Ruthenium-Catalyzed Synthesis of Biaryls through C–H Bond Functionalizations

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« Comme le prince s'endormait, je le pris dans mes bras, et me remis en route. J'étais ému. Il me semblait porter un trésor fragile. Il me semblait même qu'il n'y eût rien de plus fragile sur la Terre. Je regardais, à la lumière de la lune, ce front pâle, ces yeux clos, ces mèches de cheveux qui tremblaient au vent, et je me disais : « Ce que je vois là n'est qu'une écorce. Le plus important est invisible… » Comme ses lèvres entr'ouvertes ébauchaient un demi-sourire je me dis encore : « Ce qui m'émeut si fort de ce petit prince endormi, c'est sa fidélité pour une fleur, c'est l'image d'une rose qui rayonne en lui comme la flamme d'une lampe, même quand il dort… » Et je le devinai plus fragile encore. Il faut bien protéger les lampes : un coup de vent peut les éteindre… »

Antoine de Saint Exupéry, Le Petit Prince

A Pierre, mon petit prince. Lyline

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Abbreviations

ACE	Angiotensin Converting Enzyme	DMSO	Dimethylsulfoxide
		Ed.	Editor
AcO	Acetate	EI	Electron Ionization
Ad	Adamantyl	equiv	Equivalent(s)
Alk	Alkyl	ESI	ElectroSpray Ionization
Ar	Aryl	Et	Ethyl
ARB	Angiotension Receptors Blockers	eV	Electron volt
		FDA	Food and Drug Administration
AT_1	Angiotensin II Receptor type 1	FG	Functional Group
		g	gramm
ATR	Attenuated Total Reflectance	GC/MS	Gas chromatography–Mass sprectrometry
Bn	Benzyl	h	hours
Br	broad	HIPrCl	1,3-Bis(2,6-diisopropylphenyl)-Imidazolium chloride
n-Bu	*n*-butyl		
t-Bu	*tert*-butyl	HMBC	Heteronuclear Multiple Bond Correlation
°C	Degree Celsius		
calcd.	calculated	HRMS	High Resolution Mass Spectrometry
cat.	catalytic		
CMD	Concerted Metalation Deprotonation	HSQC	Heteronuclear Single Quantum Correlation
COSY	Homonuclear Correlation Spectroscopy	Hz	Hertz
		IES	Internal Electrophilic Substitution
Cy	Cyclohexyl		
δ	Chemical shift	IR	Infra Red Spectrocopy
d	doublet	*J*	Coupling Constant
DFT	Density Functional Theory	L	liter
		$[M^+]$	Molecular ion peak
DG	Directing Group	m	Multiplet or milli
DMA	*N*,*N*-Dimethylacetamide	M	Molar
DMEDA	*N*,*N*'-Dimethylethylenediamine	Me	Methyl
DMF	*N*,*N*-Dimethylformamide	Mes	Mesityl

MHz	Megahertz
min	minutes
MS	Massenspectrometry
m/z	Mass/Charge
N	Normal
n.r.	No reaction
NHC	N-Heterocyclic Carbene
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NOEDIFF	Nuclear Overhauser Effect Difference Spectroscopy
PEG	Polyethylene Glycol
Ph	Phenyl
PivO	Pivalate
ppm	Parts per million
pyr	Pyridine
s	singulet
sat.	saturated
SPO	Secondary Phosphine Oxide
t	triplet
T	temperature
TLC	Thin Layer Chromatography
TM	Transition Metal
TMS	Trimethylsilyl
Ts	*p*-toluenesulfonic
v	volume
X	Halogen

1 Introduction

1.1 Carboxylate-assisted ruthenium-catalyzed direct arylations

Biaryl units are among the most important scaffolds in substrates of the pharmaceutical, agrochemical and materials industry.[1] Thus, Boscalid,[2] a broad spectrum fungicide, and the hypertension medication Valsartan[3] both contain a biaryl motif (Figure 1). These molecules are billion dollar "blockbusters" for the companies that introduced them. Their sales are on the rise and, therefore, the demand for their production is up to 1000 tonnes per year.

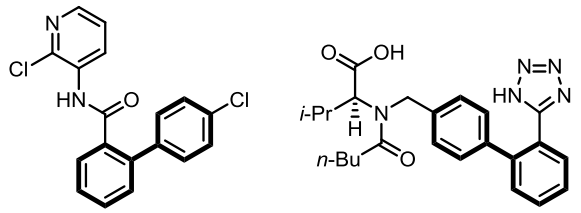
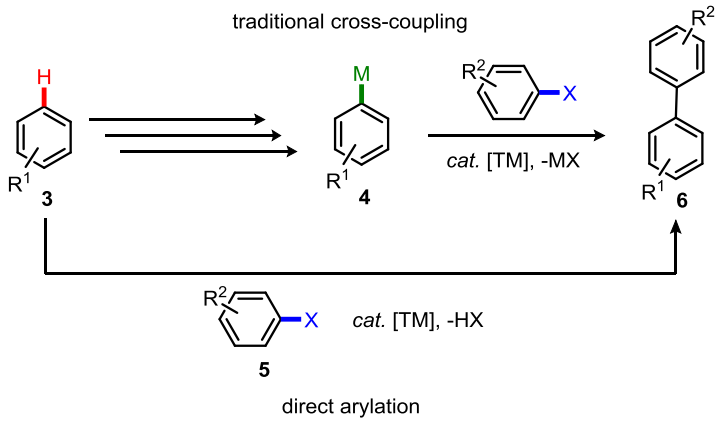


Figure 1: "Blockbusters" containing a biaryl motif.

Obviously, the design of the biaryl moiety can be considered as a key step in the synthesis of such molecules. In addition to selected non-catalytic methods, this operation can be performed applying various transition-metal-catalyzed cross-coupling reactions. Based on pionnering work by Ullmann and by Goldberg,[4] transition metal-catalyzed cross-couplings became one of the most important method for the regioselective synthesis of bi(hetero)aryls *via* C–C bond formation.[5] The importance of this chemistry was recognized when three pioneers in this field, Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki received the 2010 Nobel Prize in Chemistry, for ”providing organic chemists with efficient and useful methods for synthesizing compounds that were previously difficult to obtain”.[6]

Despite the large scope of reactions and opportunities opened by these methodologies, the starting organometallic reagents are often not commercially available, more or less toxic, and hard to synthesize or to handle. Moreover, the amount of byproducts produced, whether in the synthesis of the organometallic reagent or during the coupling step itself, remains significant (Scheme 1).



Scheme 1: Biaryl synthesis through C–H bond functionalization *vs* cross coupling chemistry.

In the last decades, transition-metal-catalyzed direct arylation of arenes through C–H bond functionalization[7] appeared as a very attractive alternative to the traditional cross-coupling reactions towards the efficient, atom- and step-economical[8] as well as environmentally friendly syntheses of biaryl units (Scheme 1).

The most challenging issue is to ensure the site-selectivity of the C–H bond functionalization in a molecule that contains other potentially reactive C–H bonds. To address this issue in heteroaromatic compounds, the difference of pK_a between various C–H bonds[9] can help to provide their selective functionalization (Figure 1).

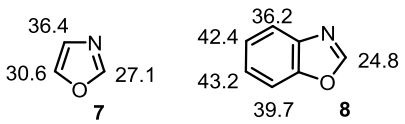
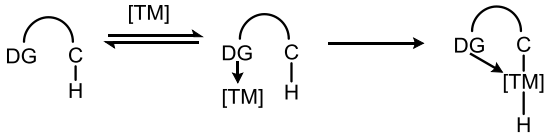


Figure 2: Control of regioselectivity of the C–H bond functionalization by their pK_a values.

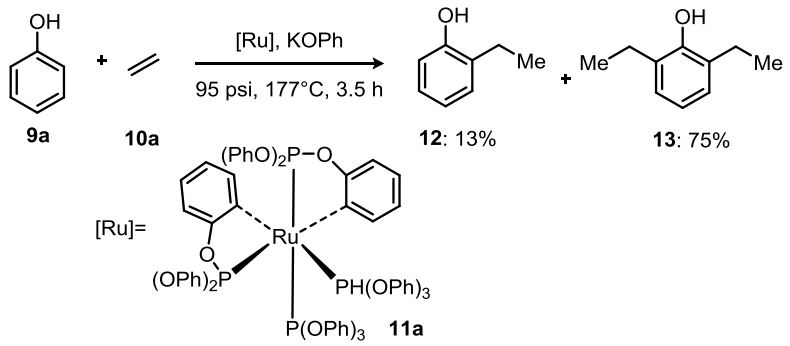
Another alternative approach is represented by the use of a directing group (DG). Nitrogen and oxygen containing groups provide the difference in reactivity between the C–H bonds in benzene derivatives, coordinating to the metal, and therefore bringing it to the proximity of the C–H bond,[10] and consequently allowing its activation/cleavage (Scheme 2).



Scheme 2: Directing group for a chelation-assisted C–H bond cleavage.

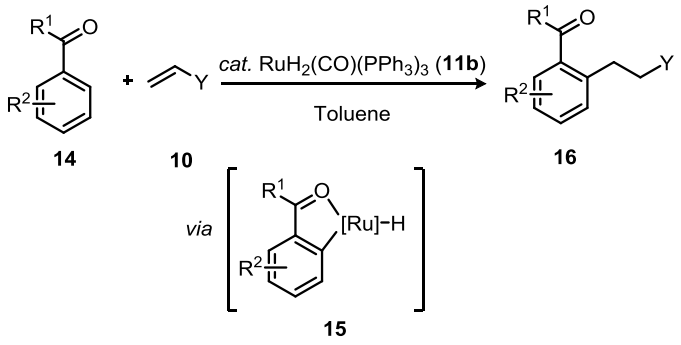
A number of synthetically useful protocols for direct C–H functionalization were developed during the last two decades,[11] mostly employing palladium. In contrast, versatile and relatively inexpensive[12] ruthenium complexes, which exhibit remarkable site selectivity and general substrate scope,[11n, 13] have only been recently exploited as catalysts for C–H bond functionalizations.

The first example of a chelation-assisted ruthenium-catalyzed C–H bond functionalization was reported by *Lewis* in 1986. The reaction consisted in an *ortho*-selective alkylation of phenol with ethylene, applying a cyclometalated ruthenium tetraphosphite as the catalyst along with catalytic amounts of potassium phenoxide (Scheme 3).[14]



Scheme 3: Chelation-assisted *ortho*-alkylation of phenol through C–H bond functionalization according to *Lewis*.

Further pioneering work by *Murai, Kakiuchi* and *Chatani* on ruthenium-catalyzed hydroarylations showed the ability of ruthenium catalysts to activate C–H bonds selectively, *via* chelation assistance (Scheme 4).[15]



Scheme 4: Chelation-assisted C–H bond functionalization according to *Murai* and coworkers.

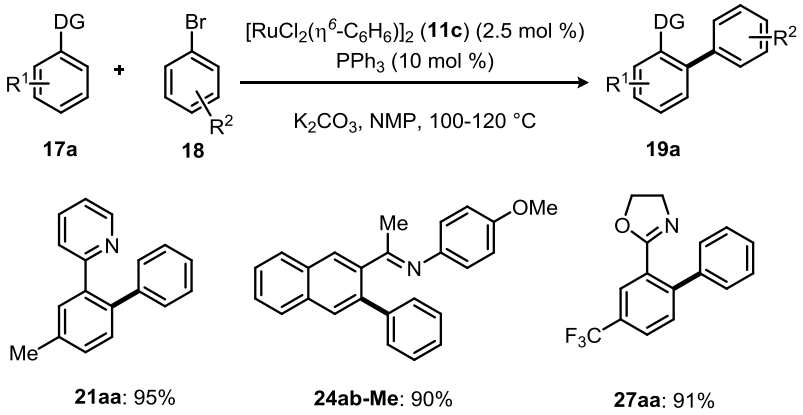
These pioneering works by *Lewis*[14] and *Murai*[15] demonstrated the synthetic potential of ruthenium complexes as catalysts for the direct C–H bond functionalization. Thereafter, considerable progress was achieved by employing ruthenium(0) catalysts for direct hydroarylations[16] and other C–H bond transformations.

On the other hand, ruthenium(II) complexes are even more attractive for organic synthesis due to their improved stability towards air and moisture.[11n, 13] Thus research was focused to the ruthenium(II)-catalyzed direct functionalization, and particularly to carboxylate-assisted direct arylation, for the sustainable synthesis of (hetero)biarenes.

1.1.1 Early studies in ruthenium-catalyzed direct arylations

In 2001, the first ruthenium(II)-catalyzed chelation-assisted direct arylation with aryl bromides was performed by *Oi*, *Inoue* and co-workers, using PPh_3 as the ligand in NMP (*N*-Methylpyrrolidinone), as the solvent (Scheme 5).[17]

Later, the *Oi* group proved that these methodologies were applicable to arenes with different directing groups, such as substituted ketimines, imidazolines, or oxazolines (Scheme 5).[18,19]



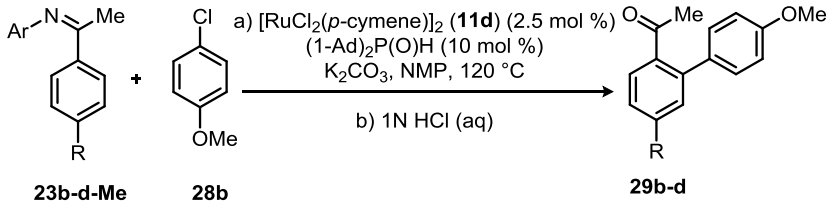
Scheme 5: Direct ruthenium(II)-catalyzed arylation according to *Oi* and *Inoue*.

The latter two products are particularly valuable, as their directing group can be transformed into other functionalities.[20] This catalytic system proved to be efficient for aryl iodides and bromides.

However, the challenge to extend those methodologies to less reactive but more abundant aryl chlorides or tosylates[11b] still remained.

1.1.2 Carboxylate-assisted direct arylations: initial observations

Starting from 2003, the scope of this reaction was extended by the *Ackermann* group as the more available and inexpensive aryl chlorides could be used as coupling partners. Those advances were achieved using a catalytic system generated from $[RuCl_2(p\text{-cymene})]_2$ and secondary phosphine oxides (SPO).[21] These conditions allowed for the efficient and selective arylation of arenes, bearing heteroatom-containing Lewis-basic derived directing groups. Notably, the reaction scope was extended to ketimines, which, after hydrolysis, gave arylated ketones as valuable tools in organic synthesis. Such substrates were arylated in a chemo-selective way, as the monoarylated product was predominantly formed (Scheme 6).[21]



R = H 74% (**29b**)
R = OMe 69% (**29c**)
R = Me 77% (**29d**)

Scheme 6: Synthesis of *ortho*-arylated ketones by *Ackermann.*

These reactions could even be applied, with a modified SPO ligand, for the selective direct arylation of arylpyrazoles, arylpyridines, and aryloxazolines with prefunctionalized phenols and aryl chlorides.[22]

Furthermore, the direct arylation employing this catalytic system could be performed in an apolar solvent like toluene.[23] This discovery brought about an important insight in the reaction mechanism. Concerning the C–H bond cleavage itself, the first insights were brought by *Davies*, who demonstrated the beneficial effect of sodium acetate in the formation of ruthenacycles at ambient temperature.[24,25]

The concept of concerted metallation-deprotonation (CMD) and the beneficial role of carboxylates for the C–H bond activation were already postulated in the palladium-catalyzed C–H bond functionalization by *Davies* and *MacGregor*,[26] *Maseras* and *Echavarren*,[27] as well as by *Gorelsky* and *Fagnou*.[28] Their findings led to advances in the field of palladium-catalyzed carboxylate-assisted C–H bond functionalizations. Based on all of those informations, a concerted metallation deprotonation (CMD) mechanism was also proposed as a key step in the ruthenium-catalyzed direct arylation with SPOs as the additives (Figure 3a).

Further DFT-calculations by *Maseras* and coworkers[29] strongly supported the hypothesis that the ruthenium catalyzed direct C–H bond functionalizations are proceeding through a proton abstraction and not through an addition of ruthenium into the C–H bond.

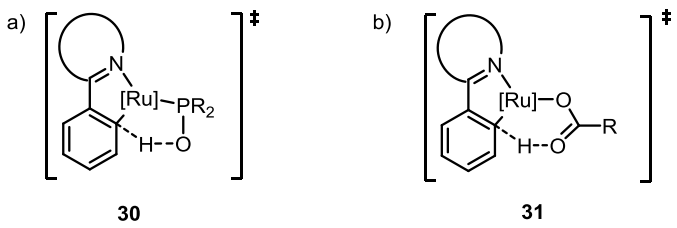


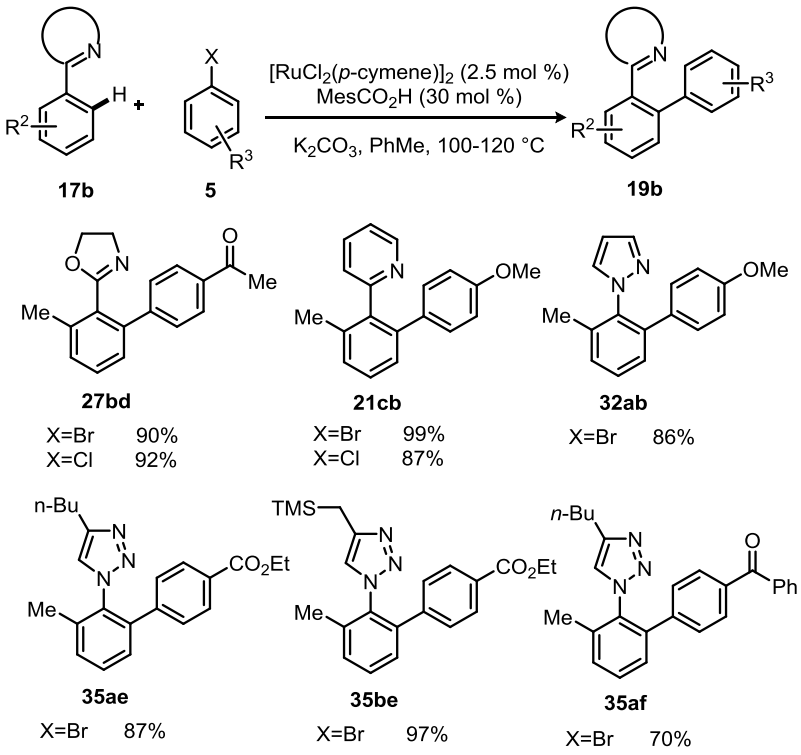
Figure 3: Proposed transition states through Concerted Metallation-Deprotonation in the presence of SPO (a) or carboxylates (b).

As this type of mechanism was most likely to occur, carboxylic acids and carboxylates (Figure 3b) were probed as additives in the ruthenium-catalyzed direct arylations by the *Ackermann* group.

1.1.3 Direct arylation through carboxylate assistance.

1.1.3.1 Direct arylation of arenes in apolar solvents

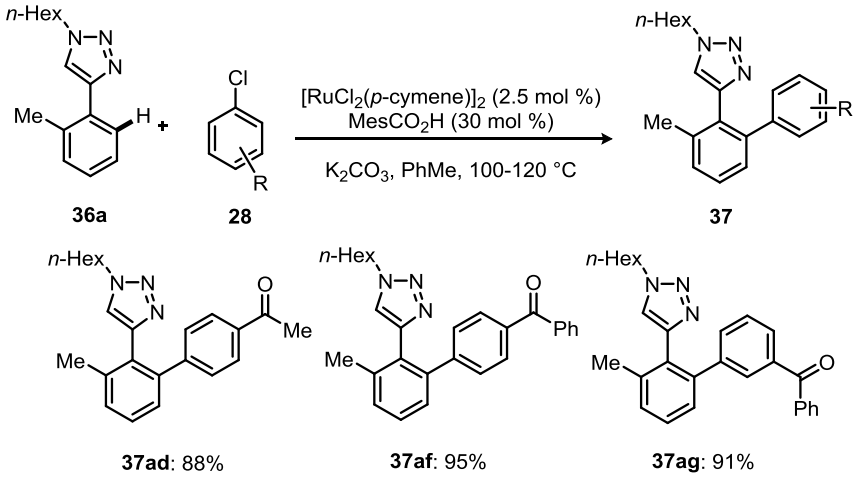
In 2008, the *Ackermann* group first described the beneficial effect of carboxylic acids in the ruthenium-catalyzed direct arylation of arenes in the apolar, less coordinating solvent toluene.
Among others, 2,4,6-trimethylbenzoic acid (mesitylic acid, $MesCO_2H$), was proved to be a reliable tool for the carboxylate-assisted direct arylation. The scope of arenes which could be arylated under these reaction conditions is very broad. Indeed, various arenes **17** with nitrogen-containing directing groups such as 2-pyridyl, oxazolin-2-yl, *N*-pyrazolyl and N-triazolyl optimally reacted with arylbromides under these reactions conditions (Scheme 7). [23]



Scheme 7: Mesitylate-assisted direct arylation in toluene.

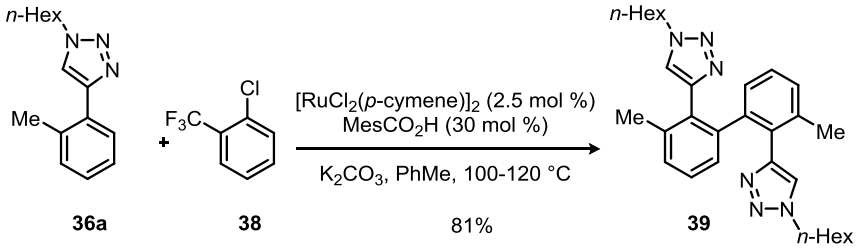
Furthermore, less expensive but also less reactive aryl chlorides gave the desired product in comparably high yields.[23] The scope was extended to 1,4-disubstituted 1,2,3-triazoles **36**, which could also be used as substrates for the direct arylation with aryl halides.[30] Contrary to the chemo-

selectivity of the palladium-[31] or copper-catalyzed[32] arylations, these functionalization took place on the carbocyclic moiety of **36a** (Scheme 8).



Scheme 8: Mesitylate-assisted direct arylation of 1,2,3-triazol-4-yl substituted arenes **36**.

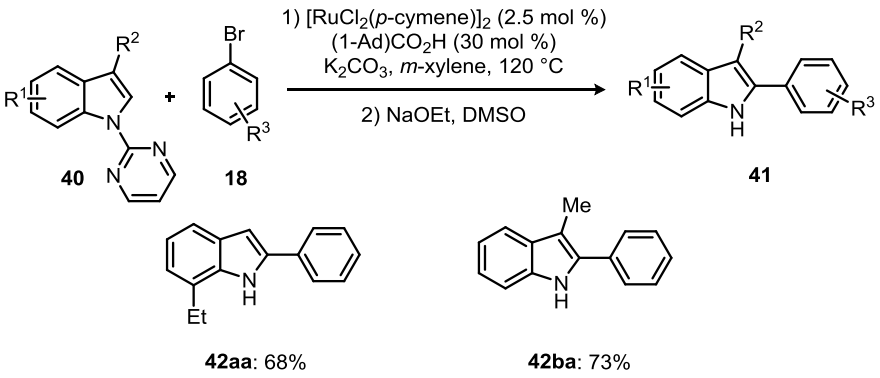
However, the direct arylation with *ortho*-substituted aryl chlorides did not occur under these reaction conditions. Thus, 2-chloro(trifluoromethyl)benzene **38** served not as an arylating agent but as an optimal sacrificial oxidant,[30] promoting the oxidative homocoupling reaction (Scheme 9).[33]



Scheme 9: Promoted oxidative homocoupling with *ortho* substituted arylchloride **38**.

1.1.3.2 Carboxylate-assisted direct arylation of heteroarenes.

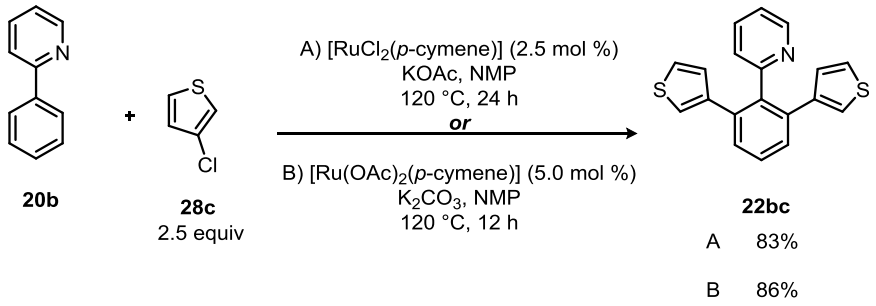
Ruthenium-catalyzed direct arylations of heteroarenes have been rarely reported until recently. The system $[RuCl_2(p\text{-cymene})]_2$/1-adamantylcarboxylic acid (1-$AdCO_2H$) showed unprecented catalytic reactivity for the direct arylation of heteroarenes.[34] Actually, indoles, pyrroles and thiophene were selectively arylated with aryl bromides in high yields (up to 91%). Moreover, the directing group could be easily removed yielding the NH free indoles **42** (Scheme 10). It should be pointed out that such a strategy of removable directing groups[35] has been previously used predominantly in palladium- and rhodium-catalyzed couplings,[36] while its application in the ruthenium-catalyzed C–H functionalizations was poorly documented.[37]



Scheme 10: One-pot synthesis of 2-arylated NH-free indoles **42**.

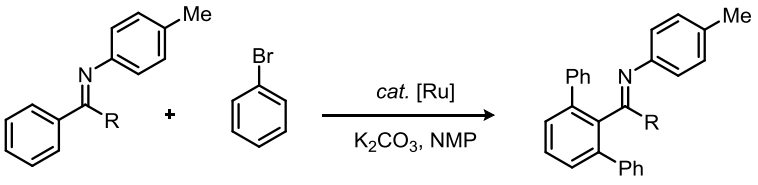
1.1.3.3 Direct arylation of arenes in polar coordinating solvents

NMP has been utilized frequently as a solvent in ruthenium-catalyzed direct arylation. For exemple, acetate was used to promote the diheterodiarylation of 2-phenylpyridine **20b** with heteroaryl chlorides or bromides in NMP as the solvent (Scheme 11).[38] Its use as an additive resulted in the *in situ* formation of the complex [Ru(OAc)$_2$(*p*-cymene)], which in combination with K_2CO_3, catalyzed the complete conversion of the substrate **20b**, yielding polyheterocycles **22bc**.



Scheme 11: Acetate-assisted direct arylation for the synthesis of polyheterocycles **22bc**.

This catalytic system was also recently applied in the efficient arylation of aldimines **23e-H** with aryl bromides.[39] The diarylated compounds **25** were obtained using [RuCl$_2$(*p*-cymene)]$_2$, KOAc as an additive and K_2CO_3 as a base in NMP. Moreover, a combination of acetate and triphenylphosphine ligands selectively gave the diarylated aldimine **25ea**-H at lower temperature (100 °C) with a reduced catalyst loading. Ketimine **23e**-Me was also a compatible susbstrate under these reaction conditions (Scheme 12).

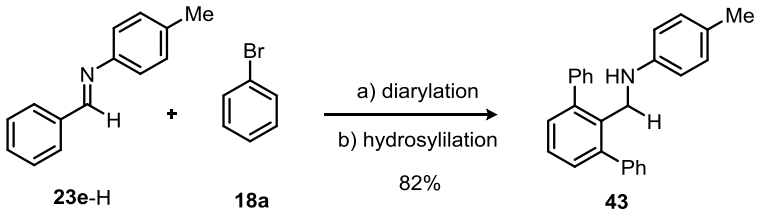


23e-R **18a** **25ea-R**

	[Ru] cat.	Isolated yield
R = H	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %) KOAc (20 mol %), 160 °C, 48 h	**25ea**-H: 75%
R = H	$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) KOAc (5.0 mol %), PPh_3 (5.0 mol %) 100 °C, 20 h	**25ea**-H: 73%
R = Me	$[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %) KOAc (20 mol %), 160 °C, 48 h	**25ea**-Me: 70%

Scheme 12: Selective diarylation of aldimines and ketimines **23**.

The complex $[RuCl_2(p\text{-cymene})]_2$ also promoted the hydrosilylation of a C=N bond with Ph_2SiH_2. This allowed the sequential diarylation/hydrosilylation of imines **23e-H** in excellent yields (Scheme 13),[39] however, after separation of KOAc and PPh_3, which inhibited the hydrosilylation. This approach was earlier used for the direct arylation/hydrosilylation sequence by *Ackermann* and coworkers.[40]



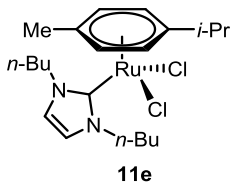
23e-H **18a** **43**

a) $[RuCl(p\text{-cymene})]_2$ (2.5 mol %) KOAc (5.0 mol %), PPh_3 (5.0 mol %) K_2CO_3, NMP, 100 °C, 20 h

b) $[RuCl(p\text{-cymene})]_2$ (2.5 mol %) Ph_2SiH_2 (2.0 equiv), EtOH then NaOH, MeOH

Scheme 13: Sequential diarylation/hydrosilylation.

Prades and *Peris* also reported the acetate-assisted arylation of 2-phenylpyridine (**20b**) in NMP using NHC-ruthenium complexes of the type **11e** (Figure 4).[41]



11e

Figure 4: NHC-ruthenium complex **11e** for the diarylation of 2-phenylpyridine.

This methodology was then extended by *Fischmeister* and *Dixneuf* for the diarylation of 2-phenylpyridine (**20b**), 2-phenyloxazoline and 1-phenylpyrazoles using such unusual ruthenium(II) precursors $[RuH(codyl)_2]BF_4$ in combination with various potassium carboxylate and K_2CO_3.[42]
On the other hand, *γ*-butyrolactone – a common impurity in NMP – or the carboxylate resulting from its hydrolysis acted as a soluble carboxylate source that enhanced the reactivity in the same extent as

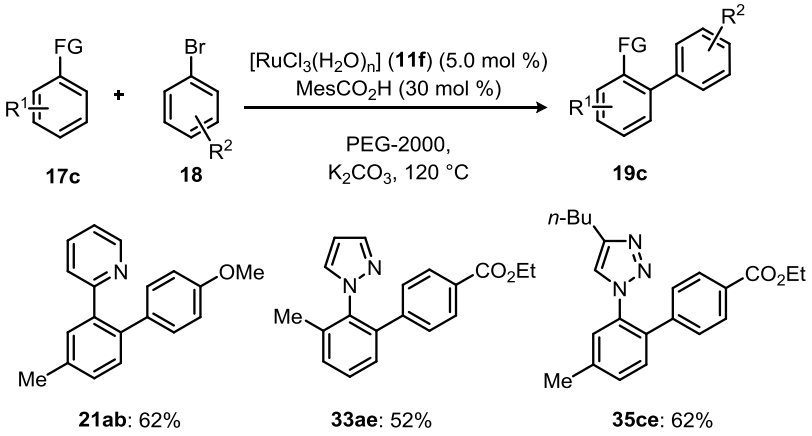
KOAc. Therefore, it is important that the results of mechanistic experiments obtained using NMP as the solvent should be accepted with care.[43]

1.1.3.4 Carboxylate assisted ruthenium catalyzed direct arylation in "green" solvents

Most of reported direct arylations were performed either in NMP or toluene as solvents. However, the demand for a more user and environmentally friendly chemistry opens a new horizon for the extended application of "green solvents" in direct C–H bond functionalizations as well.[44]

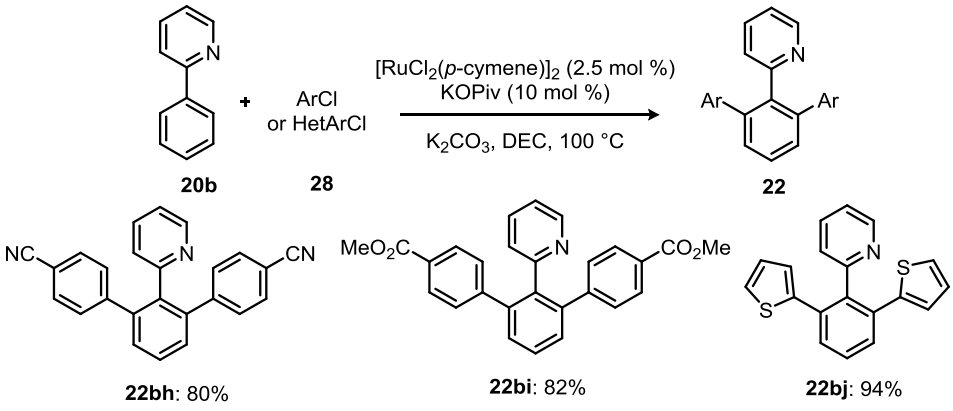
First, in 2005, the *Ackermann* group reported the chemoselectivity of the ruthenium-catalyzed direct arylation and that water could be used as a cosolvent, still with good yield of product.[21]

Additional experiments using $MesCO_2H$ as an additive were carried out in non-volatile, non toxic PEG-2000.[11p] Thereby, a number of arenes bearing various directing groups were selectively arylated with $[RuCl_3(H_2O)_n]$[45] as the least expensive ruthenium source (Scheme 14).[46]



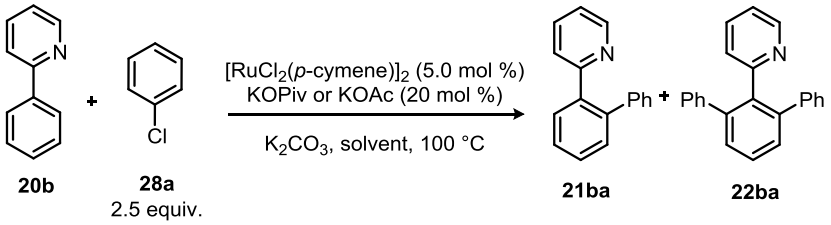
Scheme 14: Direct arylation in user-friendly PEG-2000.

Subsequently starting from 2009, several ruthenium-catalyzed direct arylations in green solvents were reported by the *Dixneuf* group. Hence, the $[RuCl_2(p\text{-cymene})]_2$/potassium pivalate catalytic system in diethylcarbonate (DEC) as the solvent ensured successful diarylation of 2-phenylpyridines **20** with aryl chlorides **28**, including heteroaryl chlorides and tolerating various functional groups like cyanide or ester (Scheme 15).[47]



Scheme 15: Direct arylations with aryl chlorides **28** in diethylcarbonate.

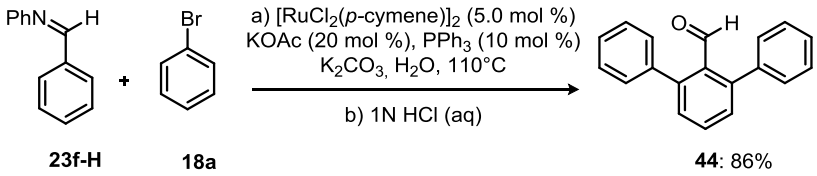
Remarkably, the twofold arylation of 2-phenylpyridine (**20b**) employing this catalytic system proved to be most effective[48] with water as the nontoxic reaction medium[49] (Scheme 16) under exceedingly mild reaction conditions. Thus, the catalyst was still active even at 60 °C.



Solvent	Potassium carboxylate	Conversion (**21ba:22ba**) (%)
Water	KOAc	100 (26:74)
Water	KOPiv	100 (0:100)
NMP	KOPiv	100 (25:75)
DEC	KOPiv	100 (45:55)

Scheme 16: Solvent effect upon ruthenium-catalyzed phenylation of 2-phenylpyridine (**20b**).

Furthermore, less expensive potassium acetate was proven again a useful additive for the direct arylation with aryl bromides of oxazolines, aldimines or ketimines in combination with PPh_3. The arylated aldimines could easily be hydrolyzed under acidic reaction conditions to give the arylated benzaldehydes **44**, showing the possibility of an efficient synthesis of functionalized aldehydes *via* temporary imine formation (Scheme 17).[50]



Scheme 17: Synthesis of diphenylated benzaldehyde 44.

Very recently, a new family of water-soluble (O,O)- and (O,N)-chelated ruthenium catalysts was synthesized by *Singh* and *Dixneuf,* by treatment of $[RuCl_2(p\text{-cymene})]_2$ with tropolone, sodium glycinate or kojic acid, respectively (Figure 5).[51] These new complexes proved to be efficient for the direct arylation of 2-phenylpyridine (**20b**) with aryl chlorides or bromides in water, in the presence of catalytic amounts of potassium acetate or pivalate in aqeous medium.[13a, 51]

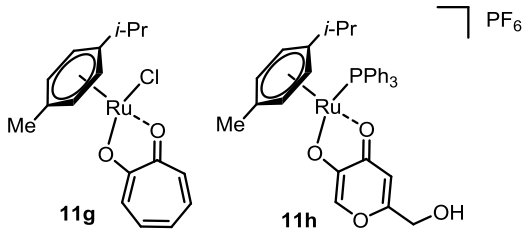


Figure 5: Water soluble ruthenium-complexes **11g-h** for the direct arylation of arenes.

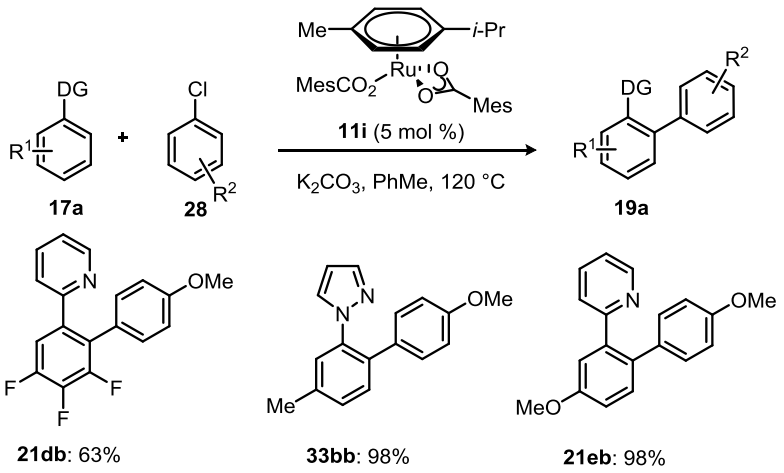
1.1.3.5 Mechanistic considerations in the ruthenium-catalyzed direct arylation

During the last decade, the mechanistic considerations of ruthenium-catalyzed direct arylation underwent rapid evolution, but yet still remain under investigation.

It was initially thought by *Oi*, *Inoue* and coworkers, [17-18] with analogy to the palladium chemistry, that the reaction was proceeding through an initial oxidative addition of the aryl halide to the ruthenium catalyst with subsequent C–H bond functionalization.[45b] But, this kind of mechanism can only be favored in particular cases.[52] Furthermore, only three years later, *Oi* and *Inoue* postulated that the cyclometalation took place first, in contrast to palladium-catalyzed direct arylations, before the oxidative addition followed then by reductive elimination. [19, 53]
Several studies including experiments with isotopically labeled starting materials,[41, 54] intermolecular competition experiments,[41, 54] determination of the inverse kinetic isotope effect as well as density functional theory (DFT) calculations[29] have been performed toward mechanistic elucidation of the carboxylate-assisted ruthenium-catalyzed direct arylations.

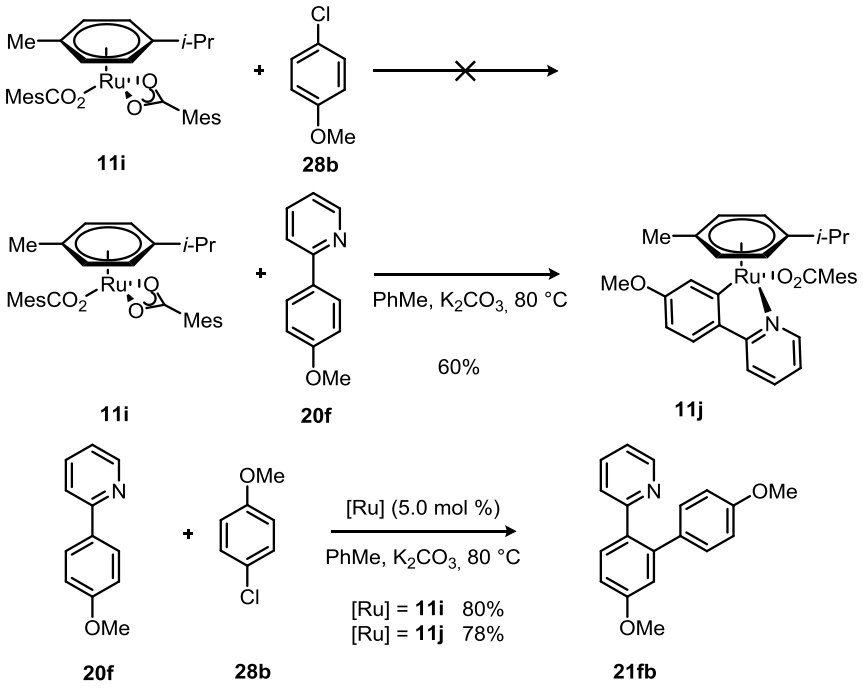
As the knowledge about the carboxylate assistance emerged, so did the interest in the nature of the active species in the catalytic cycle. As a consequence, some stoichiometric experiments were performed in order to gain a better understanding of the reaction.

Thus, the reaction of $[RuCl_2(p\text{-cymene})]_2$ with a stoichiometric amount of $MesCO_2H$ selectively gave the well defined ruthenium(II) biscarboxylate complex **11i**.[54] This complex proved to be catalytically active in a less coordinating solvent such as toluene, and a large number of arylated arenes were obtained in excellent yields (Scheme 18). Electron-deficient arenes were arylated with satisfactory results as well and even *meta*-substituted substrates reacted in a highly site-selective fashion, affording the products in great yields.



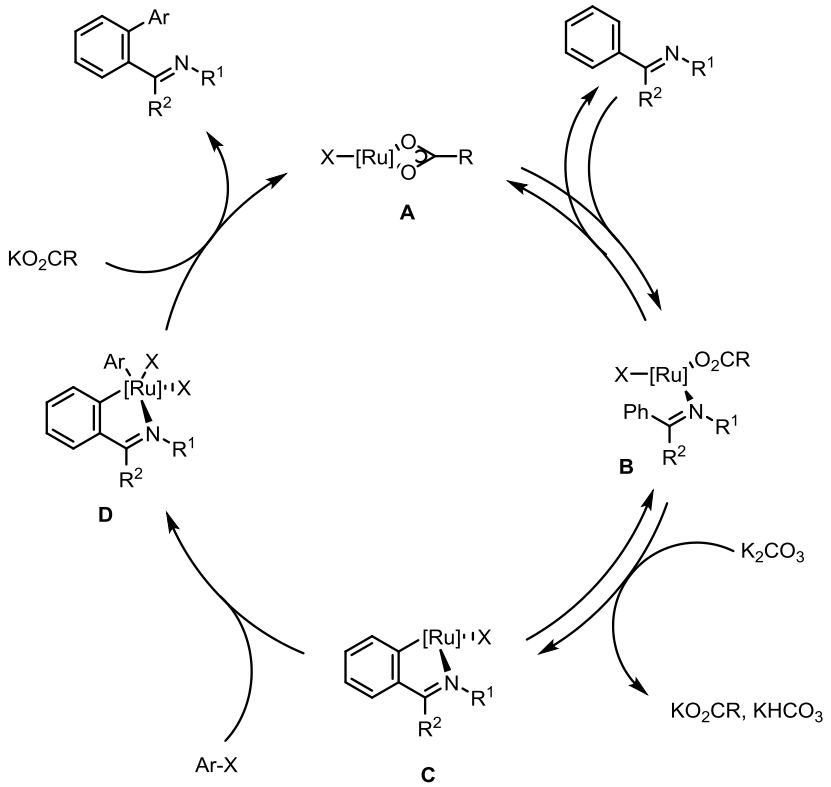
Scheme 18: Direct arylation with well-defined ruthenium(II) biscarboxylate complex **11i**.

