 (s, 3H), 2.23 (s, 6H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 190.47, 163.83, 153.61, 153.55, 149.12, 148.08, 146.41, 141.70, 133.34, 131.48, 125.08, 123.66, 123.36, 116.57, 113.35, 82.24, 59.94, 53.39, 28.15, 26.45, 13.24, 10.29; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4\text{S}_2$ $[\text{M}+\text{H}]^+$: 473.1563, found: 473.1564.

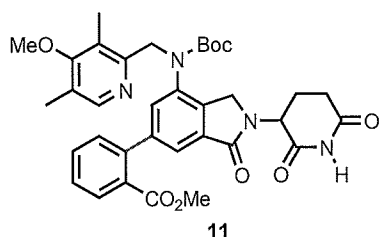


Ethyl 6-(5-((tert-butoxycarbonyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)thiophen-3-yl) -4-oxo-4H-chromene-2-carboxylate (9bh)

Substrate **2c** was arylated following the general *meta*-arylation procedure. After purification by preparative thin-layer chromatography, Compound **9bh** was obtained in 41% yield as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.25–8.18 (m, 2H), 7.87 (dd, $J = 8.8, 2.3$ Hz, 1H), 7.59 (d, $J = 8.8$ Hz, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 6.98 (s, 1H), 5.03 (s, 2H), 4.47 (q, $J = 7.2$ Hz, 2H), 3.76 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 1.47 (s, 9H), 1.44 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 178.43, 163.81, 160.49, 154.87, 153.82, 153.65, 152.09, 149.13, 146.50, 136.66, 134.12, 132.60, 125.02, 124.46, 123.63, 121.85, 119.12, 115.84, 114.55, 113.82, 82.02, 62.98, 59.93, 53.55, 28.16, 14.07, 13.23, 10.33; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_7\text{S}$ $[\text{M}+\text{H}]^+$: 565.2003, found: 565.2002.

Meta-Arylation of Lenalidomide Derivative**General Procedures for meta-Arylation of Lenalidomide:**

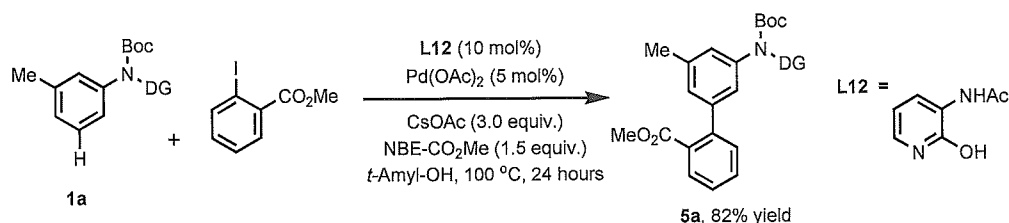
Substrate (0.05 mmol), Ar-I (0.1 mmol), Pd(OAc)2 (1.1 mg, 10 mol%), **L12** (1.5 mg, 20 mol%), AgOAc (25.0 mg, 0.15 mmol), NBE-CO2Me (11.4 mg, 0.075 mmol) and DCE (0.5 mL) were added to a 2-dram vial. The vial was capped and closed tightly. The reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC plate to afford the desired arylated product in 61% yield as a colorless solid.



Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.20 (s, 1H), 8.15 (s, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.71 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 5.7 Hz, 1H), 5.25 (dd, J = 13.3, 5.1 Hz, 1H), 4.89 (s, 2H), 4.66 (d, J = 16.5 Hz, 1H), 4.51 (d, J = 16.5 Hz, 1H), 3.71 (s, 3H), 3.58 (s, 3H), 3.00–2.78 (m, 2H), 2.38 (qd, J = 13.6, 13.0, 4.7 Hz, 1H), 2.29–2.14 (m, 7H), 1.36 (s,

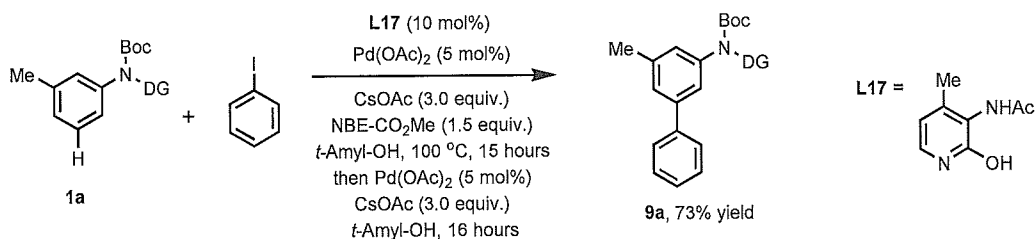
9H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.70, 168.99, 168.46, 168.02, 163.38, 153.82, 153.25, 148.36, 142.11, 140.57, 138.02, 137.33, 131.90, 131.07, 130.42, 130.15, 130.07, 129.73, 127.24, 124.61, 121.49, 80.50, 59.45, 52.42, 51.43, 51.35, 45.99, 31.15, 27.72, 23.05, 12.80, 9.95; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{35}\text{H}_{39}\text{N}_4\text{O}_8$ $[\text{M}+\text{H}]^+$: 643.2762, found: 643.2762.

3.15 Meta-Arylation of Anilines without Sliver



General procedure for arylation of 1a without sliver using methyl 2-iodobenzoate as coupling partner on gram scale:

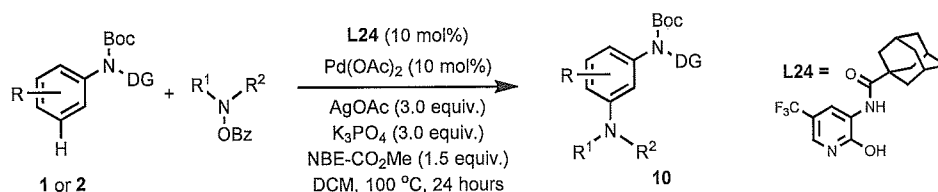
Substrate **1a** (35.6 mg, 0.1 mmol), methyl 2-iodobenzoate (30 μL , 0.2 mmol), $\text{Pd}(\text{OAc})_2$ (1.2 mg, 5 mol%), **L12** (1.5 mg, 10 mol%), CsOAc (57.6 mg, 0.3 mmol), $\text{NBE-CO}_2\text{Me}$ (21.6 mg, 0.15 mmol), and $t\text{-Amyl-OH}$ (0.2 mL) were added to a 2-dram vial. The vial was capped and closed tightly. Then the reaction mixture was stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired product Compound **5a** in 82% yield.



General procedure for arylation of 1a without sliver using iodobenzene as coupling partner: Substrate **1a** (35.6 mg,

0.1 mmol), iodobenzene (23 μ L, 0.2 mmol), Pd(OAc)₂ (1.2 mg, 5 mol%), **L17** (1.5 mg, 10 mol%), CsOAc (57.6 mg, 0.3 mmol), NBE-CO₂Me (21.6 mg, 0.15 mmol), and *t*-Amyl-OH (0.2 mL) were added to a 2-dram vial. The vial was capped and closed tightly. Then the reaction mixture was stirred at 100 °C for 15 hours. After cooling to room temperature, the mixture was diluted by DCM (5.0 mL) and stirred for 10 minutes. The mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. After concentration, CsOAc (57.6 mg, 0.3 mmol), Pd(OAc)₂ (1.2 mg, 5 mol%) and *t*-Amyl-OH (0.2 mL) were added into a 2-dram vial with the residue. The vial was capped and closed tightly, the reaction mixture was then stirred at 100 °C for another 16 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired product Compound **9a** in 73% yield.