Further, in stoichiometric experiments carried out by *Ackermann*, *Vicente*, *Potukuchi* and *Pirovano*,[54] no oxidative addition of *p*-chloroanisole (**28**) to the ruthenium catalyst **11i** was observed, even at elevated temperatures. On the contrary, cyclometallation of 2-(4-methoxyphenyl)pyridine (**20f**) with **11i** yielded the cyclometallated[55,56] complex **11j**. This complex was then proven to be catalytically active in the direct arylation chemistry (Scheme 19).[54]



Scheme 19: Synthesis of cyclometallated complex **11j** and its catalytic activity.

Further experiments with isotopically labeled starting materials or hydrogen/deuterium exchange experiments in deuteriated solvents were carried out and undoubtedly indicated the reversibility in nature of the C–H bond metallation, with a carboxylate-assisted deprotonation.[54] Based on the experimental results discussed above, the following mechanism was proposed for the ruthenium-catalyzed carboxylate-assisted direct arylation of arenes (Scheme 20).

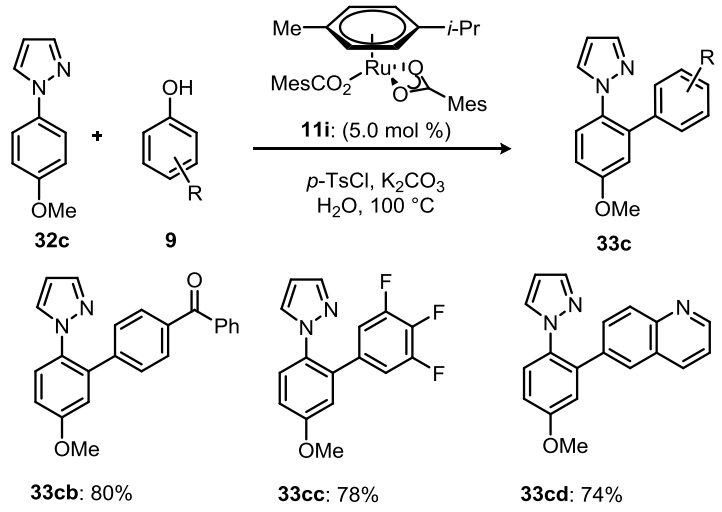


Scheme 20: Proposed mechanism for the ruthenium-catalyzed direct arylation of arenes.

Initial complex **A**, after coordination (**B**), reversibly cyclometalates the substrate through a ligated mesityl-assisted concerted deprotonation. Thereafter, complex **C** reacts in the rate-limiting step with the aryl halide Ar–X to yield the intermediate **D**. Finally, reductive elimination yields the product with regeneration of the catalytic species **A**.[54]
Importantly, while the attached carbonate ligand only favors the C–H bond deprotonation, [29] the addition of catalytic amount of carboxylate not only drastically enhances the C–H bond activation step affording **C**, [56] but also facilitates the C–C bond formation, presumably favoring the oxidation step of Ar-X furnishing **D**. Indeed, recent kinetic measurements of arylation of 2-phenylpyrazole, 2-phenyloxazoline in CD_3CN at 27 °C using [$Ru(OAc)_2$(*p*-cymene)] as pre-catalyst without additives disclosed the C–H activation step to be fast.[57] In this study, it is speculated that the C–H activation proceeds as an intermolecular process with assistance of a free acetate in an autocatalytic fashion.

1.1.3.6 Ruthenium-catalyzed biaryl synthesis through dehydrative arylation.

In spite of their lower reactivities, the user-friendly, readily available and inexpensive phenol derivatives, such as aryl tosylates and mesylates, are undoubtedly among the most synthetically useful pseudo-halide electrophiles for direct arylations of C–H bonds.[11b] The first carboxylate-assisted ruthenium-catalyzed direct arylation of arenes bearing directing groups with aryl tosylates as electrophiles through C–H bond functionalization was described by *Ackermann* and coworkers.[23] However, with respect to the overall minimization of byproduct formation upon the preparation of sulfonates from the corresponding phenols and with the aim to reduce the number of reaction steps, further improvements towards direct employment of phenols **9** without prefunctionalization have been made by the *Ackermann* group.
This highly attractive formal C–H/C–OH bond functionalization strategy was performed initially employing [$RuCl_2$(*p*-cymene)]$_2$ in DMA[58] and more successively with well-defined complex **11i** in non toxic, non flammable and user-friendly solvent water (Scheme 21). Even under neat conditions the desired products were obtained in great yields.[59]

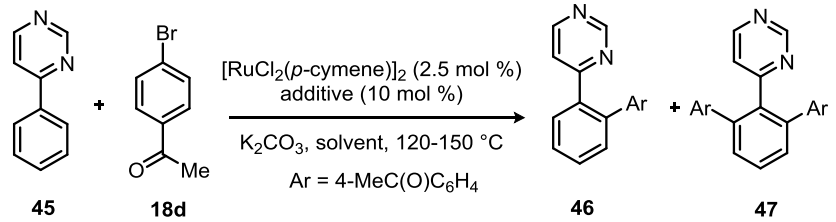


Scheme 21: Step-economical direct arylations using phenols **9** as proelectrophiles in water as a "green" solvent.

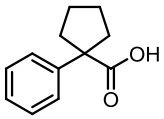
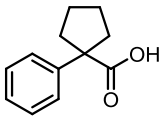
1.1.3.7 Ruthenium-catalyzed direct arylations of pyrimydyl-arenes

Most of the directing groups on the arenes employed in the direct arylation contain heteroatoms. Among them, the most commonly applied ones are pyridine, oxazoline, and pyrazole. But up to now,

few reactions have been reported on the *ortho*-directed arylation on arenes bearing a pyrimidine moiety as a directing group.[60,61,36k] Lately, *Požgan* and coworkers reported on an efficient and *ortho*-selective diarylation of 4-phenylpyrimidine **45** (Scheme 22).[62]



45 18d 46 47

Additive	Solvent	Conversion (**46**:**47**)
KOAc	NMP	13 (50:50)
KOAc	1,4-dioxane	26 (77:23)
(1-Ad)CO_2H	1,4-dioxane	53 (70:30)
 **48**	1,4-dioxane	100 (94:6)
 **48**	PhMe	100 (33:67)

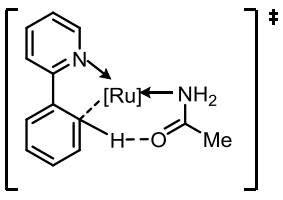
Scheme 22: Direct arylation of 4-phenylpyrimidine **45**.

The most commonly used ruthenium(II)/KOAc system displayed unsatisfactory results. While catalytic systems with benzoic or 1-adamantylcarboxylic acid demonstrated essentially the same or little better results, 1-phenyl-1-cyclopentanecarboxylic acid (**48**) formed with [$RuCl_2$(*p*-cymene)]$_2$ an excellent catalytic system, providing complete conversion with very good selectivity (Scheme 22).With this catalyst in hand, the direct arylation of 2-phenylpyrimidine was probed, and the diarylated product was obtained in 88% isolated yield.

1.1.3.8 Further additives for the ruthenium-catalyzed direct arylation.

As discussed above, carboxylates turned out as efficient additives for the direct arylation of C(sp^2)–H bonds with (pre)functionalized arenes. The role of the carboxylate as the coordinating ligand to promote the cleavage of the C–H bond cannot be doubted.

Notably, pure acetamide as additive exerts very similar chelating assistance in arylation reactions of 2-phenylpyridine (**20b**) in 1,4-dioxane, as revealed by *Li* and coworkers.[63] On the basis of previous investigations by *Dixneuf* and *Ackermann*, the authors postulated the participation of the possible intermediate **49** (Figure 6).



49

Figure 6: Postulated intermediate for the acetamide assited ruthenium-catalyzed direct arylation.

As a conclusion to this chapter, it should be emphasized that, apart from direct arylation processes, the use of carboxylates as additives set the stage for a large scope of reactions. This catalytic system could be employed for the direct *ortho* or *meta* alkylation of arenes,[64] alkyne annulations by C–H/Het–H bond formation,[65] hydroarylation with simple non-activated alkenes,[66] C–O bond formation,[67] carbonylation reactions, and for the selective direct arylation of C(sp^3)–H bonds.[68, 69]

1.2 The Angiotensin Receptors.

Hypertension, or high blood pressure, is a recurrent problem in the World. It is a public health problem as one in three adults worldwide has hypertension.[70] Through its careful control, some more serious health problems such as heart attack, stroke, and kidney failure can be prevented.[71] Hypertension – a major concern in our society – can be prevented with a healthy lifestyle and/or through prescription of drugs.[71] Among them, a class of highly efficient compounds from the family of ARBs, or Angiotensin Receptor Blockers, has attracted substantial attention as an important therapeutic and synthetic target for the researchers.[72]

1.2.1 Mode of action of the Angiotensin Receptor Blockers (ARBs).

The ARBs[73] block the activation of Angiotensin II AT_1 receptors by the polypeptide Angiotensin II. These receptors are mainly located in the heart, brain, liver and kidneys. They modulate the renin-angiotensin-aldosterone system, whose main role is to regulate the blood pressure, fluid, and electrolyte balance (Figure 7).[74]

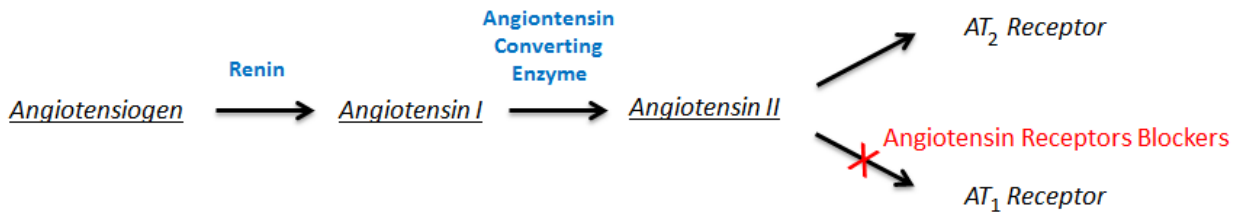


Figure 7: Mode of action of the ARBs.

The inhibition of the AT_1 receptors causes vasodilation, reduces the production of vasopressin, and decreases the production and secretion of aldosterone. The combination of all these effects reduces the blood pressure.

Another hypertension treatment consists of Angiotensin Converting Enzyme (ACE) inhibitors, which also inhibit the renin-angiotensin system. However, ACE is not a preferred target, as it also cleaves other peptides in the body, and not only angiotensin I, which can lead to undesired side effects.[73] Renin was also considered as a target, but up to now only few candidates have been used. ARBs still remain the most useful remedies to treat high blood pressure today.[3a]

1.2.2 ARBs: Blockbusters in the treatment of hypertension

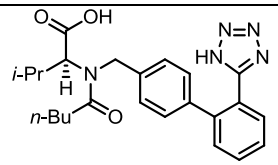
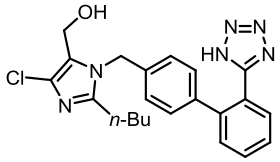
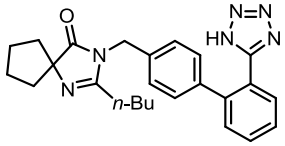
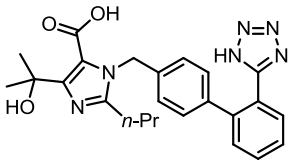
Losartan (DuP-753), the first Angiotensin II Receptor Blocker was discovered in March 1986, by researchers at *DuPont*. In 1990, the company signed joint product development and co-marketing agreement with Merck to develop Losartan and to launch it on the market. The drug was then approved by the US Food and Drug Administration in April 1995. This discovery inspired the research

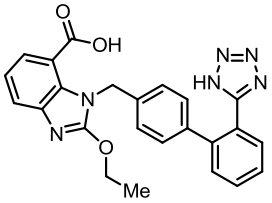
within the class of ARBs, in such a range that by 2002 the US FDA had approved seven other AT_1 receptor blockers.[75]

The basic structure of ARBs, or "sartans" consists of a biaryl unit with an attached heterocyclic moiety, such as tetrazole.

Initially, Merck first commercialized a sartan, Losartan, under the Name Cozaar®. More sartans were approved by the Food and Drug Administration for the treatment of hypertension, either alone or in combination with other drugs. They are generally classified as "blockbusters" by the firms that produced them. Those molecules are commercialized for the treatment of among others hypertension, diabetic nephropathy and congestive heart failure. These drugs generate billion dollar incomes for the companies that developed them (Table 1).

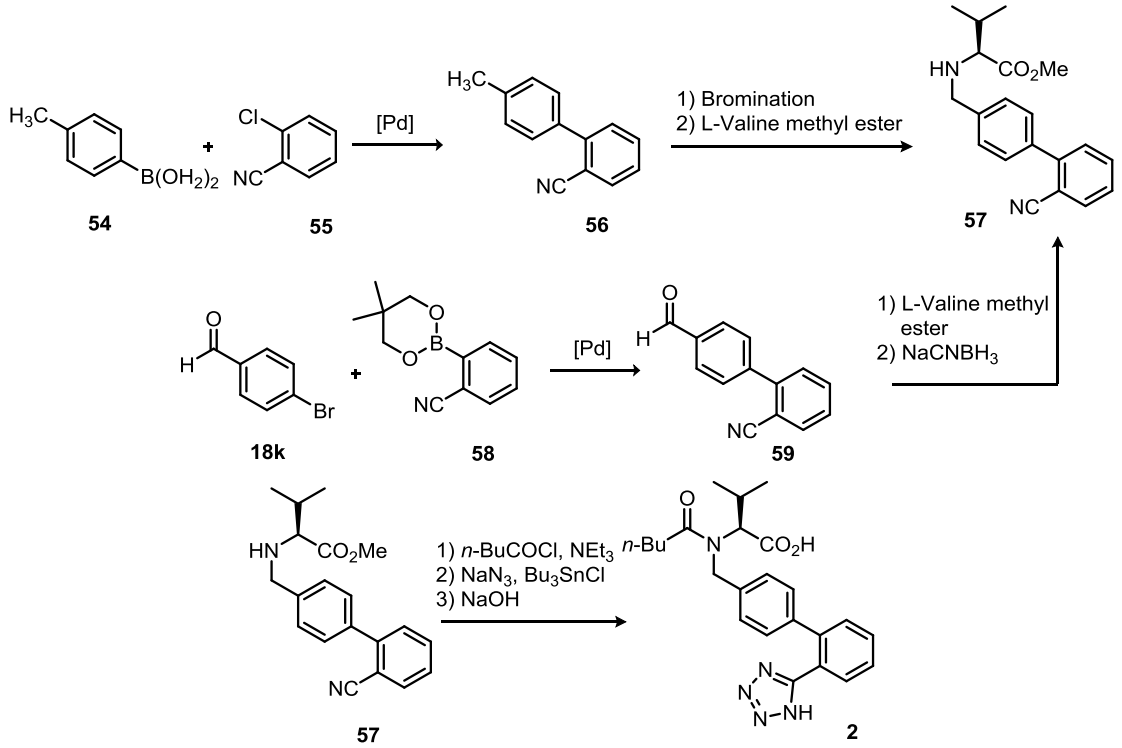
Table 1: Main ARBs drugs containing both biphenyl and tetrazole units.

Generic name	Formula	Commercial Name	Sales in 2012 (dollars)
Valsartan (**2**)		Diovan ® (Novartis)	4.4 billion
Losartan (**50**)		Cozaar ® (Merck) Active as potassium salt	1.3 billion
Irbesartan (**51**)		Aprovel® Karvea® Avapro® (Sanofi Aventis / Bristol Myers Squibb)	1.15 billion
Olmesartan (**52**)		Benicar® Olmetec® (Daiichi Sankyo)	888 million

Generic name	Formula	Commercial Name	Sales in 2012 (dollars)
Candesartan (**53**)		Blopress® Atacand® Amisa® Atacand® (Astra Zeneca / Takeda Pharmaceuticals)	Takeda: 2.0 billion (2011) AstraZeneca: 1.0 billion

1.2.3 Syntheses of ARBs

The most profitable molecule is Valsartan, which contains a biphenyl unit and a tetrazole moiety. Novartis (back then Ciba-Geigy AG) patented in 1991, the large scale synthesis *via* a Suzuki cross-coupling reaction (Scheme 23).[76]



Scheme 23: Synthesis of Valsartan.

Since then a number of different methods for an efficient and possibly useful large scale syntheses of ARBs have been elaborated.[77] In most of them, the biaryl core is directly used from commercial sources and further functionalized, or is synthesized through palladium-catalyzed cross-coupling of a boronic acid and an aryl halide, more commonly known as the Suzuki-Miyaura cross coupling.

The main drawback of this approach is the use of either expensive or not easily accessible boronic acid derivatives. Moreover, formation of undesired byproducts and waste, which need to be recovered or disposed, is not in line with the new industrial green chemistry policies.

Therefore, there are many ongoing research projects around the world to find out a new, environmentally friendly and efficient reaction for the synthesis of the appropriate biaryl unit. The

latter can be achieved employing an attractive alternative: Transition metal-catalyzed direct arylation through C–H bond cleavage, as the tetrazole moiety in **60** a priori seems to be an almost ideal directing group to construct the core structure of Valsartan (Figure 8).

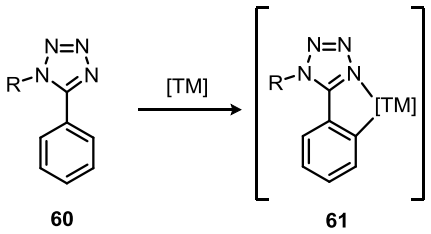
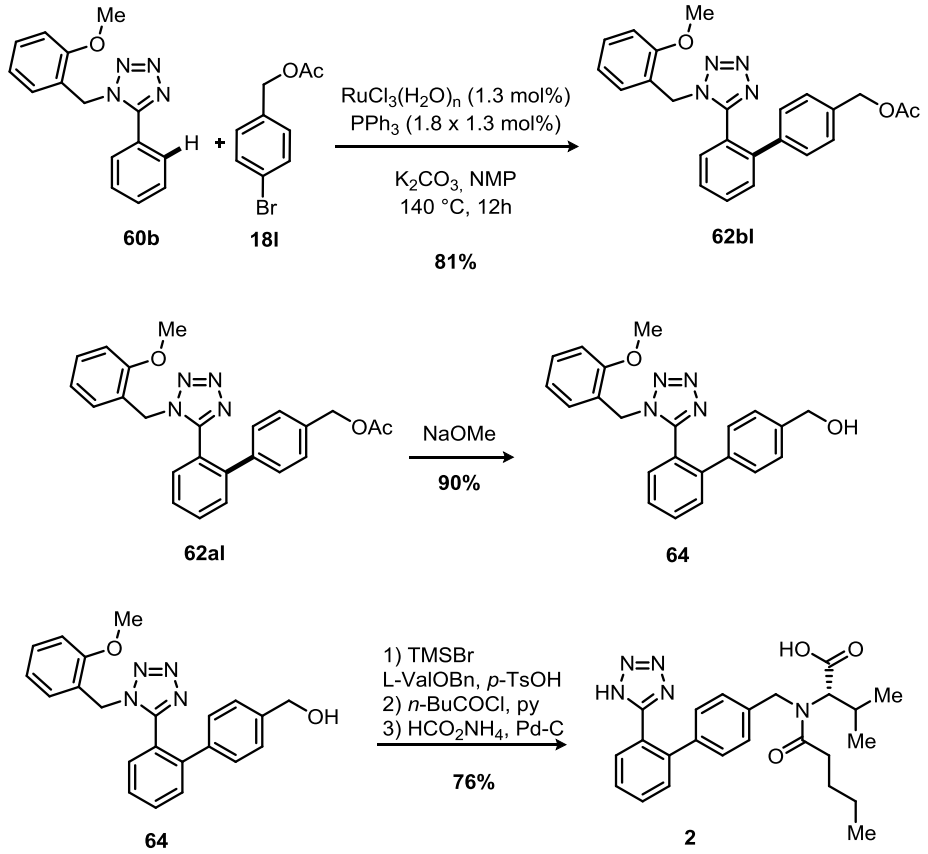


Figure 8: The possible cyclometalated complex **61** with the tetrazole core as a directing group.

The advantages of inexpensive ruthenium complexes for the design of a biaryl core along this route have been discussed above. Practically, this approach was realized by Seki for the synthesis of ARB Valsartan (**2**).[78]



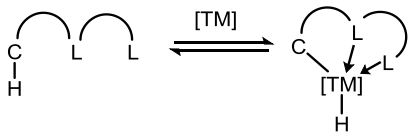
Scheme 24: Synthesis of Valsartan by *Seki.*

The catalytic system is based on the inexpensive $RuCl_3(H_2O)_n$, using triphenylphosphine as an additive and *N*-Methylpyridinone (NMP) as a solvent (Scheme 24). The biarylunit can be selectively and efficiently synthesized using low catalyst loading. However, it was recently brought to attention by researchers at *Merck* that NMP tends to content impurities that could influence the efficiency of the catalyst.[43]

1.3 Transition metal-catalyzed C–H bond functionalization using chelating bidentate systems

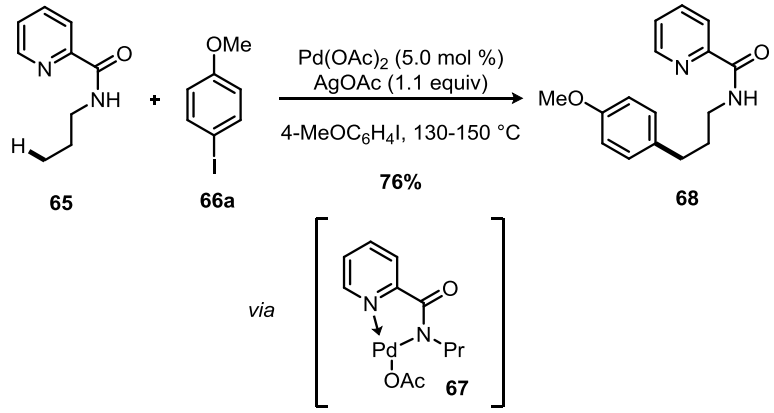
Last but not least, selectivity and efficacy of ruthenium-catalyzed direct functionalization of otherwise unreactive C–H bonds depends upon the nature and chelating ability of the directing group on an arene moietx. Most of these directing groups – pyridine, pyrrole, pyrazole, triazole, oxazoline, tetrazole, imine, ketone, and carboxylic acid – could be designated as modentate ones.

Bidentate systems can crucially modify the properties of a metal through exhaustive coordination (Scheme 25). Although these bidentate systems can pave the way towards new efficient catalytic systems, their application for the direct functionalization of C–H bonds is only poorly documented.



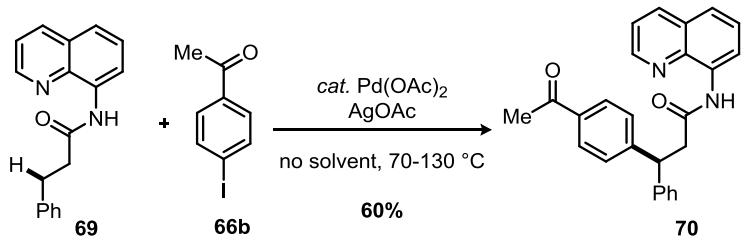
Scheme 25: Participation of a coordinating bidentate system in C–H bond activation.

First hint was discovered in 2005 by *Daugulis*, who described a bidentate-based system **65**, that allowed for the direct arylation of sp^3 C–H bond with aryl iodides (Scheme 26).[79]



Scheme 26: Palladium-catalyzed direct arylation of bidentate picolinamides **65**.

The reaction was also carried out with *N*-(quinolin-8-yl)propanamide (**69**), with good yield and selectivity (Scheme 27).

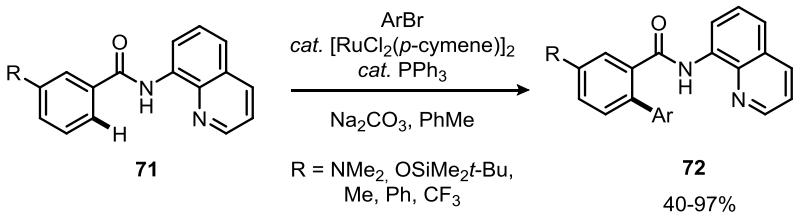


Scheme 27: Palladium-catalyzed direct arylation of *N*-(quinolin-8-yl)propanamide **69**.

Following this pioneering report, a number of reactions for the transformations of C–H bonds through the assistance of coordinating bidentate systems, were developed applying predominantly palladium catalysts.[80]

The other transition metals have been less exploited in direct C–H bond transformations applying bidentate systems. On this topic, in 2009 *Chatani* developed a new catalytic system based on a ruthenium (0) catalyst allowing for the conversion of benzamides to phtalides, with two equivalents of water, under an atmosphere of ethylene and carbon monoxide.[81] Other reactions such as alkylation,[82] carbonylation of sp^3 C–H bonds,[83] were also developed using a bidentate system and ruthenium complexes.

More recently, *Chatani* reported on the direct arylation of benzylamide derivates and extended the methodology to aminoquinoline derivates.[84] Thus, the 8-aminoquinoline derivatives **71** were successfully arylated with aryl bromides in toluene, using the commonly applied $[RuCl_2(p\text{-cymene})]_2$ complex, with triphenylphosphine PPh_3 as an additive(Scheme 28).



Scheme 28: Ruthenium-catalyzed direct arylation of benzamides **71** with 8-aminoquinoline as a directing group.

Electron rich as well as electron deficient arenes were arylated with various aryl bromides, including heteroaryl bromides, in a selective and highly efficient way.

2 Objectives

The beneficial effect of carboxylate was already proven to be widely applicable,[25, 64a, 65-66, 85] and particularly in the ruthenium-catalyzed direct arylation of arenes, through chelation assistance. However, this technique keeps lacking generality, considering their limitation to substrates that can form five membered ruthenacycles (Figure 9).

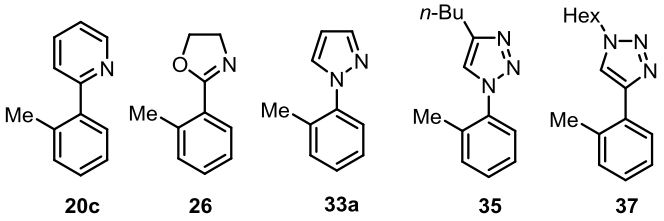
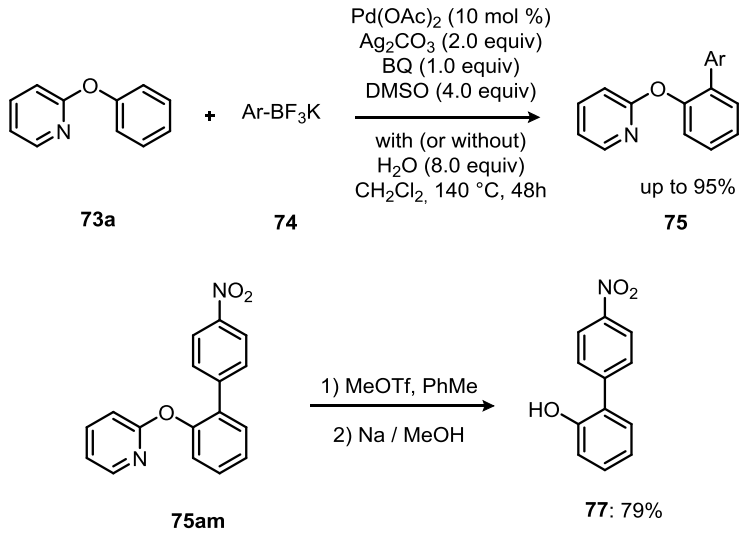


Figure 9: Selected substrates efficiently arylated through carboxylate-assisted ruthenium catalysis.

First, it should be examined if the carboxylate assistance could promote the direct arylation of substrates forming a six membered ruthenacycle as an intermediate as well. Successful solution of this problem could open the way for a novel strategy of using removable directing groups. Until recently, in ruthenium-catalyzed direct arylation, the directing groups could not be further modified and were often practically valueless in the synthesis of useful active substances.

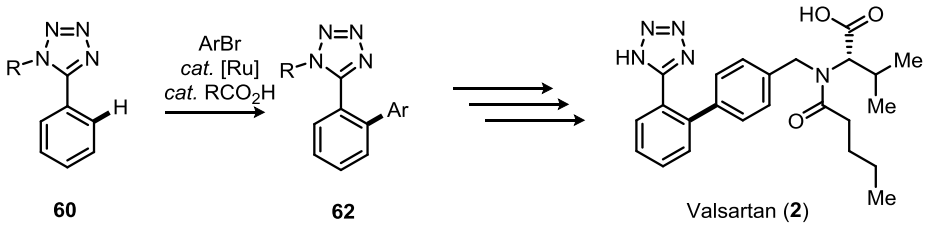
The problem of direct functionalization of substrates that can form six membered metallacycles and/or bearing removable directing groups was already treated by several research groups for palladium- or rhodium-catalyzed reactions.[35a, 36a-g, 36i, 86] Particularly, palladium-catalyzed direct arylation of phenoxypyrimidines[87] and phenoxypyridines[36h] was applied by *Wanzhi* and by *Wu* respectively, with consecutive removal of the directing group (Scheme 29).



Scheme 29: Palladium-catalyzed direct arylation of 2-phenoxypyridine (**73a**) with subsequent cleavage of the directing group by *Wu*.

In this work it was then envisaged to investigate the possibility to employ the versatile ruthenium catalysts in direct arylation with extended mechanistic studies of the reaction for its better understanding.

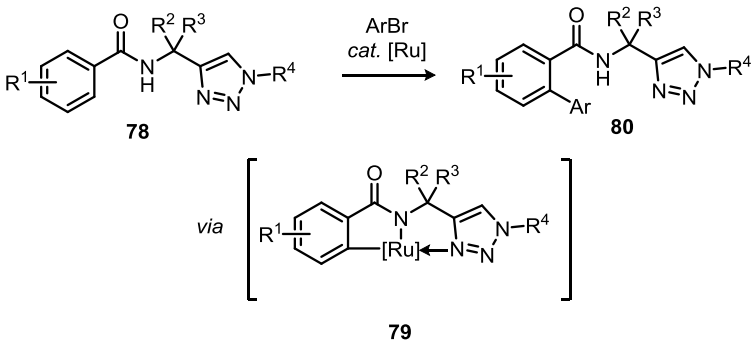
A number of intermediates for the preparation of naturally occurring intermediates were synthesized through direct C–H bond functionalizations.[88] Continuing these researches, potential applicability of carboxylate-assisted ruthenium-catalyzed direct arylation of arytetrazoles **60** as a key step towards the synthesis of pharmacologically active substance should be tested as well. For example, the Blockbuster Valsartan could possibly be synthesized employing this technique (Scheme 30). The mechanism of these direct functionalizations was also extensively studied to elucidate the peculiarities of reacting mode of tetrazoles **60**.



60 **62**

Scheme 30: Potential employment of direct arylation in the synthesis of the ARB Valsartan.

At last, most of the chelation-assisted direct C–H bond functionalizations with bidentate substrates have been performed applying palladium catalyst[79,80] while synthetic utility of less expensive and more selective ruthenium ones remains underestimated. Taking into consideration the enhanced reactivity and attractive perspectives of such better coordinating bidentate directing groups, this technique was further extended to the ruthenium-catalyzed C–H bond arylation of different bidentate coordinating directing groups **78** presumably *via* participation of intermediate **79** (Scheme 31). Investigation of this reaction covers the studies of its mechanistic aspects as well.



78 **80** **79**

Scheme 31: Intriguing direct ruthenium-catalyzed arylation of arenes **78** bearing a bidentate directing group.

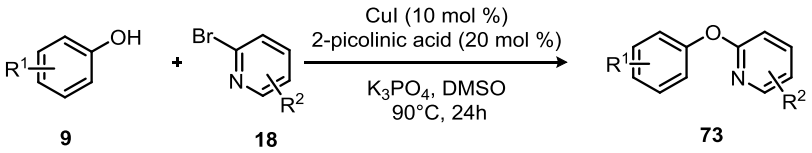
3 Results and discussion

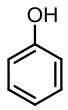
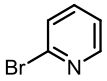
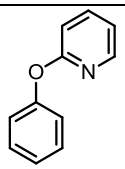
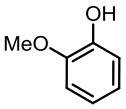
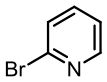
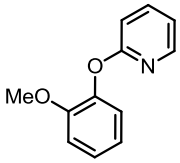
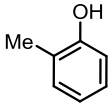
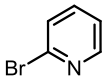
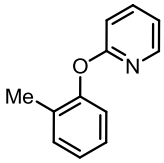
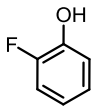
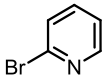
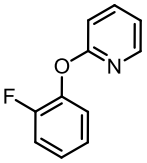
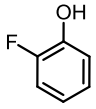
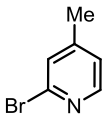
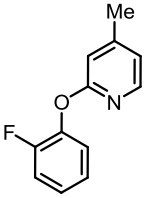
3.1 Ruthenium-catalyzed direct arylation of phenoxypyridines

3.1.1 Synthesis of starting materials

2-Phenoxypyridine (**73a**) was used as a standard substrate for the optimization of the reaction conditions. Its synthesis as well as the synthesis of substituted 2-phenoxypyridines **73** was accomplished by a copper-catalyzed reaction of phenols **9** with 2-bromopyridines **18n-o** (Table 2).

Table 2: Synthesis of phenoxypyridines **73**.[a]



Entry	9	18	73	Yield (%)
1				88
	9a	**18n**	**73a**	
2				84
	9b	**18n**	**73b**	
3				85
	9c	**18n**	**73c**	
4				92
	9d	**18n**	**72d**	
5				89
	9d	**18o**	**73do**	

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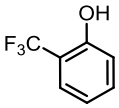
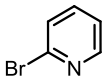
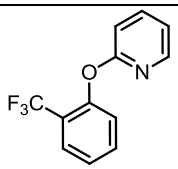
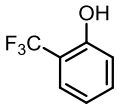
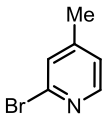
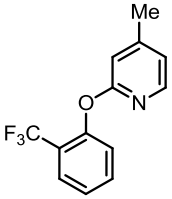
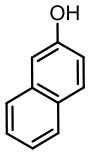
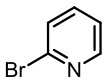
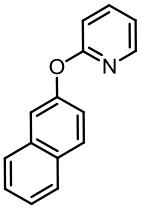
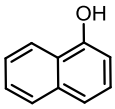
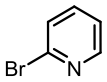
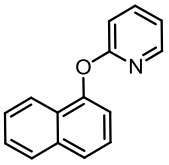
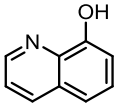
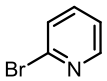
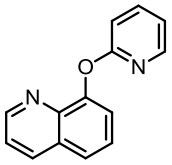
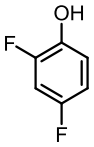
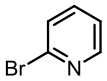
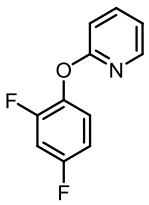
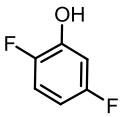
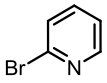
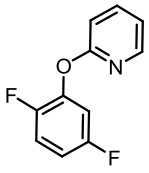
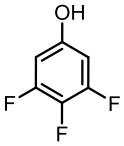
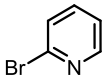
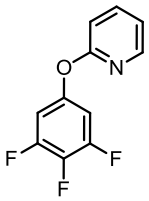
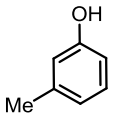
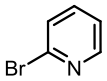
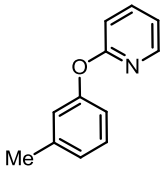
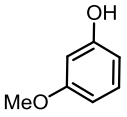
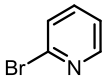
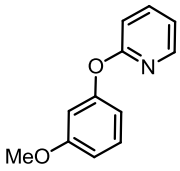
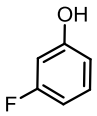
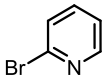
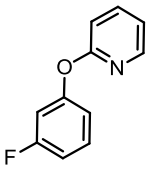
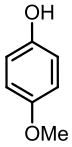
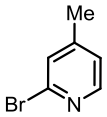
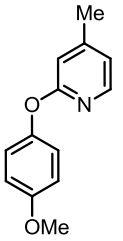
6				70
	9e	**18n**	**73e**	
7				67
	9e	**18o**	**73eo**	
8				76
	9f	**18n**	**73f**	
9				67
	9g	**18n**	**73g**	
10				85
	9h	**18n**	**73h**	
11				84
	9i	**18n**	**77i**	
12				86
	9j	**18n**	**73j**	
13				56
	9k	**18n**	**73k**	

Entry	9	18	73	Yield (%)
14				82
	9l	**18n**	**73l**	
15				89
	9m	**18n**	**73m**	
16				86
	9n	**18n**	**73n**	
17				87
	9o	**18o**	**73oo**	

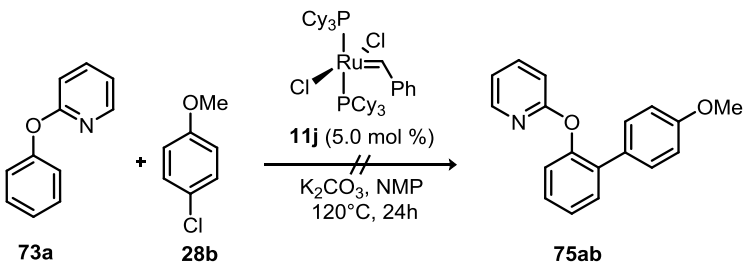
[a] Reaction conditions: Phenol **9** (1.2 equiv), 2-bromopyridine **18n-o** (1.0 equiv), CuI (10 mol %), 2-picolinic acid (20 mol %), K_3PO_4 (2.0 equiv), DMSO (0.5 M), 90 °C, 24 h; yields of isolated products.

All reactions gave satisfactory yields wether with electron-rich or -deficient arenes, or even heteroarenes.

3.1.2 Optimization studies

The optimal reaction conditions for this direct arylation in the most efficient and selective way were found through the screening of different ruthenium sources, bases, additives, solvents, at various temperatures.

First, Grubbs´ catalyst I was probed for the direct arylation of phenoxypyridine (**73a**) with aryl chloride **28b** as described in 2007 by *Born*, *Álvarez-Bercedo* and *Ackermann* for the the arylation of substrates with 2-pyridyl directing group.[40]

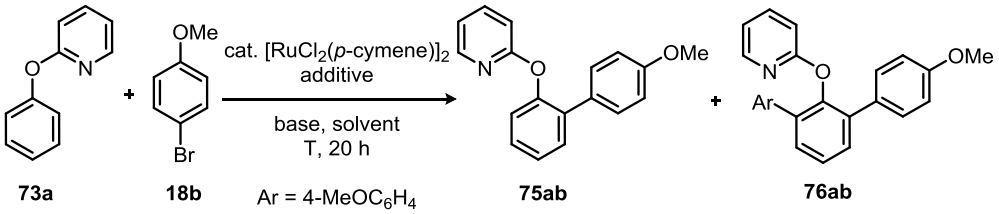


73a **28b** **75ab**

Scheme 32: Attempted direct arylation with ruthenium(IV) alkylidenes as precatalyt.

Unfortunelately, no conversion was observed in this case or with 4-bromoanisole (**18b**) (Scheme 32). Obviously, these reactions conditions, which were most potent in the direct arylations *via* five-membered ruthenacycles, are not appropriate for functionalizations through six-membered ones. $[RuCl_2(p\text{-cymene})]_2$ was then probed as another ruthenium source in combination with other bases, additives and solvents to unravel the best reaction conditions (Table 3).

Table 3: Optimisation studies for the direct arylation of 2-phenoxypyridines **73** with aryl bromide **18b.**[a]



73a **18b** **75ab** **76ab**

Entry	Additive	Base	Solvent	Temperature	**75ab**	**76ab**
1	-	K_2CO_3	NMP	140	-	-
2	HIPrCl	K_2CO_3	NMP	140	4	6
3	PCy_3	K_2CO_3	NMP	140	-	-
4	PPh_3	K_2CO_3	NMP	140	17	-
5	(*1*-Ad)$_2$P(O)H	K_2CO_3	NMP	140	54	44
6	$MesCO_2H$[b]	K_2CO_3	NMP	140	14	73
7	-	K_2CO_3	PhMe	120	-	-
8	-	K_2CO_3	H_2O	100	-	-
9	KPF_6[c]	K_2CO_3	H_2O	100	-	-
10	$MesCO_2H$[b]	K_2CO_3	H_2O	100	50	31
11	HIPrCl	K_2CO_3	PhMe	120	-	-
12	PPh_3	K_2CO_3	PhMe	120	-	-
13	(*1*-Ad)$_2$P(O)H	K_2CO_3	PhMe	120	14	-
14	KPF_6[c]	K_2CO_3	PhMe	120	-	-
15	$MesCO_2H$[b]	KOAc	PhMe	120	-	-
16	$MesCO_2H$[b]	NaOAc	PhMe	120	-	-
17	$MesCO_2H$[b]	Na_2CO_3	PhMe	120	32	-
18	$MesCO_2H$[b]	Ag_2CO_3	PhMe	120	20	-
19[d]	$MesCO_2H$[b]	K_2CO_3	PhMe	120	-	-
20	$MesCO_2H$[b]	K_2CO_3	PhMe	100	25	6
21	$MesCO_2H$[b]	K_2CO_3	PhMe	120	66	24

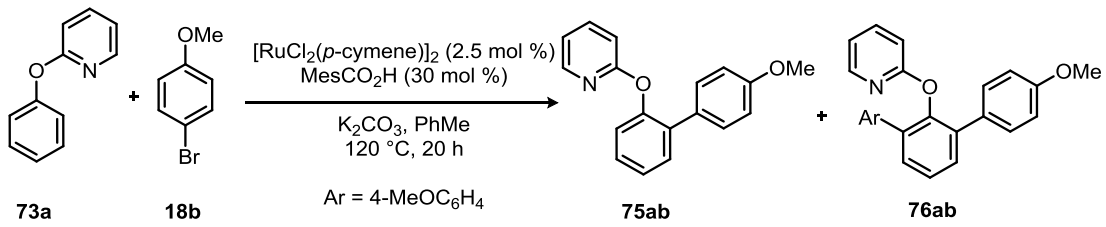
[a] Reaction conditions: Phenoxypyridine **73a** (1.5 mmol), 4-bromoanisole (**18b**) (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (10 mol %), base (1.0 mmol), solvent (2.0 mL), 20 h; HIPr = *N*,*N*´-bis(2,6-diisopropylphenyl)-imidazolium, yields of isolated products. [b] 30.0 mol %. [c] 40.0 mol %. [d] Without any source of ruthenium.

An extensive screening was accomplished to come up with the best conditions for the direct arylation of 2-phenoxypyridine (**73a**), in the most selective way.

The first reactions were carried in *N*-Methylpyrrolidinone (NMP), a solvent which was frequently employed in ruthenium-catalyzed direct arylations of arenes. The base utilized for all these reaction was potassium carbonate. The absence of additive, gave no reaction at all, while a representative carbene precursor gave low yields with low selectivity (entries 1 and 2).
The phosphine ligands used as additive by *Oi* and *Inoue*,[17-19] gave no or little conversion (entries 3 and 4). The optimized HASPO ligand enhanced the reactivity of the 2-phenoxypyridine (**73a**) with aryl bromide **18b**, giving full conversion. However the ratio of monoarylated and diarylated compounds was up to 1/1 (entry 5), which is not satisfactory enough for the direct arylation as the main objective was to obtain a selective monoarylation. The use of most commonly exploited carboxylic acid $MesCO_2H$ gave again high conversion, but the diarylated compound was selectively formed (entry 6). It was then decided to switch to a less coordinating solvent, namely toluene. The base remained K_2CO_3. Without any surprise, in the absence of additive, no product was isolated (entry 7). The carboxylate based catalyst system also showed an excellent reactivity in nontoxic user friendly water (entry 10), whereas the selectivity remained low, but the presence of a carboxylate derivative was still necessary (entries 8 and 9). The carbene precursors and phosphine derivatives yielded no product at all in those cases (entries 11 and 12), while the HASPO preligand (entry 13) favored the reaction in only 14% isolated yield of monoarylated compound. The formation of a cationic ruthenium species through the use of KPF_6 (entry 14) did not improve the reactivity. When the carboxylates were used as cocatalyst in the reaction, the improvement in the isolated yield of monoarylated compound was significant (entry 21). However, changing the base from Na_2CO_3 (entry 17), to Ag_2CO_3 (entry 18) lowered the isolated yield significantly. Moreover, acetate bases completely shut down the reaction (entries 15 and 16), showing a competitive effect of coordinating of the acetate base to the ruthenium, also showing the necessity of a combination of carbonate and carboxylic acid. Reducing the temperature to 100 °C, did not improve the selectivity, but lowered the overall yield. The best conditions were found to be the reaction of both substrates in presence of $MesCO_2H$ (30 mol %), with 2 equivalents of K_2CO_3 in toluene at 120 °C for 20 hours.

As the next step, optimization studies to identify the optimal ratio of substrate and reagent for the efficient direct arylation of 2-phenoxypyridine (**73a**) with aryl bromide **18b** were performed. The results are summarized in Table 4.

Table 4: Influence of the ratio between substrate **73a** and reagent **18b** on the ruthenium-catalyzed direct arylation of phenoxypyridine **73**.[a]



73a **18b** **75ab** **76ab**

Entry	**73a** (mmol)	**18b** (mmol)	**75ab** (%)	**76ab** (%)
1	0.5	0.75	39	16
2	3.0	0.5	77	12
3	2.0	0.5	76	20
4	1.5	0.5	66	24
5	1.0	0.5	42	20

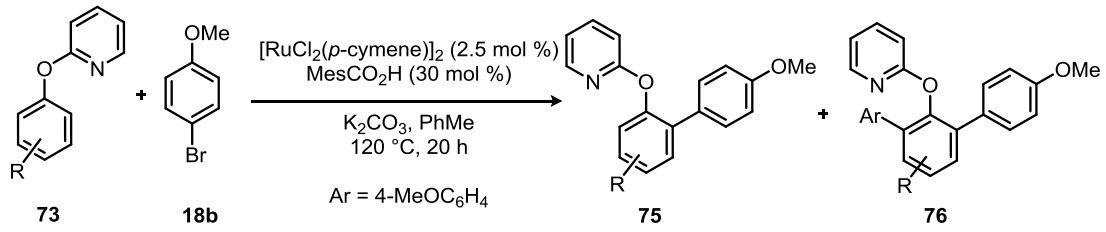
[a] Reaction conditions: Phenoxypyridine **73a**, 4-bromoanisole (**18b**), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2.0 mL), 120 °C, 20 h, isolated yields.

Using an excess of aryl bromide **18b** reduced the overall yield (entry 1). To improve the overall yield and the selectivity, the phenoxypyridine **73a** was introduced in excess (entries 2-4). Reducing the phenoxypyridine to two equivalents however resulted in a drop of the overall yield (entry 5). Whereas six or four equivalents of **73a** gave the best yield and selectivity, it was decided to continue this study with three equivalents, which yielded satisfactory results, for a matter of atom-economy.

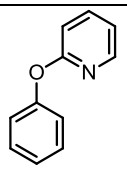
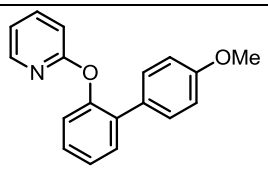
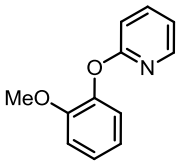
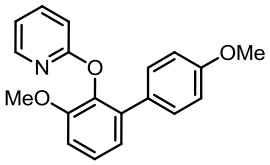
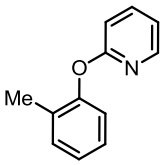
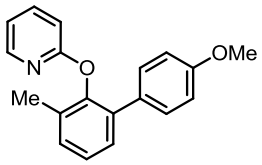
3.1.3 Scope and limitations

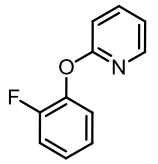
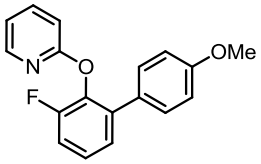
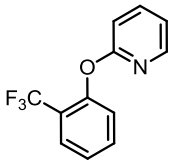
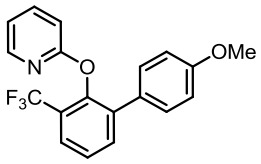
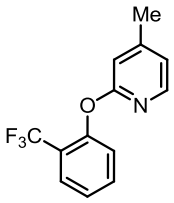
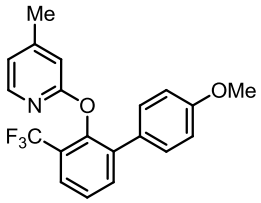
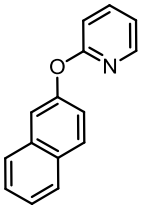
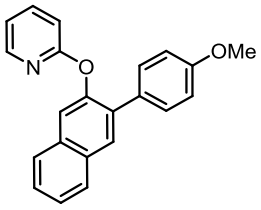
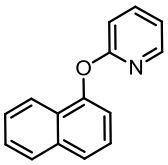
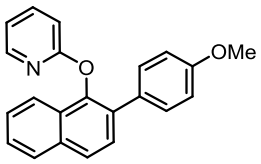
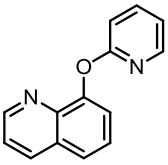
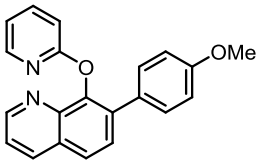
Under the optimized reaction conditions, the direct arylation of variously substituted arenes **73** was explored (Table 5).

Table 5: Scope of substrates **73** in the ruthenium-catalyzed direct arylations under the optimized conditions.[a]



73 **18b** **75** **76**

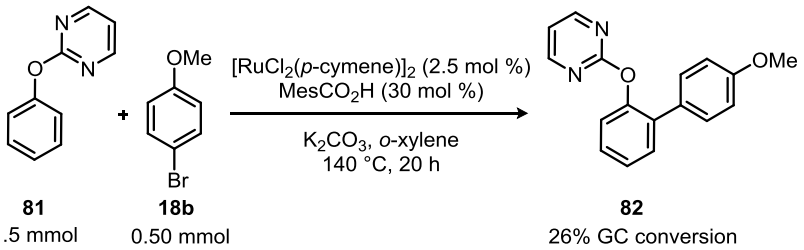
Entry	**73**	**75**	Yield (%)
1	 **73a**	 **75ab**	66 (**76ab**: 24)
2	 **73b**	 **75bb**	38
3	 **73c**	 **75cb**	44

Entry	**73**	**75**	Yield (%)
4	 **73d**	 **75db**	98
5	 **73e**	 **75eb**	42
6	 **73eo**	 **75eob**	50
7	 **73f**	 **75fb**	(<5%)[b]
8	 **73g**	 **75gb**	(<5%)[b]
9	 **73h**	 **75hb**	(11%)[b]

[a] Reaction conditions: Phenoxypyridine **73** (1.5 mmol), 4-bromoanisole (**18b**) (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe, 120 °C, 20 h, yields of isolated products. [b] GC conversion

To increase the selectivity of the direct arylation, *ortho*-substituted phenoxypyridine were probed under the optimized reaction conditions. Unfortunately, electron rich arenes bearing a methyl or a methoxy group showed a low reactivity for the arylation (entries 2 and 3).The ruthenium-catalyzed direct arylation of arenes gave the best results when the arene was bearing an electron-withdrawing group (entry 4). The phenoxypyridine bearing an electron deficient trifluoromethyl did not react as expected, probably due to steric hinderance (entry 5).

Introducing an electron donating group on the directing group did not influence the reactivity significantly (entry 6). Using more electron-rich arenes showed the limitation of this reaction. Indeed, electron-rich groups such as naphtols gave very low GC/MS-conversions (entries 7 and 8). The same result was observed in case of a substituted quinolone (entry 9). Even higher temperature or higher catalyst loading did not improve the yields.



Scheme 33: Attempted use of phenoxypyrimidine (**81**) as substrate for the ruthenium-catalyzed direct arylation.

Using the more easily removable pyrimidine as a directing group resulted in a significantly drop of yield, even at higher temperature or catalyst loading (Scheme 33).

Similar results were obtained in the additional investigations towards the use of other than oxygen tethers in direct arylations. Although the formation of a six-membered ruthenacycle as intermediate should be possible in all cases, low or no conversions of the substrates **83**–**87** were detected (Figure 10). Thus, an oxygen bridge seems to be crucial for the working mode of the developed catalytic system.

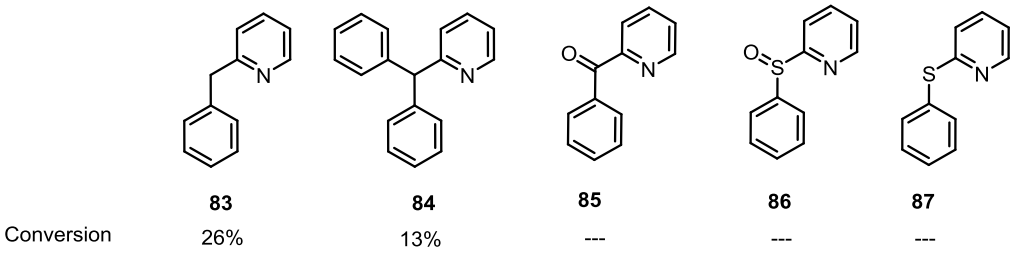


Figure 10: Tested substrates that can possibly form six-membered ruthenacycles.

The task of extending this methodology to substances which can form ruthenacycles with a larger ring size remained. Different substrates **88**–**90** were synthesized with this aim (Figure 11), but unfortunately, in attempted arylation they furnished very low or no yield at all.

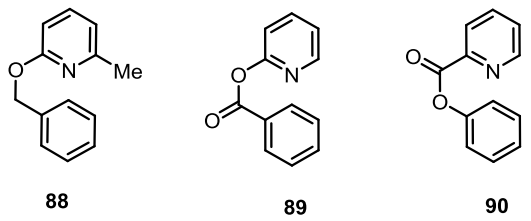
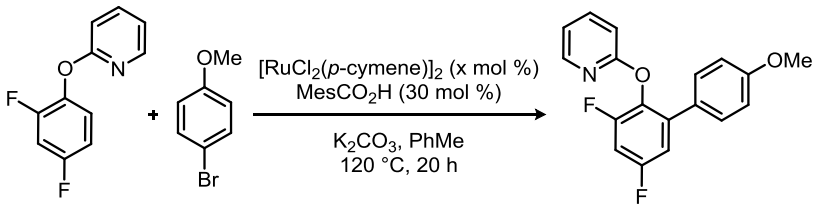


Figure 11: Tested substrates that can possibly form seven-membered ruthenacycles.

3.1.4 Direct arylation with oligofluoro-substituted substrates

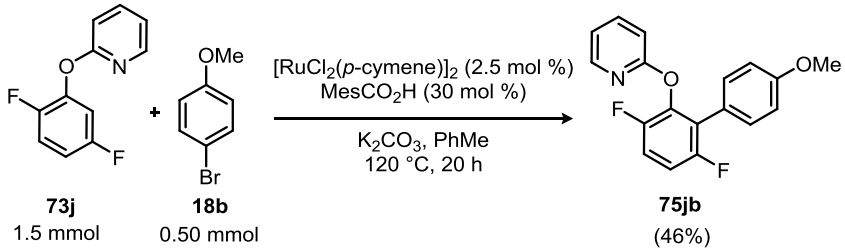
As electron-deficient substrates seemed to react preferentially, new substrates with several fluoro groups on the arenes were submitted to the optimized reaction conditions (Scheme 34).



Scheme 34: Direct arylation of **73i** with reduced catalyst loading.

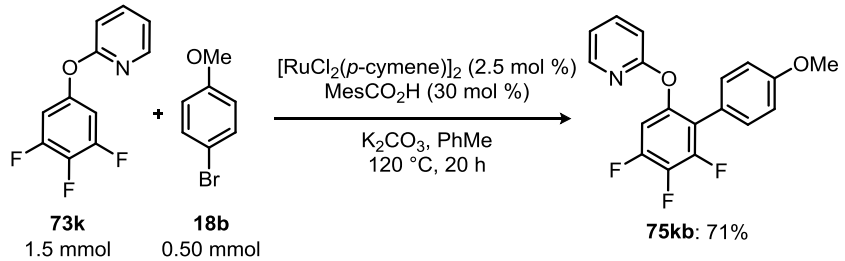
2-(2,4-difluoro)phenoxypyridine (**73i**) was submitted to the opitimized reaction conditions and the arylated product was isolated in more than 99% yield. Considering the high reactivity of this substrate, the reaction was run again with reduced catalyst loading. Reducing to 1.5 and 1.0 mol % of the ruthenium dimere did not change the result much, as the yield was still remaining higher than 90%. However, the decrease of the ruthenium dimere to 0.5 mol %, caused a significant drop in the yield.

Inserting by a fluoro group in the 2 and 5 positions caused a significant drop in yield (Scheme 35).



Scheme 35: Direct arylation of 2-(2,5-difluoro)phenoxypyridine (**73j**).

Submitting 2-(3,4,5-trifluoro)phenoxypyridine (**73k**) to the optimized reaction conditions, yielded the monoarylated product **75kb** in 71%, while 11% of the diarylated **76kb** was isolated, bringing an overall excellent yield (Scheme 36).

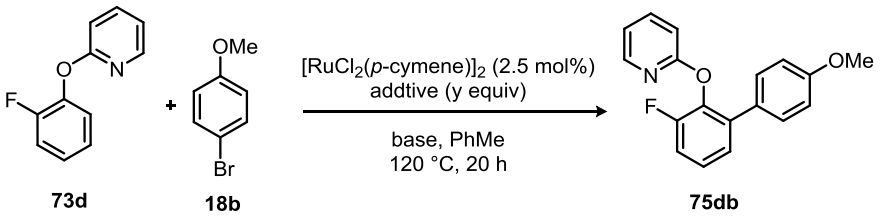


Scheme 36: Direct arylation of 2-(3,4,5-trifluoro)phenoxypyridine (**73k**).

3.1.5 Further optimization with *ortho*-fluoro substituted phenoxypyridine.

To further explore the effect of modification of the base or additive, the direct arylation of *ortho*-fluoro substituted phenoxypyridine **73d** was performed (Table 6).

Table 6: Further optimization of reactions conditions with 2-fluorophenoxypyridine (**73d**).[a]



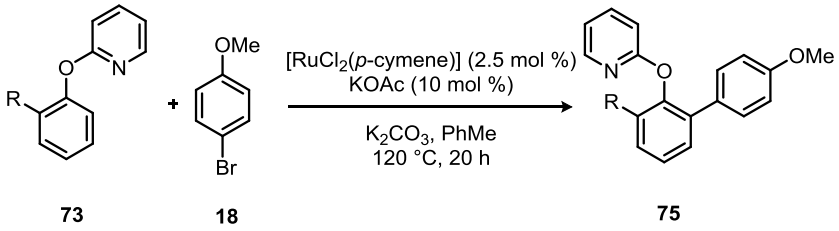
Entry	Base	Additive	Yield (%)
1	K_2CO_3 (2.0 equiv)	-	-
2	K_2CO_3 (2.0 equiv)	$MesCO_2H$ (30)	99
3	K_2CO_3 (1.2 equiv)	$MesCO_2H$ (30)	53
4	K_2CO_3 (2.0 equiv)	$MesCO_2H$ (10)	80
5	NaOAc (2.0 equiv)	$MesCO_2H$ (30)	<5
6	KOAc (2.0 equiv)	$MesCO_2H$ (30)	<5
7	CsOAc (2.0 equiv)	$MesCO_2H$ (30)	30
8	KOAc (2.0 equiv)	-	61
9	K_2CO_3 (2.0 equiv)	KOAc (60)	85
10	K_2CO_3 (2.0 equiv)	KOAc (30)	90
11	K_2CO_3 (2.0 equiv)	KOAc (10)	81
12	$MesCO_2K$ (2.0 equiv)	-	<5%

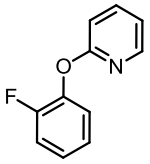
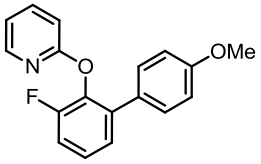
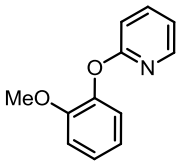
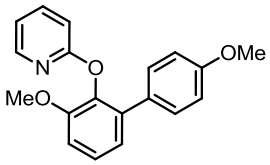
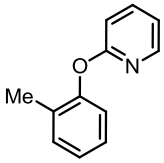
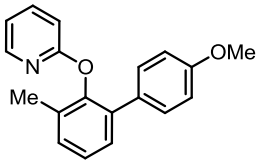
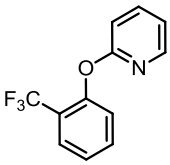
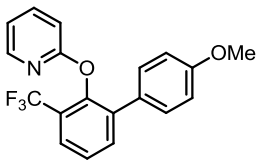
[a] Reaction conditions: 2-fluorophenoxypyridine (**73d**) (1.5 mmol), 4-bromoanisole (**18b**) (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive, base, PhMe, 120 °C, 20 h, yields of isolated products

The necessity of the carboxylate was highlighted, since no reaction occurred while the acid was not present in the reaction (entry 1). However, two equivalents of base K_2CO_3 were necessary for a good outcome of the reaction (entries 2 and 3). Even with 10 mol % of the cocatalyst, the reaction yield remained excellent (entry 4). When switching to acetate bases in combination with the mesityl carboxylic acid as cocatalyst, the yield significantly dropped (entries 5-7), showing the competiting effects of acetate and carboxylate in this reaction. Using potassium acetate alone as a base gave good yield but not as good as the one obtained with the mesitylate system (entry 8). Nevertheless, when the acetate was introduced in cocatalytic amounts, the reactivity was excellent, highlightening the beneficial effect of cocatalytic carboxylates such as acetate in the reaction (entries 9-11). Moreover, the carboxylate was not an efficient base for the reaction as less than 5% of the product was isolated (entry 12).

As potassium acetate also showed a high reactivity towards the 2-phenoxypyridine, a few reactions were carried out to get an insight into the reactivity of this catalytic system (Table 7).

Table 7: Scope of substrates with KOAc as an additive.[a]



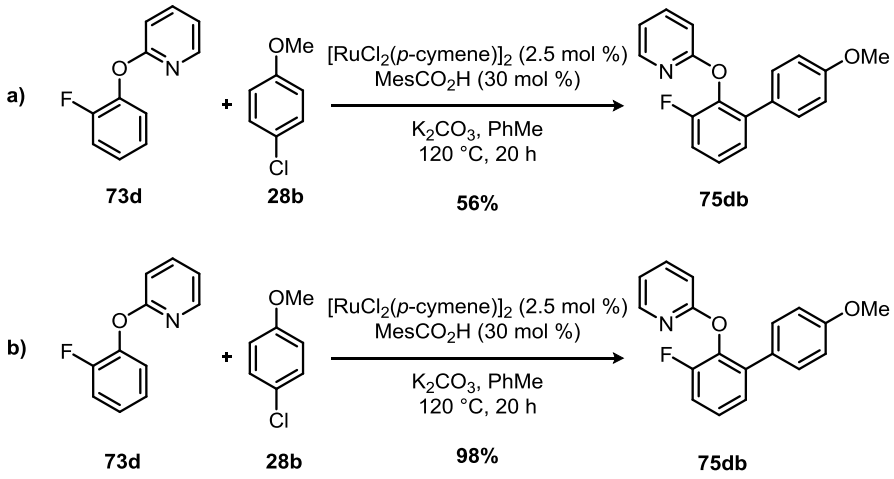
Entry	**73**	**75**	Isolated yield (%)
1	 **73d**	 **75db**	81 (98)[b]
2	 **73b**	 **75bb**	54 (38)[b]
3	 **73c**	 **75cb**	31 (44)[b]
4	 **73e**	 **75eb**	80 (42)[b]

[a] Reaction conditions: Phenoxypyridine **73** (1.5 mmol), 4-bromoanisole (**18b**) (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KOAc (10 mol %), K_2CO_3 (1.0 mmol), PhMe, 120 °C, 20 h, isolated yields. [b] The isolated yields obtained with $MesCO_2H/K_2CO_3$ system are indicated in parentheses for comparison.

The yields for *ortho*-methyl- **73c** and *ortho*-methoxy-substituted phenoxypyridine **73b** were slightly better as compared to the ones obtained with $MesCO_2H$ and K_2CO_3 system. Surprisingly, the reactivity of 2-[2-(trifluoromethyl)phenoxy]pyridine (**73e**) was dramatically increased and gave unexpectedly high yield of the monoarylated product **75eb**. Presumably, the potassium acetate being less sterically demanding than the $MesCO_2H$, electron-deficient arenes bearing a bigger group than fluor react then more efficiently.

3.1.6 Ruthenium-catalyzed direct arylation of arenes 73 with aryl chlorides 28.

Upon replacing of aryl bromides, initially tested in these arylations with less expensive and more readily available aryl chlorides, the yield of monoarylated product was not satisfaying (Scheme 37a).

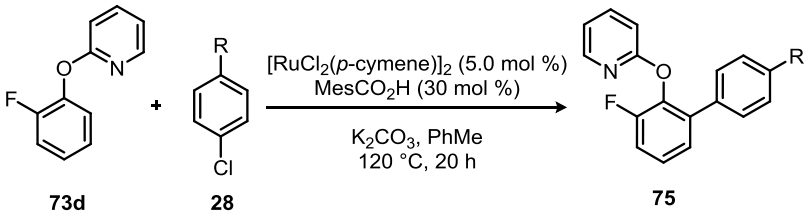


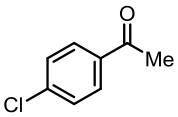
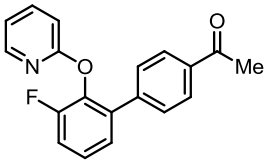
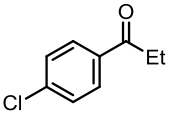
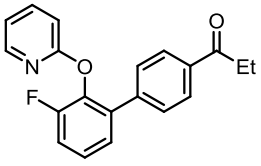
Scheme 37: Direct arylation of 2-(2-fluoro)phenoxypyridine (**73d**) with 4-chloroanisole (**28b**).

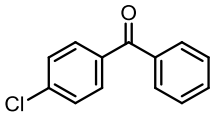
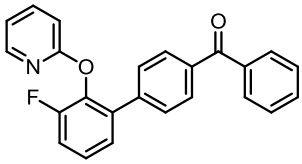
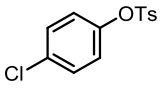
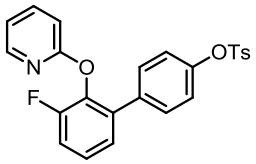
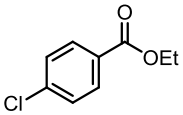
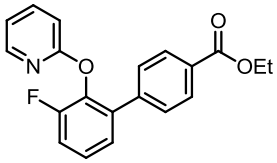
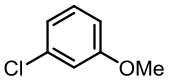
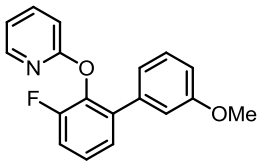
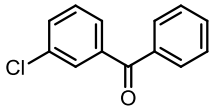
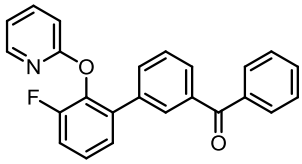
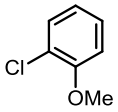
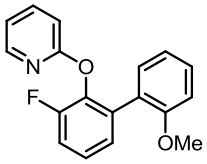
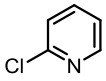
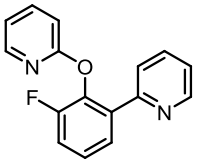
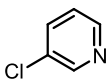
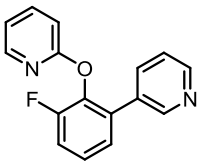
Increasing the catalyst loading to 5.0 mol % under otherwise identical conditions yielded the monoarylated product **75db** in 98% yield (Scheme 37b).

Variously substituted aryl chlorides were then tested under the newly optimized conditions to extend the scope of the reaction (Table 8).

Table 8: Scope of arylchlorides for the ruthenium catalyzed direct arylation.[a]



Entry	**28**	**75**	Yield (%)
1	 **28d**	 **75dd**	88
2	 **28p**	 **75dp**	85

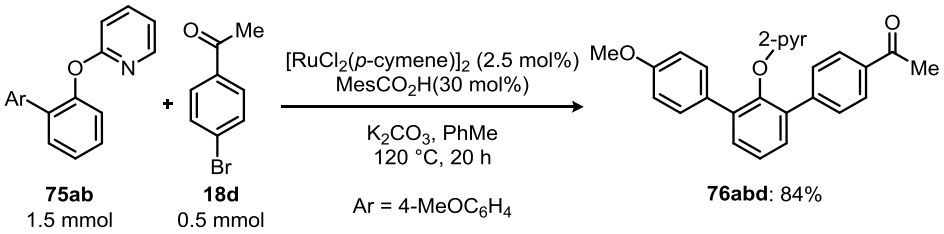
Entry	**28**	**75**	Yield (%)
3	 **28f**	 **75df**	77
4	 **28q**	 **75dq**	78
5	 **28e**	 **75de**	47
6	 **28r**	 **75dr**	69
7	 **28g**	 **75dg**	63
8	 **28s**	 **75ds**	(11)[b]
9	 **28n**	 **75dn**	(0)[b]
10	 **28t**	 **75dt**	(0)[b]

[a] Reaction conditions: 2-(2-Fluorophenoxy)pyridine (**73d**) (1.5 mmol), arylchloride **28** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $MesCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2.0 mL), 120 °C, 20 h, isolated yields. [b] Conversion by GC

Para substituted acetophenone, propiophenone and benzophenone derivatives were efficient arylating partners with high yields (entries 1-3). However, an ester functional group was tolerated but the yield still remained lower than with the other functional groups (entry 5). *meta*-Substituted arylchlorides reacted in good yields (entries 6 and 7). Moreover, considering the decreased reactivity of a tosyl moiety, *para*-substituted **28q** showed selective reactivity to the chloride (entry 5). Nonetheless, only low reactivity was observed with the *ortho*-substituted aryl chlorides and also with heterocyclic arenes (entries 8-10).

3.1.7 Synthesis of unsymmetrically trisubstituted arenes

Furthermore, a sequential C–H bond functionalization was examined with the aim of elaborating a synthetic approach for the preparation of highly unsymmetrically substituted arene **76abd** (Scheme 38).



Scheme 38: Synthesis of highly substituted arene **76abd**.

The structure of the final product **76abd** was confirmed through the analysis of its HSQC and HMBC spectra.

3.1.8 Direct functionalization with other coupling partners

Others functionalized proelectrophiles were also submitted to the optimized reaction conditions with 2-(2-fluoro)phenoxypyridine (**73d**) (Figure 12).

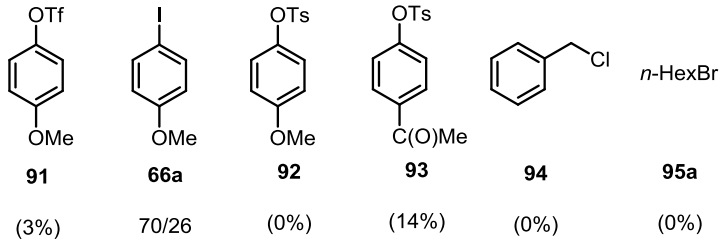


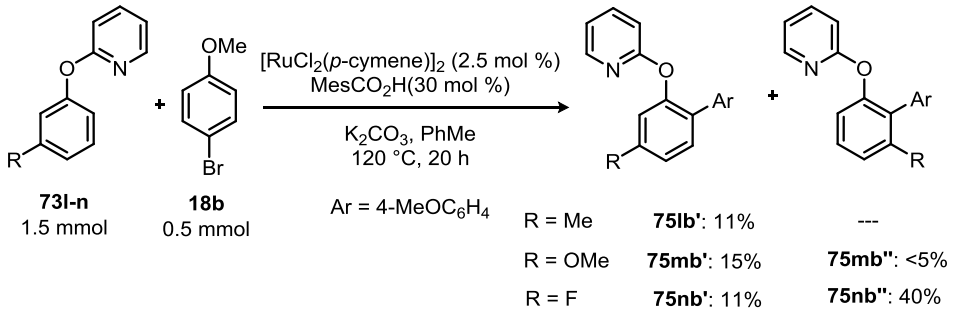
Figure 12: Yields (GC/MS conversions) in attempted arylation of phenoxypyridine **73d** with other coupling partners.

Aryl triflates and tosylates did not react efficiently. Iodoanisole gave a high yield comparable to aryl bromides. Ruthenium-catalyzed direct alkylation and benzylation as developed by *Novàk, Vicente, Hofmann* and *Ackermann* were attempted, but unfortunately did not give any satisfactory results.

3.1.9 Mechanistic studies

3.1.9.1 Intramolecular competition experiments

Intramolecular competition experiments were performed with *meta*-substituted arenes, to further evaluate the scope of the reaction, but also to gain more information about the mechanism, as here both C–H bonds can react differently.



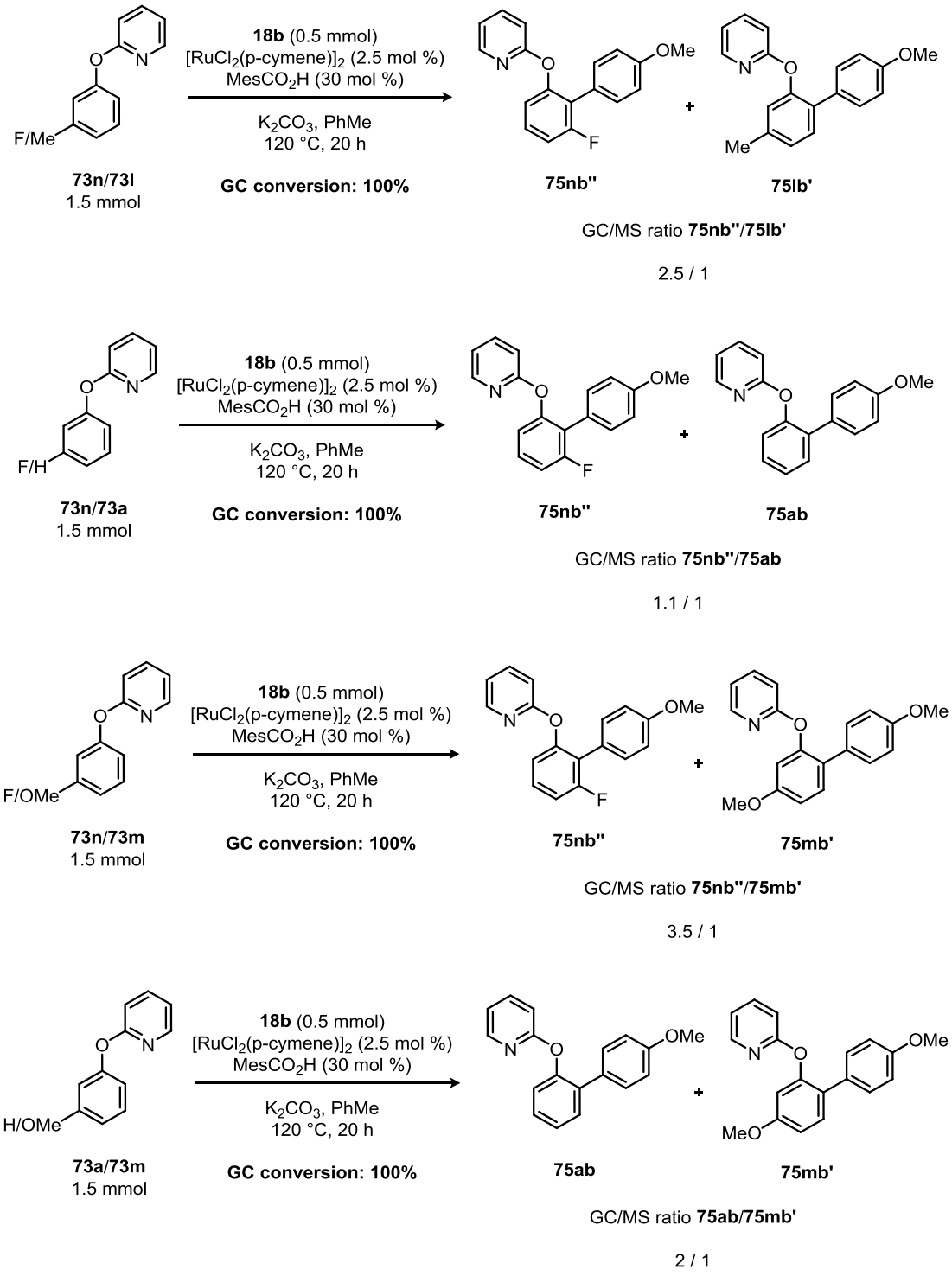
Scheme 39: Intramolecular competition experiments with *meta*-substituted arenes **73l-n**.

When the electron-rich aryloxypyridines **73l** and **73m** were subjected to the arylation under optimized reaction conditions, regiochemistry of the reaction was controlled by steric factors furnishing the products **75lb**' and **75mb**' resulting from functionalization of the C–H bonds in the less sterically hindered 6-position, however, in rather low yields of 12 and 15%, respectively. The mode of substitution in **75lb**' was confirmed by careful spectroscopic analysis of its COSY NMR spectrum. Notably, traces of 2-arylated compound **75mb"** were detected in the reaction of *met*a-methoxy-substituted substrate **73m**. Formation of this compound can be rationalized by a secondary chelating effect exerted by the methoxy substituent. The same, but more pronounced phenomenon was recently reported for direct ruthenium-catalyzed arylation via intermediacy of five-membered ruthenacycles.[59]

In contrast, the electron-deficient substrate **73n** was more reactive and furnished a mixture of the minor 6- (**75nb**') and major 2-substituted (**75nb"**) products. The structure of both compounds was elucidated by analyzing C–F coupling in their ^{13}C NMR spectra and also confirmed through detailed NMR measurements. Thus, two *ortho* couplings for the two CH fragments with the constants of 24 and 21 Hz were observed for the compound **75nb**', whereas in the spectrum of **75nb"** one discerned one *ortho* coupling for a quaternary carbon atom and one *ortho* coupling for a CH carbon with the constants of 17 and 23 Hz, respectively. Regioselectivity of the latter arylation most probably resulted from the concerted action of the directing effect of the pyridyl moiety and the well-documented *ortho*-orienting influence of the fluorine substituents.[89]

3.1.9.2 Intermolecular competition experiments

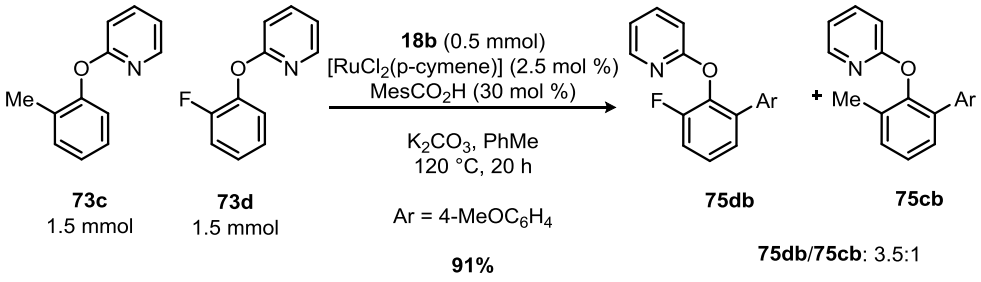
Furthermore, several intra- and intermolecular competition experiments were performed to get a better understanding of the reaction. With this purpose, different substrates **73a–73n** bearing electron-rich or electron-withdrawing substituents were applied to the optimized reaction conditions in excess with 4-bromoanisole (**18b**) (Scheme 40).



Scheme 40: Competition experiments between arenes.

According to the results of these experiments, the hierarchy of substituents in **73** from the point of view of their reactivity towards arylation can be characterized as follows: F > H >>Me>MeO.

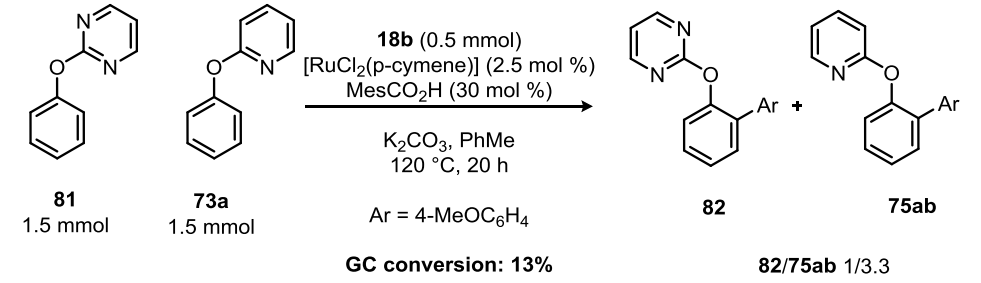
In a further competition experiment between *ortho*-substituted electron-rich and electron-deficient substrates **73c** and **73d**, a mixture of the desired products **75cb** and **75db** was isolated. Careful NMR analysis of the mixture undoubtedly indicated that the aryl bromide **18b** was mostly converted to **75db** (Scheme 41).



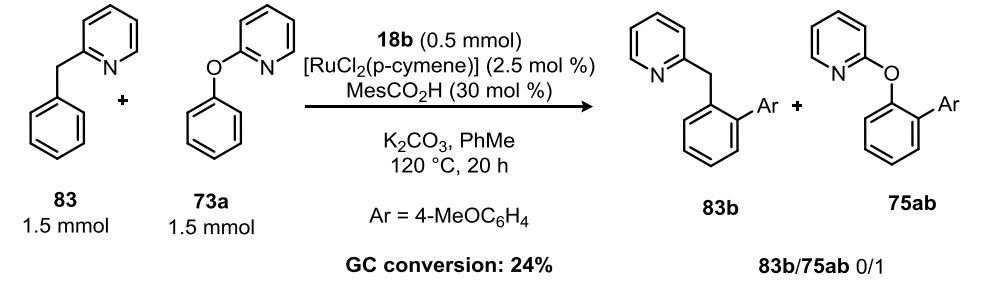
Scheme 41: Competition experiment between **73c** and **73d**.

These experiments highlight the fact that electron-deficient arenes react preferentially compared to electron rich ones. This observation stands in contrast to phenomena observed up to now in the field of direct arylation of arenes with aryl halides.[25, 54] Furthermore, this observation also excluded an electrophilic substitution on the arene from the possible mechanistic pathways of arylation.

Since both 2-phenoxypyrimidine (**81**) and 2-benzylpyridine (**83**) did not react in a satisfactory yield, a competition experiment was carried out between those substrates and 2-phenoxypyridine (**73a**), to observe if the reaction is inhibited by those substrates under the optimized conditions (Scheme 42 and Scheme 43) or if the observed extremely low reactivity of **81** and **83** had another reason.



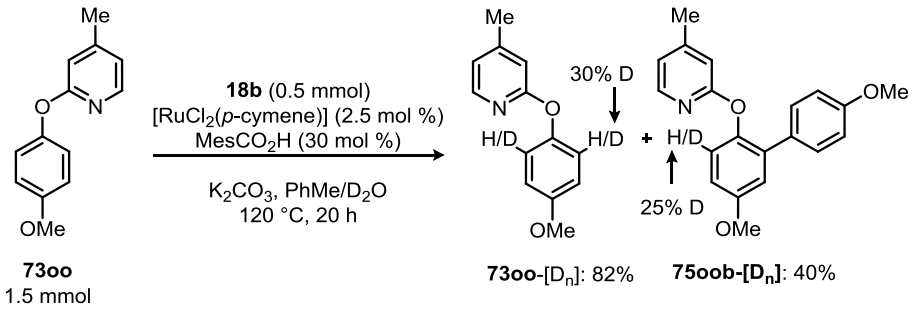
Scheme 42: Competition experiment between **81** and **73a**.



Scheme 43: Competition experiment between **83** and **73a**.

When a equimolar mixture of 2-phenoxypyridine (**73a**) with 2-phenoxypyrimidine (**81**) or with 2-benzylpyridine (**83**), respectively, was reacted with 4-bromoanisole (**18b**) under the optimized conditions, the overall conversion was very low in each case. In spite of the predominant formation of monoarylated phenoxypyridine **75ab**, its extremely low yields (cf Table 5, entry 1) indicated deactivation of the catalyst in each case, presumable *via* chelation with 2-phenoxypyrimidine (**81**) or with 2-benzylpyridine (**83**).

3.1.9.3 H/D exchange



Scheme 44: H/D exchange, in D_2O as the cosolvent.

The substrate **73oo** was submitted to the optimized reaction conditions with D_2O as the cosolvent (Scheme 44). 82% of the **73oo**-[D_n] was reisolated, with a deuterium incorporation in the *ortho*-position of 30%. Almost the same percentage of deuterium incorporation was observed in the isolated product **75oob**-[D_n]. This observation established the C–H bond cleavage to be reversible in nature.

3.1.9.4 Comparison between substrates forming five-membered and six membered ruthenacycles.

Competition experiments were performed to compare the reactivity of substrates reacting through different intermediates of different ruthenacycle size (Figure 13).

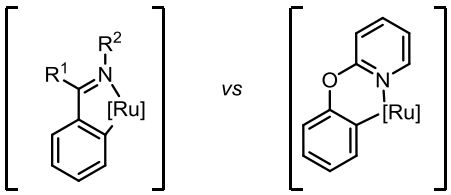
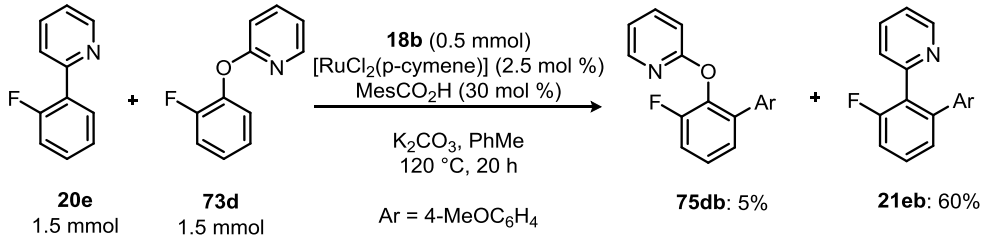


Figure 13: Different reaction intermediates.

Thus, 2-Fluoro 2-phenylpyridine (**20e**) (five-membered ruthenacycle as intermediate) was compared to 2-fluoro 2-phenoxypyridine (**73d**) (six-membered ruthenacycle as intermediate).