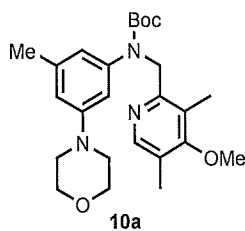
Meta-Amination of Anilines



General procedure for amination of anilines:

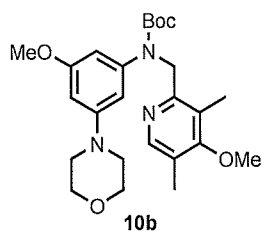
Substrate **1** or **2** (0.1 mmol), aminating reagent (0.15 mmol), Pd(OAc)₂ (2.2 mg, 10 mol%), **L24** (3.4 mg, 10 mol%), AgOAc (33.4 mg, 0.2 mmol), NBE-CO₂Me (21.6 mg, 0.15 mmol), K₃PO₄ (62.8 mg, 0.3 mmol) and DCM (1.0 mL) were added to a 2-dram vial. The vial was capped and closed tightly. Then the reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting

solution was concentrated and purified by preparative TLC to afford the desired product Compound **10**.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-morpholinophenyl) carbamate (10a)

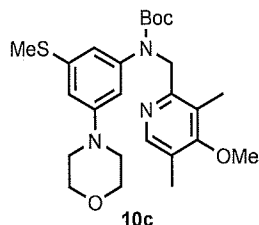
Substrate **1a** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10a** was obtained in 77% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 6.49 (s, 1H), 4.87 (s, 2H), 3.80 (t, $J = 4.8$ Hz, 4H), 3.72 (s, 3H), 3.04 (t, $J = 4.8$ Hz, 4H), 2.23 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.59, 155.36, 154.75, 151.28, 148.87, 143.53, 138.55, 124.54, 123.72, 119.03, 114.16, 111.84, 80.06, 66.90, 59.81, 53.60, 49.52, 28.29, 21.72, 13.19, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 442.2700, found: 442.2700.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methoxy-5-morpholinophenyl) carbamate (10b)

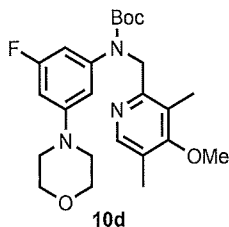
Substrate **1b** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10b** was obtained in 65% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 6.46 (s, 1H), 6.37 (s, 1H), 6.22 (t, $J = 2.2$ Hz, 1H), 4.88 (s, 2H), 3.80 (t, $J = 4.7$ Hz, 4H), 3.72 (s, 3H), 3.70 (s, 3H), 3.05 (t, $J = 4.6$ Hz, 4H), 2.21 (s, 3H),

2.20 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.57, 160.15, 155.20, 154.64, 152.11, 148.88, 144.47, 124.57, 123.70, 107.47, 103.88, 99.79, 80.17, 66.81, 59.82, 55.20, 53.57, 49.31, 28.29, 13.19, 10.41; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 458.2649, found: 458.2650.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-(methylthio)-5-morpholinophenyl)-carbamate (10c)

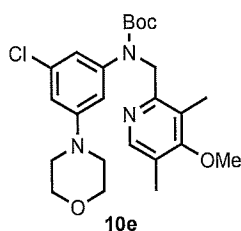
Substrate **1c** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10c** was obtained in 57% yield as a colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 6.67 (s, 1H), 6.65 (s, 1H), 6.57 (t, $J = 2.0$ Hz, 1H), 4.87 (s, 2H), 3.84–3.76 (m, 4H), 3.72 (s, 3H), 3.10–3.01 (m, 4H), 2.38 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.63, 155.09, 154.59, 151.51, 148.89, 144.05, 138.70, 124.67, 123.76, 116.61, 111.87, 111.62, 80.31, 66.79, 59.85, 53.43, 49.24, 28.29, 16.01, 13.20, 10.43; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 474.2421, found: 474.2421.



tert-Butyl (3-fluoro-5-morpholinophenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (10d)

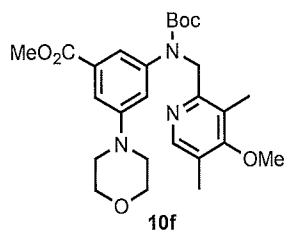
Substrate **1e** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10d** was obtained in

63% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 6.65 (s, 1H), 6.51 (dt, $J = 10.0, 2.1$ Hz, 1H), 6.35 (dt, $J = 11.7, 2.3$ Hz, 1H), 4.86 (s, 2H), 3.84–3.77 (m, 4H), 3.73 (s, 3H), 3.10–3.03 (m, 4H), 2.22 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 164.00, 163.65, 162.40, 154.84, 152.24, 152.16, 148.93, 144.78, 144.69, 124.72, 123.61, 109.47, 105.05, 104.89, 99.91, 99.74, 80.54, 66.64, 59.85, 53.35, 28.21, 13.20, 10.37; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{24}\text{H}_{33}\text{FN}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 446.2450, found: 446.2452.



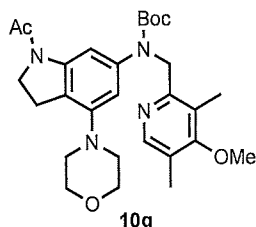
tert-Butyl (3-chloro-5-morpholinophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (10e)

Substrate **1f** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10e** was obtained in 63% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 6.77 (s, 2H), 6.63 (t, $J = 2.1$ Hz, 1H), 4.85 (s, 2H), 3.84–3.77 (m, 4H), 3.73 (s, 3H), 3.10–3.02 (m, 4H), 2.22 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.66, 154.80, 154.35, 151.92, 148.94, 144.54, 134.17, 124.75, 123.62, 117.94, 112.84, 112.50, 80.58, 66.66, 59.86, 53.30, 48.87, 28.22, 13.21, 10.39; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{24}\text{H}_{33}\text{ClN}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 462.2154, found: 462.2155.



Methyl 3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5-morpholino-benzoate (10f)

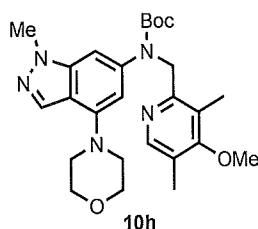
Substrate **1h** was aminated following the general *meta*-amination procedure using Pd(OAc)₂ (3.4 mg, 15 mol%), **L24** (5.1 mg, 15 mol%), AgOAc (50.1 mg, 0.3 mmol) and NBE-CO₂Me (45.7 mg, 0.3 mmol). After purification by preparative thin-layer chromatography, Compound **10f** was obtained in 60% yield as a colorless solid, ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.42 (s, 1H), 7.36-7.32 (m, 1H), 7.08 (s, 1H), 4.91 (s, 2H), 3.86 (s, 3H), 3.84-3.80 (m, 4H), 3.72 (s, 3H), 3.15-3.08 (m, 4H), 2.23-2.19 (m, 6H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 166.97, 163.71, 154.89, 154.48, 151.26, 148.90, 143.71, 130.80, 124.78, 123.86, 119.26, 118.86, 113.76, 80.55, 66.74, 59.85, 53.24, 52.09, 49.06, 28.23, 13.21, 10.46; HRMS (ESI-TOF) *m/z* Calcd for C₂₆H₃₆N₃O₆ [M+H]⁺: 486.2599, found: 486.2600.



tert-Butyl (1-acetyl-4-morpholinoindolin-6-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (10g)

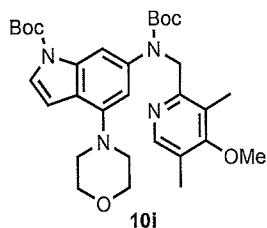
Substrate **2g** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10g** was obtained in 76% yield as a light yellow solid, Rotameric mixture, ratio of the rotamers = 74/26; ¹H NMR (500 MHz, CDCl₃) δ 8.14 (s, 1H), 7.87 (s, 0.74H), 6.86 (s, 0.26H), 6.68-6.52 (m, 1H), 4.97-4.81 (m, 2H), 4.09 (t, *J* = 8.4 Hz, 0.52H), 4.01 (t, *J* = 8.2 Hz, 1.48H), 3.84-3.76 (m, 4H), 3.76-3.69 (m, 3H), 3.02 (t, *J* = 8.3 Hz, 1.42H), 2.97-2.82 (m, 4.52H), 2.28-2.13 (m, 9H), 1.41 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) resonances for the minor rotamer are enclosed in parenthesis (): δ 168.21, 163.64 (163.71), 155.27

(155.13), 154.74, 148.77 (148.88), 147.80, 143.81, 143.21 (142.78), 124.56 (124.83), 123.96 (123.43), 120.93, 112.74 (111.75), 110.80 (108.80), 80.22 (80.41), 67.15 (67.10), 59.82, 53.53 (53.68), 50.91 (50.71), 49.41 (48.60), 28.29, 26.61 (25.61), 24.21 (24.00), 13.18, 10.48 (10.45); HRMS (ESI-TOF) m/z Calcd for $C_{28}H_{39}N_4O_5$ $[M+H]^+$: 511.2915, found: 511.2914.