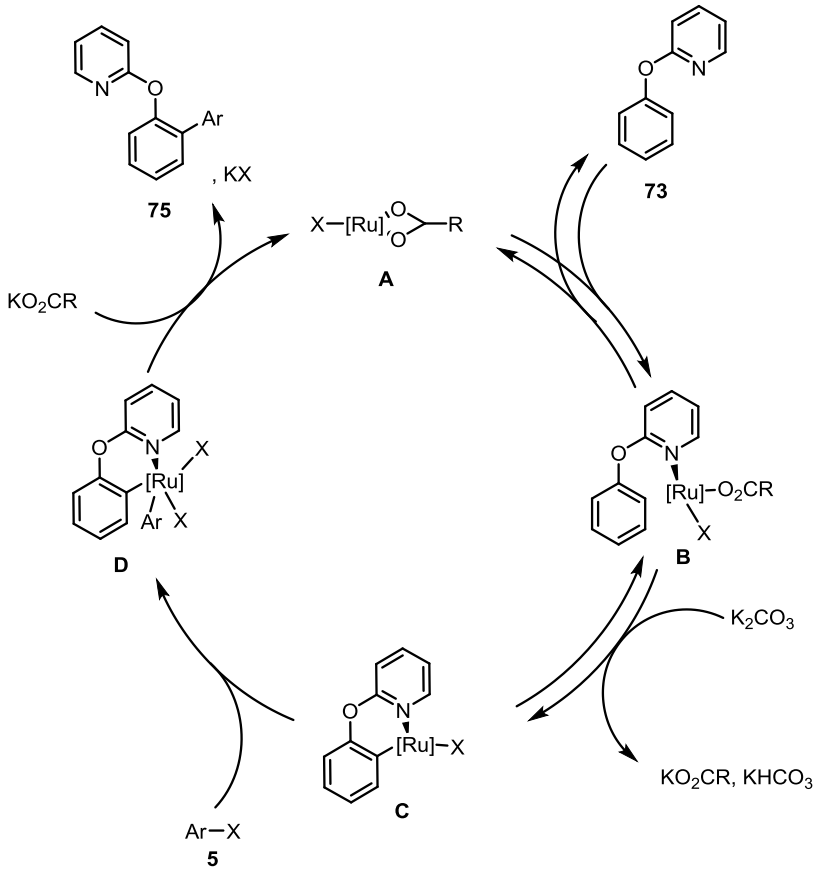
Scheme 45: Competition experiments between 2-fluoro-2-phenylpyridine (**20e**) and 2-fluorophenoxypyridine (**73d**).

Without surprise, the arylation product from 2-fluoro-2-phenylpyridine was formed preferentially (Scheme 45). This observation confirmed that the five-membered ruthenacycles are more easily formed, and suits with the huge number of examples of ruthenium-catalyzed direct arylation of substrates through five membered ruthenacycles that have been published.

Furthermore, a non negligeable quantity of monoarylated phenylpyridine **21bb** was isolated. It highlighted the capacity of ruthenium to perform C–F bond functionalization.[90]

3.1.10 Proposed mechanism

Summarising all these observations, the following mechanism for ruthenium-catalyzed direct arylation of 2-phenoxypyridine **73** was proposed (Scheme 46).



Scheme 46: Proposed mechanism for the ruthenium-catalyzed direct arylation of phenoxypyridine **73**.

The catalytic species **A** is formed *in situ* by the reaction of $[RuCl_2(p\text{-cymeme})]_2$ with $MesCO_2H$, and then coordinates to the phenoxypyridine **73**, followed by a reversible C–H bond cleavage to **B**. Through the formal oxidative addition of the aryl bromide to the ruthenium, the species **D** is formed. The following reductive elimination yields the product and regenerates the catalytic species.

3.1.11 Removal of the directing group

Importantly, it was possible to remove the directing group to yield the *ortho*-arylated phenols (Scheme 47). The arylated product was activated for an efficient cleavage, through methylation of the pyridine. Whereas methyl iodide did not afford full conversion, **75** was completely methylated with methyl triflate to the product **75b-Me** as indicated by ^1H NMR of the crude product (Figure 14 and Figure 15). The signal shift of the proton next to the nitrogen was actually shifted downfield, from 8.1 ppm to 8.9 ppm.

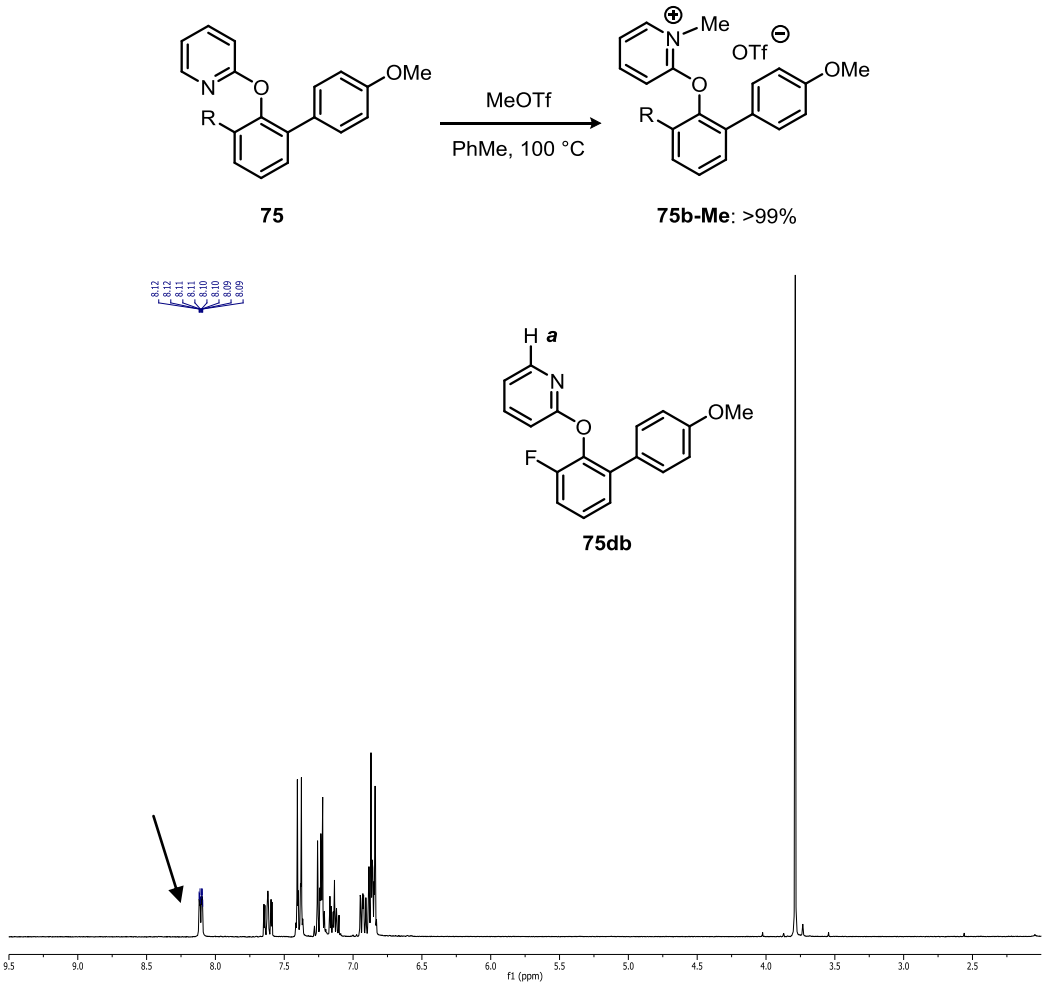


Figure 14: Proton NMR of **75db**.

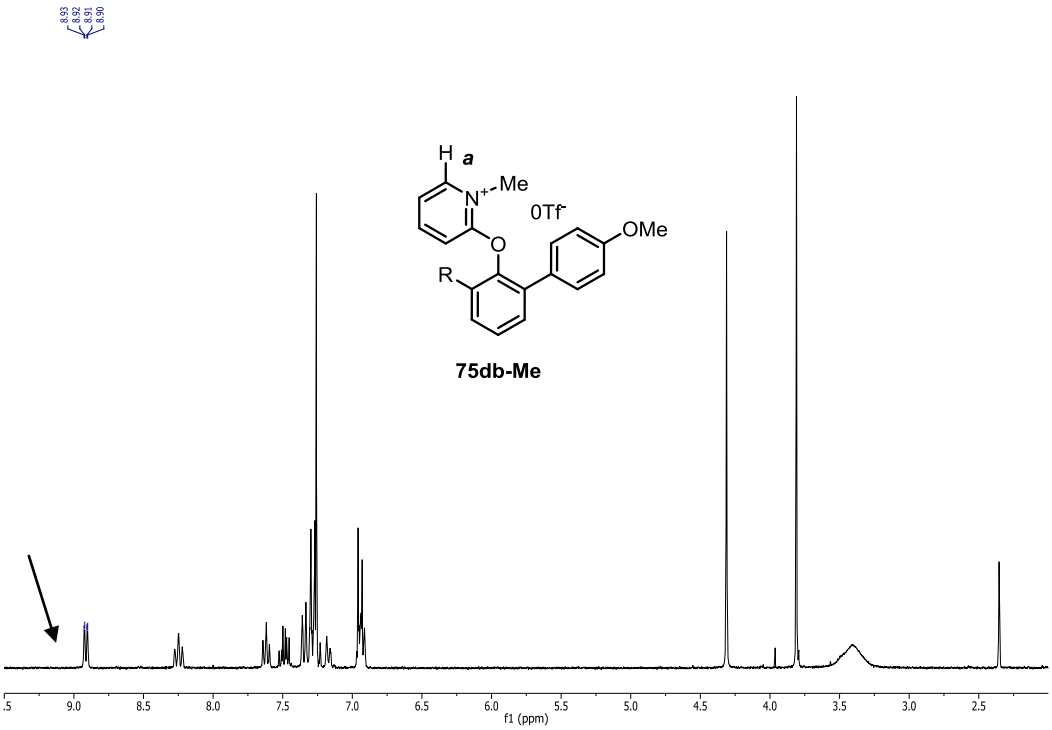
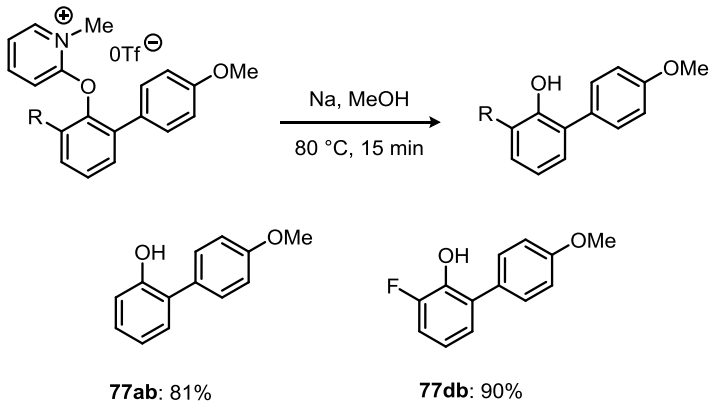


Figure 15: Proton NMR of **75db-Me**.

The crude was then treated with sodium methanolate in methanol, which efficiently cleaved the methylated pyridinimium fragment. This procedure yielded the *ortho* arylated phenols **77** in up to 90% yields.[36j, 91]



Scheme 47: Cleavage of the directing group.

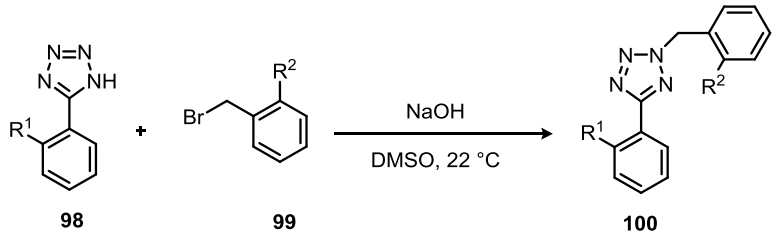
The structure of the final product **77** and, hence, the siteselectivity of substitution in the arylated product **75**, was then confirmed through HSQC and HMBC measurements.

3.2 Ruthenium-catalyzed direct arlytion of phenyltetrazoles

3.2.1 Preliminary results

The simplest synthetic route towards the preparation of *N*-benzyl-protected phenyltetrazoles **60**, would be a benzylation of the free N–H tetrazoles **98** with benzylic derivatives. Unfortunately, this reaction did not give the expected result, as isomeric tetrazoles **100** with different physical and chemical properties were formed (Table 9)

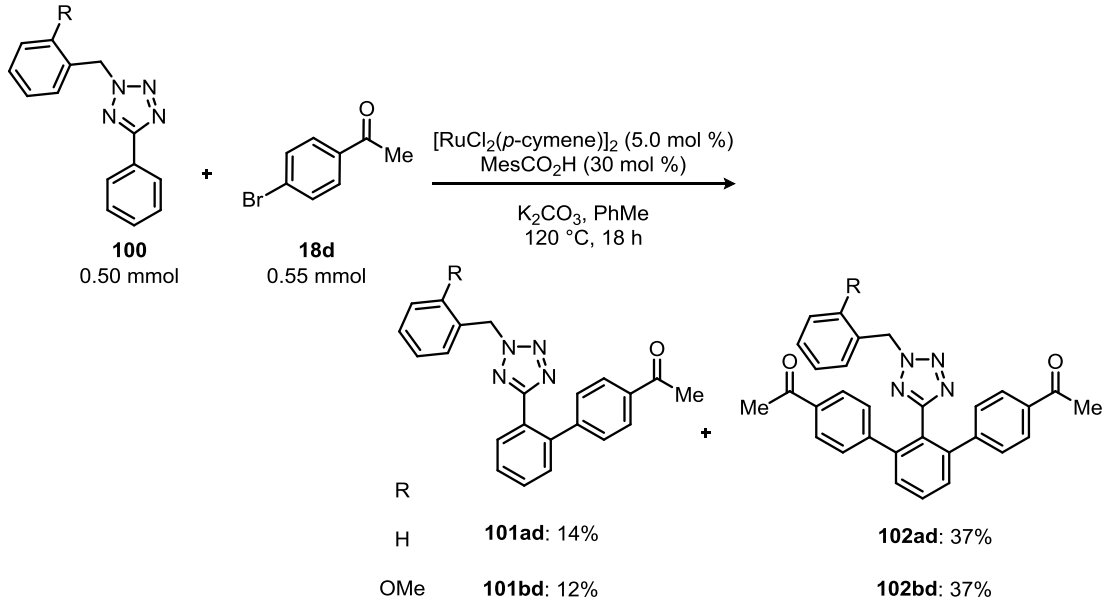
Table 9: Attempted *N*-benzylation of phenyltetrazoles **98**.



98 **99** **100**

R^1	R^2	Isolated yield
H	H	71% (**100a**)
H	OMe	68% (**100b**)
F	H	41% (**100c**)
OMe	H	27% (**100d**)

Under modified conditions, as reported by *Seki* and coworkers[78d] or applying Mitsunobu-type benzylation on the tetrazole ring in **98**,[92] a mixture of substituted 1*H*-tetrazoles **60** and 2*H*-tetrazoles **100** was obtained.

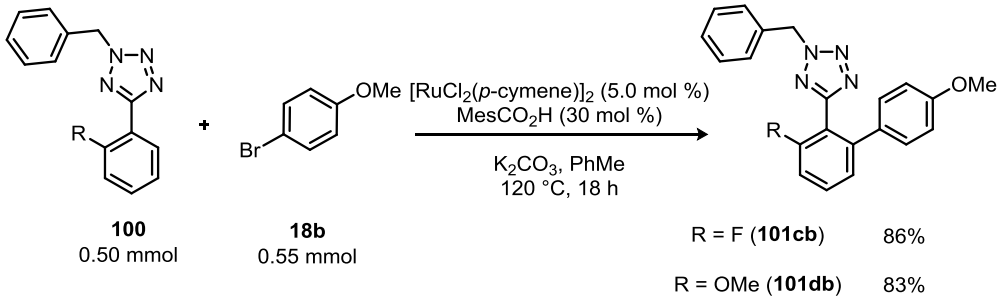


100 0.50 mmol **18d** 0.55 mmol

R		
H	**101ad**: 14%	**102ad**: 37%
OMe	**101bd**: 12%	**102bd**: 37%

Scheme 48: Direct arylation on 2-benzyl-5-phenyl-*2H*-tetrazole **100**.

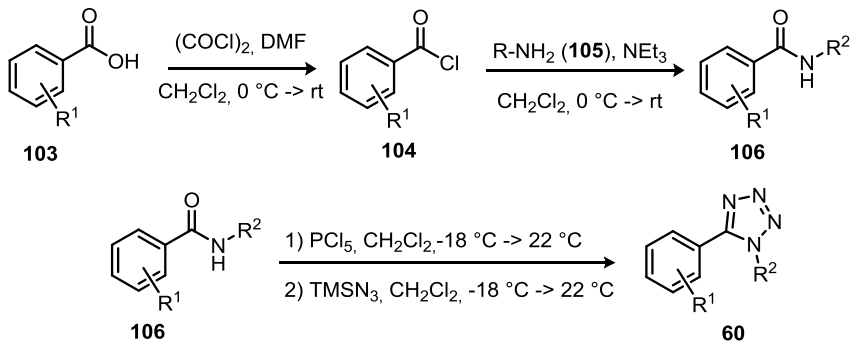
Then, these undesired substrates were submitted to the direct arylation reaction conditions, but the results were not satisfactory (Scheme 48). The yields were too low and the selectivity was disapointing. Blocking the *ortho* position brought better results (Scheme 49).

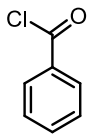
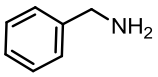
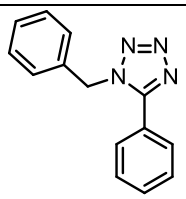
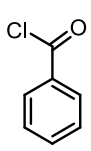
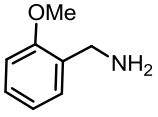
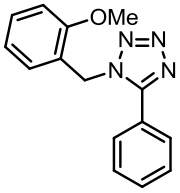
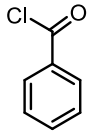
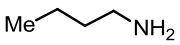
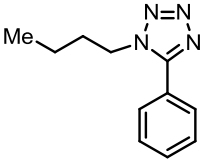


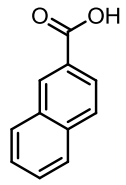
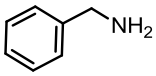
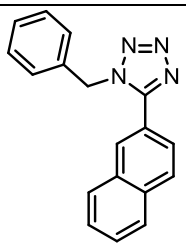
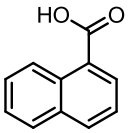
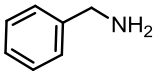
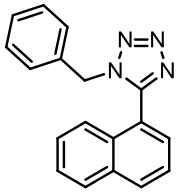
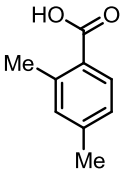
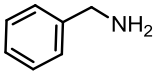
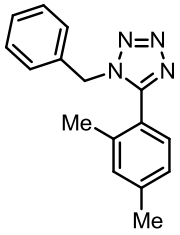
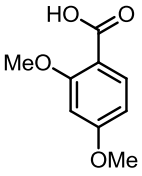
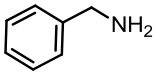
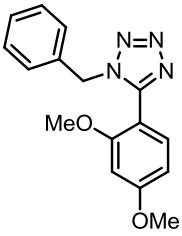
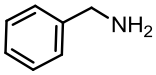
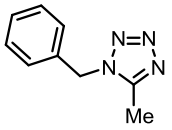
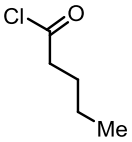
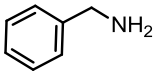
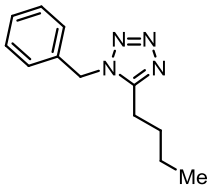
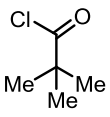
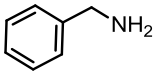
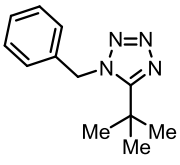
Scheme 49: Selective direct arylation of *ortho*-substituted 2-benzyl-5-phenyl-*2H*-tetrazole.

Another alternative to obtain the originally desired isomer was applied to synthesize 1,2-substituted tetrazoles (Table 10).[78c]

Table 10: Synthesis of differently substituted 5-phenyl-1*H*-tetrazole.[a]



Entry	**103/104**	**105**	**60**	yield (%)
1				63
	104a	**105a**	**60a**	
2				38
	104a	**105b**	**60b**	
3				20
	104a	**105c**	**60c**	

Entry	**103/104**	**105**	**60**	yield (%)
4				55
	103b	**105a**	**60d**	
5				14
	103c	**105a**	**60e**	
6				traces
	103d	**105a**	**60f**	
7				traces
	103e	**105a**	**60g**	
8				81
	104h	**105a**	**107a**	
9				62
	104i	**105a**	**107b**	
10				75
	104j	**105a**	**107c**	

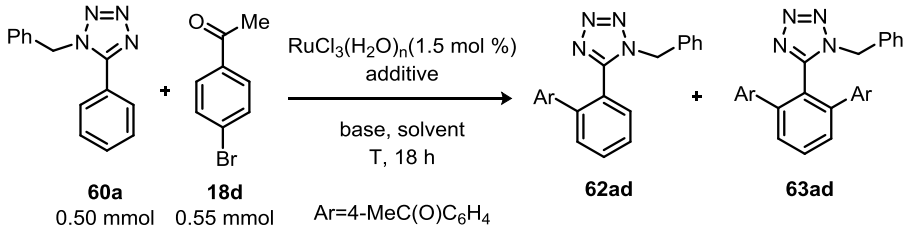
[a] Reaction conditions: acid **103** or acid chloride **104** (1.0 equiv), benzylamine **105** (1.0 equiv), NEt_3 (1.0 equiv), CH_2Cl_2 (0.5 M), 0 °C → 22 °C, 16-20 h, then 1) benzylamide **106** (1.0 equiv), PCl_5 (1.5 equiv), CH_2Cl_2, -18 °C → 22 °C 2) $TMSN_3$ (2.0 equiv), -18 °C → 22 °C,16-20h, isolated yields.

This method appeared to be widely applicable for various substrates with different substituents on the benzylic group (entries 1 and 2). Even an alkyl chain was tolerated (entry 3). Concerning the substitution on the arene, different arenes reacted well (entries 4 and 5). The only exception were *ortho*-substituted benzoic acids (entries 6 and 7). In those cases, only traces could be isolated. 5-Alkyl-1*H*-tetrazoles were also obtained with this method in good yields (entries 8-10). The structure of 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) was indirectly confirmed by X-ray crystal structure analysis of its arylated derivative **62ad** (see below).

3.2.2 Optimization of the reaction conditions

Tetrazole **60a** was selected as the standard substrate for the optimization of the reaction conditions for the ruthenium-catalyzed direct arylations. Because of economic reasons, the inexpensive $RuCl_3(H_2O)_n$ was first tested as a catalyst for these transformations (Table 11).

Table 11: Optimisation for the best reaction conditions with the inexpensive $RuCl_3$ $(H_2O)_n$.[a]



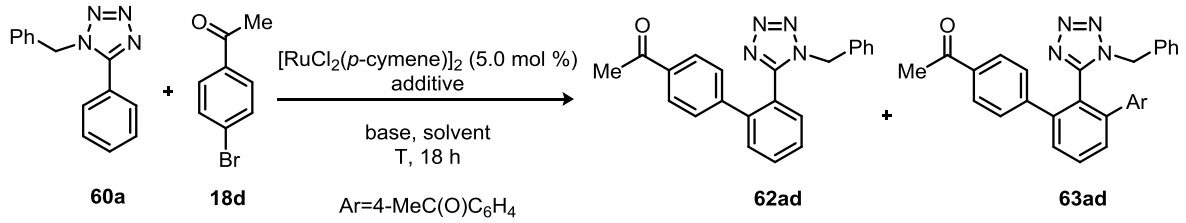
Entry	Base	Additive (mol %)	Solvent	Temperature (°C)	**62ad** (%)	**63ad**(%)
1	K_2CO_3	PPh_3(5)	NMP	140	60	-
2	K_2CO_3	PPh_3 (6)	PhMe	120	traces	-
3	K_2CO_3	-	NMP	140	traces	-
4	K_2CO_3	$MesCO_2H$ (30)	PhMe	120	traces	-

[a] Reaction conditions: **60a** (0.50 mmol), **18d** (0.55 mmol), $RuCl_3(H_2O)_n$ (1.5 mol %), additive, K_2CO_3 (1.0 mmol), solvent (2.0 mL), 120–140 °C, 18 h, yields of isolated products.

Attempted reactions in NMP without any additives gave only traces of the product (entry 1). In analogy to the results reported by *Seki*,[78c, 78d] the arylation in NMP with PPh_3 as a cocatalyst gave selectively the monoarylated product **62ad** in 60%. Switching the solvent to apolar toluene dramatically decreased the yield (entry 3). Even the carboxylate assistance did not change the situation (entry 4).

The more applicable $[RuCl_2(p\text{-cymene})]_2$ was then used as catalyst, in combination with different bases, solvents and additives to determine the optimal conditions for the direct arylation (Table 12).

Table 12: Optimisation of reaction condition with $[RuCl_2(p\text{-cymene})]_2$.[a]



Entry	Base	Additive (mol %)	Solvent	Temperature (°C)	**62ad** (%)	**63ad** (%)
1	K_2CO_3	Without	PhMe	120	34	2
2[b]	K_2CO_3	$MesCO_2H$ (30)	PhMe	120	-	-
3	K_2CO_3	PPh_3 (10)	PhMe	120	47	-
4	K_2CO_3	PPh_3 (10)	NMP	140	75	-
5	K_2CO_3	KOAc (30)	PhMe	120	52	8
6	K_2CO_3	*t*-$BuCO_2H$	PhMe	120	60	10
7	K_2CO_3	(1-Ad)CO_2H	PhMe	120	61	9
8	$MesCO_2K$	-	PhMe	120	-	-
9	-	$MesCO_2K$ (30)	PhMe	120	<5	-
10	KOAc	Without	PhMe	120	70	2
11	KOAc	KPF_6 (20)	PhMe	120	46	-
12	KOAc	$MesCO_2H$ (30)	PhMe	120	<10	-
13	Ag_2CO_3	$MesCO_2H$ (30)	PhMe	120	-	-
14	Na_2CO_3	$MesCO_2H$ (30)	PhMe	120	34	-
15	Cs_2CO_3	$MesCO_2H$ (30)	PhMe	120	41	8
16	K_2CO_3	$MesCO_2H$ (30)	DMA	120	50	19
17	K_2CO_3	$MesCO_2H$ (30)	1,4-dioxane	100	45	12
18	K_2CO_3	$MesCO_2H$ (30)	NMP	140	46	15
19	K_2CO_3	$MesCO_2H$ (30)	H_2O	100	-	-
20[c]	K_2CO_3	$MesCO_2H$ (30)	PhMe	120	58	7
21	K_2CO_3	$MesCO_2K$ (30)	PhMe	120	64	8
22	K_2CO_3	$MesCO_2H$ (30)	PhMe	120	64	9

[a] Reaction conditions: **60a** (0.50 mmol), **18d** (0.55 mmol), $[RuCl_2(p\text{-cymene}]_2$ (5.0 mol %), additive, base (1.0 mmol), solvent (2.0 mL), 100–140 °C, 18 h, isolated yields. [b] Without ruthenium. [c] [Ru] = $[RuBr_2(p\text{-cymene})]_2$ (5.0 mol %).

No product formation was observed without a ruthenium source (entry 2). Additionally, it is also shown that the reaction occurred in the presence of carbonate, in spite of low yield of the product (entry 1). Using triphenylphosphine as a cocatalyst proved to be inefficient in the apolar solvent toluene, but showed excellent yield in the more coordinating solvent NMP (entries 3 and 4). Upon catalysis with $[RuCl_2(p\text{-cymene})]_2$, the carboxylate assistance was found to be of prime necessity. Other carboxylic acids such as acetate, pivalic acid, or adamantyl carboxylic acid (entries 5-7) showed high conversion but were not as efficient as the $MesCO_2H$ or the potassium salt of $MesCO_2H$ (entries 21-22). Application of the $MesCO_2K$ in either stoichiometric or cocatalytic amounts, gave unsatisfactory results (entries 8 and 9). In contrast, potassium acetate as a base without any additives (entries 11 and 12), gave high yield of the monoarylated product **62ad** in a highly selective

manner (entry 10). Among different carbonate bases, potassium carbonate proved to be the best (entries 13-15). Other solvents were tested, such as NMP, DMA and 1,4-dioxane but the results were not better as the one in toluene (entries 16-18). Unfortunately less toxic solvents, such as water, were not applicable, probably based on a difference of solubility between the reagents (entry 19). Moreover, a different ruthenium source $[RuBr_2(p\text{-cymene})]_2$ was employed but did not gave better results (entry 20). Summarizing the results presented in Table 11, a combination of potassium carbonate as a base, and mesityl carboxylic acid as a cocatalyst in the less polar solvent toluene was found to be optimal for the direct arylation of phenyltetrazoles **60**. The structure of **62ad** was confirmed through X-Ray crystal structure analysis. The reaction is shown to be regioselective as the arylation takes place in the *ortho* position exclusively (Figure 18).

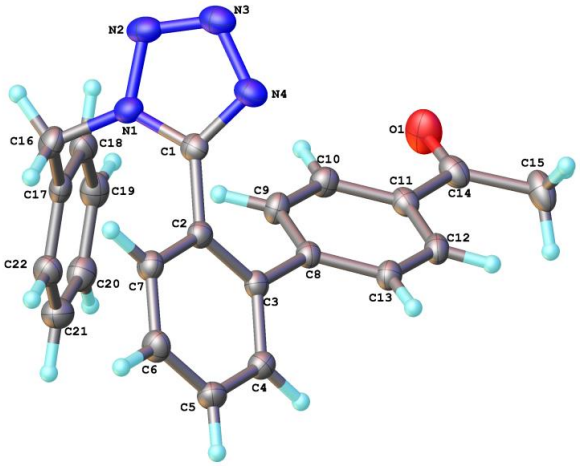
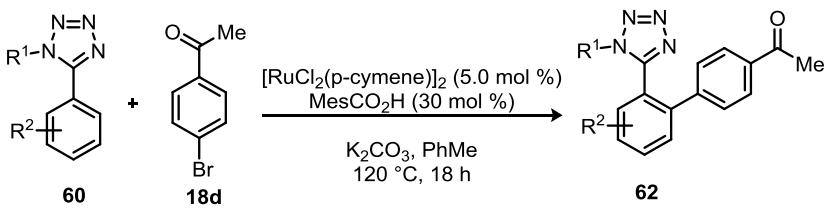


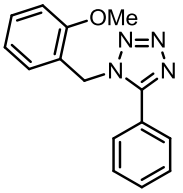
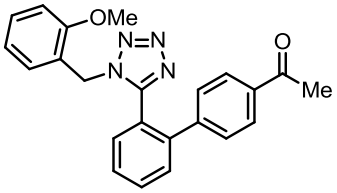
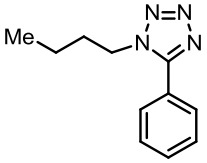
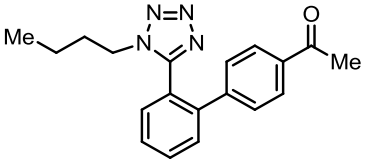
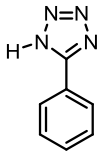
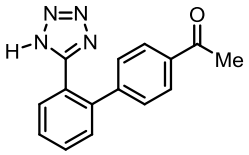
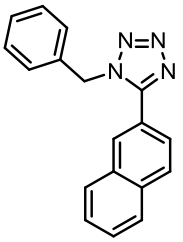
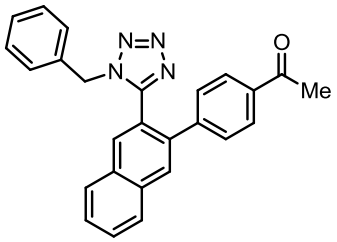
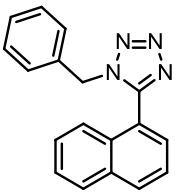
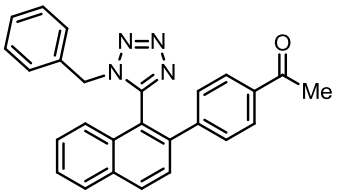
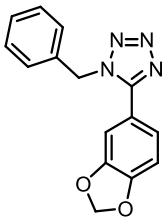
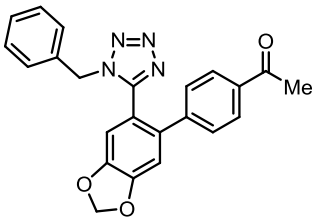
Figure 16: Molecular structure of 1-[2'-(1-benzyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]ethanone (**62ad**) in the crystal. The numbering does not correspond to the IUPAC rules.

3.2.3 Scope of phenyltetrazoles in the ruthenium catalyzed direct arylation with 4-bromoacetophenone (18d).

The scope of the direct arylations under the optimized reaction conditions was tested with differently substituted tetrazoles **62** (Table 13).

Table 13: Scope of the arylation with 4-bromoacetophenone (**18d**).[a]



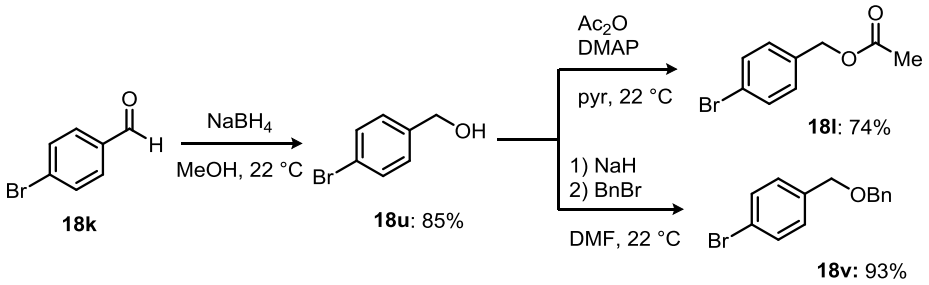
Entry	**60**	**62**	Yield (%)
1	 **60b**	 **62bd**	65 (diarylated **63bd**: 11)
2	 **60c**	 **62cd**	53 (diarylated **63cd**: 16)
3	 **98a**	 **62bd-H**	n.r.
4	 **60d**	 **62dd**	48
5	 **60e**	 **62ed**	24
6	 **60h**	 **62hd**	26

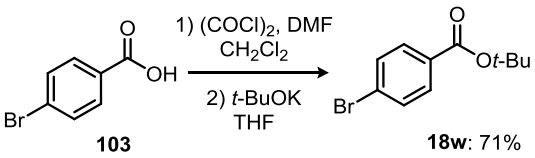
[a] Reaction conditions: **60** (0.50 mmol), **18d** (0.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $MesCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2.0 mL), 120 °C, 18 h, isolated yields.

The yield was not influenced by the introduction of a methoxy group in the *ortho*-position of the benzyl group (entry 1). If the tetrazole is bearing an alkyl chain (entry 2), the yield still remains satisfactory, but the group is however more difficult to remove as compared to a benzyl group, to finally obtain the desired free N–H tetrazole. Unfortunately, the unprotected phenyltetrazole **98a** did not react at all (entry 3). The naphthalene rings were arylated in a selective manner, but with a low yield (entries 3 and 4). When the substrate **60h** was subjected to the optimized condition, only one product was obtained, but with a low yield, where the more accessible C–H bond reacted (entry 6).

3.2.4 Scope of proelectrophiles.

With the aim of further extending the reaction scope, a diverse set of (pro)electrophiles were tested in direct arylations of the tetrazole **60a**. The appropriate arylating reagents **18u**-**18w** were synthesized from the 4-bromobenzaldehyde (**18k**) and 4-bromobenzoic acid (**103**) as indicated in Scheme 50.

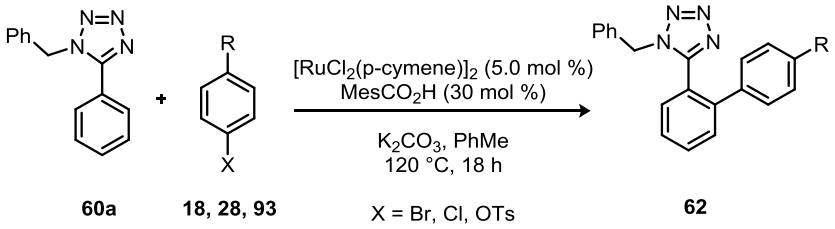


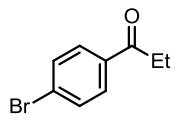
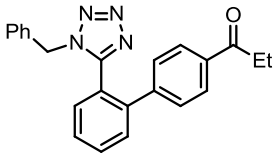
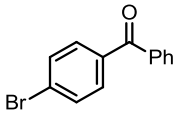
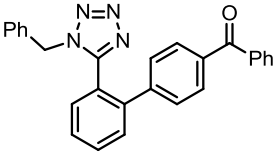


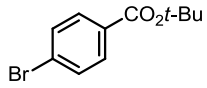
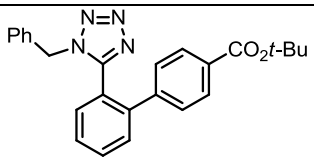
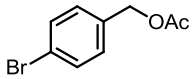
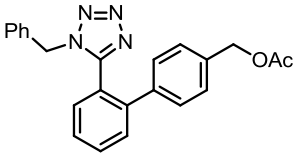
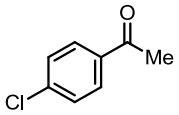
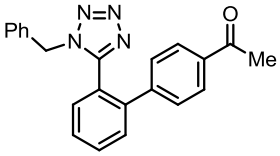
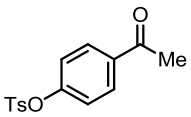
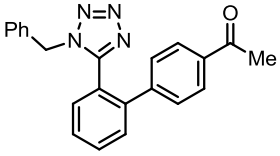
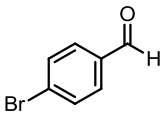
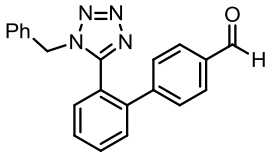
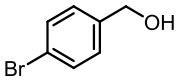
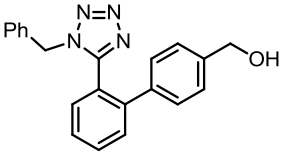
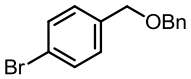
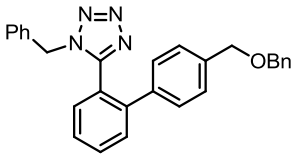
Scheme 50: Preparation of diverse (pro)electrophiles for direct arylations of the tetrazole **60a**.

The results of arylations with (pro)electrophiles **18**, **28** and **93** under the optimized conditions are summarized in Table 14.

Table 14: Scope of (pro)electrophiles.[a]



Entry	**18, 28, 93**	**62**	Yield (%)
1	 **18p**	 **62ap**	63
2	 **18f**	 **62af**	70

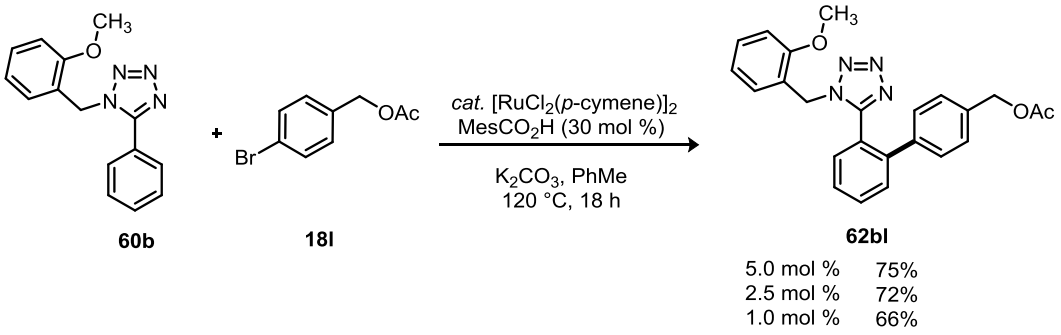
Entry	**18, 28, 93**	**62**	Yield (%)
3	 **18w**	 **62aw**	58
4	 **18l**	 **62al**	59
5	 **28d**	 **62ad**	10
6	 **93**	 **62ad**	n.r.
7	 **18k**	 **62ak**	traces
8	 **18u**	 **62au**	traces
9	 **18v**	 **62av**	traces

[a] Reaction conditions: **60a** (0.50 mmol), **18, 28, 93** (0.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $MesCO_2H$ (30 mol %), K_2CO_3 (1.0 mmol), PhMe (2.0 mL), 120 °C, 18 h, isolated yields.

Overall, the aryl bromides were efficient coupling partners with different functional groups being tolerated such as ketones and ester (entries 1-4). Yet, aryl chlorides and tosylates showed reduced or no reactivity (entries 5 and 6). On the other hand, 4-bromobenzaldehyde **18k**, (4-bromophenyl)methanol **18u** and its benzyl-protected derivative **18v** appeared to be almost inert in direct arylations under the optimized conditions (entries 7-9).

3.2.5 Synthesis of the key precursor for the ARB Valsartan

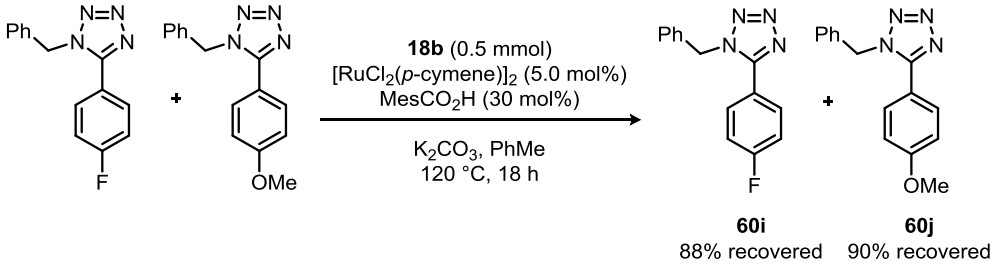
After studying the scope of arenes and electrophiles, the methodology was then probed to be applied to the synthesis of the intermediate **62bl** to Valsartan (**2**). The optimized conditions were then applied to the synthesis of the biaryl core, with high yields. More interestingly, the catalyst loading could be reduced up to one percent, yielding the target product in 66% (Scheme 51).



Scheme 51: Reduction of the catalyst loading in the synthesis of the Valsartan intermediate **62bl**.

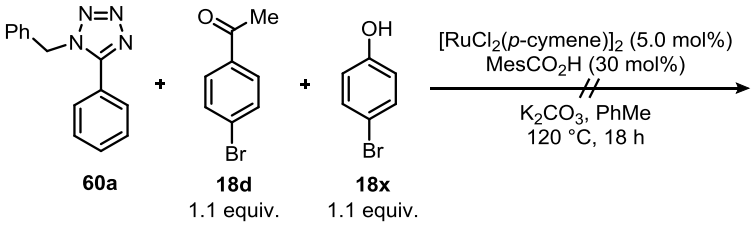
3.2.6 Mechanistic studies.

3.2.6.1 Intermolecular competition experiments between arenes



A competition experiment was attempted between the electron-deficient arene **60i** and the electron-rich arene **60j**. After 18 hours of heating under nitrogen, up to 80 % of both starting materials were recovered. According to the previous experience (Table 12, entries 7 and 8), electron-rich arenes demonstrated moderate reactivity in arylations with aryl bromides, whereas electron-deficient exhibited no reactivity (see below Scheme 53). It is still an opened question, if the electron-deficient arene **60i** indeed inhibited the arylation.

3.2.6.2 Competition experiments between aryl bromides 18d and 18x

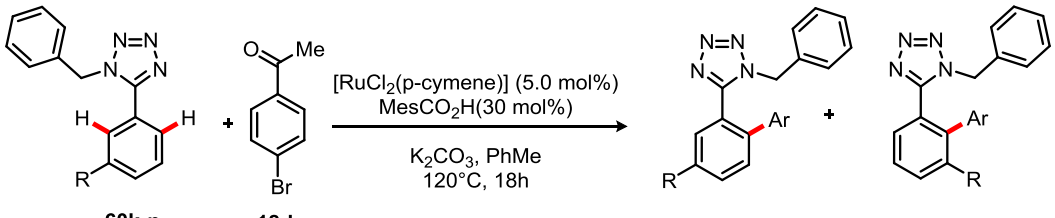


Scheme 52: Competition experiment between **18d** and **18x**.

The reaction of tetrazole **60a** with a mixture of 4-bromoacetophenone (**18d**) and 4-bromophenol (**18x**) gave no arylated product. Most probably, the 4-bromophenol (**18x**) inhibits the reaction by chelating the catalyst.This is in line with the previously discussed result (entry 8, Table 14), showing the necessity of the use of protected alcohols for such reactions.

3.2.6.3 Intramolecular competition experiments

Intramolecular competition experiments were performed with *meta*-substituted substrates. Whereas tetrazoles **60m** and **60n** with electron-deficient substituents exhibited no reactivity, the site selectivity of arylations with electron-rich arenes **60k** and **60l** was controlled by steric factors furnishing predominantly the products **62kd'** and **62ld'** *via* functionalization of the C–H bonds at the less sterically hindered 6-position (Scheme 53).



Scheme 53: Intramolecular competition experiments with *meta*-substituted substrates **60k-n**.

Nonetheless, a non negligeable amount of product **62ld''**, where the more congested C–H bond reacted, was obtained in the case of the arene bearing a methoxy group. This observation can be accounted for the effect of a secondary directing group.

The structure of **62kd'** was confirmed through ^{1}H NMR, in combination with HMBC and HSQC measurements, as well as NOEDIFF experiments[93] which confirmed the proposed structure. In the ^{1}H NMR spectrum (Figure 17), protons a, x, y and c were assigned with help from the HMBC analysis. When the CH_2 group signal was irradiated, the protons a and y saw their intensities change, which makes sense as the protons a are in direct neighborhood of the CH_2 group. Moreover, the fact that the intensity of the protons of the aryl rest (y) changed confirmed the fact that the arylation took place in the *ortho* position.

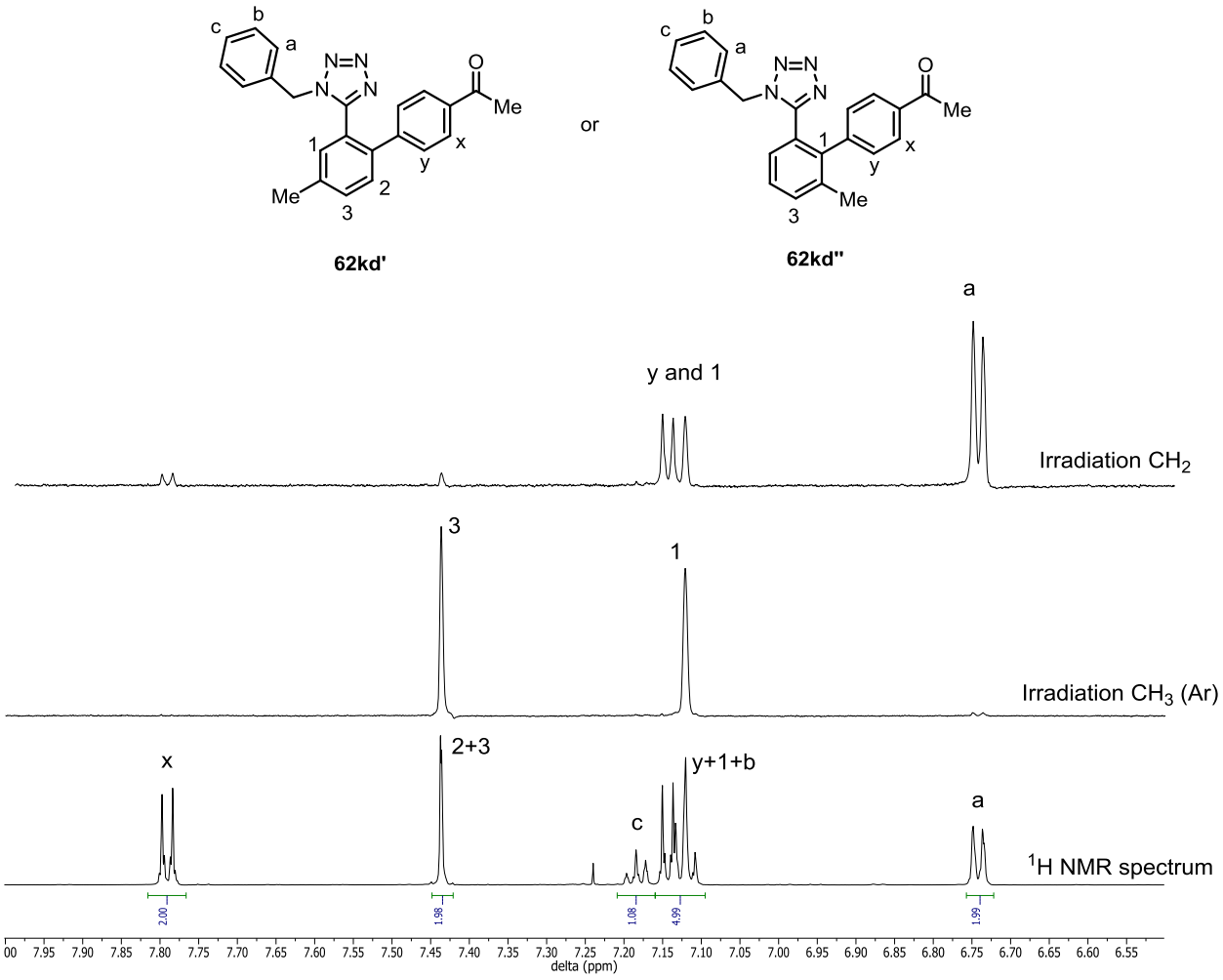
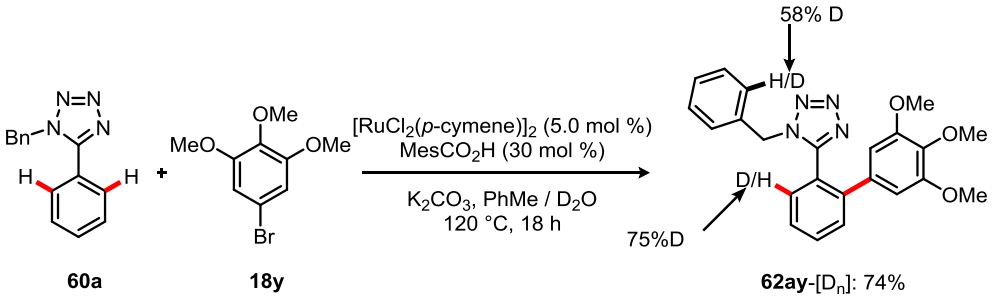


Figure 17: NOE experiments on **62kd**'.

Irradiation of a signal at the *resonance* frequency of the methyl group resulted in the intensity changes of two signals (Figure 17), but did not affect the intensity of the signals of the hydrogen atom **y**, thus excluding its neighborhood to the methyl group and ruling the structure **62kd"** from consideration.

3.2.6.4 H/D exchange



Scheme 54: H/D exchange experiment with D_2O as the cosolvent.

Reaction of substrate **60a** and **18y** under the optimized conditions, with deuteriated water as the cosolvent, lead to the observation of a H/D exchange (75%) in the *ortho*-position, confirming the reversibility of the C–H bond cleavage (Scheme 54). It was unexpected to observe also an exchange on the ring of the benzylgroup.

This observation undoubtedly indicated potential reactivity of the latter towards ruthenium-catalyzed arylation under appropriately selected reaction conditions and prompted us to synthesize tetrazole-containing substrates **107a**–**107c** (Figure 18) in order to check their reactivity towards arylation *via* six-membered ruthenacycles.

Unfortunately, none of the substrates **107a**–**107c** afforded even traces of the desired arylated products applying either mesytilate-assisted catalytic system or acetate-assisted ruthenium catalysis (see below). This result shows once again that the arylation occurring through six-membered ruthenacycles still remains an intriguing challenge for the future.

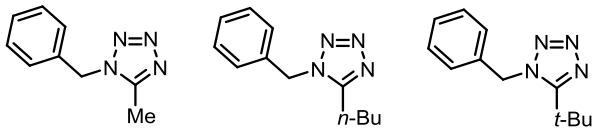
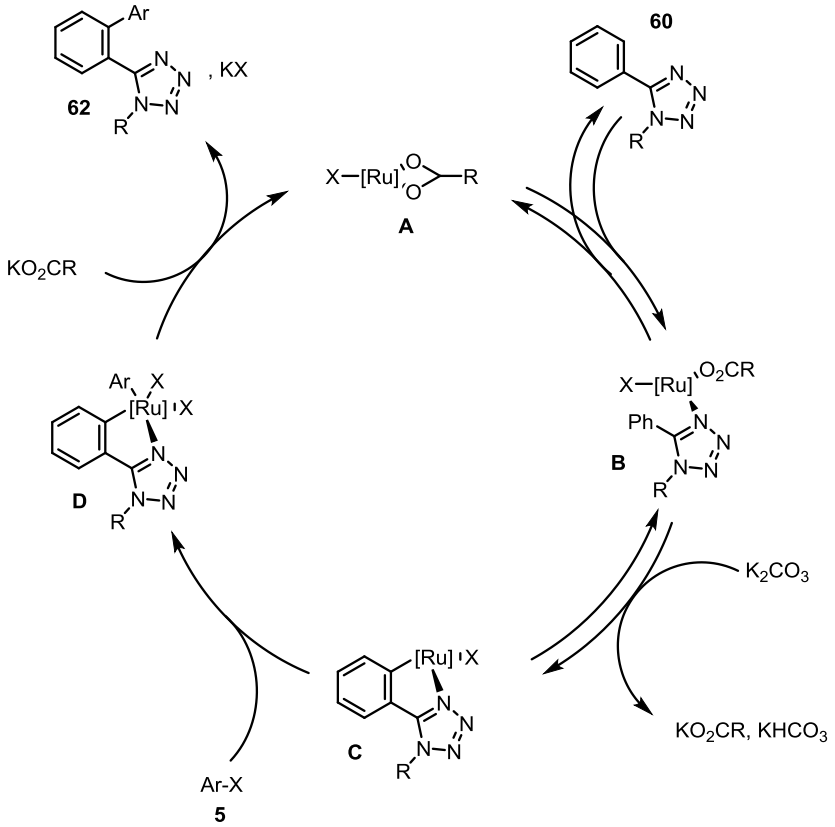


Figure 18: Substrates for potential direct arylation forming six membered ruthenacycles.

3.2.7 Proposed mechanism

Based on the studies, the following mechanism was proposed (Scheme 55).



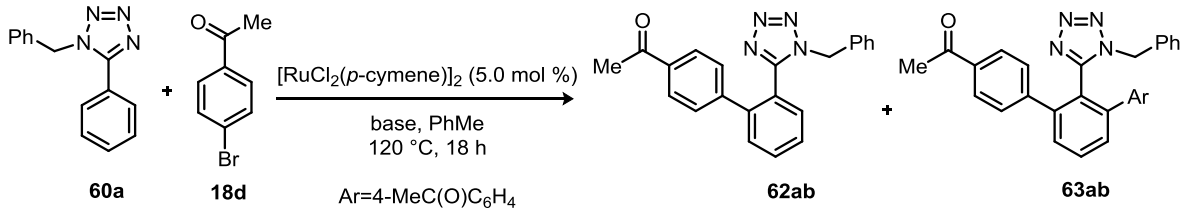
Scheme 55: Proposed mechanism.

It was shown by *N.Y.P. Kumar* that the isolated complex [Ru(*p*-cymene)($MesCO_2$)$_2$] **11i** was efficient as a catalyst for the direct arylation of phenyltetrazoles, which supports the fact that this complex is formed *in situ* during the reaction from [$RuCl_2$(*p*-cymene)]$_2$ and $MesCO_2H$ and then coordinates to the tetrazole core. A reversible C–H deprotonation is followed by the rate determining addition of the aryl bromide to the ruthenium complex. Up to now, there is no detailed knowledge on how the aryl bromide is adding to the ruthenium. The reductive elimination is then yielding the product and regenerates the active catalyst **A**.

3.2.8 Base-assisted ruthenium catalyzed direct arylation of phenyltetrazoles.

In spite of satisfactory results provided by the mesitylate-assisted catalytic system, the excellent isolated yield and high selectivity upon employment of KOAc as the base (Table 12, entry 12) prompted us to examine further organic and inorganic bases in these direct arylations (Table 15).

Table 15: Optimization studies of direct arylations with various bases.[a]



60a **18d** **62ab** **63ab**

Entry	Base	**62ab** (%)[a]	**63ab** (%)[a]
1	K_2CO_3	34	2
2	$CsCO_3$	14	-
3	$RbCO_3$	28	-
4	Na_2CO_3	5	-
5	$CsHCO_3$	45	-
6	$KHCO_3$	27	-
7	$NaHCO_3$	2	-
8	NEt_3	-	-
9	DMAP	-	-
10	Pyridine	-	-
11	$MesCO_2K$	-	-
12	NaOPiv	36	-
13	CsOPiv	44	-
14	MgO*t*-Bu_2	-	-
15	LiO*t*-Bu	-	-
16	NaO*t*-Bu	-	-
17	KO*t*-Bu	-	-
18	NH_4OAc	-	-
19	KOAc	70	2
20	NaOAc	13	-
21	CsOAc	60	2
22	RbOAc	71	9

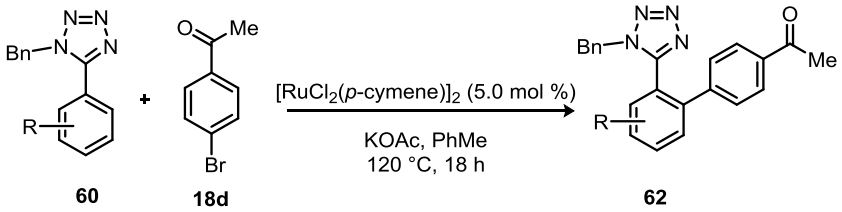
23	*n*-Bu_4NOAc	56	6

[a] Reaction conditions: **60a** (0.50 mmol), **18d** (0.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), base (1.0 mmol), PhMe (2.0 mL), 120 °C, 18 h, yields of isolated products.

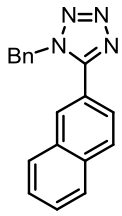
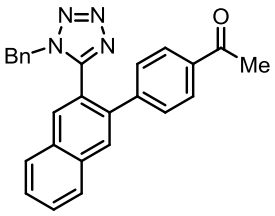
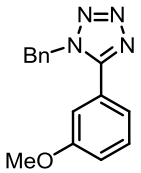
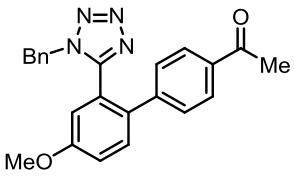
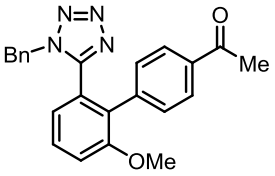
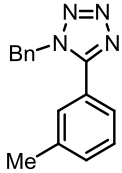
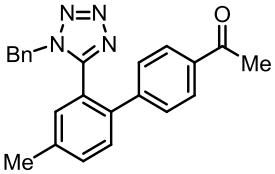
Inorganic bases, like carbonate or hydrocarbonate gave low to moderate yields (entries 1-7), while organic bases such as triethylamine, pyridine, yielded no product at all (entries 8-10). In addition, when pivalate derivatives were used as bases the reaction was working, while no product was obtained with mesitylate potassium salt (entries 11-13). Using stronger bases such as different *tert*-butoxides did not bring better results (entries 14-17). The acetate bases gave the best results, with potassium acetate and rubidium acetate yielding the highest conversion to the desired product (entries 19-22). Surprisingly, the tetra alkylammonium acetate yielded the product in a satisfactory yield (entry 23), while the ammonium acetate gave only traces of product (entry 18).

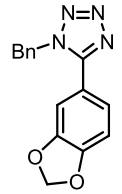
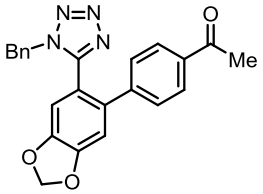
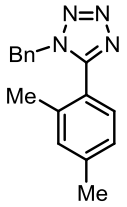
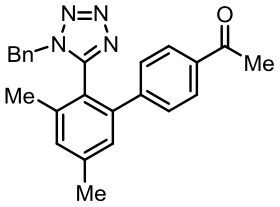
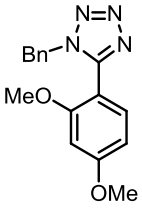
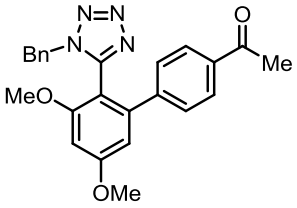
With these new optimized conditions in hand, the scope of substrates was extended using less expensive potassium acetate as the base (Table 16).

Table 16: Scope of arenes with KOAc as the base.[a]



60 **18d** **62**

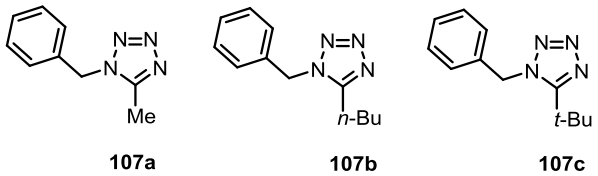
Entry	**60**	**62**	Yield (%)
1	 **60d**	 **62dd**	52
2	 **60l**	 **62ld‘**  **62ld“**	45/15
3	 **60k**	 **62kd‘**	45

Entry	**60**	**62**	Yield (%)
4	 **60h**	 **62hd**	6
5	 **60f**	 **62fd**	n.r.
6	 **60g**	 **62gd**	35

[a] Reaction conditions: **60** (0.50 mmol), **18d** (0.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), KOAc (1.0 mmol), PhMe (2.0 mL), 120 °C, 18 h, isolated yields.

Unfortunantely, the high yield of arylation obtained above (Table 14, entry 19) was rather not general. The yields of the arylated aryltetrazoles **62** were not as high as expected, and significantly lower compared to the mesitylate-based system. This demonstrated the synthetic versatility of bulky carboxylates in ruthenium-catalyzed arylations.

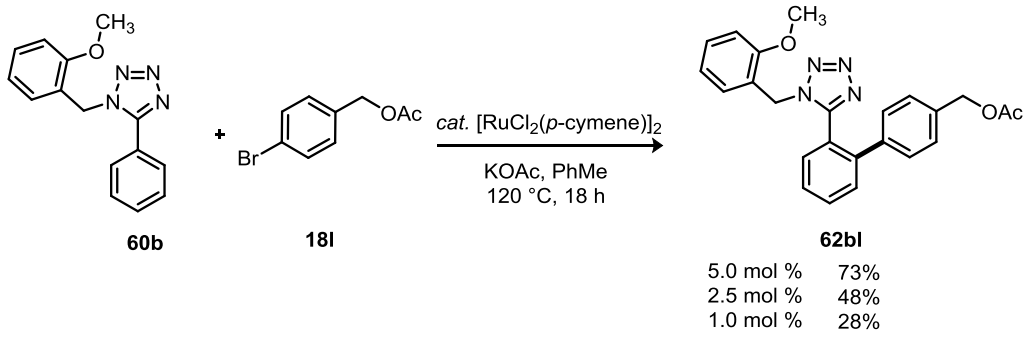
Furthermore, the optimal reaction conditions with acetate as a base were not applicable to the direct arylation of substrates that can form six membered ruthenacycles (Figure 19).



107a **107b** **107c**

Figure 19: Tested substrates that potentially form six-membered ruthenacycles.

3.2.9 Synthesis of the Valsartan precursors with potassium acetate as the base.

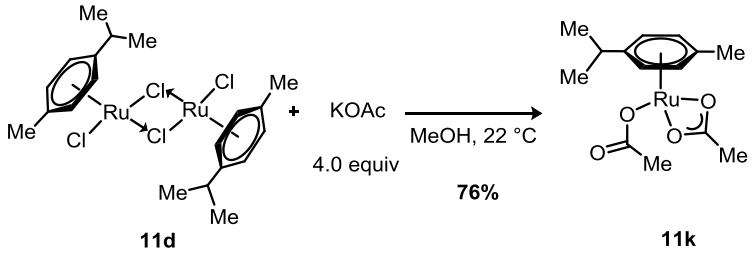


Scheme 56: Preparation of the building block **62bl** for the synthesis of Valsartan (**2**) applying KOAc.

The intermediate for the synthesis of Valsartan was efficiently synthesized under the new conditions (Scheme 56). Unfortunately, the reduction of the catalyst loading resulted in a significant decreased yield once again indicating the superiority of the ruthenium/$MesCO_2H$ catalytic system.

3.2.10 Arylation with the isolated complex 11k

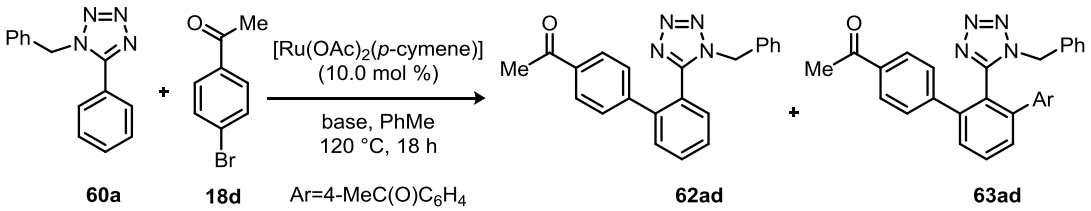
The reaction of $[RuCl_2(p\text{-cymene})]_2$ with 4 equivalents of KOAc gave the well-defined complex $[Ru(p\text{-cymene})(OAc)_2]$ (Scheme 57).[57b, 94]



Scheme 57: Synthesis of isolated complex **11k**.

The complex **11k** was then probed as the catalyst in the direct arylation of phenyltetrazole (Table 17).

Table 17: Direct arylation of **60a** with the isolated complex **11k**.[a]



Entry	Base	**62ad** (%)	**63ad** (%)
1	-	13	---
2	K_2CO_3	54	11
3	KOAc	38	---
4	KOAc + KCl(20 mol %)	73	4

[a] Reaction conditions: **60a** (0.50 mmol), **18d** (0.55 mmol), [$Ru(OAc)_2$(*p*-cymene)] (10 mol %), base (1.0 mmol), PhMe (2.0 mL), 120 °C, 18 h, isolated yields.

In the absence of a base, the isolated complex **11k** displayed a low catalytic activity towards the direct arylation (Table 17, entry 1). Addition of potassium carbonate (K_2CO_3) as the base afforded the expected result (Table 17, entry 2) similar to those obtained wit [$RuCl_2$(*p*-cymene)]$_2$ and bulky organic acids (Table 12, entries 6-7 and 22). Surprisingly, employing potassium acetate as a base in combination with the complex **11k** (Table 17, entry 3) furnished lower yield than by use of [$RuCl_2$(*p*-cymene)]$_2$/KOAc catalytic system. This result indicated the possible participation of chloride anions from [$RuCl_2$(*p*-cymene)]$_2$ in the catalytic cycle. Indeed, under essentially the same conditions, but in the presence of potassium chloride (20 mol %), the arylated phenyltetrazole **62ad** was obtained with essentially the same efficacy (73% yield) as applying [$RuCl_2$(*p*-cymene)]$_2$/KOAc catalyst (Table 12, entry 10). Presumably, the mechanism of the acetate-assisted direct ruthenium-catalyzed arylation slightly differs from the mesitylate-assisted from the point of view of more active chloride participation as a ligand in the intermediates **A**–**C** (Scheme 55) in the former case.

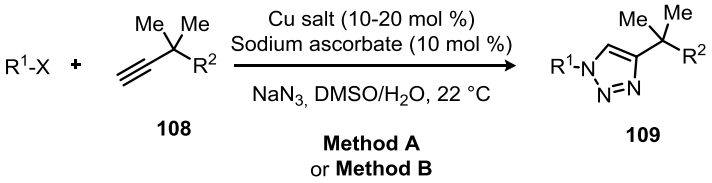
3.3 Ruthenium-catalyzed direct arylation of arenes with a bidentate directing group

3.3.1 Synthesis of starting materials

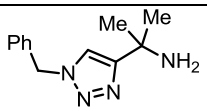
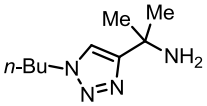
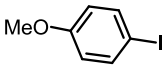
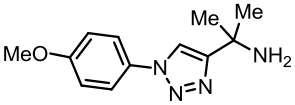
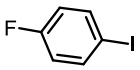
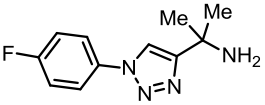
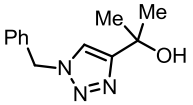
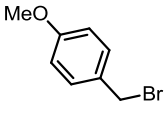
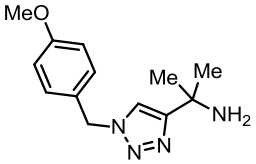
3.3.1.1 Synthesis of amines or alcohols

Variously substituted triazoles **109** were synthesized using the copper-catalyzed 1,3-dipolar cycloaddition[95] of alkynes **108** with alkyl or benzyl bromide. With modified methods whether an alkyl, benzyl[96] or aryl rest[97] was introduced (Table 18).

Table 18: Synthesis of amine or alcohol derivatives **109**.[a]



108 109

Entry	R^1–X	R^2	**109**	Yield (%)	Method
1		NH_2		76	A
	99a	**108a**	**109a**		
2	*n*-Bu–Br	NH_2		76	A
	95b	**108a**	**109b**		
3		NH_2		82	B
	66a	**108a**	**109c**		
4		NH_2		86	B
	66c	**108a**	**109d**		
5		OH		92	A
	99a	**108b**	**109e**		
6		NH_2		73	A
	99c	**108a**	**109f**		

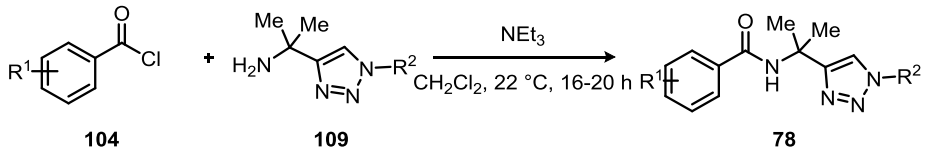
[a] Method A: Alkylbromide or benzylbromide (1.0 equiv), NaN_3 (1.0 equiv), DMSO (0.50 M), 22°C, 16 h then, sodium ascorbate (10 mol %), $Cu(SO_4)_2.5H_2O$ (20 mol %), alkyne (1.0 equiv), degassed H_2O (2 x V_{DMSO}), 22 °C, 18–20 h. Method B: Aryliodide (1.0 equiv), NaN_3 (1.1 equiv), sodium ascorbate (10 mol %), CuI (10 mol %), alkyne (1.0 equiv), DMEDA (15 mol %), degassed DMSO/degassed H_2O (0.30 M, 5/1, v/v), 16–20 h, 22 °C, yields of isolated compounds.

In most cases, these simple and easily performable syntheses furnished the triazole derivatives **109,** which did not required any further purification. The purity of **109** was verified applying ^{1}H NMR spectroscopy.

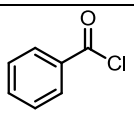
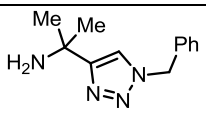
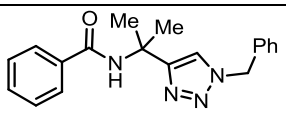
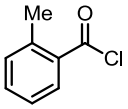
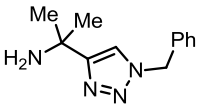
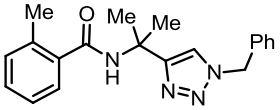
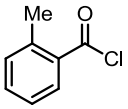
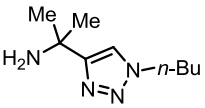
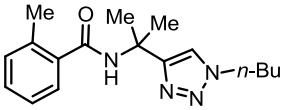
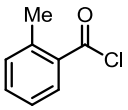
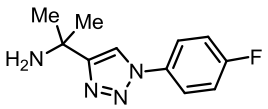
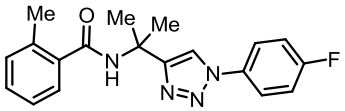
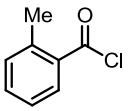
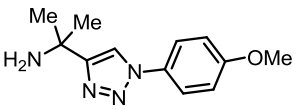
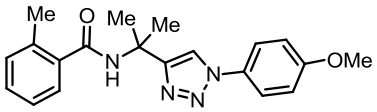
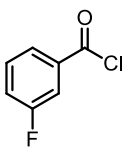
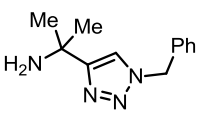
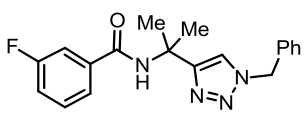
3.3.1.2 Synthesis of bidentate substrates starting from acid or acid chloride.

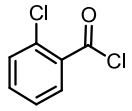
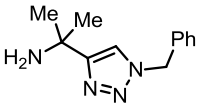
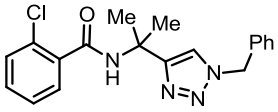
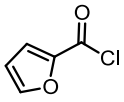
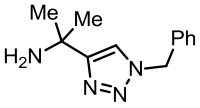
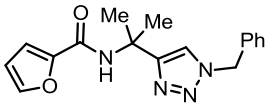
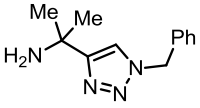
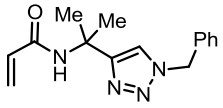
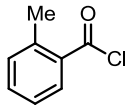
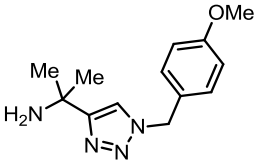
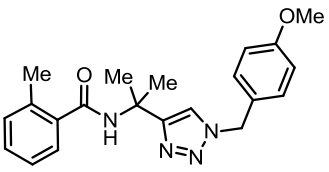
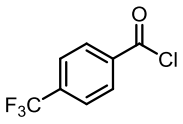
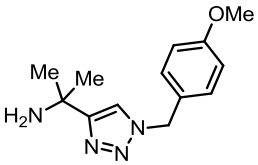
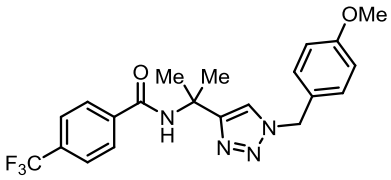
The synthesis of benzamides succeeded through the reaction of already available acid chlorides **104**, or prepared from the benzoic acid **103** and then used immediately, utilizing the amine **109**, and NEt_3 in CH_2Cl_2. Aromatic or non-aromatic acids were easily converted to the benzamides in good yields. Even heteroaromatic acids reacted to yield the corresponding benzamides (Table 19 and 20).

Table 19: Synthesis of starting materials **78** starting from acid chlorides **104**.[a]



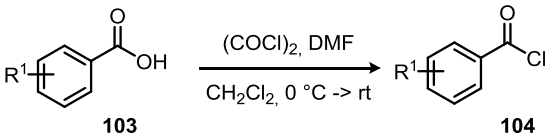
104 **109** **78**

Entry	**104**	**109**	**78**	Yield (%)
1				85
	104a	**109a**	**78a**	
2				86
	104b	**109a**	**78b**	
3				70
	104b	**109b**	**78c**	
4				62
	104b	**109d**	**78d**	
5				61
	104b	**109c**	**78e**	
6				73
	104c	**109a**	**78f**	

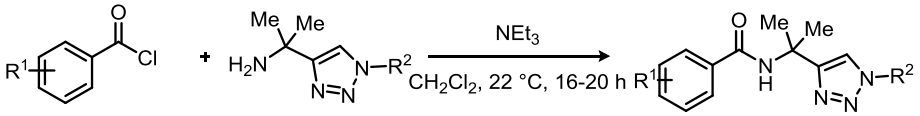
Entry	104	109	78	Yield (%)
7	 **104d**	 **109a**	 **78g**	85
8	 **104e**	 **109a**	 **78h**	64
9	 **104f**	 **109a**	 **78i**	79
10	 **104b**	 **109f**	 **78j**	79
11	 **104g**	 **109f**	 **78k**	85

[a] Reaction conditions: **104** (1.0 equiv), **109** (1.0 equiv), NEt_3 (1.0 equiv), CH_2Cl_2, 0→22 °C, 16–20 h, isolated yields.

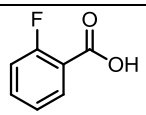
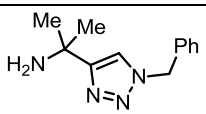
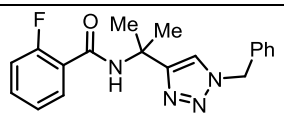
Table 20: Synthesis of starting materials **78** starting from acid chlorides **103**.[a]

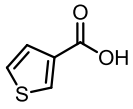
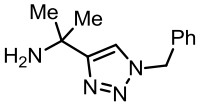
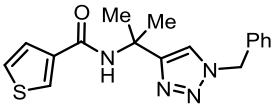
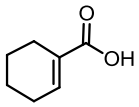
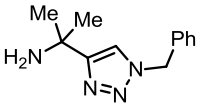
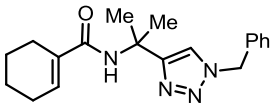


103 **104**



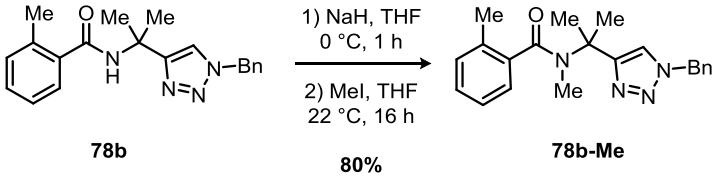
104 **109** **78**

Entry	103	109	78	Yield (%)
1	 **103f**	 **109a**	 **78l**	68

Entry	103	109	78	Yield (%)
2				55
	103h	**109a**	**78m**	
3				65
	103i	**109a**	**78n**	

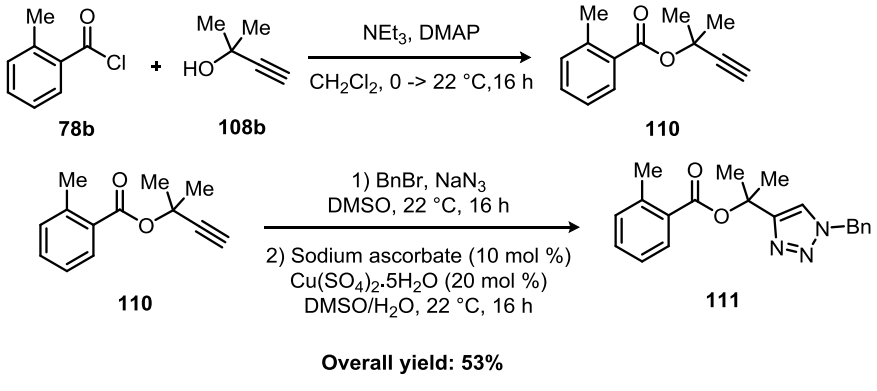
[a] Benzoic acid **103** (1.0 equiv), oxalylchloride (1.2 equiv), DMF (10 mol %), CH_2Cl_2, 0→22 °C, 2 h amine **109** (1.0 equiv), NEt_3 (1.0 equiv), CH_2Cl_2, 0→22 °C, 16–20 h, isolated yields.

Taking into account the previous experience, the free amine function in **78b** was also blocked efficiently with methyl iodide, to check the necessity of a free NH in the desired C–H bond functionalization reaction (Scheme 58).



Scheme 58: Methylation of the NH moiety.

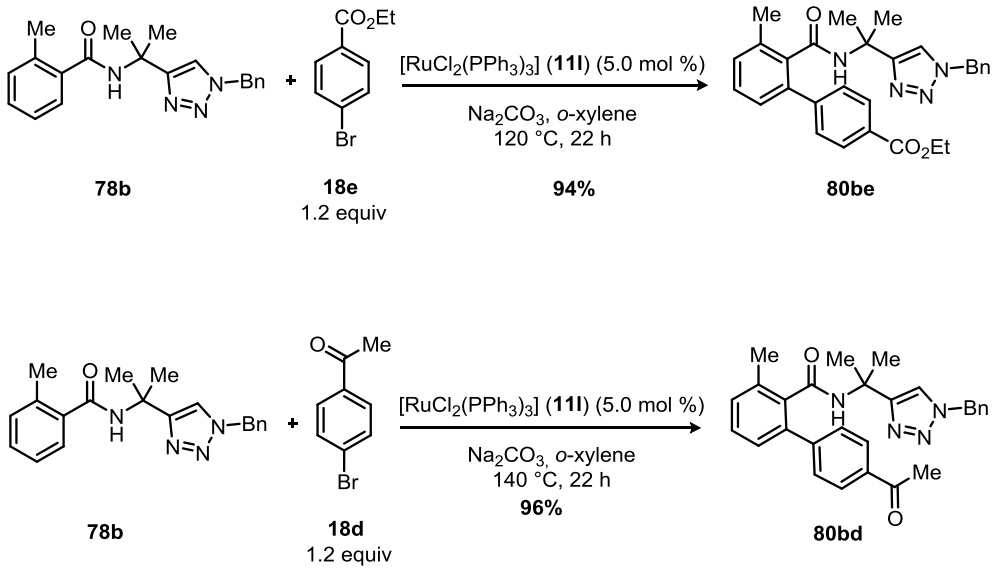
Unfortunately, the ester **111** could not be directly prepared from the direct reaction of *o*-toluyl chloride **78b** and the alcohol **109e**. The typical coupling procedure for the preparation of ester using *N*,*N*-Dicyclohexylcarbodiimide (DCC) with catalytic amount of 4-Dimethylaminopyridine (DMAP) also gave no satisfactory yields. On the contrary, changing the synthetic route, more precisely preparing first the ester unit, and then converting the alkyne to the triazole through 1,3-dipolar cycloaddition, enabled the synthesis of the ester derivative (Scheme 59).



Scheme 59: Two-step **s**ynthesis of the ester **111**.

3.3.2 Scope of the reactions

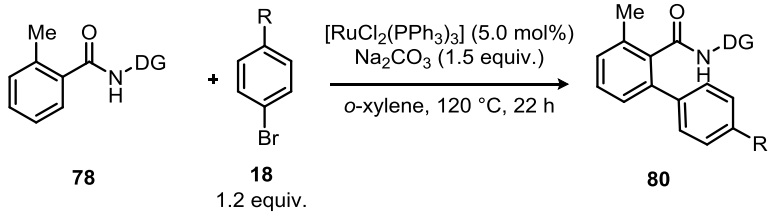
The optimal reaction conditions for the direct arylation of benzamides **78** were discovered by *Dr. Hamad Al Mamari* in the Ackermann research group (Scheme 60).

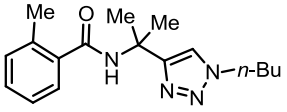
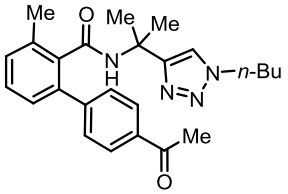
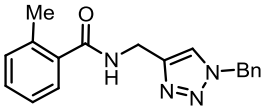
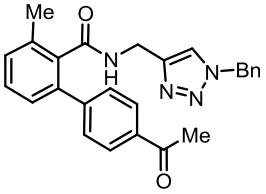


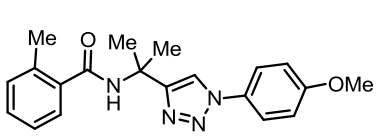
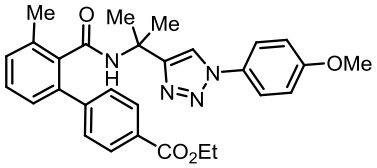
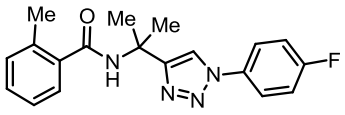
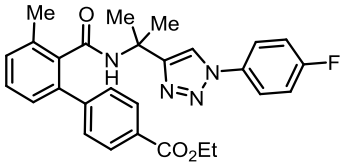
Scheme 60: Optimized reaction conditions for the ruthenium-catalyzed direct arylation of benzamide **78**.

With the optimized reaction conditions in hand, the scope of the reaction was then extended to different arenes and to substrates with modified directing groups (Table 21).

Table 21: Scope of arenes bearing modified directing groups.[a]

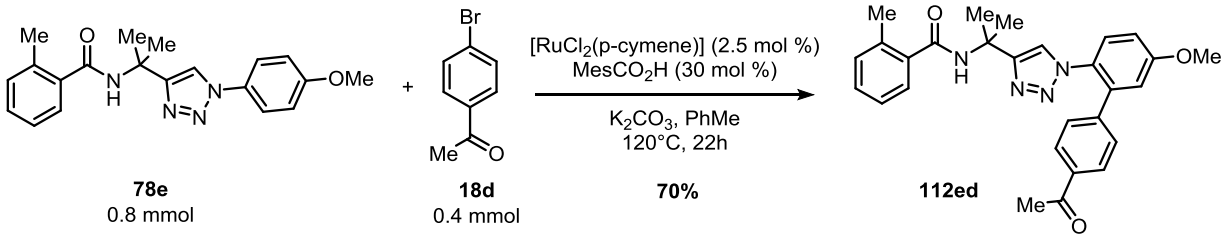


Entry	**78**	**80**	Yield (%)
1	 **78c**	 **80cd**	41
2	 **78o**	 **80od**	54

Entry	**78**	**80**	Yield (%)
3	 **78e**	 **80ee**	n.r.
4	 **78d**	 **80de**	n.r

[a] Reaction conditions: **78** (0.50 mmol), **18** (0.60 mmol), $[RuCl_2(PPh_3)_3]$ (5.0 mol %), Na_2CO_3 (0.75 mmol), *o*-xylene (2.0 mL), 120 °C, 22 h, isolated yields.

Upon testing modified directing groups, the *N*-alkylated substrate **78c** (entry 1) did not react as efficiently as its *N*-benzylated analogue **78b** (Scheme 60), whereas substrates **78d** and **78e** with *N*-arylated triazole cores were quantitatively re-isolated from the reaction mixture (entries 2 and 3). This can be explained by predominant formation of monodentate complex with participation of triazole and aryl moieties rather than of the bidentate complex. This should lead to a ruthenium-catalyzed direct arylation of phenyltetrazole fragment, and such a reaction was indeed observed applying $[RuCl_2(p\text{-cymene})]_2/MesCO_2H/K_2CO_3$ catalytic system, as discussed above (Table 12). To check this idea, the substrate **78e** was submitted to the reaction conditions developed by *Vicente, Althammer* and *Ackermann*.[23]



Scheme 61: Carboxylate-assisted direct arylation of substrate **78e**.

Under these conditions, the arylation indeed took place on the aryl moiety connected to the triazole core (Scheme 61). This result could be rationalized by the favored formation of a five-membered ruthenacycle, over the formation of a ruthenium species coordinated by the bidentate system.