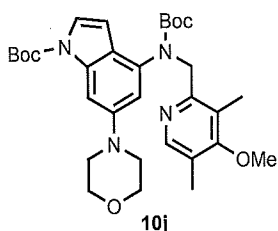
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(1-methyl-4-morpholino-1H-indazol-6-yl)-carbamate (10h)

Substrate **2j** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10h** was obtained in 62% yield as a colorless solid, 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.86–7.79 (m, 2H), 6.93 (s, 1H), 6.44 (s, 1H), 4.95 (s, 2H), 3.94 (s, 3H), 3.92–3.88 (m, 4H), 3.73 (s, 3H), 3.25–3.16 (m, 4H), 2.23 (s, 3H), 2.22 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.67, 155.14, 154.75, 148.88, 145.25, 142.42, 141.34, 130.99, 124.73, 123.82, 115.44, 106.64, 100.31, 80.40, 66.89, 59.83, 53.94, 51.40, 35.64, 28.29, 13.21, 10.48; HRMS (ESI-TOF) m/z Calcd for $C_{26}H_{36}N_5O_4$ $[M+H]^+$: 482.2762, found: 482.2766.



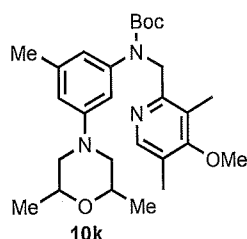
tert-Butyl 6-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4-morpholino-1H-indole-1-carboxylate (10i)

Substrate **2h** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10i** was obtained in 53% yield as a colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.67 (s, 1H), 7.49 (d, $J = 3.7$ Hz, 1H), 6.66 (s, 1H), 6.48 (d, $J = 3.7$ Hz, 1H), 4.97 (s, 2H), 3.89 (t, $J = 4.5$ Hz, 4H), 3.72 (s, 3H), 3.06 (t, $J = 4.6$ Hz, 4H), 2.23 (s, 3H), 2.20 (s, 3H), 1.57 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.67, 155.32, 154.97, 149.52, 148.85, 144.70, 140.07, 135.82, 124.76, 124.63, 124.02, 121.87, 110.77, 108.56, 105.03, 83.54, 80.10, 67.12, 59.78, 54.13, 52.06, 28.34, 28.02, 28.01, 13.15, 10.50; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{31}\text{H}_{43}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 567.3177, found: 567.3179.



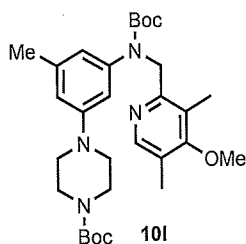
tert-Butyl 4-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-6-morpholino-1H-indole-1-carboxylate (10j)

Substrate **2i** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10j** was obtained in 44% yield as a colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.11 (s, 1H), 7.60 (s, 1H), 7.38 (d, $J = 3.7$ Hz, 1H), 6.69 (s, 1H), 6.41 (d, $J = 3.8$ Hz, 1H), 4.95 (s, 2H), 3.86-3.78 (m, 4H), 3.68 (s, 3H), 3.12-3.01 (m, 4H), 2.23-2.13 (m, 6H), 1.64 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.63, 155.23, 154.80, 149.81, 149.28, 148.83, 136.84, 135.05, 124.71, 124.42, 124.05, 122.23, 112.58, 105.50, 101.10, 83.29, 80.10, 66.95, 59.75, 53.28, 50.54, 28.22, 28.17, 13.16, 10.57; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{31}\text{H}_{43}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 567.3177, found: 567.3174.



tert-Butyl (3-(2,6-dimethylmorpholino)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-carbamate (10k)

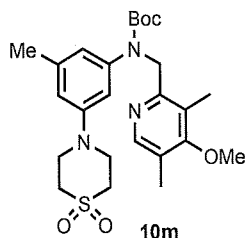
Substrate **1a** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10k** was obtained in 81% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 6.57 (s, 2H), 6.48 (s, 1H), 4.87 (s, 2H), 3.80–3.67 (m, 5H), 3.30 (d, $J = 10.4$ Hz, 2H), 2.31 (t, $J = 11.1$ Hz, 2H), 2.25–2.18 (m, 9H), 1.39 (s, 9H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.58, 155.40, 154.76, 150.94, 148.83, 143.42, 138.55, 124.52, 123.79, 118.79, 114.24, 112.01, 80.02, 71.55, 59.81, 54.99, 53.62, 28.28, 21.71, 19.01, 13.18, 10.43; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{27}\text{H}_{40}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 470.3013, found: 470.3014.



tert-Butyl 4-(3-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5-methylphenyl)piperazine-1-carboxylate (10l)

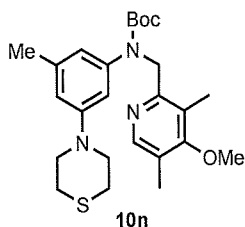
Substrate **1a** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10l** was obtained in 84% yield as a colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 6.63 (s, 1H), 6.61 (s, 1H), 6.50 (s, 1H), 4.87 (s, 2H), 3.72 (s, 3H), 3.52 (t, $J = 5.1$ Hz, 4H), 3.01 (t, $J = 5.2$ Hz, 4H), 2.23 (s, 3H), 2.21 (s, 3H), 2.20 (s,

3H), 1.48 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.56, 155.30, 154.67, 151.23, 148.85, 143.46, 138.54, 124.54, 123.68, 119.20, 115.09, 112.60, 80.06, 79.78, 59.80, 53.57, 49.53, 44.01, 42.98, 28.38, 28.26, 21.68, 13.18, 10.40; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{30}\text{H}_{45}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 541.3384, found: 541.3387.



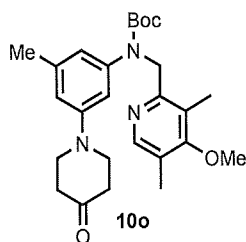
tert-Butyl (3-(1,1-dioxidothiomorpholino)-5-methylphenyl)-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-carbamate (10m)

Substrate **1a** was aminated following the general *meta*-amination procedure. After purification by preparative thin-layer chromatography, Compound **10m** was obtained in 70% yield as a light yellow solid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 6.71 (s, 1H), 6.66 (s, 1H), 6.48 (s, 1H), 4.87 (s, 2H), 3.81-3.69 (m, 7H), 3.07-2.98 (m, 4H), 2.24 (s, 3H), 2.23-2.19 (m, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.64, 155.16, 154.51, 148.83, 147.34, 143.93, 139.30, 124.76, 123.78, 119.61, 114.42, 112.37, 80.32, 59.85, 53.40, 50.33, 47.62, 28.24, 21.74, 13.21, 10.42; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 490.2370, found: 490.2368.



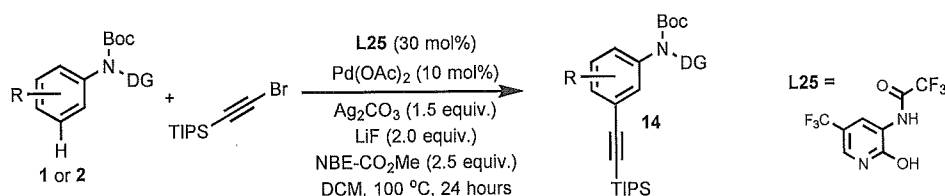
tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-thiomorpholinophenyl)carbamate (10n)

Substrate **1a** was aminated following the general *meta*-amination procedure using Pd(OAc)₂ (3.4 mg, 15 mol%), **L24** (5.1 mg, 15 mol%), AgOAc (50.1 mg, 0.3 mmol) and NBE-CO₂Me (45.7 mg, 0.3 mmol). After purification by preparative thin-layer chromatography, Compound **10n** was obtained in 62% yield as a colorless solid, ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 6.58 (s, 2H), 6.47 (s, 1H), 4.87 (s, 2H), 3.72 (s, 3H), 3.45-3.38 (m, 4H), 2.71-2.64 (m, 4H), 2.24-2.18 (m, 9H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 163.61, 155.34, 154.74, 151.33, 148.85, 143.49, 138.66, 124.60, 123.78, 118.82, 115.65, 113.26, 80.10, 59.84, 53.59, 52.27, 28.30, 26.79, 21.71, 13.21, 10.44; HRMS (ESI-TOF) *m/z* Calcd for C₂₅H₃₆N₃O₃S [M+H]⁺: 458.2472, found: 458.2469.