Replacing of dimethylmethylene tether in **78b** with a methylene one (entry 2) caused a drop in yield, probably due to a less favorable formation of the bidentate complex, in absence of the two methyl groups.

The structure of product **112ed** was confirmed through ^1H COSY, HSQC and HMBC measurement (Figure 20).

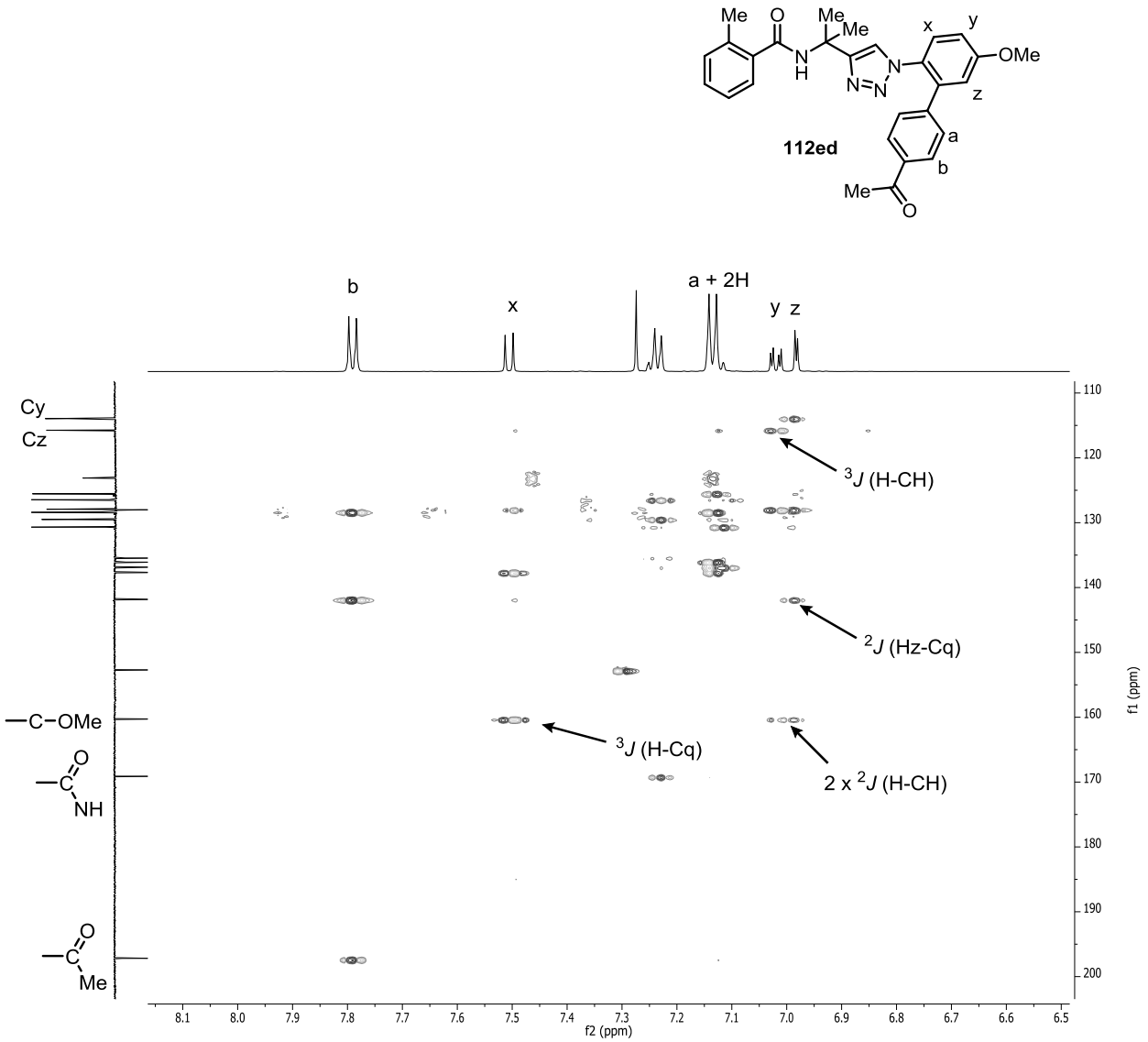
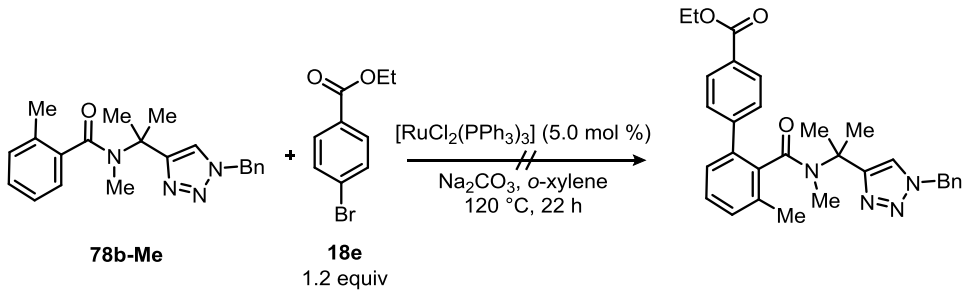


Figure 20: HMBC spectrum of **112ed**.

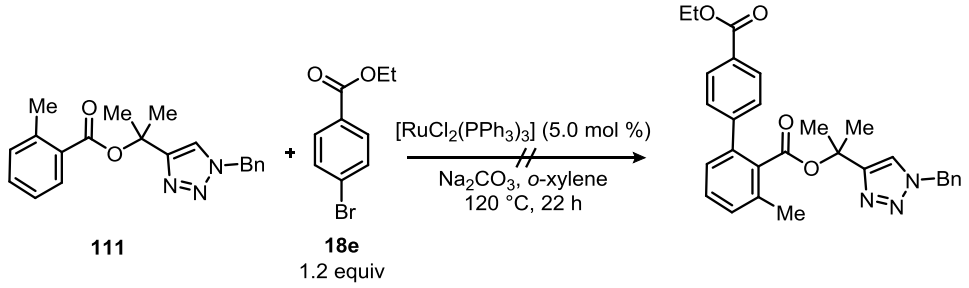
The chemical shift of protons and carbons were assigned through the analysis of the COSY, HSQC and HMBC sprectra. For example, the proton z is not correlating with any other proton in COSY. All the protons x,y and z are showing correlation to the carbon directly bond to the methoxy group. The proton z is also correlating to a second quaternary carbon from the aryl–aryl bond and to Cy.

Additionally, the *N*–substituted substrate did not react at all, showing the necessity of the free N–H bond for the viability of the reaction, or the difficulty for the ruthenium to coordinate to a sterically hindered substrate (Scheme 62).



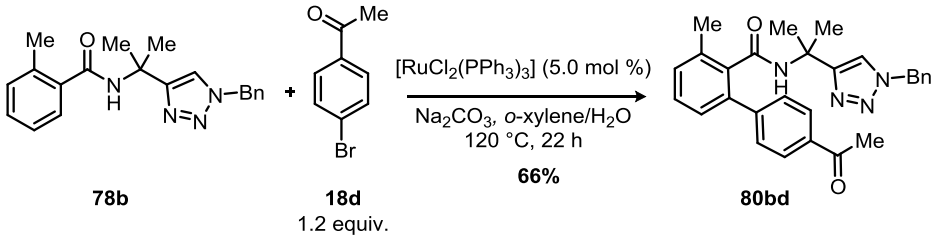
Scheme 62: Attempted direct arylation of tertiary amide **78b-Me**.

Another experiment was then set up with the ester **111**. No product was isolated, proving again the necessecity of a free N–H function for the working mode of the reaction (Scheme 63).



Scheme 63: Attempted direct arylation of the ester **111**.

Furthermore, water was tolerated under the optimized reaction conditions (Scheme 64).

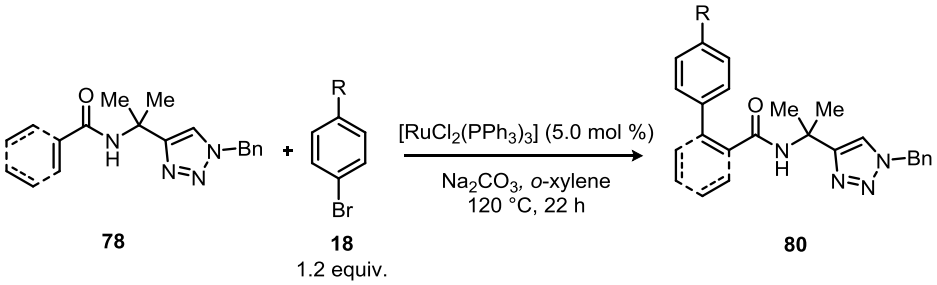


Scheme 64: Direct arylation of the amide **78b** in presence of water.

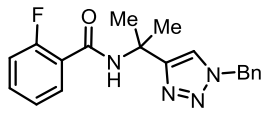
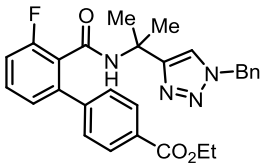
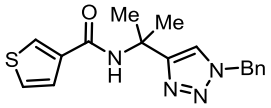
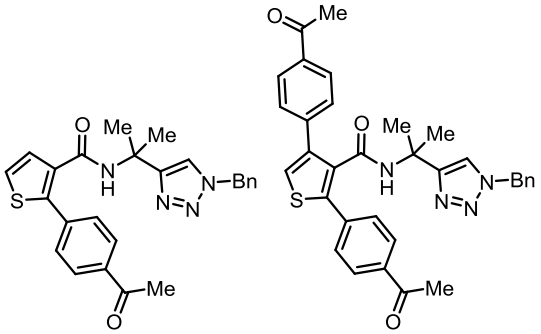
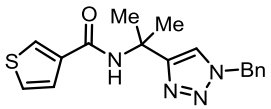
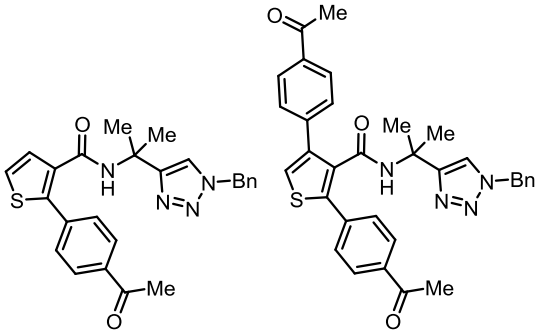
3.3.3 Scope of (hetero)arenes

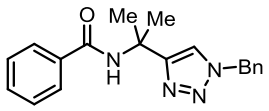
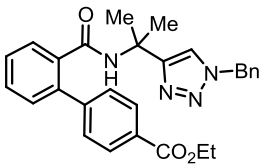
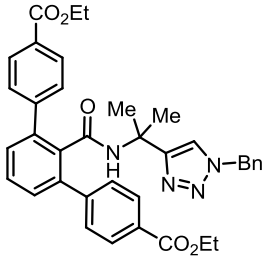
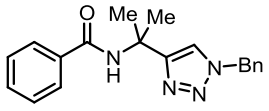
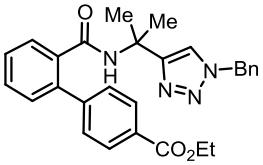
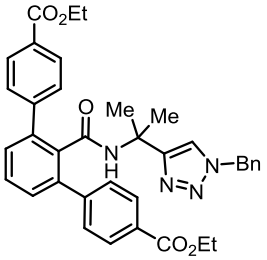
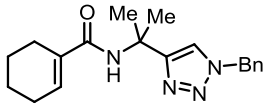
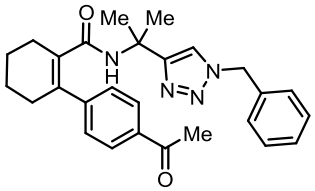
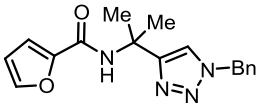
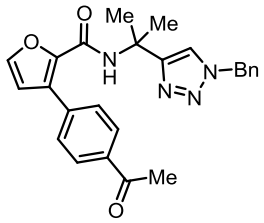
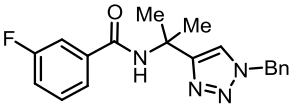
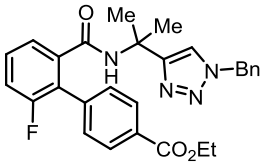
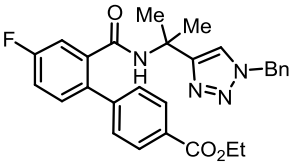
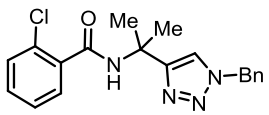
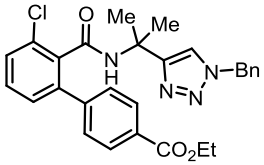
Differently substituted substrates **78** were submitted to the optimized reaction conditions (Table 22)

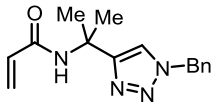
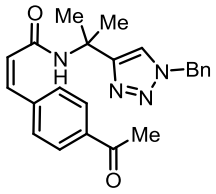
Table 22: Scope of (hetero)arenes.[a]



78 **18** 1.2 equiv. **80**

Entry	**78**	**80**	Yield (%)
1			95
	78l	**80le**	
2			39 / 24
	78m	**80md** **81md**	
3[b]			43 / 43
	78m	**80md** **81md**	

Entry	78	80		Yield (%)
4				54 / 22
	78a	**80ae**	**81ae**	
5[b]				70 / 22
	78a	**80ae**	**81ae**	
6				34 48[c]
	78n	**80nd**		
7				50[d]
	78m	**80md**		
8				99 (1.6/1 by ^{1}H NMR)
	78f	**80fe"**	**80fe'**	
9				<5
	78g	**80ge**		

Entry	**78**	**80**	Yield (%)
10			n.r.
	78i	**80id**	

[a] Reaction conditions: **78** (0.50 mmol), **18** (0.60 mmol), $[RuCl_2(PPh_3)_3]$ (5.0 mol %), Na_2CO_3 (0.75 mmol), *o*-xylene (2.0 mL), 120 °C, 22 h, isolated yields. [b] **78** (1.0 mmol), **18** (0.50 mmol) $[RuCl_2(PPh_3)_3]$ (5.0 mol %), Na_2CO_3 (0.75 mmol), *o*-xylene (2.0 mL), 120 °C, 22 h. [c] With 10 mol % $RuCl_2(PPh_3)_3$ at 140 °C. [d] ^1H NMR conversion

Electron-deficient arenes were arylated in excellent yields (entry 1). The capacity of ruthenium to perform C–F bond activation is known.[90] However, no product from the activation of the C–F bond was isolated. Another *ortho*-substituted arene with halogen was also tested but gave less than 5% isolated product (entry 9). Unsubstituted arene **78a** was also submitted to the optimized reaction conditions but both monoarylated and diarylated compounds were obtained, with an excellent overall yield (entry 4). Using the aryl bromide **18e** as the limiting reagent, the selectivity was improved yielding the monoarylated compound in 70% yield (entry 5).

Cyclic alkenes could also be arylated, requiring however a higher catalyst loading and reaction temperature to obtain a reasonable yield (entry 6). Unfortunately uncyclic alkenes did not show any reactivity under the optimized reaction conditions for the direct arylation (entry 10) and hereby showed one limitation of this reaction.

Introducing a fluorine substituent in the *meta* position of the arene, led in high yields to the formation of two isomers (ratio determined by ^1H NMR), which proved to be difficult to separate through chromatography (entry 8). Further reactions with *meta*-substitutents such as methoxy, methyl, and trifluoromethyl groups, were performed by *Dr. Hamad Al Mamari*, and showed the site-selectivity to be controlled by sterics, as the major isolated isomer was the one where the arylation took place in the less congested position. In the case of the fluoro substituent (entry 8), the site-selectivity of the reaction can be explained by the *ortho*-orienting effect of the fluorine substituent. [89]

Heterocycles, such as furanes (entry 7) or thiophenes (entries 2 and 3), were also capable to undergo the direct arylation, but in the case of the thiophene derivatives, the diarylated compound was also isolated in a non negligeable amount, as two C–H bonds can potentially react. The structure of the monoarylated compound **80md** was confirmed by the ^1H NMR spectrum. The coupling constant of the two protons, typical for the thiophene core are observable at 7.27 and 7.30 ppm (Figure 21).[98]

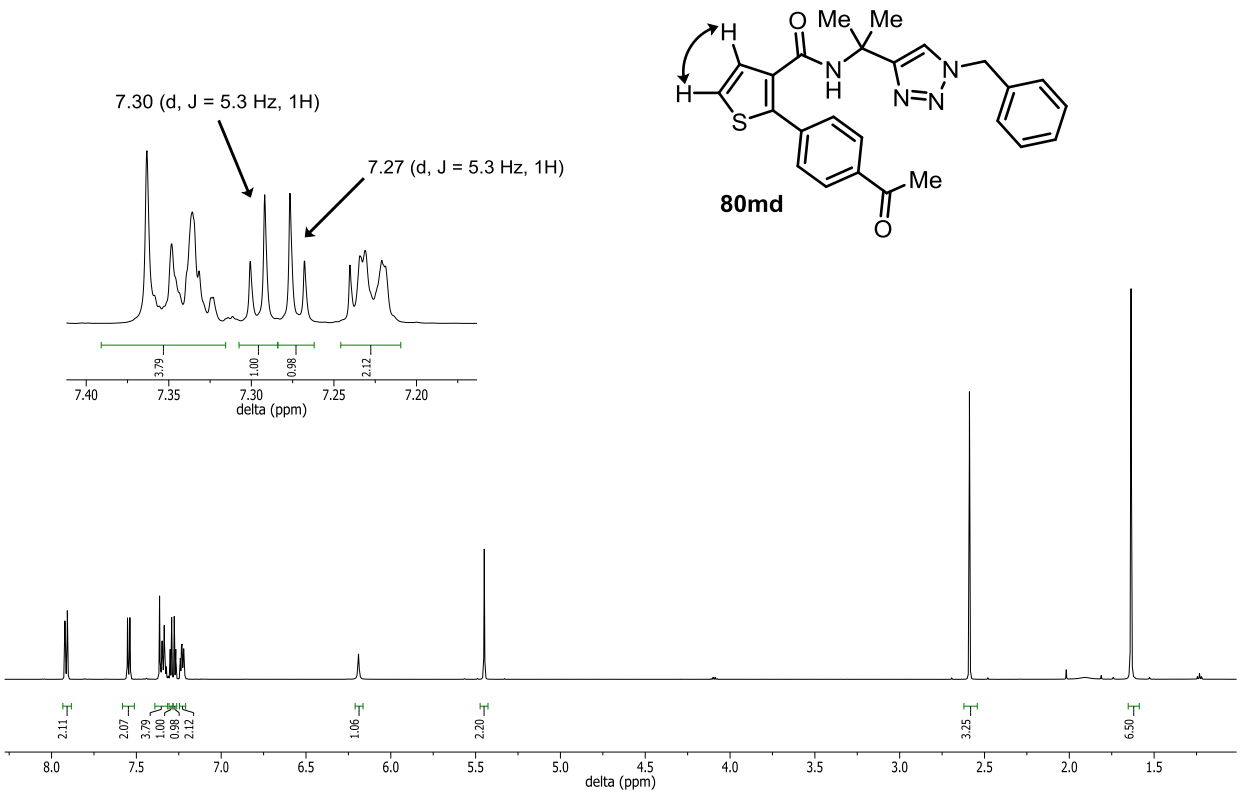
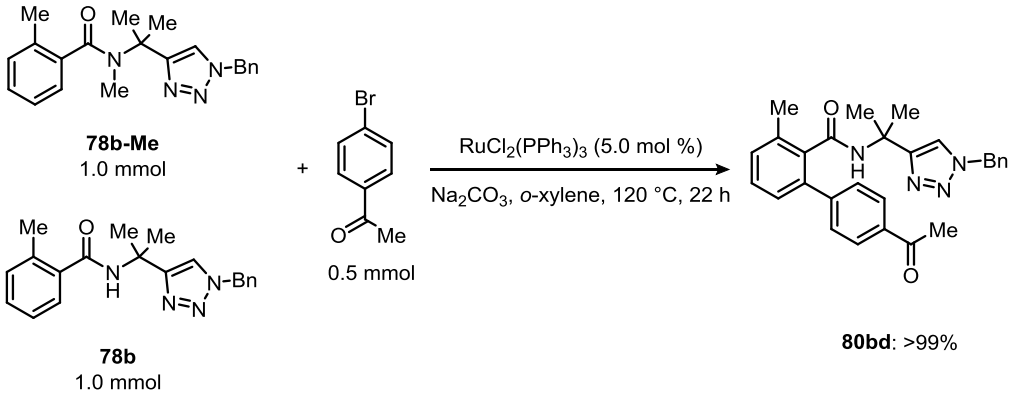


Figure 21: ^{1}H NMR (600 MHz, $CDCl_3$) of compound **80md**.

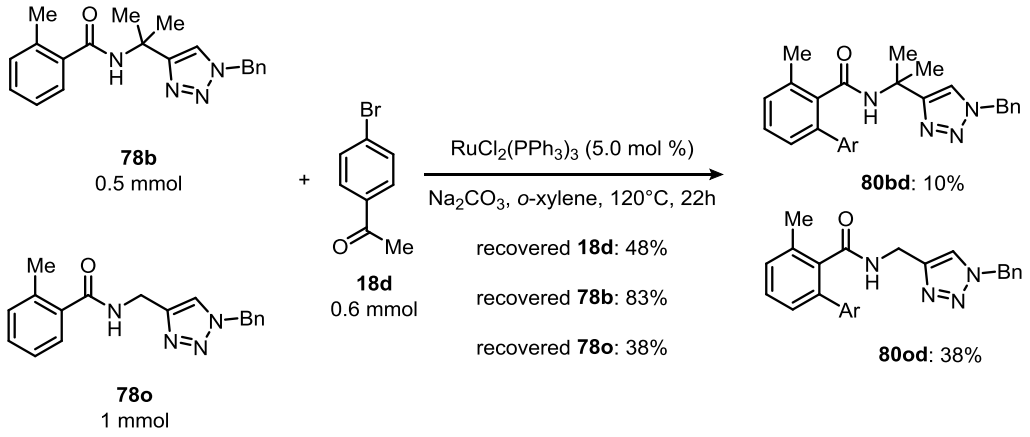
3.3.4 Competition experiments

Different competition experiments were performed to get a more detailed insight on how the reaction is proceeding.



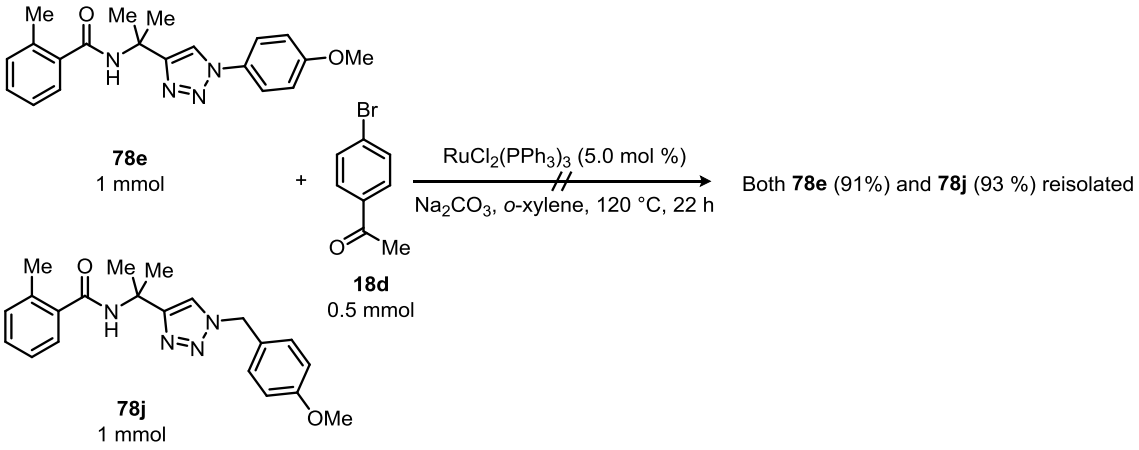
Scheme 65: Intermolecular competition experiment between substrates **78b-Me** and **78b**.

A first competition experiment was carried out between substrates **78b-Me** and **78b**. As expected the product **80bd** was formed in more than 99% yield, with no reactivity shown for the *N*-methylated substrate **78b-Me**. This result showed that the NH-free substrate reacts selectively and can consequently better coordinate to the ruthenium complex (Scheme 65).



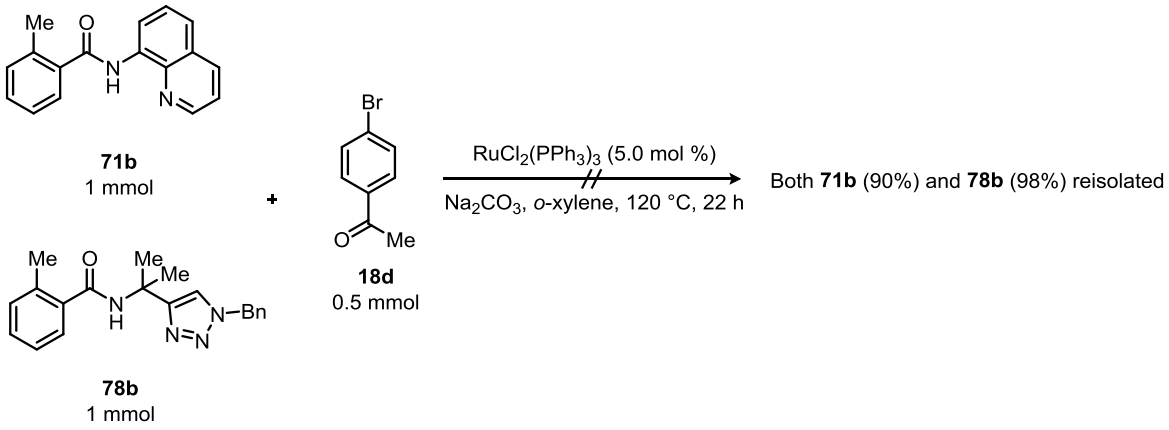
Scheme 66: Intermolecular competition experiment between substrates **78b** and **78o**.

The competition experiment showed that the substrate without any methylgroups **78o** is reacting preferentially compared to the one with two methyl groups attached, probably due to steric hinderance (Scheme 66).



Scheme 67: Competition experiment between **78e** and **78j**.

Then, the difference of reactivity between substrates **78e** and **78j** was probed. In this reaction, both substrates were subjected to the optimized reaction conditions with 4-bromoacetophenone (**18d**) as a coupling partner. No reaction was observed, as both starting materials could be reisolated in more than 90% (Scheme 67). When submitted separately to the optimized reaction conditions, **78j** is supposed to react in high yield and **78e** is not (Scheme 60 and Scheme 61). This observation can be rationalized by the fact that a five membered ruthenacycle is preferentially formed in the reaction, but will not yield any product under these reaction conditions, blocking then the access to the formation of the bidentate chelated ruthenacycle.

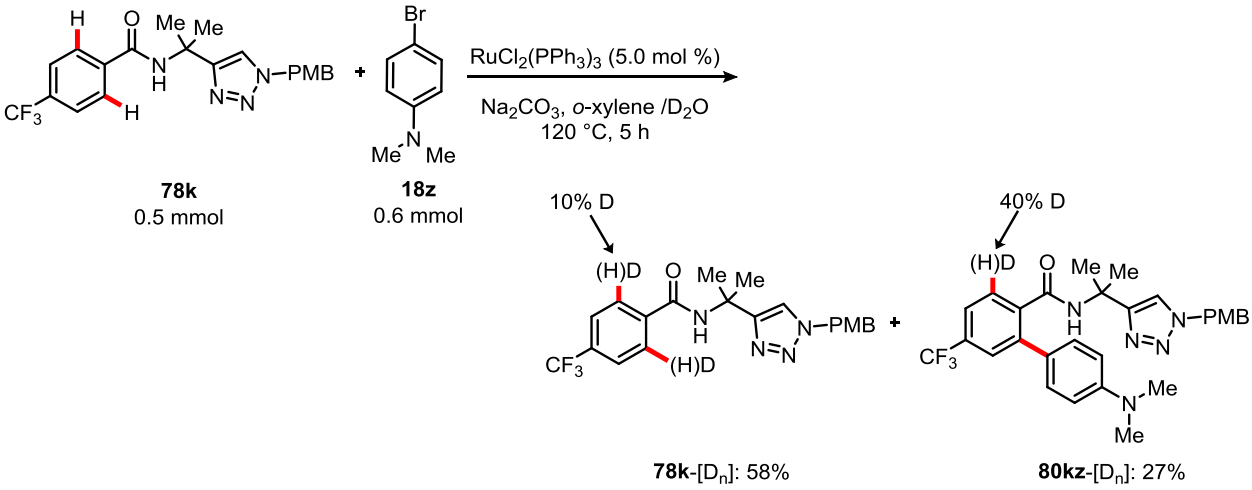


Scheme 68: Competition experiment between substrates **71b** and **78b**.

Furthermore, the difference of reactivity between **71b** and **78b** extensively studied by *Daugulis*[79] and *Chatani*[84] was subjected to our optimized reaction conditions. It was already proven before by *Dr. Hamad Al Mamari* that the 8-aminoquinoline derivative did not react under our optimized conditions. Consequently, as previously observed, the triazole derivative should react preferentially. Surprisingly, no reaction occurred in this case, allowing the reisolation of both starting materials (Scheme 68). Again, in this case, it seems that the ruthenium has a tendency of coordinating to the 8-aminoquinoline benzamide, but without reacting any further, preventing the reaction of **78b** with **18d**, and hence shuting down the reaction.

3.3.5 Deuterium experiments

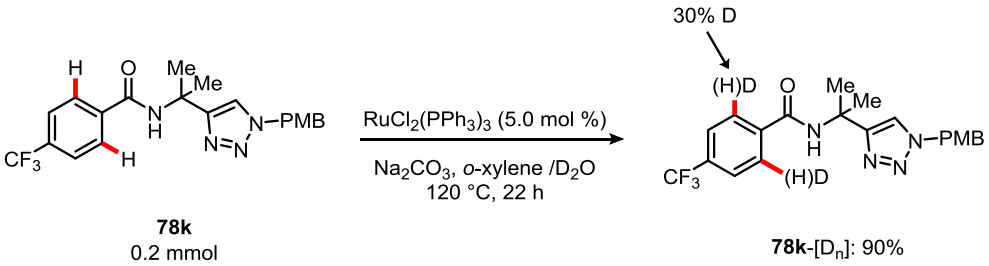
The substrate **78k** was submitted to the optimized reaction conditions in the presence of a deuteriated solvent.



Scheme 69: Isotopic labeling experiment for **78k** with deuteriated cosolvent.

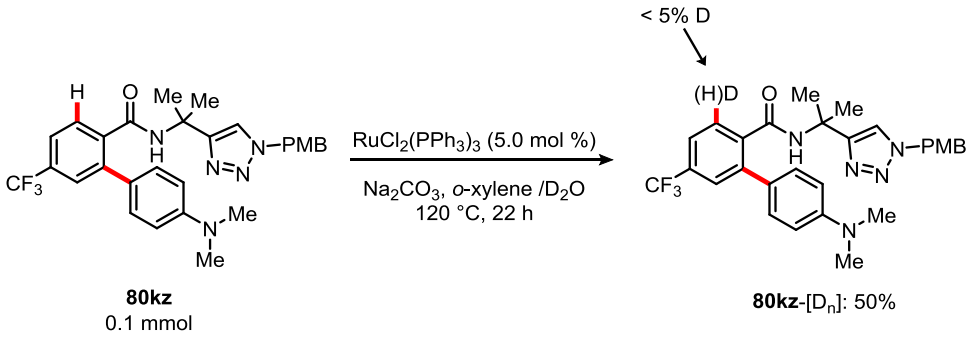
The reisolation of the starting material and isolation of the product were carried out after 5 hours to obtain an incomplete conversion. The deuterium incorporation was determined by ^{1}H NMR. The integration was up to 10% on the *ortho*-position of the arene in **78k**-[D_n] and 40% on the second available ortho position in the product **80kz**-[D_n] (Scheme 69). These results cannot prove completely the reversibility of the C–H bond cleavage.

Significant deuterium incorporation was observed when the starting material **78k** was submitted to the optimized reaction conditions with deuteriated water as a cosolvent, but in the absence of arylbromide (Scheme 70). This observation can be rationalized with the reversibility of the C–H bond metalation.



Scheme 70: Isotopic labeling experiment for **78k** with deuteriated cosolvent.

However, no deuterium incorporation was observed when the arylation product **80kd** was again submitted to the optimized reaction conditions, without arylbromide but in the presence of deuteriated water as a cosolvent (Scheme 71), ruling out the reversibility of the metalation to the product.



Scheme 71: Isotopic labeling experiment for **80kz** with deuteriated cosolvent.

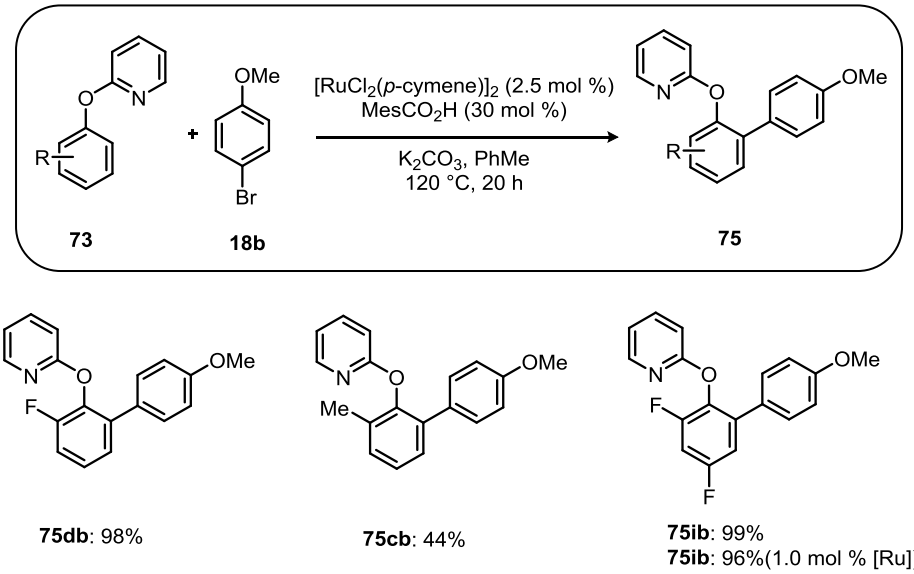
Contrary to the phenomena observed in the tetrazole chemistry (Scheme 54), such as a deuterium integration on the arene of the benzyl protecting group, here no deuterium integration was observed on the benzyl ring.

4 Summary and Outlook

During the last decade, transition-metal-catalyzed direct C–H bond functionalizations have appeared as an appealing alternative to the most commonly used cross-coupling reactions, which allowed for the synthesis of biaryls present in many bioactive pharmaceuticals, agrochemicals or materials. Thus the main focus of this work was set on the development of new methodologies for the efficient and step-economical synthesis of biaryl cores by direct arylation through direct C–H bond cleavage.

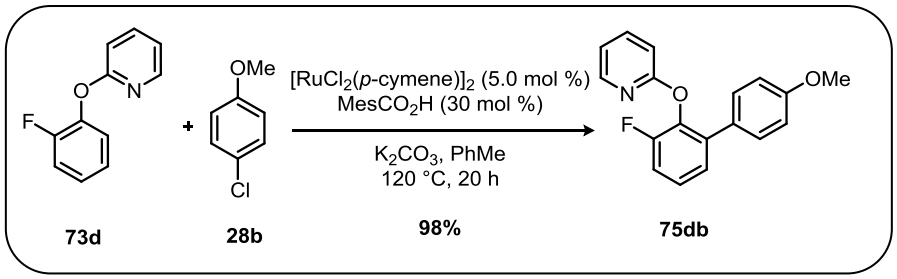
In the first part of this work, the first ruthenium-catalyzed direct arylation of an arene bearing a removable directing group was achieved. In fact, ruthenium catalysts have been developed for the direct functionalization of otherwise unreactive C–H bonds *via* chelation assistance. However, these methodologies kept lacking generality as they were only efficient with substrates that can form five-membered ruthenacycles, and were not achievable with substrates bearing removable directing groups.
Recently, the beneficial effect of carboxylate in the direct arylation was brought up by our group.[23, 30, 34, 54, 59]

2-Phenoxypyridines **73** reacted optimally under these reaction conditions with aryl bromides, with electron-deficient arenes reacting preferentially (Scheme 72).



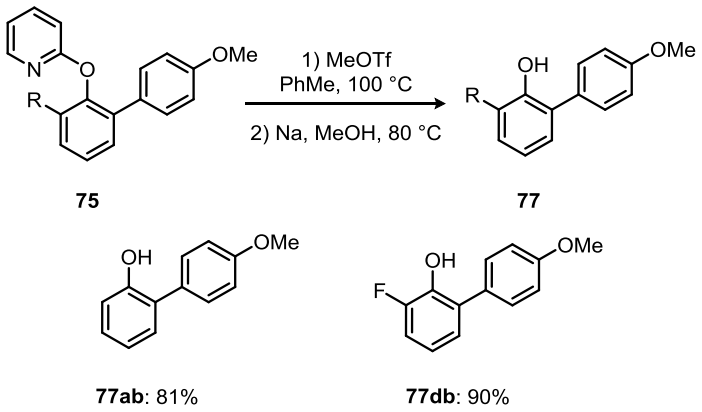
Scheme 72: Scope of direct arylation of phenoxypyridines **73**.

The direct arylation was achieved under the optimized reaction conditions with the more easily accessible and less expensive aryl chlorides, as well (Scheme 73).



Scheme 73: Direct arylation of 2-(2-fluoro)phenoxypyridine (**73d**) with 4-chloroanisole (**28b**).

Importantly, the directing group could be easily cleaved yielding the *ortho*-arylated phenols (Scheme 74).



Scheme 74: Removal of the directing group.

A reliable catalytic system for the ruthenium-catalyzed direct arylation of phenols or an in situ cleavable directing group would be, in the future, highly desirable.

In a second project, the ruthenium-catalyzed direct C–H bond arylation was applied to the synthesis of important intermediates, namely Valsartan (**2**) preconized in the treatment of high blood pressure (Figure 22).

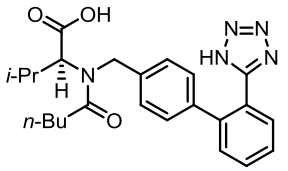
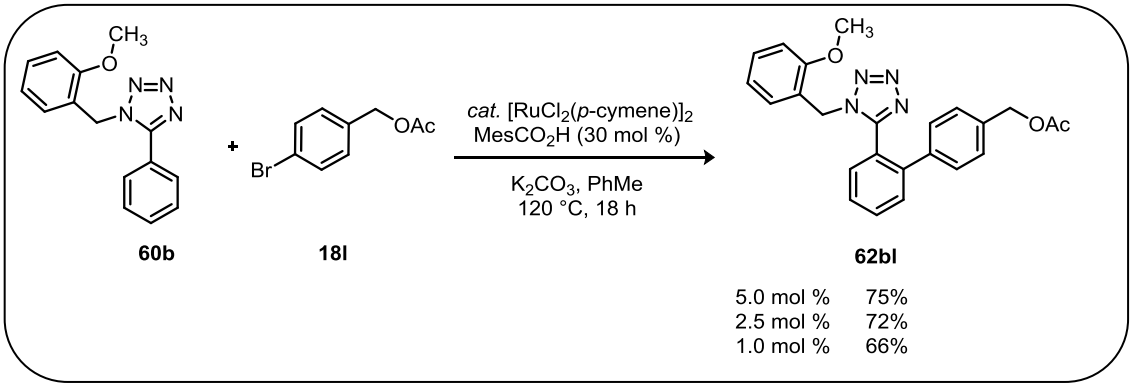


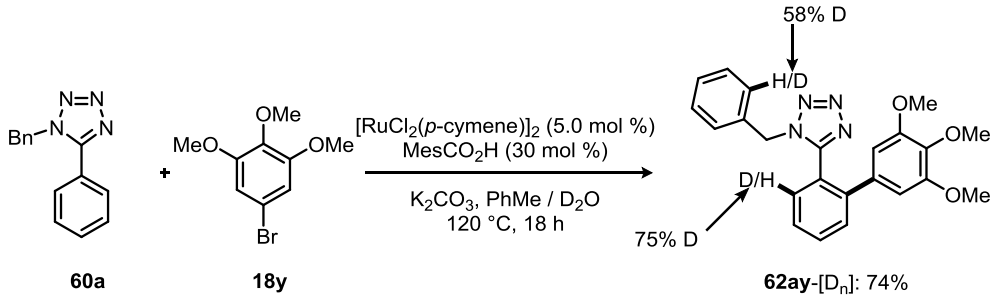
Figure 22: Angiotensin Receptor Blocker, Valsartan (**2**).

The carboxylate assistance proved to be a valuable asset for this reaction, leading to the intermediate **62bl** even with a reduced catalyst loading (Scheme 75).



Scheme 75: Synthesis of a Valsartan intermediate **62bl** with reduced catalyst loadings.

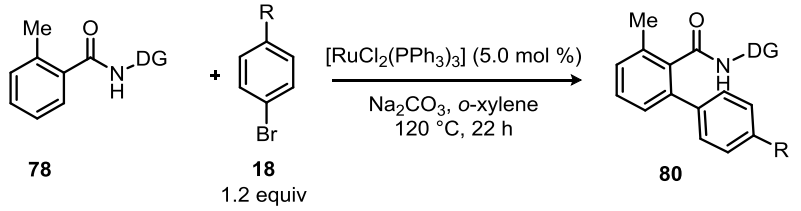
In order to understand the reaction mechanisms, reactions with isotopically labeled solvents were carried out, and proved the cyclometalation with ruthenium to be reversible (Scheme 76).

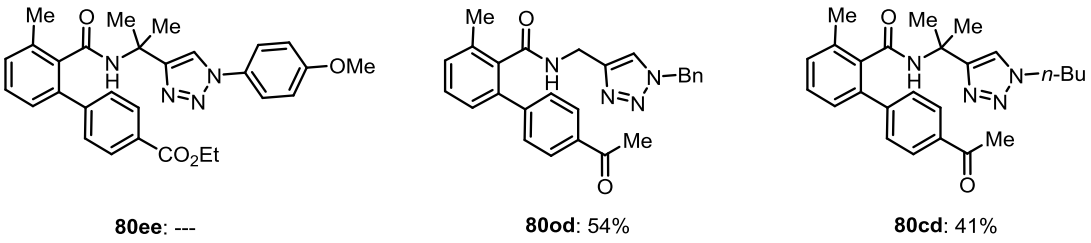


Scheme 76: Isotopic labeling experiment on **60a**.

Moreover, a deuterium incorporation was also observed on the phenylring of the benzyl group, showing the possibility of a functionalization in this position. However, the achievement of catalytic reactions still remains a big challenge. A more step-economical way to Valsartan would be preferred, if a free alcohol could be tolerated under the reactions conditions.

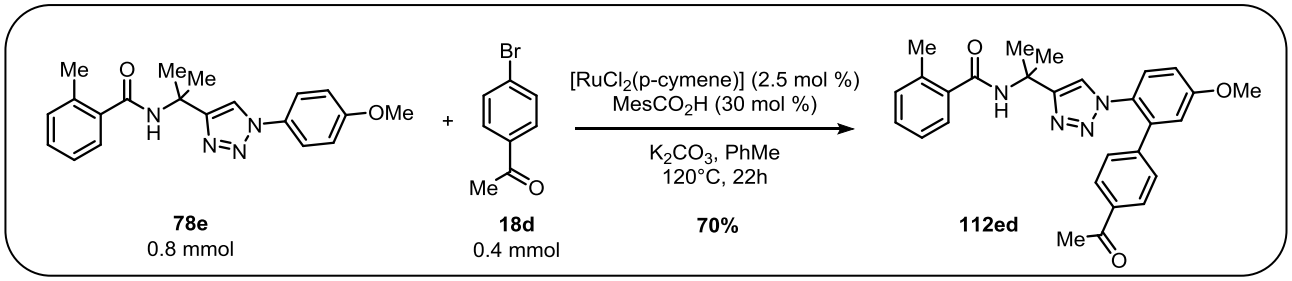
The research was then focused on the extension of the ruthenium-catalyzed direct arylation to a different system, such as a bidentate coordinating directing group. Up to now, most of the the directing group in the direct arylation chemistry, were described as monodentate (pyridine, pyrimidine, oxazoline for exemple).
A new bidentate system was optimized in the Ackermann group by *Dr. Hamad El Mamari,* and showed high reactivity towards aryl bromides **18** with differently substituted arenes. The effect of change in the directing group was carefully studied (Scheme 77).





Scheme 77: Variation of the directing group.

When an aryl rest was connected to the triazole, a simple change in the reaction conditions gave the arylated product but in another position, (Scheme 78) as previously described by the *Ackermann* group.[23]



Scheme 78: Carboxylate-assisted direct arylation of **78e**.

Future propects could include the direct functionalizations through C–H bond cleavage using this bidentate directing group, other than arylation and using other transition metals. Research on these topics is currently ongoing in the Ackermann group.

5 Experimental Section

5.1 General Remarks

All catalytic reactions were carried out under a dry nitrogen atmosphere using standard Schlenk techniques and pre-dried glassware. Syringes for handling of dry solvents or liquid reagents were flushed with dry nitrogen three times prior to use. Analytical data of substances, known in the literature (marked by the corresponding references) were compared with those described in the literature.

- Solvents

All solvents for reactions were purified using a M. Braun SPS-800 solvent purification system, or alternatively, dried, distilled and stored under an inert atmosphere (argon or nitrogen) according to the following standard procedures.

Dichloromethane (CH_2Cl_2) was purified using M. Braun SPS-800 solvent purification system.

***N*,*N*-Dimethylacetamide** was dried over KH and distilled under ambient pressure.

***N*,*N*-Dimethylformamide** was dried over CaH_2 for eight hours, degassed and distilled under reduced pressure.

Dimethylsulfoxide was dried over CaH_2 for four hours, degassed and distilled under reduced pressure.

Methanol was stirred over magnesium for three hours at 65 °C prior to distillation.

***N*-Methyl-2-pyrrolidone** (NMP) was stirred for four hours at 150 °C and subsequently distilled under reduced pressure.

Tetrahydrofuran was purified using a M. Braun SPS-800 solvent purification system.

Toluene was pre-dried over KH and distilled over sodium/benzophenone.

***o*-Xylene** was stirred at 160 °C over sodium /benzophenone and distilled under ambient pressure.

Water was degased before its use applying repeated Freeze-Pump-Thaw degasing procedure.

Dimethylsulfoxide for the copper-catalyzed cycloaddition was p.a. quality and degassed prior to use for 5-8 hours.

Distilled water for the copper-catalyzed cycloaddition was degassed prior to use for 5-8 hours.

- Vacuum

Following pressures were measured on the used vacuum pump and are not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

- Melting Points

Melting points were measured using a BÜCHI 540 Melting Point Apparatus. Reported values are uncorrected.

- Chromatography

Analytical TLC was performed on 0.25 mm silica gel 60F plated (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were visualized under ultraviolet light. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040-0.063 mm and 0.063-0.200 mm, 70-230 mesh ASTM).

- Gas Chromatography

Monitoring of reactions processes via coupled gas chromatography-mass spectrometry was performed using a G1800C GCDplus with mass detector HP 5971, 5890 Series II with mass detector HP5972 from HEWLETT-PACKARD and 7890A GC-System with mass detector 5975C (Triplex-Axis-Detector) from AGILENT TECHNOLOGIES. HP-5MS Columns (30 m x 0.25 mm, film 0.25 µm) were used.

- Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectra were recorded at 300, or 600 MHz (^{1}H NMR) and at 75 or 125 MHz (^{13}C NMR, APT) and at 283 Hz (^{19}F NMR) on BRUKER *AM 250*, VARIAN *Unity-300* and *Inova 500* instruments. Chemical shifts are reported as *δ*-values in ppm relative to the residual peak of the deuterated solvent or its carbon atom, respectively.

	^{1}H NMR	^{13}C-NMR
$CDCl_3$	7.26 ppm	77.0 ppm

For characterization of the observed signal multiplicities, the following abbreviations were applied: s (singulet), brs (broad singulet), d (doublet), t (triplet), q (quartet), hept (heptet), m (multiplet). Coupling constants *J* are reported in Hertz (Hz).

- Infrared Spectroscopy

Infrared spectra were recorded using a BRUKER Alpha-P spectrometer; liquid probes were measured as films and solid probes neat. Analysis of the spectra was carried out using OPUS 6. Absorption is given in wave numbers (cm^{-1}). Spectra were recorded in the range from 4000 to 400 cm^{-1}.

- Mass Spectrometry

EI- and EI-HRMS spectra were measured on a Time-of- Flight mass spectrometer AccuTOF from JOEL. ESI-mass spectra were recorded on an Ion-Trap mass spectrometer LCQ from FINNIGAN or on a Time-of-Flight mass spectrometer microTOF from BRUKER. ESI-HRMS spectra were recorded on a BRUKER APEX IV or a BRUKER DALTONIC (7T, Transform Ion Cyclotron Resonance (FTCIR) mass spectrometer. The ratio of mass to charge are indicated, intensities relative to the base peak (I=100) are written in parentheses.

- Crystal Structure Analysis

Crystals for X-ray diffraction of compound **62ad** were obtained by slow evaporation of its solution in $CHCl_3$/*n*-octane. The single crystal X-ray data were collected on a Bruker *SMART-CCD 6000* diffractometer at 120.0(2) K using graphite monochromator with Mo-Kα radiation (λ = 0.71073 Å). All structures were solved by direct method and refined full-matrix least squares on F^2 for all data. All non-hydrogen atoms were refined with anisotropic displacement parameters. H-atoms were located on the difference map and refined isotropically. Structure of **62ad** was confirmed on the basis of X-ray data. Crystal and data collection parameters are summarized in Table S1.

- Reagents

Chemicals obtained from commercial sources (purity > 95%) were used without further purification. The following compounds were synthesized according to known literature procedures.

Dichloro-(*p*-cymene)-ruthenium(II) dimer (**11d**), dibromo-(*p*-cymene)-ruthenium(II) dimer, H*i*PrCl by courtesy of Karsten Rauch.

Potassium 2,4,6-trimethylbenzoate and dichlorotris(triphenylphosphine)ruthenium(II) (**11l**) by courtesy of Dr. Marvin Schinkel.

2-Benzhydrylpyridine (**84**) by courtesy of B.Sc. Christian Kuper.

2-Fluoro-2-phenylpyridine (**20e**) by courtesy of Dr. Alexander Lygin.

5-(2-Methoxyphenyl)-1*H*-tetrazole (**98d**) and 5-(2-Fluorophenyl)-1*H*-tetrazole (**98c**) by courtesy of Dr. Tom Mejuch.

1-Benzyl-5-[3-(trifluoromethyl)phenyl]-1*H*-tetrazole (**60n**), 1-Benzyl-5-(3-methylphenyl)-1*H*-tetrazole (**60k**), 1-Benzyl-5-(4-methoxyphenyl)-1*H*-tetrazole (**60j**), 1-Benzyl-5-(4-fluorophenyl)-1*H*-tetrazole (**60i**) by courtesy of N.Y. Phani Kumar.

1-Benzyl-5-(2,4-dimethylphenyl)-1*H*-tetrazole (**60f**), 1-Benzyl-5-(2,4-dimethylphenyl)-1*H*-tetrazole (**60g**), 5-(Benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-1*H*-tetrazole (**60h**) by courtesy of B.Sc. Nicolas Sauermann.

1-Benzyl-5-(3-fluorophenyl)-1*H*-tetrazole (**60m**) by courtesy of B.Sc. Grigory Shevchenko.

1-Benzyl-5-(3-methoxyphenyl)-1*H*-tetrazole (**60l**) by courtesy of BSc. Susanne Löffler.

2-Methyl-*N*-(quinolin-8-yl)benzamide (**71b**), *N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methylbenzamide (**78b**) by courtesy of Dr. Hamad Hamdan Mohamed Al Mamari.

N-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-2-methylbenzamide (**78o**), *N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]benzamide (**78a**) by courtesy of B.Sc. Benjamin Schröder.

Phenyl(pyridin-2-yl)methanone (**85**), Benzylpyridine (**83**), 5-Phenyl-1*H*-tetrazole (**98a**) were purchased and used without any further purification.

All those compounds were prepared according to or in analogy to described literature procedures: Phenoxypyridines **73**,[99] 2-Phenoxypyrimidine (**81**), [87] 2-(Phenylsulfinyl)pyridine (**86**),[100] 2-(Phenylthio)pyridine (**87**),[100a] 2-(Benzyloxy)-6-methylpyridine (**88**),[101] Phenylpicolinate (**90**),[102] Pyridine-2-yl benzoate (**89**),[103] 4-acetylphenyl 4-methylbenzensulfonate (**93**), [104] 4-Methoxyphenyl trifluoromethanesulfonate (**91**),[105] 2-Bromo-4-methylpyridine (**18o**),[106] 2-Methoxybenzylbromide (**99a**),[107] 4-(Bromophenyl)methanol (**18u**),[108] 4-Bromobenzyl acetate (**18l**),[109] 1-[(Benzyloxy)methyl]-4-bromobenzene (**18v**),[110] *tert*-Butyl 4-bromobenzoate (**18w**),[111] 4-Methoxybenzylbromide (**99c**),[112] 2-Methylbut-3-yn-2-yl 2-methylbenzoate (**110**).[113]

5.2 General Procedures

5.2.1 General Procedure A: synthesis of phenoxypyridines 73

A suspension of phenol (1.2 equiv), 2-bromopyridine (1.0 equiv), CuI (10 mol %), 2-picolinic acid (20 mol %) and K_3PO_4 (2.0 equiv) in DMSO (0.5 M) was stirred overnight at 90 °C under N_2. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (50 mL) and H_2O (50 mL) and stirred for 30 minutes at ambient temperature. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with a NH_4Cl / NH_3 (v/v: 1/1) solution (3 x 50 mL), then with a aqueous NaOH solution (2N, 50 mL) and finally with brine (50 mL). The extracts were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.2.2 General Procedure B: Ruthenium-catalyzed direct arylations of phenoxypyridines 73 with aryl bromides 18 or aryl chlorides 28

A suspension of phenoxypyridine **73** (3.0 equiv), aryl bromide **18** or aryl chloride **28** (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5-5.0 mol %), $MesCO_2H$ (30 mol %) and K_2CO_3 (2.0 equiv) in PhMe (2.0 mL) was stirred at 120 °C for 20 h under N_2. At ambient temperature, the reaction mixture was diluted with EtOAc (50 mL) and H_2O (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.2.3 General Procedure C1: Synthesis of substituted phenyltetrazoles 60 from benzoic acids 103

To a solution of benzoic acid **103** (1.0 equiv) in CH_2Cl_2 (1.2 M) and *N*,*N*-Dimethylformamide (0.2 equiv), was added oxalylchloride (1.1 equiv) at 0 °C dropwise. The reaction mixture was stirred further at 0 °C until the gas evolution disappeared, then for one more hour at ambient temperature. The reaction mixture was afterwards concentrated at ambient temperature *in vacuo*. To remove the excess of oxalylchloride, CH_2Cl_2 (5 mL) was added and evaporated again at ambient temperature. This operation was repeated three times. The crude acid chloride was used directly, without any further purification.

The crude acid chloride (1.0 equiv) **104** was dissolved in CH_2Cl_2 (1.0 M), and then added to a solution of benzylamine **105** (1.0 equiv), NEt_3 (1.0 equiv) in CH_2Cl_2 (2.0 M) at 0 °C. The reaction mixture was allowed to warm up to 20°C and stirred under N_2 till the TLC control showed complete consumption of one of the starting materials or no further evolution of the reaction. The reaction mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the benzamide was obtained and was used without further purification (purity was more than 95% by ^{1}H-NMR).

To a solution of benzamide **106** (1.0 equiv) in CH_2Cl_2 (0.5 M) was added PCl_5 (1.2 equiv) portionwise, at a temperature below -18 °C. The reaction mixture was allowed to warm up and stirred at ambient temperature for 1 h. Then $TMSN_3$ (1.7 equiv) was added at a rate, so that the temperature remained under -15 °C. The reaction mixture was allowed to warm up, and stirred at ambient temperature overnight. To the reaction mixture was added an aqueous saturated $NaHCO_3$ solution (200 mL) dropwise. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield the tetrazoles **60**.

5.2.4 General Procedure C2: Synthesis of substituted phenyltetrazoles 60 from acid chlorides 104

To a solution of benzylamine **105** (1.0 equiv), NEt_3 (1.0 equiv) in CH_2Cl_2 (0.67 M) was added dropwise benzoylchloride (**104a**) (1.0 equiv) at a temperature below 16 °C. The reaction mixture was allowed to warm up and stirred under N_2 at 20 °C until the TLC control showed complete consumption of one of the two starting materials or no further evolution of the reaction. The reaction mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the benzamide was obtained and was used without further purification (purity was superior to 95% by ^{1}H-NMR).

To a solution of benzamide **106** (1.0 equiv) in CH_2Cl_2 (0.5 M) was added PCl_5 (1.2 equiv) portionwise, at a temperature below -18 °C. The reaction mixture was allowed to warm up and stirred at ambient temperature for 1 h. Then $TMSN_3$ (1.7 equiv) was added at a rate, so that the temperature remained under -15 °C. The reaction mixture was allowed to warm up, and stirred at ambient temperature

overnight. To the reaction mixture was added an aqueous saturated $NaHCO_3$ solution (200 mL) dropwise. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to yield the tetrazoles.

5.2.5 General Procedure D1: Ruthenium-catalyzed direct arylation of phenyltetrazoles 60

A mixture of tetrazole **60** (1.00 equiv), arylbromide **18** (1.05 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $MesCO_2H$ (30 mol %) and K_2CO_3 (2.00 equiv) in PhMe (2.0 mL) was stirred at 120 °C for 18 h under N_2. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.2.6 General Procedure D2: Ruthenium-catalyzed direct arylation of phenyltetrazoles 60 with KOAc as a base

A mixture of tetrazole **60** (1.00 equiv), arylbromide **18** (1.05 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), and KOAc (2.00 equiv) in PhMe (2.0 mL) was stirred at 120 °C for 18 h under N_2. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.2.7 General Procedure E1: Copper-catalyzed synthesis of benzyltriazoles and alkyltriazoles 109

Alkyl/benzylbromide (1.0 equiv) was added to a solution of sodium azide (1.0 equiv) in degassed DMSO (0.5 M). The reaction mixture was stirred overnight at ambient temperature. Degassed water ($2xV_{DMSO}$) was then added, followed by $Cu(SO_4)_2{\cdot}5H_2O$ (20 mol %), sodium ascorbate (10 mol %) and finally the alkyne (1.0 equiv). After an exothermic reaction, the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then diluted with an aqueous solution of NH_3/NH_4Cl (1/1, v/v) and EtOAc. The aqueous phase was extracted with EtOAc. The gathered organic phases were washed with NH_3/NH_4Cl (1/1, v/v), until disappearance of the blue color, brine, dried over Na_2SO_4, and finally evaporated *in vacuo*. Purity was checked with ^{1}H-NMR spectroscopy and the product was used without further purification.

5.2.8 General Procedure E2: Copper catalyzed synthesis of phenyltriazoles 109c-d

A mixture of aryl iodide (1.00 equiv), NaN_3 (1.05 equiv), sodium ascorbate (10.0 mol %), CuI (10.0 mol %), alkyne (1.00 equiv) in a mixture of degassed DMSO and H_2O (0.3 M, 5/1, v/v) was stirred at ambient temperature. DMEDA (15.0 mol %), was then added at ambient temperature. The reaction mixture was further stirred at ambient temperature overnight, and afterwards diluted with an

aqueous solution of NH_3/NH_4Cl (1/1, v/v) and EtOAc. The aqueous phase was extracted with EtOAc. The gathered organic phases were washed with NH_3/NH_4Cl (1/1, v/v) until disappearance of the blue color, brine, dried over Na_2SO_4 and finally evaporated *in vacuo*. Purity was checked with ^{1}H-NMR and the product was used without further purification.

5.2.9 General Procedure F1: Synthesis of benzamides 78 from acid chlorides 104

The acid chloride **104** was added at 0 °C to a solution of amine (1.0 equiv) and NEt_3 (1.0 equiv) in CH_2Cl_2 (1.0 M). The reaction mixture was allowed to warm up to ambient temperature and stirred under N_2 overnight. The reaction mixture was diluted with water and EtOAc. The organic phase was separated, the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the residue was purified either by column chromatography on silica gel or by recrystallization.

5.2.10 General Procedure F2: Synthesis of benzamides 78 from the acids 103

To a solution of benzoic acid **103** (1.0 equiv) in CH_2Cl_2 (1.2 M) and *N*,*N*-Dimethylformamide (0.2 equiv), was added oxalylchloride (1.1 equiv) at 0 °C dropwise. The reaction mixture was stirred further at 0 °C until the gas evolution disappeared, then for one more hour at ambient temperature. The reaction mixture was afterwards concentrated at ambient temperature *in vacuo*. To remove the excess of oxalylchloride, CH_2Cl_2 (5 mL) was added and evaporated again at ambient temperature. This operation was repeated three times. The crude acid chloride was used directly, without any further purification.

The crude acid chloride **104** was dissolved in CH_2Cl_2 (1.0 M), and then added at 0 °C to a solution of amine (1.0 equiv), and NEt_3 (1.0 equiv) in CH_2Cl_2 (2.0 M). The reaction mixture was allowed to warm up to ambient temperature and stirred under N_2 overnight. The reaction mixture was diluted with H_2O (50 mL) and EtOAc (50 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the residue was purified either by column chromatography on silica gel or by recrystallization.

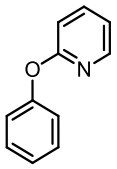
5.2.11 General Procedure G: Ruthenium-catalyzed direct arylation of benzamides 78.

A mixture of benzamide **78** (1.00 equiv), arylbromide **18** (1.05 equiv), $[RuCl_2(PPh_3)_3]$ (2.5 mol %) Na_2CO_3 (1.50 equiv) and *o*-xylene (2.0 mL) was stirred at 120 °C for 22 h under N_2. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

5.3 Synthesis and Analytical Data

5.3.1 Ruthenium-catalyzed direct arylation of 2-phenoxypyridine derivatives.

Synthesis of 2-Phenoxypyridine (73a)



The general procedure A was followed using phenol (**9a**) (3.54 g, 37.5 mmol), 2-bromopyridine (**18n**) (4.85 g, 30.7 mmol), CuI (614 mg, 3.20 mmol), 2-picolinic acid (789 mg, 6.50 mmol) and K_3PO_4 (13.0 g, 61.3 mmol) in DMSO (60 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) yielded **73a** (4.63 g, 88%) as a white solid.

M. p.: 41–44 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.68 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.46–7.35 (m, 2H), 7.24–7.10 (m, 3H), 6.99 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.90 (dt, *J* = 8.3, 0.9 Hz, 1H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 163.7 (C_q), 154.2 (C_q), 147.8 (CH), 139.3 (CH), 129.6 (CH), 124.6 (CH), 121.1 (CH), 118.4 (CH), 111.5 (CH).

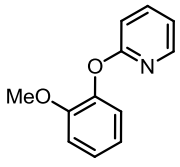
MS (EI) *m/z* (relative intensity): 171 (85) [M^+], 170 (100), 143 (45), 115 (25), 78 (22), 51 (32).

HRMS (ESI) *m/z* for $C_{11}H_{10}NO^+$ [$M+H^+$] calcd. 172.0757

found 172.0761

The spectral data were in accordance with those reported in the literature.[114]

Synthesis of 2-(2-Methoxyphenoxy)pyridine (73b)



The general procedure A was followed using 2-methoxyphenol (**9b**)(1.5 g, 12.0 mmol), 2-bromopyridine (**18n**) (1.58 g, 10.0 mmol), CuI (193 mg, 1.00 mmol), 2-picolinic acid (251 mg, 2.00 mmol) and K_3PO_4 (4.30 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography (*n*-hexane/EtOAc 20/1) yielded **73b** (1.70 g, 84%) as a white powder.

M. p.: 92–93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.66 (ddd, *J* = 8.2, 7.2, 2.0 Hz, 1H), 7.21 (ddd, *J* = 8.3, 7.3, 1.7 Hz, 1H), 7.14 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.01 (ddd, *J* = 7.5, 4.0, 1.5 Hz, 2H), 6.98–6.88 (m, 2H), 3.77 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C_q), 151.7 (C_q), 147.4 (CH), 142.5 (C_q), 139.0 (CH), 125.9 (CH), 123.0 (CH), 121.0 (CH), 117.9 (CH), 112.9 (CH), 110.6 (CH), 55.9 (CH_3).

IR (neat): 1595, 1568, 1467, 1456, 1425, 1270, 1240, 1174, 1110, 1041, 882, 782, 771, 747 cm^{-1}.

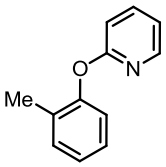
MS (EI) *m/z* (relative intensity): 201 (8) [M^+], 184 (7), 171 (15), 170 (100), 78 (15), 52 (10), 51 (12).

HRMS (EI) *m/z* for $C_{12}H_{11}NO_2^+$[M^+] calcd. 201.0790

found 201.0790

The spectral data were in accordance with those reported in the literature.[115]

Synthesis of 2-(2-Methylphenoxy)pyridine (73c)



The general procedure A was followed using 2-methylphenol (**9c**) (1.30 g, 12.0 mmol), 2-bromopyridine (**18n**) (1.60 g, 10.0 mmol), CuI (194 mg, 1.00 mmol), 2-picolinic acid (247 mg, 2.00 mmol) and K_3PO_4 (4.30 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30/1) yielded **73c** (1.60 g, 85%) as a white solid.

M. p.: 44–45 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (ddd, *J* = 5.0, 2.0, 0.7 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.25 (ddd, *J* = 9.3, 7.4, 4.1 Hz, 2H), 7.14 (td, *J* = 7.4, 1.4 Hz, 1H), 7.06 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.96 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.85 (dt, *J* = 8.3, 0.8 Hz, 1H), 2.19 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C_q), 152.1 (C_q), 147.7 (CH), 139.2 (CH), 131.3 (CH), 130.6 (C_q), 127.0 (CH), 125.1 (CH), 121.7 (CH), 117.9 (CH), 110.5 (CH), 16.4 (CH_3).

IR (neat): 1568, 1463, 1425, 1261, 1246, 1176, 1110, 882, 775, 740, 713 cm^{-1}.

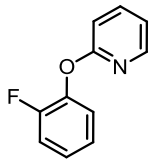
MS (EI) *m/z* (relative intensity): 185 (77) [M^+], 170 (40) [M–CH_3^+], 168 (100), 156 (20).

HRMS (EI) *m/z* for $C_{12}H_{11}NO^+$ [M^+] calcd. 185.0841

found 185.0842

The spectral data were in accordance with those reported in the literature.[114]

Synthesis of 2-(2-Fluorophenoxy)pyridine (73d)



The general procedure A was followed using 2-fluorophenol (**9d**) (4.20 g, 37.5 mmol), 2-bromopyridine (**18n**) (4.80 g, 30.1 mmol), CuI (578 mg, 3.00 mmol), 2-picolinic acid (739 mg, 6.00 mmol) and K_3PO_4 (12.7 g, 60.0 mmol) in DMSO (60 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30/1) yielded **73d** (5.20 g, 92%) as a white solid.

M. p.: 49–52 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.10 (m, 1H), 7.70 (ddd, *J* = 7.9, 7.4, 2.0 Hz, 1H), 7.30–7.12 (m, 4H), 7.00 (ddd, *J* = 5.6, 4.1, 1.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (C_q), 154.9 (C_q, d, $J_{C–F}$ = 248 Hz), 147.5 (CH), 141.0 (C_q, $J_{C–F}$ = 12 Hz), 139.4 (CH), 126.0 (CH, $J_{C–F}$ = 7 Hz), 124.5 (CH, $J_{C–F}$ = 4 Hz), 123.9 (CH), 118.6 (CH), 116.8 (CH, $J_{C–F}$ = 19 Hz), 110.8 (CH).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -(128.2–128.4) (m).

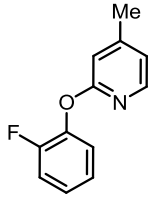
IR (neat): 1494, 1464, 1425, 1273, 1184, 1099, 888, 776, 749 cm^{-1}.

MS (EI) *m/z* (relative intensity): 189 (40) [M^+], 171 (15) [M-F^+], 170 (100).

HRMS (ESI) *m/z* for $C_{11}H_8FNONa^+$ [M+Na^+] calcd. 212.0488

found 212.0489

Synthesis of 2-(2-Fluorophenoxy)-4-methylpyridine (73do)



The general procedure A was followed using 2-fluorophenol (**9d**) (564 mg, 5.00 mmol), 4-methyl-2-bromopyridine (**18o**) (685 mg, 4.00 mmol), CuI (79 mg, 0.40 mmol), 2-picolinic acid (99 mg, 0.80 mmol) and K_3PO_4 (1.70 g, 8.00 mmol) in DMSO (10 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30/1) yielded **73do** (719 mg, 89 %) as a white solid.

M. p.: 48–50 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, J = 5.2 Hz, 1H), 7.28–7.11 (m, 4H), 6.84–6.76 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4 (C_q), 154.9 (C_q, J_{C-F} = 249.0 Hz), 151.1 (C_q), 147.0 (CH), 141.2 (C_q, J_{C-F} = 12 Hz), 125.9 (CH, J_{C-F} = 7 Hz), 124.6 (CH, J_{C-F} = 4 Hz), 124.0 (CH, J_{C-F} = 1 Hz), 120.1 (CH), 116.8 (CH, J_{C-F} = 18 Hz), 111.0 (CH), 20.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = –(128.4–128.6) (m).

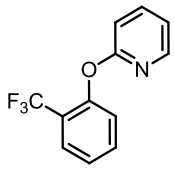
IR (neat): 1612, 1566, 1496, 1396, 1189, 1147, 948, 753 cm^{-1}.

MS (EI) *m/z* (relative intensity): 203 (35) [M^+], 184 (100), 174 (54), 92 (10), 65 (20).

HRMS (EI) *m/z* for $C_{12}H_{10}FNO^+$ [M^+] calcd 203.0746

found 203.0743

Synthesis of 2-{2-(Trifluoromethyl)phenoxy}pyridine (73e)



The general procedure A was followed using 2-(trifluoromethyl)phenol (**9e**) (2.0 g, 12.2 mmol), 2-bromopyridine (**18n**) (1.6 g, 10.2 mmol), CuI (193 mg, 1.00 mmol), 2-picolinic acid (247 mg, 2.00 mmol) and K_3PO_4 (4.30 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30/1) yielded **73e** (1.7 g, 70%) as a pale yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (ddd, J = 5.0, 2.0, 0.8 Hz, 1H), 7.79–7.66 (m, 2H), 7.57 (ddd, J = 7.6, 4.6, 1.1 Hz, 1H), 7.36–7.20 (m, 2H), 7.08–6.96 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q), 151.7 (C_q, m), 147.5 (CH), 139.6 (CH), 132.9 (CH), 127.1 (CH, J_{C-F} = 5.0 Hz), 124.5 (CH), 123.6 (CH), 123.2 (C_q, J_{C-F} = 273 Hz), 122.8 (C_q, J_{C-F} = 31 Hz), 119.0 (CH), 111.9 (CH).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -61.7 (s).

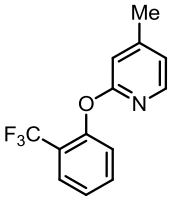
IR (film): 1587, 1574, 1457, 1427, 1318, 1239, 1110, 1054, 887, 757 cm^{-1}.

MS (EI) *m/z* (relative intensity): 239 (100) [M^+], 238 (25) [$M–H^+$], 220 (15), 190 (10), 171 (30), 170 (100).

HRMS (EI) *m/z* for $C_{12}H_8F_3NO^+$ [M^+] calcd. 239.0558

found 239.0566

Synthesis of 4-Methyl-2-[2-(trifluoromethyl)phenoxy]pyridine (73eo)



The general procedure A was followed using 2-trifluoromethylphenol (**9e**) (977 mg, 6.00 mmol), 4-methyl-2-bromopyridine (**18o**) (899 mg, 5.20 mmol), CuI (96 mg, 0.50 mmol), 2-picolinic acid (125 mg, 1.00 mmol) and K_3PO_4 (2.20 g, 10.0 mmol) in DMSO (10 ml). Purification by column chromatography (*n*-hexane/EtOAc 30/1) yielded **73eo** (878 mg, 67%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.56 (dddd, *J* = 8.2, 7.4, 1.6, 0.8 Hz, 1H), 7.28 (tt, *J* = 7.6, 0.9 Hz, 1H), 7.22 (dt, *J* = 8.3, 1.0 Hz, 1H), 6.90–6.79 (m, 2H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6 (C_q), 152.1 (C_q, m), 151.5 (C_q), 147.2 (CH), 133.1 (CH), 127.3 (CH, $J_{C–F}$ = 5.0 Hz), 124.5 (CH), 123.7 (CH), 123.5 (C_q, $J_{C–F}$ = 273 Hz), 123.1 (C_q, $J_{C–F}$ = 31 Hz), 120.7 (CH), 112.4 (CH), 21.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –61.7 (s).

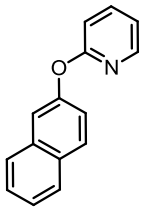
IR (ATR): 1611, 1490, 1451, 1396, 1299, 1288, 1219, 1122, 1054, 947, 815, 797, 762, 583 cm^{-1}.

MS (EI) *m/z* (relative intensity): 252 (10) [M^+], 224 (15), 185 (18), 184 (100), 92 (10), 65 (18).

HRMS (EI) *m/z* for $C_{13}H_{11}F_3NO^+$ [$M+H^+$] calcd. 253.0714

found 253.0710

Synthesis of 2-(Naphtalen-2-yloxy)pyridine (73f)



The general procedure A was followed using 2-naphtol (**9f**) (1.70 g, 12.0 mmol), 2-bromopyridine (**18n**) (1.60 g, 10.3 mmol), CuI (193 mg, 1.00 mmol), 2-picolinic acid (246 mg, 2.00 mmol) and K_3PO_4 (4.25 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography (*n*-hexane/EtOAc 30/1) and wash with *n*-hexane (10 mL) yielded **73f** (1.70 g, 76%) as an orange solid.

M. p.: 56–58 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.22 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.92–7.76 (m, 3H), 7.71 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.53–7.39 (m, 2H), 7.31 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.02 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.97 (dt, *J* = 8.3, 0.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ= 136.7 (C_q), 151.7 (C_q), 147.7 (CH), 139.3 (CH), 134.1 (C_q), 138.9 (C_q), 129.5 (CH), 127.7 (CH), 127.3 (CH), 126.3 (CH), 125.1(CH), 121.3 (CH), 118.4 (CH), 117.3 (CH), 111.5 (CH).

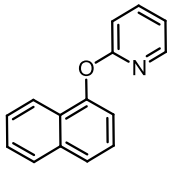
IR (neat): 1587, 1508, 1460, 1426, 1240, 1208, 1158, 961, 868, 752 cm^{-1}.

MS (EI) *m/z* (relative intensity): 221 (75) [M^+], 220 (100), 193 (35), 192 (25), 165 (20), 127 (15), 115 (28), 78 (20).

HRMS (EI) *m/z* for $C_{15}H_{11}NO^+$ [M^+] calcd. 221.0841

found 221.0847

Synthesis of 2-(Naphtalen-1-yloxy)pyridine (73g)



The general procedure A was followed using 1-naphtol (**9g**) (1.75 g, 12.0 mmol), 2-bromopyridine (**18n**) (1.6 g, 10.0 mmol), CuI (195 mg, 1.00 mmol), 2-picolinic acid (251 mg, 2.00 mmol) and K_3PO_4 (4.26 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography (*n*-hexane/EtOAc 30/1) and wash with *n*-hexane (10 mL) yielded **73g** (1.50 g, 67%) as a yellow solid.

M. p.: 89–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 8.04–7.97 (m, 1H), 7.89 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.77–7.63 (m, 2H), 7.55–7.39 (m, 3H), 7.28–7.21 (m, 1H), 7.00 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.95 (dt, *J* = 8.3, 0.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.2 (C_q), 150.0 (C_q), 147.9 (CH), 139.4 (CH), 134.9 (C_q), 127.9 (CH), 127.4 (C_q), 126.3 (CH), 126.0 (CH), 125.7 (CH), 124.9 (CH), 122.0 (CH), 118.3 (CH), 117.0 (CH), 110.9 (CH).

IR (neat): 1591, 1568, 1465, 1425, 1386, 1238, 1039, 867, 770 cm^{-1}.

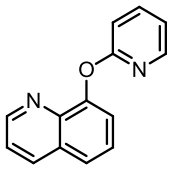
MS (EI) *m/z* (relative intensity): 221 (50) [M^+], 220 (100), 204 (15), 192 (22), 115 (24), 78 (15).

HRMS (EI) *m/z* for $C_{15}H_{11}NO^+$ [M^+] calcd. 221.0841

found 221.0845

The spectral data were in accordance with those reported in the literature.[87]

Synthesis of 8-(Pyridine-2-yloxy)quinoline (73h)



The general procedure A was followed using 8-hydroxyquinoline (**73h**) (875 mg, 6.00 mmol), 2-bromopyridine (**18n**) (801 mg, 5.10 mmol), CuI (95 mg, 0.50 mmol), 2-picolinic acid (124 mg, 1.00 mmol) and K_3PO_4 (2.10 g, 10.0 mmol). Purification by column chromatography on silica gel (EtOAc) yielded **73h** (957 mg, 85%) as a white solid.

M. p.: 166–168 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.86 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.08 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.76–7.67 (m, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.16 (dt, *J* = 8.2, 0.9 Hz, 1H), 6.97 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3 (C_q), 150.2 (C_q), 150.1 (CH), 147.3 (C_q), 141.8 (CH), 139.2 (CH), 135.9 (C_q), 129.7 (CH), 126.4 (CH), 124.6 (CH), 121.4 (CH), 120.8 (CH), 118.2 (CH), 111.7 (CH).

IR (neat): 1594, 1465, 1425, 1270, 1247, 1076, 851, 779, 765 cm^{-1}.

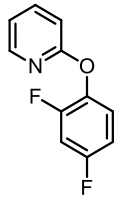
MS (EI) *m/z* (relative intensity): 222 (100) [M^+], 221 (75), 194 (40), 193 (93), 168 (20), 129 (40), 89 (20), 78 (24), 63 (12), 51 (21).

HRMS (EI) *m/z* for $C_{14}H_{10}N_2O^+$ [M^+] calcd. 222.0793

found 222.0787

The spectral data were in accordance with those reported in the literature.[87]

Synthesis of 2-(2,4-Difluorophenoxy)pyridine (77i)



The general procedure A was followed using 2,4-difluorophenol (**9i**) (818 mg, 6.30 mmol), 2-bromopyridine (**18n**) (868 mg, 5.50 mmol), CuI (97 mg, 0.50 mmol), 2-picolinic acid (126 mg, 1.00 mmol) and K_3PO_4 (2.10 g, 10.0 mmol) in DMSO (10 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 40/1) yielded **77i** (960 mg, 84%) as a white solid.

M. p.: 55–57 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17–8.09 (m, 1H), 7.71 (ddd, J = 9.2, 7.5, 2.0 Hz, 1H), 7.19 (ddd, J = 7.2, 6.3, 3.2 Hz, 1H), 7.01 (ddd, J = 7.8, 5.0, 3.0 Hz, 2H), 6.96–6.85 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7 (C_q), 159.3 (C_q, $J_{C–F}$ = 245, 11 Hz), 154.6 (C_q, $J_{C–F}$ = 249, 15 Hz), 147.2 (CH), 139.4 (CH), 137.1 (C_q, $J_{C–F}$ = 13, 4 Hz), 124.4 (CH, $J_{C–F}$ = 9, 3 Hz), 118.7 (CH), 111.2 (CH, $J_{C–F}$ = 22, 4 Hz), 110.8 (CH), 105.1 (CH, $J_{C–F}$ = 26, 22 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –114.1 (tt, J = 8.1, 5.4 Hz), –123.3 (tdd, J = 10.2, 5.2, 1.3 Hz).

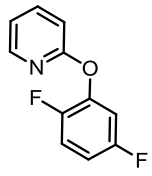
IR (neat): 1502, 1464, 1424, 1236, 1188, 1134, 860, 822, 780 cm^{-1}.

MS (EI) *m/z* (relative intensity): 207 (45) [M^+], 188 (100), 179 (40), 151 (28).

HR-MS (EI) *m/z* for $C_{11}H_7F_2NO^+$ [M^+] calcd. 207.0496

found 207.0492

Synthesis of 2-(2,5-Difluorophenoxy)pyridine (77j)



The general procedure A was followed using 2,5-difluorophenol (**9j**) (807 mg, 6.20 mmol), 2-bromopyridine (**18n**) (788 mg, 5.00 mmol), CuI (99 mg, 0.50 mmol), 2-picolinic acid (126 mg, 1.00 mmol) and K_3PO_4 (2.20 g, 10.0 mmol) in DMSO (10 mL). Purification by column chromatography (*n*-hexane/EtOAc 40/1) yielded **77j** (891 mg, 86%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (ddd, J = 5.1, 1.9, 0.9 Hz, 1H), 7.72 (tdd, J = 7.3, 2.0, 1.0 Hz, 1H), 7.13 (ddd, J = 9.3, 9.5, 5.2 Hz, 1H), 7.07–6.94 (m, 3H), 6.94–6.84 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (C_q), 158.4 (C_q, J_{C-F} = 245, 3 Hz), 151.2 (C_q, J_{C-F} = 244, 3 Hz), 147.4 (CH), 141.5 (C_q, J_{C-F} = 13 Hz), 139.6 (CH), 119.0 (CH), 117.0 (CH, J_{C-F} = 21, 10 Hz), 112.2 (CH, J_{C-F} = 24, 7 Hz), 111.4 (CH, J_{C-F} = 26, 2 Hz), 111.1 (CH).

^{19}F NMR (283 MHz): δ = -(116.8–117.0) (m), -(133.6–133.8) (m).

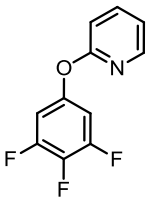
IR (film): 1597, 1503, 1467, 1424, 1296, 1233, 1193, 1138, 1095, 992, 868, 809, 771 cm^{-1}.

MS (EI) *m/z* (relative intensity): 207 (60) [M^+], 188 (100), 179 (45), 151 (35), 140 (10), 101 (12), 78 (50), 51 (39), 43 (32).

HRMS (EI) *m/z* for $C_{11}H_7F_2NO^+$ [M^+] calcd. 207.0496

found 207.0492

Synthesis of 2-(3,4,5-Trifluorophenoxy)pyridine (73k)



The general procedure A was followed using 3,4,5-trifluorophenol (**9k**) (920 mg, 6.20 mmol), 2-bromopyridine (**18n**) (834 mg, 5.20 mmol), CuI (955 mg, 0.50 mmol), 2-picolinic acid (125 mg, 1.00 mmol) and K_3PO_4 (2.20 g, 10.0 mmol) in DMSO (10 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 40/1) yielded **73k** (666 mg, 56%) as a white solid.

M. p.: 59–61 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (ddd, J = 4.9, 1.9, 0.7 Hz, 1H), 7.74 (m, 1H), 7.12–7.01 (m, 1H), 6.96 (dt, J = 8.3, 0.8 Hz, 1H), 6.90–6.73 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.4 (C_q), 151.2 (C_q, J_{C-F} = 249, 11, 5 Hz), 148.9 (C_q, J_{C-F} = 11, 3 Hz), 147.3 (CH), 139.8 (CH), 137.2 (C_q, J_{C-F} = 248, 15, 15 Hz), 119.4 (CH), 111.9 (CH), 106.2 (CH, J_{C-F} = 18, 6 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -(133.1–133.4) (m), -(165.7–165.9) (m).

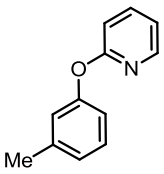
IR (neat): 1520, 1469, 1447, 1427, 1220, 1144, 1037, 993, 865, 831, 769 cm^{-1}.

MS (EI) *m/z* (relative intensity): 225 (100) [M^+], 197 (98) [$M–H^+$], 170 (18), 169 (35).

HRMS (EI) *m/z* for $C_{11}H_6F_3NO^+$ [M^+] calcd. 225.0401

found 225.0398

Synthesis of 2-(3-Methylphenoxy)pyridine (73l)



The general procedure A was followed using 3-methylphenol (**9l**) (1.30 g, 12.0 mmol), 2-bromopyridine (**18n**) (1.57 g, 10.0 mmol), CuI (192 mg, 1.00 mmol), 2-picolinic acid (249 mg, 2.00 mmol) and K_3PO_4 (4.30 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography (*n*-hexane/EtOAc 30/1) yielded **73l** (1.5 g, 82%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.67 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.40–7.17 (m, 1H), 7.14–6.81 (m, 5H), 2.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8 (C_q), 154.1 (C_q), 147.8 (CH), 139.8 (C_q), 139.3 (CH), 129.3 (CH), 125.5 (CH), 121.7 (CH), 118.3 (CH), 118.1 (CH), 111.4 (CH), 21.4 (CH_3).

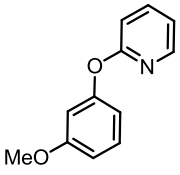
IR (ATR): 1586, 1570, 1465, 1425, 1240, 1141, 936, 773, 737, 691 cm^{-1}.

MS (EI) m/z (relative intensity): 185 (68), 184 (98), 157 (30), 78 (18), 43 (42).

HRMS (EI) m/z for $C_{12}H_{11}NO^+$ [M^+] calcd. 185.0841

found 185.0835

Synthesis of 2-(3-Methoxyphenoxy)pyridine (73m)



The general procedure A was followed using 3-methoxyphenol (**9m**) (1.50 g, 12.0 mmol), 2-bromopyridine (**18n**) (1.60 g, 10.0 mmol), CuI (192 mg, 1.00 mmol), 2-picolinic acid (249 mg, 2.00 mmol) and K_3PO_4 (4.30 g, 20.0 mmol) in DMSO (20 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 30/1) yielded **73m** (1.80 g, 89%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.22 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.68 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.29 (ddd, *J* = 8.5, 8.3, 0.8 Hz, 1H), 6.99 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.90 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.77 (dd, *J* = 2.4 Hz, 0.9 Hz, 1H), 6.74 (dd, *J* = 2.2, 0.8 Hz, 1H), 6.72–6.68 (m, 1H), 3.80 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5 (C_q), 160.7 (C_q), 155.2 (C_q), 147.8 (CH), 139.3 (CH), 130.0 (CH), 118.5 (CH), 113.2 (CH), 111.5 (CH), 110.3 (CH), 107.0 (CH), 55.2 (CH_3).