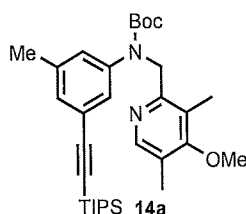


tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-(4-oxopiperidin-1-yl)phenyl)-carbamate (10o)

Substrate **1a** was aminated following the general *meta*-amination procedure using Pd(OAc)₂ (3.4 mg, 15 mol%), **L24** (5.1 mg, 15 mol%), AgOAc (50.1 mg, 0.3 mmol) and NBE-CO₂Me (45.7 mg, 0.3 mmol). After purification by preparative thin-layer chromatography, Compound **10o** was obtained in 53% yield as a colorless liquid, ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 6.71 (s, 1H), 6.61 (s, 1H), 6.56 (s, 1H), 4.88 (s, 2H), 3.73 (s, 3H), 3.50 (t, *J* = 6.0 Hz, 4H), 2.47 (t, *J* = 6.0 Hz, 4H), 2.25 (s, 3H), 2.21 (s, 6H), 1.39 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 208.41, 163.61, 155.33, 154.69, 148.97, 148.83, 143.73, 138.94, 124.63, 123.77, 118.81, 114.26, 112.10, 80.16, 59.84, 53.57, 49.00, 40.69, 28.29, 21.77, 13.20, 10.43; HRMS (ESI-TOF) *m/z* Calcd for C₂₆H₃₆N₃O₄ [M+H]⁺: 454.2700, found: 454.2699.

Meta-Alkynylation of Anilines**General procedure for alkynylation of anilines:**

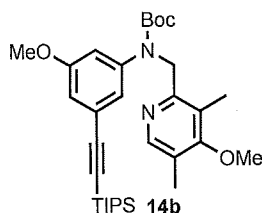
Substrate **1** or **2** (0.1 mmol), alkynyating reagent (52.2 mg, 0.2 mmol), Pd(OAc)₂ (2.2 mg, 10 mol%), **L25** (8.2 mg, 30 mol%), Ag₂CO₃ (41.1 mg, 0.15 mmol), NBE-CO₂Me (38.0 mg, 0.25 mmol), LiF (5.2 mg, 0.2 mmol) and DCM (1.0 mL) were added to a 2-dram vial. The vial was capped and closed tightly. Then the reaction mixture was then stirred at 100 °C for 24 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired product Compound **14**.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methyl-5-((triisopropylsilyl)ethynyl)phenyl)-carbamate (14a)

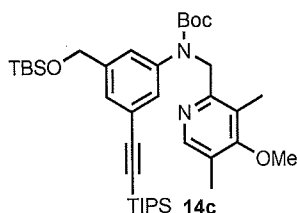
Substrate **1a** was alkynyated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14a** was obtained in 72% yield as a colorless liquid, ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.11 (s, 1H), 7.05 (s, 2H), 4.87 (s, 2H), 3.72 (s, 3H), 2.24 (s, 3H), 2.21 (s, 6H), 1.40 (s, 9H), 1.10 (s, 21H); ¹³C NMR (150 MHz, CDCl₃) δ 163.70, 154.94, 154.59, 148.95, 142.57, 138.08, 129.93, 127.64, 127.31, 124.69, 123.75, 123.25, 107.04, 89.82, 80.42, 59.83, 53.32, 28.22, 21.10, 18.63, 13.18, 11.29, 10.44; HRMS

(ESI-TOF) m/z Calcd for $C_{32}H_{49}N_2O_3Si$ $[M+H]^+$: 537.3507, found: 537.3506.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (3-methoxy-5-((triisopropylsilyl)ethynyl)phenyl)-carbamate (14b)**

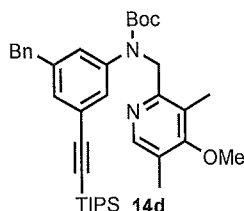
Substrate **1b** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14b** was obtained in 62% yield as a colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.94 (s, 1H), 6.83 (s, 1H), 6.75 (s, 1H), 4.87 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.23–2.18 (m, 6H), 1.41 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.70, 159.17, 154.78, 154.49, 148.97, 143.84, 124.70, 123.95, 123.70, 122.97, 114.24, 113.82, 106.82, 90.18, 80.56, 59.84, 55.39, 53.26, 28.23, 18.63, 13.18, 11.27, 10.41; HRMS (ESI-TOF) m/z Calcd for $C_{32}H_{49}N_2O_4Si$ $[M+H]^+$: 553.3456, found: 553.3457.



***tert*-Butyl (3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-((triisopropylsilyl)ethynyl)phenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (14c)**

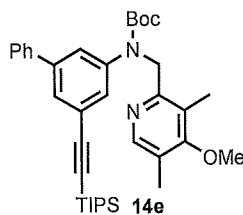
Substrate **1x** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14c** was obtained in 70% yield as a colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.20 (s, 1H), 7.19–7.14 (m, 2H), 4.88 (s,

2H), 4.62 (s, 2H), 3.72 (s, 3H), 2.23-2.17 (m, 6H), 1.40 (s, 9H), 1.10 (s, 21H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.67, 154.81, 154.61, 149.02, 142.77, 141.83, 128.46, 126.71, 124.63, 124.27, 123.63, 123.26, 107.06, 90.03, 80.45, 64.15, 59.82, 53.28, 28.23, 25.86, 18.63, 18.31, 13.17, 11.29, 10.39, -5.35; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{38}\text{H}_{63}\text{N}_2\text{O}_4\text{Si}_2$ $[\text{M}+\text{H}]^+$: 667.4321, found: 667.4322.



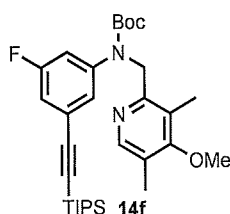
tert-Butyl (3-benzyl-5-((triisopropylsilyl)ethynyl)-phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-carbamate (14d)

Substrate **1y** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14d** was obtained in 50% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 7.28-7.22 (m, 2H), 7.18 (t, $J = 7.2$ Hz, 1H), 7.14 (s, 1H), 7.11-7.05 (m, 3H), 7.00 (s, 1H), 4.86 (s, 2H), 3.86 (s, 2H), 3.69 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.36 (s, 9H), 1.09 (s, 21H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.72, 154.80, 154.56, 148.94, 142.65, 141.02, 140.40, 129.77, 128.85, 128.39, 128.10, 127.89, 126.10, 124.69, 123.86, 123.56, 106.87, 90.22, 80.49, 59.82, 53.22, 41.40, 28.21, 18.64, 13.20, 11.29, 10.44; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{38}\text{H}_{53}\text{N}_2\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 613.3820, found: 613.3820.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (5-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-3-yl) carbamate (14e)**

Substrate **1z** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14e** was obtained in 61% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.45–7.36 (m, 4H), 7.33 (d, J = 7.2 Hz, 1H), 7.31 (s, 1H), 4.94 (s, 2H), 3.71 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.43 (s, 9H), 1.12 (s, 21H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.76, 154.86, 154.55, 149.02, 143.01, 141.45, 140.14, 128.90, 128.68, 127.99, 127.53, 127.10, 126.01, 124.81, 123.89, 106.78, 90.51, 80.62, 59.83, 53.28, 28.29, 28.26, 18.65, 13.19, 11.30, 10.48; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{37}\text{H}_{51}\text{N}_2\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 599.3663, found: 599.3662.

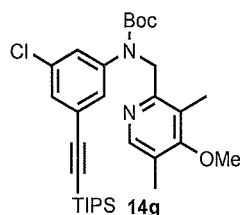


***tert*-Butyl (3-fluoro-5-((triisopropylsilyl)ethynyl)-phenyl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) carbamate (14f)**

Substrate **1e** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14f** was obtained in 44% yield as a colorless liquid, ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.15 (s, 1H), 7.03 (d, J = 10.3 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 4.86 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.74, 161.84 (d, J = 245.3 Hz), 154.42, 154.21, 149.09, 144.41 (d, J = 11.1 Hz), 125.76, 124.84, 124.54 (d, J = 10.9 Hz), 123.53, 115.79 (d, J = 23.0 Hz), 114.50 (d, J = 23.3 Hz), 105.59 (d, J = 3.3 Hz), 91.74, 80.96, 59.88, 53.09, 28.18, 18.60,

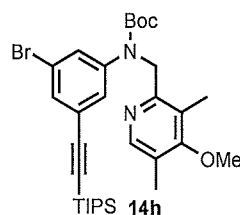
13.20 , 11.23 , 10.38; HRMS (ESI-TOF) m/z Calcd for

$C_{31}H_{46}FN_2O_3Si$ $[M+H]^+$: 541.3256, found: 541.3257.



tert-Butyl (3-chloro-5-((triisopropylsilyl)ethynyl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) carbamate (14g)

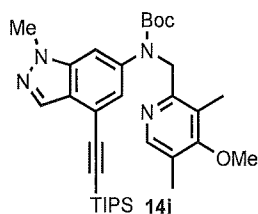
Substrate **1f** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14g** was obtained in 59% yield as a colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.28 (s, 1H), 7.27–2.24 (m, 1H), 7.20 (s, 1H), 4.85 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.75, 154.40, 154.18, 149.10, 144.00, 133.45, 128.83, 128.22, 127.03, 124.85, 124.70, 123.53, 105.31, 92.05, 80.98, 59.89, 53.06, 28.17, 18.61, 13.20, 11.23, 10.39; HRMS (ESI-TOF) m/z Calcd for $C_{31}H_{46}ClN_2O_3Si$ $[M+H]^+$: 557.2961, found: 557.2960.



tert-Butyl (3-bromo-5-((triisopropylsilyl)ethynyl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) carbamate (14h)

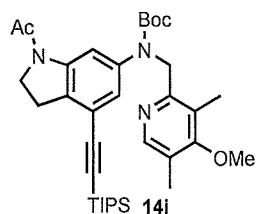
Substrate **1aa** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14h** was obtained in 56% yield as a colorless liquid, 1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.43 (s, 1H), 7.35 (s, 1H), 7.29 (s, 1H),

4.85 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H),
 1.40 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (151 MHz, CDCl_3) δ
 163.76, 154.38, 154.16, 149.10, 144.04, 131.65, 129.88,
 128.69, 125.00, 124.86, 123.55, 121.16, 105.14, 92.19,
 81.00, 59.89, 53.05, 28.17, 18.61, 13.20, 11.23, 10.40;
 HRMS (ESI-TOF) m/z Calcd for $\text{C}_{31}\text{H}_{46}\text{BrN}_2\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 601.2456,
 found: 601.2456.



tert-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl) (1-methyl-4-((triisopropylsilyl)ethynyl)-1H-indazol-6-yl)carbamate (14i)

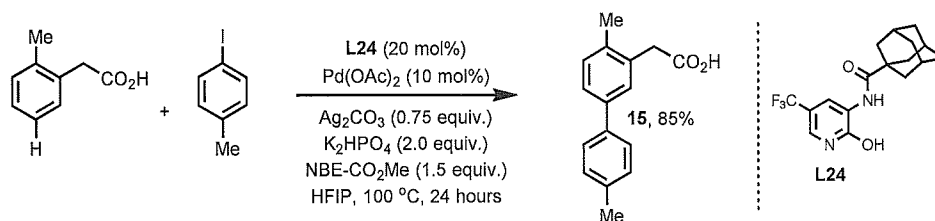
Substrate **2j** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14i** was obtained in 53% yield as a colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.96 (s, 1H), 7.35 (s, 1H), 7.17 (s, 1H), 4.95 (s, 2H), 3.98 (s, 3H), 3.72 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.41 (s, 9H), 1.15 (s, 21H); ^{13}C NMR (150 MHz, CDCl_3) δ 163.79, 154.81, 154.68, 148.93, 141.15, 139.74, 132.28, 125.06, 124.86, 123.91, 123.35, 115.60, 107.69, 103.86, 94.66, 80.72, 59.84, 53.70, 35.69, 28.23, 18.66, 13.18, 11.26, 10.50; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{33}\text{H}_{49}\text{N}_4\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$: 577.3568, found: 577.3568.



tert-Butyl (1-acetyl-4-((triisopropylsilyl)ethynyl)-indolin-6-yl) ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (14j)

Substrate **2g** was alkynylated following the general *meta*-alkynylation procedure. After purification by preparative thin-layer chromatography, Compound **14j** was obtained in 46% yield as a light yellow solid, Rotameric mixture, ratio of the rotamers = 84/16; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 8.11 (s, 0.84H), 7.19 (s, 0.16H), 6.97 (s, 1H), 4.93–4.82 (m, 2H), 4.18–4.96 (m, 2H), 3.72 (s, 3H), 3.17 (t, J = 8.5 Hz, 1.68H), 3.05 (t, J = 8.4 Hz, 0.32H), 2.33–2.14 (m, 9H), 1.40 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (150 MHz, CDCl_3) resonances for the minor rotamer are enclosed in parenthesis (): ^{13}C NMR (150 MHz, CDCl_3) δ 168.55 (168.27), 163.74, 154.98 (154.84), 154.67, 148.88, 142.87 (142.36), 142.27 (141.67), 131.84 (134.48), 125.21 (124.90), 124.68 (124.64), 123.98, 119.35 (120.76), 116.60 (114.42), 104.10 (103.69), 94.27 (95.13), 80.46 (80.63), 59.82, 53.49, 48.97 (48.06), 28.24, 27.72 (26.48), 24.11 (24.34), 18.62, 13.17, 11.18, 10.52 (10.45); HRMS (ESI-TOF) m/z Calcd for $\text{C}_{35}\text{H}_{52}\text{N}_3\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$: 606.3722, found: 606.3722.

3.18 Meta-Arylation of Phenylacetic Acid

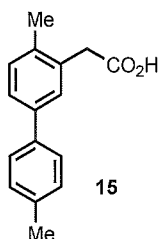


General procedure for arylation of phenylacetic acid:

2-Methyl phenylacetic acid (0.1 mmol), Ar-I (0.25 mmol), $\text{Pd}(\text{OAc})_2$ (2.2 mg, 10 mol%), **L24** (6.8 mg, 20 mol%), Ag_2CO_3 (20.7 mg, 0.075 mmol), $\text{NBE-CO}_2\text{Me}$ (38.0 mg, 0.25 mmol), K_2HPO_4 (35 mg, 0.2 mmol) and HFIP (1.0 mL) were added to a 10 mL vial. The vial was capped and closed tightly. Then the reaction mixture was first stirred at room temperature for 5 minutes and then heated to 100 °C for 24 hours. After cooling to room temperature, 0.05 mL HOAc was added. Then the mixture was passed through a pad of Celite[®] with

DCM as the eluent to remove the insoluble precipitate.

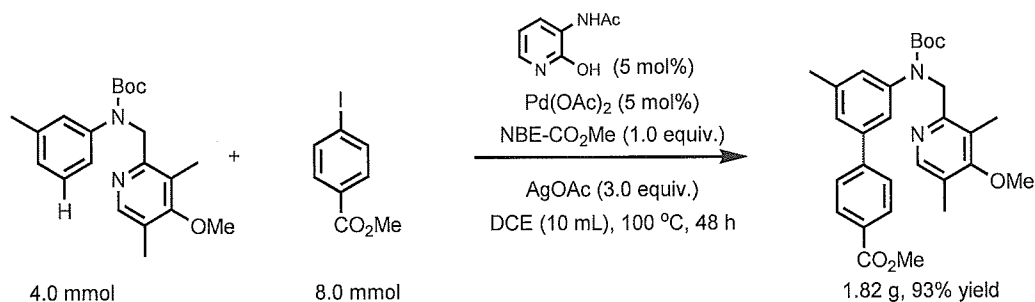
The resulting solution was concentrated and purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent to afford the desired product Compound **15**.



2-(4,4'-dimethyl-[1,1'-biphenyl]-3-yl)acetic acid

Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.43–7.36 (m, 2H), 7.27–7.15 (m, 3H), 3.72 (s, 2H), 2.38 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.3, 139.2, 137.8, 136.9, 135.7, 132.3, 130.8, 129.4, 128.9, 126.8, 126.2, 39.0, 21.1, 19.2; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{17}\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 241.1223, found: 241.1223.

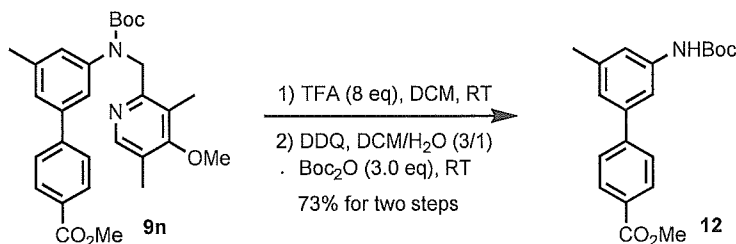
Gram-Scale Reaction for meta-Arylation of Anilines



Compound **1a** (1.43 g, 4.0 mmol), methyl 4-iodobenzoate (2.1 g, 8.0 mmol), $\text{Pd}(\text{OAc})_2$ (44.8 mg, 0.2 mmol, 5 mol%), Ligand **L12** (30.4 mg, 0.2 mmol, 5 mol%), AgOAc (2.0 g, 12.0 mmol), $\text{NBE-CO}_2\text{Me}$ (608.8 mg, 4.0 mmol) and DCE (10.0 mL) were added to a 150 mL sealed tube. Then the reaction mixture was stirred at 100 °C for 48 hours. After cooling to room temperature, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and

purified by silica gel column chromatography to afford the desired arylated product in 93% yield as a colorless liquid.

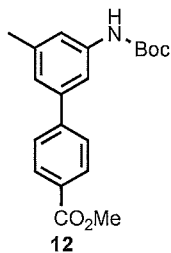
Directing Group Removal for Amines



General procedure for directing group removal from amines:

To a solution of **9n** (981.2 mg, 2.0 mmol) in DCM (8.0 mL) was added TFA (1.2 mL, 16.0 mmol) at room temperature. The mixture was stirring at room temperature for another 24 hours. The resulting solution was diluted by DCM (50 mL), and washed by with a saturated sodium carbonate solution. The aqueous phase was extracted with DCM (3×10 mL). The combined organic phases were dried by Na₂SO₄ and concentrated to afford a solid, which was used for next step without purification.

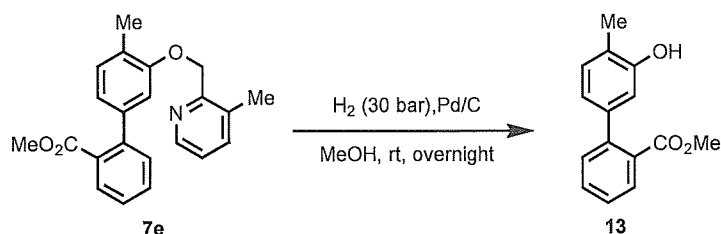
To a mixture of the solid amine obtained in the previous step (39.0 mg, 0.1 mmol), was added DDQ (22.7 mg, 0.1 mmol), DCM/H₂O (0.6 mL/0.2 mL) and Boc₂O (69 μL, 0.3 mmol). The mixture was stirred at room temperature for another 24 hours. Next, the mixture was passed through a pad of Celite® with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative TLC to afford the desired arylated product (Hexane/EA = 3/1) as a colorless solid (25.2 mg, 74% yield).



Methyl 3'-((*tert*-butoxycarbonyl)amino)-5'-methyl-[1,1'-biphenyl]-4-carboxylate (12)

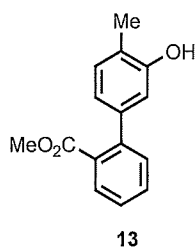
^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, $J = 8.3$ Hz, 2H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.47 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 6.60 (s, 1H), 3.95 (s, 3H), 2.41 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.00, 152.74, 145.45, 140.75, 139.45, 138.85, 129.96, 128.88, 127.07, 127.04, 122.83, 118.79, 114.53, 80.61, 52.09, 28.33, 21.57.

Directing Group Removal for Phenols



General Procedure for directing group hydrogenolysis

(phenols): Substrate **7e** (0.1 mmol) and 10% Pd/C (30.0 mg), were charged to a 10 mL vial equipped with a stir bar and a rubber septa. The vial was evacuated and purged with nitrogen, followed by addition of 2.0 mL of MeOH. The vial was then placed in an autoclave with a needle piercing the septa. The autoclave was purged with hydrogen three times then filled to a pressure of 30 bar H_2 . The autoclave was placed on a stirring plate at room temperature overnight with good stirring. The resulting solution was diluted with EtOAc (5.0 mL) and passed through a plug of Celite® with EtOAc as the eluent. The filtrate was concentrated and purified by preparative TLC to provide the desired phenol **13** in 79% yield.



Methyl 4'-methyl-3'-((3-methylpyridin-2-yl)methoxy)-[1,1'-biphenyl]-2-carboxylate (13)

Colorless solid, ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.7$ Hz, 1H), 7.53–7.44 (t, $J = 7.6$ Hz, 1H), 7.41–7.32 (m, 2H), 7.13 (d, $J = 7.6$ Hz, 1H), 6.79 (dd, $J = 7.5, 1.7$ Hz, 1H), 6.74 (d, $J = 1.7$ Hz, 1H), 5.02 (s, 1H), 3.68 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.56, 153.56, 141.87, 140.18, 131.17, 130.84, 130.69, 130.53, 129.53, 127.02, 122.91, 120.66, 114.86, 52.12, 15.56; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3$ $[\text{M}+\text{H}]^+$: 243.1016, found: 243.1017.

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Each of the patents, patent applications and articles cited herein is incorporated by reference.

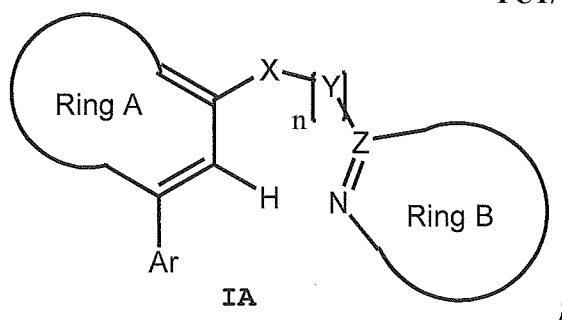
The foregoing description and the examples are intended as illustrative and are not to be taken as limiting. Still other variations within the spirit and scope of this invention are possible and will readily present themselves to those skilled in the art.

CLAIMS:

1. A method of forming a reaction product containing carbon-to-carbon (C-C) bond to an aryl or heteroaryl substituent at a position *meta* to a substituent previously present on the ring of an aromatic reactive substrate compound comprising the steps of

a) heating a reaction mixture to a temperature of about 70° to about 120° C, said reaction mixture containing i) said aromatic reactive substrate compound of Formula **I** dissolved or dispersed in a non-aqueous solvent having a boiling point at 1 atmosphere of about 40° to about 200° C, that further contains dissolved or dispersed therein ii) a catalytic amount of a Pd(II) catalyst, iii) a ligand of Formula **III** is present at about 10 to about 50 mole percent based on the moles of reactive substrate, iv) an ethylenically unsaturated bicyclic compound of Formula **II** as a transient mediator present in excess over the amount of reactive substrate, v) about 1.5 to about 5 equivalents of an oxidant based on the amount of said reactive substrate, and vi) about 1.1 to about 10 equivalents of a iodo-substituted aryl or heteroaryl coupling agent (Ar-I); and

b) maintaining said temperature for a time period sufficient to carry out the C-C bond formation at a position *meta* to said substituent and form a reaction product whose structural formula is shown in Formula **IA**



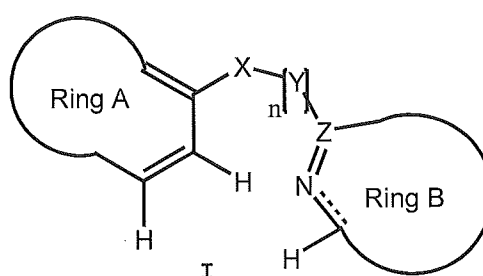
wherein

said iodo-substituted aryl or heteroaryl coupling agent being additionally unsubstituted, or said iodo-substituted aryl coupling agent being further substituted at the *meta* and *para* positions with one or two substituents independently selected from the group consisting of halogen (fluoro, chloro, bromo or iodo), C₁-C₇-hydrocarbyl that is straight, branched or cyclic, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), cyano, nitro, perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarboyl (acyl), protected hydroxyl, protected hydroxyl-substituted C₁-C₇-hydrocarbyl that is straight, branched or cyclic, di-(C₁-C₇-hydrocarbyl) C₁-C₇-hydrocarbylphosphonate, protected amino wherein the protecting group(s) contains up to 10 carbon atoms and the amine nitrogen has no reactive hydrogen, and a fused ring that includes 3 or 4 added ring atoms, and at the *ortho* position by a carboxy C₁-C₇-hydrocarbyl or NH-C₁-C₇-hydrocarboyl group;

or said iodo-substituted heteroaryl coupling agent being further substituted with one or two substituents independently selected from the group consisting of halogen other than iodo, C₁-

C₇-hydrocarbyl that is straight, branched or cyclic,
 C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-
 C₇-hydrocarbylthioxy (C₁-C₇-S-), perfluoro-C₁-
 C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-
 C₇-hydrocarboyl (acyl), a fused ring that includes 3
 or 4 added ring atoms and in which any nitrogen atom
 present is free of reactive hydrogens;

said aromatic reactive substrate compound
 has a structural formula shown in Formula I, below:



wherein, Ring A is a heteroaromatic or carbocyclic aromatic ring structure in which the bond shown to X is at the 1-position of the ring and the substituent bonded at the 1-position constitutes the substituent previously present on the ring, the ring position rotated clock-wise from the 1-position is the *ortho*-position at which a hydrogen (H) is bonded, and the next position clock-wise from the *ortho*-position at which another hydrogen (H) is bonded is the *meta*-position and is the position at which the new C-C bond is formed,

said Ring A containing a single ring or two fused rings having a total of 5 to 10 ring atoms and in which the ring bonded to X is aromatic and any other ring fused to that aromatic ring is independently aromatic or aliphatic, and in which a

heteroaromatic ring structure contains one, two or three heteroatoms that can independently be nitrogen, oxygen or sulfur atoms,

said Ring A optionally further containing 1, 2 or 3 substituents other than hydrido (H) bonded to the ring atoms, which substituents are selected from the group consisting of halo other than iodo (fluoro, chloro or bromo), C₁-C₇-hydrocarbyl that is straight, branched or includes a 4- to 6-membered ring bonded to a straight or branched chain, C₁-C₇-hydrocarbyloxy (C₁-C₇-O-), C₁-C₇-hydrocarbylthioxy (C₁-C₇-S-), C₁-C₂-hydrocarbyldioxy, cyano, nitro, perfluoro-C₁-C₃-hydrocarbyl, carboxy C₁-C₇-hydrocarbyl, C₁-C₇-hydrocarbonyl (acyl), protected amino wherein the protecting group(s) contains up to 10 carbon atoms, and a fused ring;

n is zero (0) or one, such that the methylene group Y within the brackets is absent when n is zero, and present when n is one,

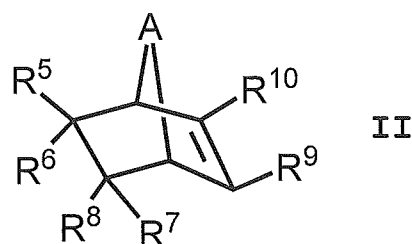
X is O (oxygen) or NPG (a nitrogen bonded to a protecting group) when n is 1, and NPG or CH₂ (methylene) when n is zero,

Ring B is a heteroaromatic single 6-membered ring or a fused 6,6- or 5,6-membered ring system containing the depicted nitrogen atom and 1 or 2 other nitrogen ring atoms, Z is carbon when n is zero or 1, and Z is nitrogen (a) when n is zero, and (b) the double bond depicted is absent and replaced by a double bond at the position of the dashed line,

said Ring B optionally further containing 1, 2 or 3 substituents other than hydrido (H) bonded to the ring atoms, which substituents are selected

from the group consisting of C₁-C₇-hydrocarbyl that is straight, branched or includes a 4- to 6-membered ring bonded to a straight or branched chain C₁-C₃-substituent, C₁-C₇-hydrocarbyloxy, trifluoromethyl-C₁-C₃-hydrocarbyl, trifluoromethyl-C₁-C₃-hydrocarbyloxy, and a fused ring;

said transient mediator is an ethylenically unsaturated bicyclic compound of Formula **II**



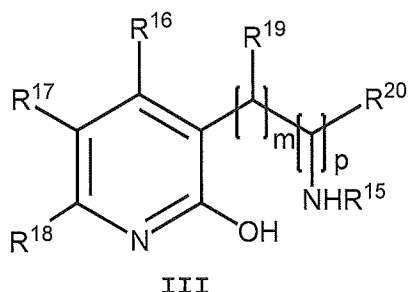
wherein

A is CH₂, C=O or O,

each of R⁵, R⁶, R⁷, R⁸, R⁹, and R¹⁰ is independently H, C₁-C₆-hydrocarbyl, C₁-C₆-hydrocarbyloxy, C₁-C₆-hydrocarbyl carboxylate, C₁-C₆-hydrocarbonyl, one or both of R⁵ plus R⁶ and R⁷ plus R⁸ together with the carbon atom to which they are bonded form one or two carbonyl groups, or one each of R⁵ and R⁶, or R⁷ and R⁸ together with the atoms to which they are bonded form a further 4- to 6-membered aliphatic or aromatic ring that itself can be independently substituted with one or two substituent groups selected from the group consisting of a C₁-C₆-hydrocarbyl, a C₁-C₆-hydrocarbyloxy, a C₁-C₆-hydrocarbyl carboxylate and a nitro group; and

said ligand having the structure of Formula

III

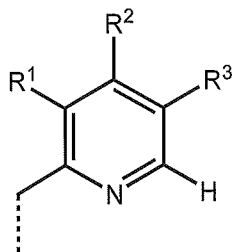


wherein R^{15} is an acyl group containing 2 to about 12 carbon atoms or a perfluorinated acyl group containing 2 to about 6 carbon atoms, R^{16} is hydrido or C_1 - C_6 -hydrocarbyl, R^{17} is hydrido, C_1 - C_6 -hydrocarbyl or trifluoromethyl, R^{18} is hydrido or C_1 - C_6 -hydrocarbyl, or R^{16} and R^{17} or R^{17} and R^{18} together with the carbon atoms to which they are bonded form a 6-membered ring with the depicted pyridine ring, m and p are the same and are zero or 1, such that when m and p are zero, the bracketed carbon atoms are absent and the NHR^{15} group is bonded directly to the depicted pyridine ring, and when m and p are both one, R^{19} and R^{20} together with the carbons to which they are bonded form a phenyl ring.

2. The method according to claim 1, wherein n is 1.

3. The method according to claim 2, wherein Ring B is a heteroaromatic single 6-membered ring and Z is a carbon atom.

4. The method according to claim 3, wherein Ring B has the structural formula shown below, wherein the dotted line



denotes a bond to methylene group Y, and R¹, R² and R³ are independently hydrido, C₁-C₆-hydrocarbyl, C₁-C₆-hydrocarbyloxy or trifluoromethyl-C₁-C₃-hydrocarbyloxy, but at least one is other than hydrido.

5. The method according to claim 4, wherein Ring A is a single ring structure.

6. The method according to claim 5, wherein said single ring structure is a heteroaromatic ring.

7. The method according to claim 7, wherein said single heteroaromatic ring contains a ring hetero atom or a ring substituent in the meta-position rotated counter clock-wise from said 1-position.

8. The method according to claim 4, wherein Ring A is a fused ring structure containing two rings.

9. The method according to claim 5, wherein said single ring structure is a carbocyclic aromatic ring.

10. The method according to claim 9, wherein said carbocyclic aromatic ring contains at least one substituent group.

11. The method according to claim 1, wherein R¹⁵ is acetyl or 1-adamantoyl.

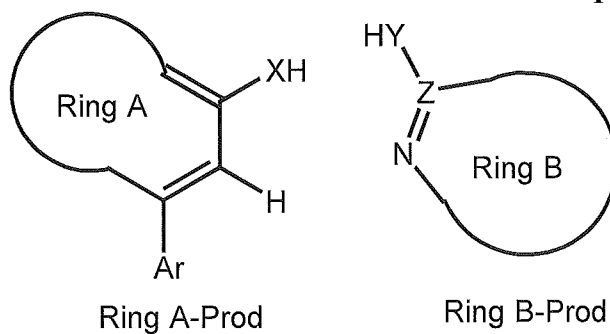
12. The method according to claim 11, wherein R¹⁶ is hydrido, R¹⁷ is C₁-C₆-hydrocarbyl or trifluoromethyl and R¹⁸ is hydrido.

13. The method according to claim 1, wherein A is CH₂ and R¹⁰ is C₁-C₆-hydrocarbyl carboxylate in a transient mediator compound of Formula II.

14. The method according to claim 13, wherein the remaining substituent R groups of a transient mediator compound of Formula II are hydrido.

15. The method according to claim 1 including the further step of recovering said reaction product of Formula **IA**.

16. The method according to claim 2 including the further step of reductively cleaving said reaction product of Formula **IA** to form products Ring A-Prod and Ring B-Prod whose structural formulas are shown below

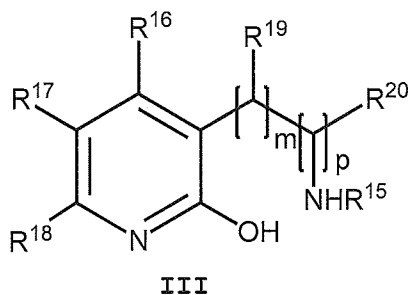


17. The method according to claim 4, wherein X is O.

18. The method according to claim 4, wherein X is NPG.

19. The method according to claim 1, wherein n is zero.

20. A substituted 3-amino-2-hydroxypyridine ligand having the structure of of Formula **III**



wherein R¹⁵ is an acyl group containing 2 to about 12 carbon atoms or a perfluorinated acyl group containing 2 to about 6 carbon atoms,

R¹⁶ is hydrido or C₁-C₆-hydrocarbyl,

R¹⁷ is hydrido, C₁-C₆-hydrocarbyl or trifluoromethyl,

R¹⁸ is hydrido or C₁-C₆-hydrocarbyl, or R¹⁶ and R¹⁷ or R¹⁷ and R¹⁸ together with the carbon atoms to which they are bonded form a 6-membered ring with the depicted pyridine ring,

m and p are the same and are zero or 1 such that m and p are zero, the bracketed carbon atoms are absent and the NHR¹⁵ group is bonded directly to the depicted pyridine ring, and when m and p are both one, R¹⁹ and R²⁰ together with the carbons to which they are bonded form a phenyl ring.

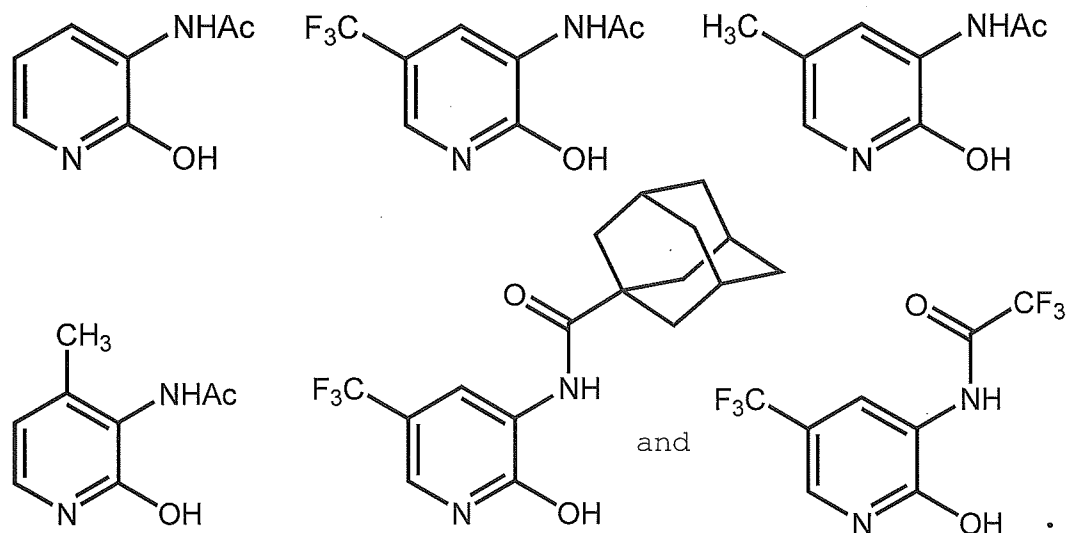
21. The substituted 3-amino-2-hydroxypyridine ligand according to claim 20, wherein m and p are both zero, and at least one of R¹⁶, R¹⁷ and R¹⁸ is other than hydrido.

22. The substituted 3-amino-2-hydroxypyridine ligand according to claim 21, wherein R¹⁵ is acetyl, 1-adamantoyl or trifluoroacetyl and R¹⁶ and R¹⁸ are hydrido.

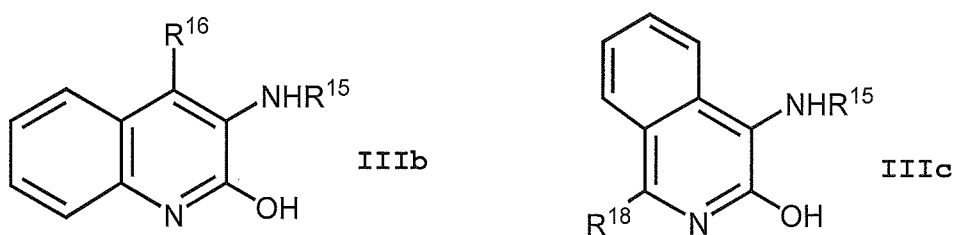
23. The substituted 3-amino-2-hydroxypyridine ligand according to claim 21, wherein one of R¹⁶ and R¹⁷ is C₁-C₆-hydrocarbyl, the other is hydrido, R¹⁸ is hydrido and R¹⁵ is acetyl.

24. The substituted 3-amino-2-hydroxypyridine ligand according to claim 21,

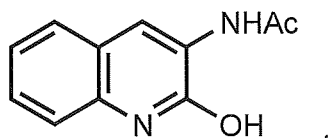
selected from the group consisting of one or more of the ligands having a structural formula shown below



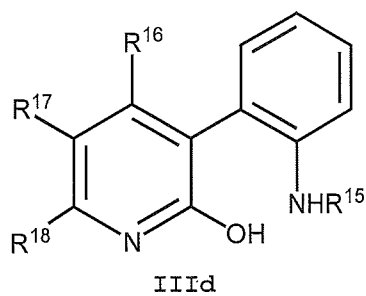
25. The substituted 3-amino-2-hydroxypyridine ligand according to claim 20, wherein R^{16} and R^{17} , or R^{17} and R^{18} together with their bonded carbons form a 6-membered aromatic ring so that the ligand is a derivative of a quinoline or isoquinoline of Formulas **IIIb** and **IIIc**, respectively,



26. The substituted 3-amino-2-hydroxypyridine ligand according to claim 25, whose structural formula is shown below



27. The substituted 3-amino-2-hydroxypyridine ligand according to claim 20, wherein m and p are both one and R¹⁹ and R²⁰ together with the carbons to which they are bonded form a phenyl ring whose structure is shown in Formula **IIId**, below



A. CLASSIFICATION OF SUBJECT MATTER**C07D 213/26(2006.01)i, C07D 213/36(2006.01)i, C07D 215/38(2006.01)i**

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 213/26; C07D 213/36; C07D 215/38

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(Registry, CAplus), Google & Keywords: versatile ligand, palladium catalyst, ligand, meta

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PIOTROWSKI, H. et al., "Self-assembled organometallic [12]metallacrown-3 complexes", Chemistry : A European journal, 2001, Vol. 7, No. 15, pp. 3196-3208 See page 3198, right column, 4th paragraph - page 3199, left column, 1st paragraph; and compound 8	20, 24
A		1-19, 21-23, 25-27
A	WANG, X.-C. et al., "Ligand-enabled meta-C-H activation using a transient mediator", Nature, 19 March 2015, Vol. 519, No. 7543, pp. 334-338 See abstract; and figures 1-4.	1-27
A	LI, S. et al., "Pd(II)-catalysed meta-C-H functionalizations of benzoic acid derivatives", Nature Communications, E-Pub. 27 January 2016, Vol. 7, Article no. 10443, pp. 1-8 See the whole document.	1-27
A	LEOW, D. et al., "Activation of remote meta-C-H bonds assisted by an end-on template", Nature, 28 June 2012, Vol. 486, pp. 518-522 See the whole document.	1-27

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

27 July 2017 (27.07.2017)

Date of mailing of the international search report

28 July 2017 (28.07.2017)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/028116

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SONG, B., "Palladium-catalyzed C-C bond formations via activation of carboxylic acids and their derivatives", Doctoral Thesis of Technische Universitat Kaiserslautern, 2013, pp. 1-293 See the whole document.	1-27
PX	WANG, P. et al. "Ligand-promoted meta-C-H arylation of anilines, phenols, and heterocycles", Journal of the American Chemical Society, E-Pub. 6 july 2016, Vol. 138, No. 29, pp. 9269-9276 See abstract; figures 1, 2; tables 1-3; and scheme 1.	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/028116Patent document
cited in search reportPublication
datePatent family
member(s)Publication
date

None