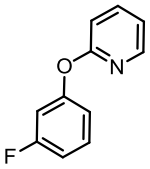
IR (film): 1586, 1465, 1424, 1238, 1135, 1038, 950, 770, 688 cm^{-1}.

MS (EI) *m/z* (relative intensity): 201 (88) [M^+], 200 (100), 185 (22), 173 (25), 171 (15), 130 (15), 78 (29), 63 (13), 51 (20).

HRMS (EI) for $C_{12}H_{11}NO_2^+$ [M^+] calcd. 201.0790

found 201.0788

Synthesis of 2-(3-Fluorophenoxy)pyridine (73n)



The general procedure A was followed using 3-fluorophenol (**9n**) (685 mg, 6.10 mmol), 2-bromopyridine (**18n**) (857 mg, 5.40 mmol), CuI (96 mg, 0.50 mmol), 2-picolinic acid (125 mg, 1.00 mmol) and K_3PO_4 (2.2 g, 10.0 mmol) in DMSO (10 mL). Purification by column chromatography (*n*-hexane/EtOAc 30/1) yielded **73n** (878mg, 86%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26–8.17 (m, 1H), 7.77–7.65 (m, 1H), 7.34 (tdt, *J* = 10.5, 7.8, 1.5 Hz, 1H), 7.09–6.98 (m, 1H), 6.98–6.83 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (C_q, J_{C-F} = 249 Hz), 163.1 (C_q), 155.3 (C_q, J_{C-F} = 8 Hz), 147.8 (CH), 139.6 (CH), 130.3 (CH, J_{C-F} = 10 Hz), 119.0 (CH), 116.6 (CH, J_{C-F} = 3 Hz), 111.9 (CH), 111.5 (CH, J_{C-F} = 21 Hz), 108.8 (CH, J_{C-F} = 24 Hz).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -(111.07 – 111.25) (m).

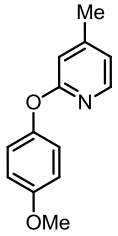
IR (film): 1589, 1571, 1484, 1465, 1446, 1425, 1266, 1236, 1118, 957, 863, 770, 685 cm^{-1}.

MS (EI) *m/z* (relative intensity): 189 (85) [M^+], 188 (100) [$M–H^+$], 161 (90), 133 (38).

HRMS (EI) *m/z* for $C_{11}H_8FNO^+$ [M^+] calcd. 189.0590

found 189.0591

Synthesis of 2-(4-Methoxyphenoxy)-4-methylpyridine (73oo)



The general procedure A was followed using 4-methoxyphenol (**9o**) (751 mg, 6.10 mmol), 4-methyl-2-bromopyridine (**18o**) (879 mg, 5.1 mmol), CuI (95 mg, 0.50 mmol), 2-picolinic acid (126 mg, 1.00 mmol) and K_3PO_4 (2.10 g, 10.0 mmol) in DMSO (10 mL). Purification by column chromatography (*n*-hexane/EtOAc 20/1) yielded **73oo** (950 mg, 86%) as a beige solid.

M. p.: 97–99 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 5.1 Hz, 1H), 7.11–7.00 (m, 2H), 6.98–6.87 (m, 2H), 6.83–6.74 (m, 1H), 6.66 (dq, *J* = 1.5, 0.7 Hz, 1H), 3.81 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6 (C_q), 156.5 (C_q), 150.8 (C_q), 147.3 (C_q), 147.2 (CH), 122.3 (CH), 119.5 (CH), 114.7 (CH), 111.2 (CH), 55.6 (CH_3), 21.0 (CH_3).

IR (neat): 1609, 1502, 1392, 1203, 1146, 1101, 1028, 828, 752 cm^{-1}.

MS (EI) *m/z* (relative intensity): 215 (100) [M^+], 214 (68), 187 (20), 172 (65), 92 (31), 65 (33).

HRMS (EI) *m/z* for $C_{13}H_{13}NO_2^+$ [M^+] calcd. 215.0946

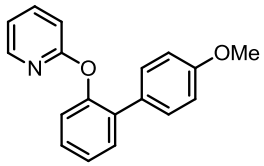
found 215.0941

Ruthenium Catalyzed Direct Arylation of 2-Phenoxypyridine with Arylbromides

Synthesis of 2-{(4'-Methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75ab) and 2-{(4',4''-Dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)oxy}pyridine (76ab)

The general procedure B was followed using 2-phenoxypyridine (**73a**) (256 mg, 1.50 mmol), 4-bromoanisole (**18b**) (90 mg, 0.50 mmol) K_2CO_3 (139 mg, 1.0 mmol), $MesCO_2H$ (26 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column

chromatography on silica gel (*n*-hexane/EtOAc 10/1 → 5/1) yielded **75ab** (89 mg, 66%) and **76ab** (23 mg, 24%) as white solids.



75ab:

M. p.: 65–67 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.48–7.23 (m, 5H), 7.16 (ddd, *J* = 7.9, 1.5, 0.8 Hz, 1H), 6.91–6.80 (m, 3H), 6.75 (dt, *J* = 8.3, 0.8 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.8 (C_q), 158.7 (C_q), 150.9 (C_q), 147.6 (CH), 139.1 (CH), 134.3 (C_q), 131.0 (CH), 130.2 (C_q), 130.1 (CH), 128.1 (CH), 125.3 (CH), 122.6 (CH), 117.9 (CH), 113.5 (CH), 111.2 (CH), 55.1 (CH_3).

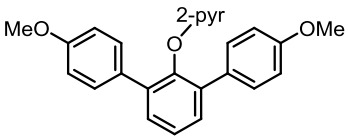
IR (neat): 1483, 1425, 1241, 1193, 1178, 1034, 881, 782, 753, 550 cm^{-1}.

MS (EI) *m/z* (relative intensity): 277 (100) [M^+], 276 (100) [$M–H^+$], 260 (90), 170 (15).

HRMS (EI) *m/z* for $C_{18}H_{14}NO_2^+$ [$M–H^+$] calcd 276.1025

found 276.1030

The spectral data were in accordance with those reported in the literature.[36h]



76ab:

M. p.: 135–136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.43–7.29 (m, 8H), 6.83–6.75 (m, 4H), 6.65 (ddd, *J* = 7.1, 5.0, 0.5 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 3.76 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3 (C_q), 158.6 (C_q), 147.8 (C_q), 147.1 (CH), 138.5 (CH), 135.7 (C_q), 130.6 (C_q), 130.2 (CH), 129.9 (CH), 125.7 (CH), 117.2 (CH), 113.4 (CH), 110.6 (CH), 55.1 (CH_3).

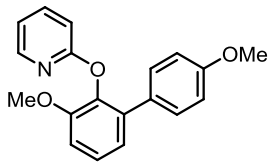
IR (neat): 1511, 1464, 1427, 1288, 1239, 1173, 1032, 796, 779, 559, 537 cm^{-1}.

MS (EI) *m/z* (relative intensity): 383 (75) [M^+], 366 (100), 354 (10), 276 (15).

HRMS (EI) *m/z* for $C_{25}H_{21}NO_3^+$ [M^+] calcd. 383.1521

found 383.1509.

Synthesis of 2-{(3,4'-dimethoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75bb)



The general procedure B was followed using 2-(2-methoxyphenoxy)pyridine (**73b**) (305 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (118 mg, 0.60 mmol) K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 15/1) yielded **75bb** (75 mg, 38%) as a white solid.

The general procedure B was followed using 2-(2-methoxyphenoxy)pyridine (**73b**) (302 mg, 1.50 mmol), 4-bromoanisole (**18b**) (115 mg, 0.60 mmol), K_2CO_3 (139 mg, 1.00 mmol), KOAc (5.2 mg, 0.05 mmol, 10 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (8.0 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **75bb** (102 mg, 54%) as a white solid.

M.p.: 145–147 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.09 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.43–7.35 (m, 2H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.90–6.75 (m, 4H), 3.77 (s, 3H), 3.75 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.7 (C_q), 158.8 (C_q), 152.4 (C_q), 147.4 (CH), 139.6 (C_q), 138.9 (CH), 136.0 (C_q), 130.2 (CH), 130.1 (CH), 125.7 (CH), 122.7 (CH), 117.6 (CH), 133.5 (CH), 111.4 (CH), 110.3 (C_q), 56.1 (CH_3), 55.2 (CH_3).

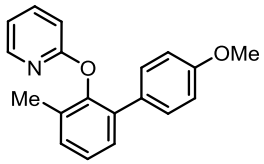
IR (ATR): 1609, 1513, 1459, 1297, 1263, 1119, 1081, 1025, 842, 778, 743 cm^{-1}.

MS (EI) *m/z* (relative intensity): 307 (18) [M^+], 276 (100), 261 (15), 233 (10).

HRMS (EI) m/z for $C_{19}H_{17}NO_3^+$ [M^+] calcd 307.1208

found 307.1211

Synthesis of 2-{(4'-Methoxy-3-methyl-[1,1'-biphenyl]-2-yl)oxy}pyridine (75cb)



The general procedure B was followed using 2-(2-methylphenoxy)pyridine (**73c**) (278 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (102 mg, 0.50 mmol) K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 15/1) yielded **75cb** (70 mg, 44%) as a white solid.

The general procedure B was followed using 2-(2-methylphenoxy)pyridine (**73c**) (281 mg, 1.50 mmol), 4-bromoanisole (**18b**) (120 mg, 0.65 mmol), K_2CO_3 (138 mg, 1.00 mmol), KOAc (4.9 mg, 0.05 mmol, 10 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (8.0 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **75cb** (53 mg, 31%) as a white solid.
M. p.: 100–101 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.52–7.46 (m, 1H), 7.36–7.31 (m, 1H), 7.25–7.17 (m, 4H), 6.78 (m, 3H), 6.63 (d, *J* = 8.4 Hz, 1H), 3.74 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (C_q), 158.6 (C_q), 148.9 (C_q), 147.6 (CH), 139.0 (CH), 135.1 (C_q), 131.9 (C_q), 130.6 (C_q), 130.1 (CH), 130.0 (CH), 128.6 (CH), 125.6 (CH), 117.4 (CH), 113.4 (CH), 110.0 (CH), 55.1 (CH_3), 16.9 (CH_3).

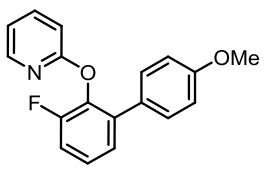
IR (neat): 1509, 1468, 1421, 1237, 1178, 1031, 840, 777, 576 cm^{-1}.

MS (EI) *m/z* (relative intensity): 291 (70) [M^+], 276 (30), 274 (100).

HRMS (EI) *m/z* for $C_{19}H_{17}NO_2^+$ [M^+] calcd. 291.1259

found 291.1255

Synthesis of 2-{(3-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75db)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (851 mg, 4.50 mmol), 4-bromoanisole (**18b**) (280 mg, 1.50 mmol) K_2CO_3 (415 mg, 3.00 mmol), $MesCO_2H$ (74 mg, 0.45 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (23 mg, 0.038 mmol, 2.5 mol %) in PhMe (6.0 mL). Purification by

column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **75db** (437 mg, 98%) as a white solid.

The general procedure B was followed using 2-(2-fluorphenoxy)pyridine (**73d**) (286 mg, 1.50 mmol), 4-bromoanisole (**18b**) (98 mg, 0.53 mmol), K_2CO_3 (139 mg, 1.00 mmol), KOAc (5.2 mg, 0.05 mmol, 10 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **75db** (126 mg, 81%) as a white solid.

The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (286 mg, 1.50 mmol), 4-chloroanisole (**28b**) (71 mg, 0.50 mmol) K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **75db** (140 mg, 98%) as a white solid.

M. p.: 92–94 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (dd, J = 5.0, 1.9 Hz, 1H), 7.62 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.42–7.36 (m, 2H), 7.29–7.19 (m, 2H), 7.13 (ddd, J = 9.9, 6.3, 3.5 Hz, 1H), 6.93 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 6.90–6.82 (m, 3H), 3.79 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (C_q), 159.1 (C_q), 155.5 (C_q, J_{C-F} = 248 Hz), 147.4 (CH), 139.3 (CH), 138.2 (C_q, J_{C-F} = 12 Hz), 137.0 (C_q), 130.1 (CH), 129.2 (C_q), 125.8 (CH, J_{C-F} = 8 Hz), 125.8 (CH, J_{C-F} = 3 Hz), 118.3 (CH), 115.0 (CH, J_{C-F} = 19 Hz), 113.6 (CH), 110.5 (CH), 55.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -(126.92–127.13) (m).

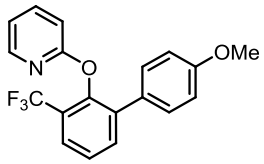
IR (neat): 1573, 1514, 1457, 1423, 1248, 1230, 1094, 1026, 874, 845, 785, 774, 567 cm^{-1}.

MS (EI) *m/z* (relative intensity): 295 (100) [M^+], 294 (55) [$M–H^+$], 278 (80), 276 (60), 235 (18), 157 (15), 146 (23), 78 (30).

HRMS (EI) *m/z* for $C_{18}H_{14}FNO_2^+$ [M^+] calcd. 295.1009

found 295.1008

Synthesis of 2-{(4'-Methoxy-3-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy}pyridine (75eb)



The general procedure B was followed using 2-(2-trifluoromethylphenoxy)pyridine (**73e**) (364 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (99 mg, 0.50 mmol) K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL).

Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 15/1) yielded **75eb** (76 mg, 42%) as a white solid.

The general procedure B was followed using 2-(2-trifluoromethylphenoxy)pyridine (**73e**) (409 mg, 1.70 mmol), 4-bromoanisole (**18b**) (96 mg, 0.51 mmol), K_2CO_3 (139 mg, 1.00 mmol), KOAc (5.3 mg, 0.05 mmol, 10 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 20/1) yielded **75eb** (141 mg, 80%) as a white solid.

M. p.: 72–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (ddd, J = 5.0, 2.0, 0.7 Hz, 1H), 7.72–7.66 (m, 1H), 7.61–7.55 (m, 1H), 7.46 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.40 (dt, J = 7.8, 3.9 Hz, 1H), 7.36–7.29 (m, 2H), 6.79–6.68 (m, 4H), 3.74 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (C_q), 158.9 (C_q), 148.5 (C_q), 146.9 (CH), 138.8 (CH), 137.2 (C_q), 134.8 (CH), 130.1 (CH), 129.2 (C_q), 125.8 (CH, J_{C-F} = 6 Hz), 125.4 (CH), 124.6 (C_q, J_{C-F} = 31 Hz), 125.0 (C_q, J_{C-F} = 274 Hz), 117.9 (CH), 113.5 (CH), 110.7 (CH), 55.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -61.5 (s).

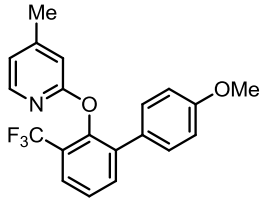
IR (film): 1517, 1469, 1453, 1329, 1237, 1122, 1045, 882, 827, 797, 772, 754 cm^{-1}.

MS (EI) *m/z* (relative intensity): 345 (32) [M$^+$], 328 (41), 276 (100), 261 (15), 238 (10).

HRMS (EI) *m/z* for $C_{19}H_{14}F_3NO_2^+$ [M$^+$] calcd. 345.0977

found 345.0979

Synthesis of 2-{(4'-methoxy-3-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy}-4-methylpyridine 75eob



The general procedure B was followed using 4-methyl-2-[2-(trifluoromethyl)phenoxy]pyridine (**73eo**) (384 mg, 1.52 mmol), 4-bromoanisole (**18b**) (122 mg, 0.65 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (24.9 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) yielded **75eob** (116 mg, 50%) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 5.2 Hz, 1H), 7.68 (dd, J = 7.8, 1.6 Hz, 1H), 7.57 (dd, J = 7.8, 1.6 Hz, 1H), 7.42–7.35 (m, 1H), 7.35–7.30 (m, 2H), 6.81–6.69 (m, 2H), 6.63–6.55 (m, 1H), 6.54 (dt, J = 1.4, 0.8 Hz, 1H), 3.75 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q), 158.9 (C_q), 150.3 (C_q), 148.6 (C_q, m), 146.4 (CH), 137.3 (C_q), 134.8 (CH), 130.1 (CH), 129.3 (C_q), 125.8 (CH, J_{C-F} = 5 Hz), 125.3 (CH), 124.5 (C_q, J_{C-F} = 31 Hz), 123.3 (C_q, J_{C-F} = 273 Hz), 119.4 (CH), 113.4 (CH), 110.9 (CH), 55.2 (CH_3), 20.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ = –61.4 (s).

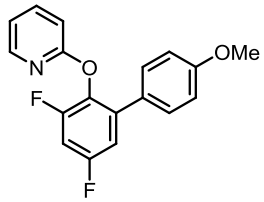
IR (ATR): 1613, 1518, 1453, 1394, 1328, 1250, 1198, 1121, 1024, 947, 812, 795 cm^{-1}.

MS (EI) *m/z* (relative intensity): 359 (23), 342 (38), 290 (100), 252 (10), 145 (5), 92 (8), 65 (10).

HRMS (EI) *m/z* for $C_{20}H_{16}F_3NO_2$ [M^+] calcd. 359.1133

found 359.1140

Synthesis of 2-{(3,5-Difluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75ib)



The general procedure B was followed using 2-(2,4-difluorophenoxy)pyridine (**73i**) (311 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (93 mg, 0.50 mmol) K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **75ib** (157 mg, 99%) as a white solid.

The general procedure B was followed using 2-(2,4-difluorophenoxy)pyridine (**73i**) (312 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (97 mg, 0.51 mmol) K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (4.6 mg, 0.0075 mmol, 1.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 30/1) yielded **75ib** (146 mg, 90%) as a white solid.

The general procedure B was followed using 2-(2,4-difluorophenoxy)pyridine (**73i**) (314 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (97 mg, 0.51 mmol) K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (3.9 mg, 0.006 mmol, 1.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 40/1) yielded **75ib** (155 mg, 96%) as a white solid.

M. p.: 98–99 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (ddd, *J* = 5.0, 1.9, 0.7 Hz, 1H), 7.67–7.57 (m, 1H), 7.42–7.32 (m, 2H), 7.01–6.81 (m, 6H), 3.79 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6 (C_q), 159.3 (C_q), 159.0 (C_q, J_{C-F} = 245, 12 Hz), 155.4 (C_q, J_{C-F} = 248, 13 Hz), 147.2 (CH), 139.3 (CH), 137.6 (C_q, J_{C-F} = 10, 2 Hz), 134.5 (C_q, J_{C-F} = 13, 4 Hz), 129.9 (CH), 128.3 (C_q, J_{C-F} = 3, 2 Hz), 118.4 (CH), 113.7 (CH), 112.1 (CH, J_{C-F} = 23, 3 Hz), 110.5 (CH), 103.3 (CH, J_{C-F} = 27, 23 Hz), 55.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -114.30 (td, J = 8.6, 5.4 Hz), -(122.02–122.60) (m).

IR (neat): 1598, 1517, 1463, 1425, 1250, 1237, 1182, 1141, 1099, 1003, 865, 828, 799, 587, 532 cm^{-1}.

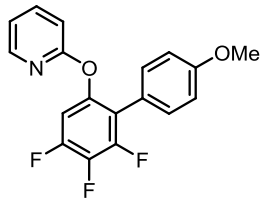
MS (EI) *m/z* (relative intensity): 313 (70) [M^+], 296 (40), 294 (100), 253 (15).

HRMS (ESI) *m/z* for $C_{18}H_{13}F_2NO_2^+$ [M^+] calcd. 313.0914

found 313.0913

Synthesis of 2-{(4,5,6-Trifluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75kb) and 2-{(4',5',6'-Trifluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)oxy}pyridine (76kb):

The general procedure B was followed using 2-(3,4,5-trifluorophenoxy)pyridine (**73k**) (339 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (102 mg, 0.50 mmol) K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) yielded **75kb** (129 mg, 71%) as a colorless liquid and **76kb** (14 mg, 11%) as a white solid.



75kb:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (ddd, J = 5.0, 2.0, 0.7 Hz, 1H), 7.59 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.26 (m, 2H), 6.93 (ddd, J = 7.2, 5.0, 0.9 Hz, 1H), 6.90–6.81 (m, 3H), 6.74 (dt, J = 8.3, 0.8 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (C_q), 159.3 (C_q), 149.5 (C_q, J_{C-F} = 249, 10, 6 Hz), 149.2 (C_q, J_{C-F} = 248, 11, 5 Hz), 144.2 (CH), 146.4 (C_q, J_{C-F} = 11, 6, 4 Hz), 139.4 (CH), 137.8 (C_q, J_{C-F} = 248, 18, 17 Hz), 131.2 (CH), 121.5 (C_q), 120.9 (C_q, J_{C-F} = 15, 4 Hz), 118.7 (CH), 113.6 (CH), 111.5 (CH), 106.9 (CH, J_{C-F} = 21, 5 Hz), 55.2 (CH_3).

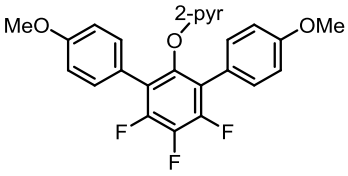
^{19}F NMR (283 MHz, $CDCl_3$): δ = -135.2 (ddd, J = 21.7, 10.7, 5.2 Hz), -(135.8–136.0) (m), -164.10 (td, J = 21.9, 6.6 Hz).

IR (film): 1499, 1454, 1427, 1236, 1178, 1141, 1046, 883, 830, 776, 545 cm^{-1}.

MS (EI) *m/z* (relative intensity): 331 (95) [M^+], 330 (93) [$M–H^+$], 314 (100), 302 (22), 271 (25).

HRMS (ESI) *m/z* for $C_{18}H_{13}F_3NO_2^+$ [$M+H^+$] calcd. 332.0898

found 332.0893



76kb:

M. p.: 169–171 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (ddd, *J* = 5.0, 1.9, 0.7 Hz, 1H), 7.34 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.29–7.21 (d, *J* = 8.7 Hz, 4H), 6.85–6.76 (d, *J* = 8.7 Hz, 4H), 6.73 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.42 (dt, *J* = 8.3, 0.7 Hz, 1H), 3.76 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.7 (C_q), 159.2 (C_q), 147.8 (C_q, $J_{C–F}$ = 247, 11, 5 Hz), 146.7 (CH), 144.3 (C_q, m), 138.8 (CH), 138.4 (C_q, $J_{C–F}$ = 248, 16 Hz), 131.2 (CH), 121.8 (C_q, $J_{C–F}$ = 2 Hz), 121.3 (C_q, m), 113.3 (CH), 113.3 (CH), 110.8 (CH), 55.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -137.56 (d, *J* = 23.0 Hz), -163.07 (t, *J* = 23.1 Hz).

IR (neat): 1604, 1458, 1424, 1405, 1294, 1250, 1223, 1046, 1022, 909, 831, 552, 538 cm^{-1}.

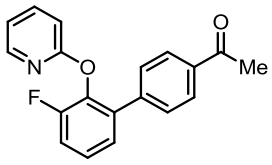
MS (EI) *m/z* (relative intensity): 437 (60) [M^+], 420 (100), 408 (20), 225 (15).

HRMS (EI) *m/z* for $C_{25}H_{18}F_3NO_3^+$ [M^+] calcd. 437.1239

found 437.1256

Ruthenium-Catalyzed Direct Arylation of 2-Phenoxypyridine with Aryl chlorides 28

Synthesis of 1-{3'-Fluoro-2'-(pyridin-2-yloxy)-[1,1'-biphenyl]-4-yl}ethanone (75dd)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (287 mg, 1.50 mmol) and 4-chloroacetophenone (**28d**) (99 mg, 0.60 mmol) K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL).. Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **75dd** (173 mg, 88%) as a white solid.

M. p.: 114–115 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (ddd, J = 5.0, 2.0, 0.7 Hz, 1H), 7.97–7.86 (m, 2H), 7.63 (ddd, J = 8.2, 7.2, 2.0 Hz, 1H), 7.59–7.50 (m, 2H), 7.37–7.13 (m, 3H), 6.95 (ddd, J = 7.1, 5.0, 0.9 Hz, 1H), 6.88 (dt, J = 8.4, 0.9 Hz, 1H), 2.58 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7 (C_q), 162.76 (C_q), 155.5 (C_q, J_{C-F} = 250 Hz), 147.4 (CH), 141.7 (C_q), 141.7 (C_q), 139.4 (CH), 138.4 (C_q, J_{C-F} = 13 Hz), 136.2 (C_q, J_{C-F} = 15 Hz), 129.2 (CH), 128.2 (CH), 126.0 (CH, J_{C-F} = 8 Hz), 125.7 (CH, J_{C-F} = 3 Hz), 118.5 (CH), 116.3 (CH, J_{C-F} = 19 Hz), 110.6 (CH), 26.6 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –(126.1–126.4) (m).

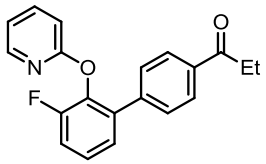
IR (neat): 1685, 1594, 1573, 1459, 1424, 1402, 1264, 1235, 773, 734 cm^{-1}.

MS (EI) *m/z* (relative intensity): 307 (100) [M^+], 290 (85), 288 (92), 264 (20).

HRMS (EI) *m/z* for $C_{19}H_{14}FNO_2^+$ [M^+] calcd. 307.1009

found 307.1013

Synthesis of 1-{3'-Fluoro-2'-(pyridin-2-yloxy)-[1,1'-biphenyl]-4-yl}propan-1-one (75dp)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (288 mg, 1.50 mmol), 4-chloropropiophenone (**28p**) (86 mg, 0.50 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10/1) yielded **75dp** (140 mg, 85%) as a white solid.

M. p.: 87–89 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.06 (m, 1H), 7.96–7.87 (m, 2H), 7.63 (ddd, *J* = 8.2, 7.2, 2.0 Hz, 1H), 7.59–7.49 (m, 2H), 7.37–7.14 (m, 3H), 6.99–6.90 (m, 1H), 6.90–6.83 (m, 1H), 2.98 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4 (C_q), 162.8 (C_q), 155.5 (C_q, $J_{C–F}$ = 249 Hz), 147.4 (CH), 141.4 (C_q, $J_{C–F}$ = 3 Hz), 139.4 (CH), 138.4 (C_q, $J_{C–F}$ = 13 Hz), 136.3 (C_q), 135.9 (C_q), 129.2 (CH), 127.9 (CH), 126.0 (CH, $J_{C–F}$ = 8 Hz), 125.7 (CH, $J_{C–F}$ = 3 Hz), 118.5 (CH), 116.3 (CH, $J_{C–F}$ = 19 Hz), 110.6 (CH), 31.8 (CH_2), 8.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -126.4 (dd, *J* = 9.7, 4.6 Hz).

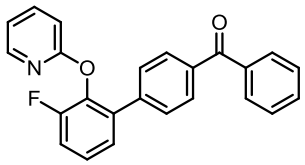
IR (neat): 1686, 1460, 1424, 1404, 1220, 1203, 860, 792, 769 cm^{-1}.

MS (EI) *m/z* (relative intensity): 321 (75) [M^+], 304 (50), 292 (100), 264 (20), 247 (40), 244 (65).

HRMS (EI) *m/z* for $C_{20}H_{16}FNO_2^+$ [M^+] calcd. 321.1165

found 321.1160

Synthesis of {3'-Fluoro-2'-(pyridin-2-yloxy)-[1,1'-biphenyl]-4-yl}(phenyl)methanone (75df)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (287 mg, 1.50 mmol), 4-chlorobenzophenone (**28f**) (109 mg, 0.50 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **75df** (142 mg, 77%) as a light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.05 (m, 1H), 7.85–7.71 (m, 4H), 7.64 (ddd, *J* = 8.3, 7.3, 2.1 Hz, 1H), 7.60–7.54 (m, 3H), 7.51–7.43 (m, 2H), 7.36–7.16 (m, 3H), 6.95 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.90 (dt, *J* = 8.4, 0.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3 (C_q), 162.8 (C_q), 155.5 (C_q, $J_{C–F}$ = 249 Hz), 147.4 (CH), 141.1 (C_q, $J_{C–F}$ = 3 Hz), 139.4 (CH), 138.5 (C_q, $J_{C–F}$ = 13 Hz), 137.6 (C_q), 136.5 (C_q), 136.3 (C_q), 132.4 (CH), 129.9 (CH), 129.9 (CH), 128.9 (CH), 128.2 (CH), 126.0 (CH, $J_{C–F}$ = 8 Hz), 125.8 (CH, $J_{C–F}$ = 3 Hz), 118.5 (CH), 116.3 (CH, $J_{C–F}$ = 19 Hz), 110.6 (CH).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -126.3 (dd, *J* = 9.8, 3.9 Hz).

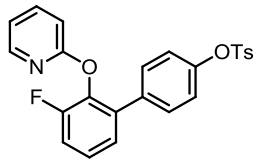
IR (film): 1655, 1594, 1574, 1459, 1426, 1262, 1233, 774, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 369 (40) [M^+], 352 (35), 350 (32), 275 (60), 260 (100), 233 (70).

HRMS (EI) *m/z* for $C_{24}H_{16}FNO_2^+$ [M^+] calcd. 369.1165

found 369.1173

Synthesis of 3'-Fluoro-2'-(pyridin-2-yloxy)-[1,1'-biphenyl]-4-yl 4-methylbenzenesulfonate (75dq)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (287 mg, 1.50 mmol), 4-chlorophenyl 4-methylbenzenesulfonate (**28q**) (142 mg, 0.50 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.6 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **75dq** (171 mg, 78%) as a white solid.

M. p.: 85–87 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (ddd, *J* = 5.0, 1.9, 0.6 Hz, 1H), 7.69–7.57 (m, 3H), 7.39–7.31 (m, 2H), 7.31–7.12 (m, 5H), 6.98–6.88 (m, 3H), 6.84 (d, *J* = 8.3 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (C_q), 155.5 (C_q, J_{C-F} = 249 Hz), 149.1 (C_q), 147.4 (CH), 145.3 (C_q), 139.3 (CH), 138.3 (C_q), 136.1 (C_q), 135.8 (C_q, J_{C-F} = 3 Hz), 132.6 (C_q), 130.2 (CH), 129.7 (CH), 128.5 (CH), 125.9 (CH, J_{C-F} = 8 Hz), 125.7 (CH, J_{C-F} = 3 Hz), 122.1 (CH), 118.4 (CH), 115.9 (CH, J_{C-F} = 19 Hz), 110.6 (CH), 21.7 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -126.7 (ddd, *J* = 9.5, 5.0, 1.4 Hz).

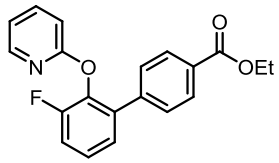
IR (neat): 1596, 1460, 1427, 1366, 1236, 1151, 867, 848, 777, 748, 731, 562, 548 cm^{-1}.

MS (EI) *m/z* (relative intensity): 435 (10) [M^+], 281(20), 280 (100), 252 (10).

HRMS (EI) *m/z* for $C_{24}H_{18}FNO_4S^+$ [M^+] calcd 435.0941

found 435.0924

Synthesis of Ethyl 3'-fluoro-2'-(pyridine-2-yloxy)-[1,1'-biphenyl]-4-carboxylate (75de)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (289 mg, 1.50 mmol), 4-ethylchlorobenzoate (**28e**) (103 mg, 0.55 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (26 mg, 0.15 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (15.6 mg, 0.025 mmol, 5.0 mol %). Purification by column chromatography (*n*-hexane/EtOAc 20/1) yielded **75de** (88 mg, 47%) as a white solid.

M. p.: 105–107 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12–8.05 (m, 1H), 8.02–7.96 (m, 2H), 7.62 (ddd, J = 7.9, 7.1, 2.0 Hz, 1H), 7.56–7.47 (m, 2H), 7.32–7.17 (m, 3H), 6.93 (ddt, J = 7.0, 4.9, 0.6 Hz, 1H), 6.87 (dq, J = 8.3, 0.8 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (C_q), 162.8 (C_q), 155.5 (C_q, J_{C-F} = 249 Hz), 147.4 (CH), 141.4 (C_q, J_{C-F} = 3 Hz), 139.4 (CH), 138.4 (C_q, J_{C-F} = 13 Hz), 136.5 (C_q), 129.5 (C_q), 129.4 (CH), 129.0 (CH), 126.0 (CH, J_{C-F} = 8 Hz), 125.8 (CH, J_{C-F} = 3 Hz), 118.5 (CH), 116.2 (CH, J_{C-F} = 19 Hz), 110.6 (CH), 61.0 (CH_2), 14.3 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$) δ =–126.47 (dd, J = 9.6, 4.4 Hz).

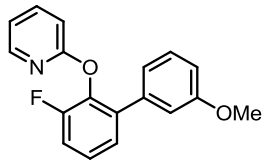
IR (ATR): 1708, 1606, 1594, 1575, 1461, 1426, 1313, 1261, 896, 879, 858, 766 cm^{-1}.

MS (EI) *m/z* (relative intensity): 337 (100) [M^+], 318 (80), 292 (60), 235 (30), 188 (35), 157 (40), 78 (50).

HRMS (EI) *m/z* for $C_{20}H_{16}FNO_3$ [M^+] calcd. 337.1114

found 337.1100

Synthesis of 2-{(3-Fluoro-3'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75dr)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (288 mg, 1.50 mmol), 3-chloroanisole (**28r**) (71.0 mg, 0.50 mmol) , K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.6 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) yielded **75dr** (102 mg, 70%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (dd, J = 5.1, 1.8 Hz, 1H), 7.63 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.30–7.12 (m, 4H), 7.07–6.99 (m, 1H), 6.97 (td, J = 2.8, 1.2 Hz, 1H), 6.95–6.87 (m, 2H), 6.86–6.78 (m, 1H), 3.65 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (C_q), 159.2 (C_q), 155.5 (C_q, $J_{C–F}$ = 249 Hz), 147.4 (CH), 139.3 (CH), 138.2 (C_q, $J_{C–F}$ = 15 Hz), 138.1 (C_q, $J_{C–F}$ = 3 Hz), 137.3 (C_q), 129.2 (CH), 125.8 (CH, $J_{C–F}$ = 9 Hz), 125.7 (CH), 121.3 (CH), 118.3 (CH), 115.6 (CH, $J_{C–F}$ = 19 Hz), 114.0 (CH), 113.8 (CH), 110.7 (CH), 55.0 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –(126.7–127.1) (m).

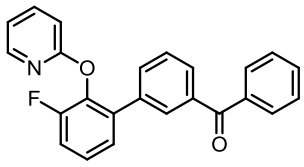
IR (film): 1596, 1573, 1459, 1425, 1262, 1226, 1203, 1038, 769, 741, 698 cm^{-1}.

MS (EI) *m/z* (relative intensity): 295 (100) [M^+], 294 (80), 278 (75), 276 (73), 266 (30), 235 (20).

HRMS (EI) *m/z* for $C_{18}H_{14}FNO_2^+$ [M^+] calcd. 295.1009

found 295.0998

Synthesis of {3'-Fluoro-2'-(pyridin-2-yloxy)-[1,1'-biphenyl]-3-yl}(phenyl)methanone (75dg)



The general procedure B was followed using 2-(2-fluorophenoxy)pyridine (**73d**) (287 mg, 1.50 mmol), 3-chlorobenzophenone (**28g**) (109 mg, 0.50 mmol) , K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 10/1) yielded **75dg** (116 mg, 63%) as a yellow solid.

M. p.: 110–112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (ddd, J = 5.0, 1.9, 0.6 Hz, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.78–7.52 (m, 6H), 7.48–7.39 (m, 3H), 7.33–7.14 (m, 3H), 6.95–6.85 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3 (C_q), 162.8 (C_q), 155.4 (C_q, $J_{C–F}$ = 249 Hz), 147.3 (CH), 139.3 (CH), 138.4 (C_q, $J_{C–F}$ = 13 Hz), 137.4 (C_q, $J_{C–F}$ = 19 Hz), 136.8 (C_q, $J_{C–F}$ = 3 Hz), 136.3 (C_q), 136.3 (C_q), 132.8 (CH), 132.3 (CH), 130.6 (CH), 129.8 (CH), 129.1 (CH), 128.2 (CH), 128.2 (CH), 125.9 (CH, $J_{C–F}$ = 8 Hz), 125.8 (CH, $J_{C–F}$ = 3 Hz), 118.4 (CH), 116.0 (CH, $J_{C–F}$ = 19 Hz), 110.5 (CH).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -126.5 (m).

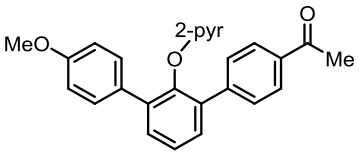
IR (neat): 1655, 1598, 1574, 1427, 1268, 1240, 877, 777, 721, 699, 640 cm^{-1}.

MS (EI) *m/z* (relative intensity): 369 (100) [M^+], 368 (55) [$M–H^+$], 349 (50), 350 (95), 292 (20), 264 (20), 236 (35), 188 (25), 157 (25), 105 (65), 77 (92).

HRMS (EI) *m/z* for $C_{24}H_{16}FNO_2^+$ [M^+] calcd. 369.1165

found 369.1167

Synthesis of 1-{4''-Methoxy-2'-(pyridine-2-yloxy)-[1,1':3',1''-terphenyl]-4-yl}ethanone (76abd)



The general procedure B was followed using 2-{(4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (**75ab**) (417 mg, 1.50 mmol) and 4-bromoacetophenone (**18d**) (100 mg, 0.50 mmol) K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (26 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.8 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc: 5/1) yielded **76abd** (169 mg, 84%) as a white solid.

M. p.: 128–130 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.87 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.85–7.82 (m, 2H), 7.59–7.54 (m, 2H), 7.45 (dd, *J* = 6.1, 3.3 Hz, 1H), 7.40–7.35 (m, 4H), 7.31 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 6.80–6.76 (m, 2H), 6.64 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.48 (dt, *J* = 8.3, 0.9 Hz, 1H), 3.74 (s, 3H), 2.54 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8 (C_q), 163.0 (C_q), 158.8 (C_q), 147.7 (C_q), 147.1 (CH), 143.3 (C_q), 138.7 (CH), 136.0 (C_q), 135.6 (C_q), 135.0 (C_q), 131.1 (CH), 130.2 (C_q), 130.2 (CH), 129.7 (CH), 129.4 (CH), 128.0 (CH), 125.9 (CH), 117.4 (CH), 113.4 (CH), 110.7 (CH), 55.1 (CH_3), 26.5 (CH_3).

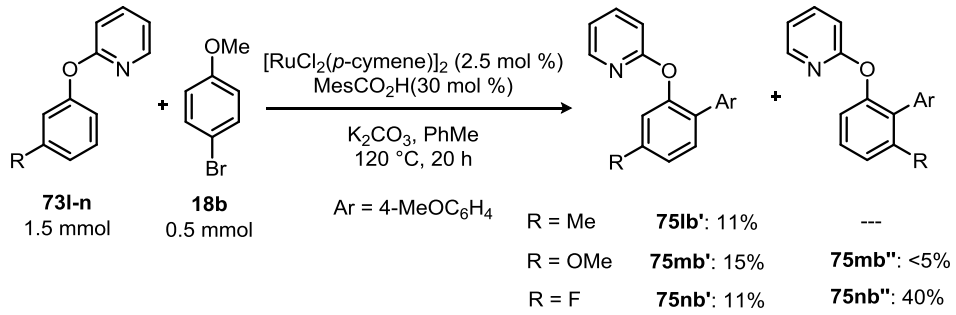
IR (ATR): 1677, 1593, 1572, 1425, 1264, 1239, 1036, 879, 792, 779, 753 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 394 (30) [$M–H^+$], 383 (15), 373 (20), 293 (40), 283 (30), 255 (40), 171 (10), 135 (100) 113 (60).

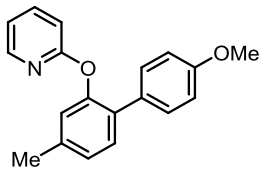
HRMS (ESI) *m/z* for $C_{26}H_{21}NO_3Na^+$ [$M+Na^+$] calcd. 418.1419

found 418.1414.

Intramolecular Competition Experiments



Synthesis of 2-{(4´-methoxy-4-methyl-[1,1'-biphenyl]-2-yl)oxy}pyridine (75lb')



The general procedure B was followed using 2-(3-methylphenoxy)pyridine (**73l**) (287 mg, 1.55 mmol), 4-bromoanisole (**18b**) (96 mg, 0.50 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10/1) yielded **75lb'** (16 mg, 11%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1H), 7.44–7.37 (m, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.09 (ddd, *J* = 7.8, 1.8, 0.8 Hz, 1H), 7.00–6.96 (m, 1H), 6.87 (ddd, *J* = 7.2, 4.9, 0.9 Hz, 1H), 6.85–6.79 (m, 2H), 6.74 (dt, *J* = 8.3, 0.9 Hz, 1H), 3.77 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0 (C_q), 158.7 (C_q), 150.7 (C_q), 147.7 (CH), 139.2 (CH), 138.4 (C_q), 131.4 (C_q), 130.8 (CH), 130.3 (C_q), 130.1 (CH), 126.3 (CH), 123.1 (CH), 117.9 (CH), 113.5 (CH), 111.2 (CH), 55.1 (CH_3), 21.0 (CH_3).

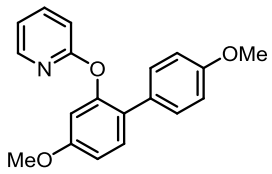
IR (ATR): 1597, 1493, 1466, 1427, 1241, 1177, 1038, 908, 814, 778, 727 cm^{-1}.

MS (EI) *m/z* (relative intensity): 291 (90) [M^+], 290 (100), 274 (80), 231 (15), 184 (15).

HRMS (EI) *m/z* for $C_{19}H_{17}NO_2^+$ [M^+] calcd 291.1259

found 291.1259

Synthesis of 2-{(4,4'-dimethoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75mb')



The general procedure B was followed using 2-(3-methoxyphenoxy)pyridine (**73m**) (304 mg, 1.5 mmol), 4-bromoanisole (**18b**) (119 mg, 0.6 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10/1) yielded **75mb'** (30 mg, 15%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.56 (ddd, *J* = 8.4, 7.3, 2.0 Hz, 1H), 7.41–7.32 (m, 3H), 6.93–6.78 (m, 4H), 6.74 (dt, *J* = 8.3, 0.8 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C_q), 159.6 (C_q), 158.5 (C_q), 151.6 (C_q), 147.6 (CH), 139.3 (CH), 131.5 (CH), 130.1 (CH), 130.1 (C_q), 126.9 (C_q), 118.1 (CH), 113.5 (CH), 111.4 (CH), 111.2 (CH), 108.2 (CH), 55.5 (CH_3), 55.2 (CH_3).

IR (ATR): 1597, 1492, 1465, 1424, 1239, 1177, 1155, 1078, 1044, 776 cm^{-1}.

MS (EI) m/z (relative intensity): 307 (100), 306 (85), 290 (63), 270 (100), 200 (15), 115 (10), 78 (18).

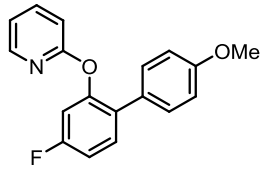
HRMS (EI) m/z for $C_{19}H_{16}NO_3$ [M-H$^+$] calcd. 306.1130

found 306.1126

Synthesis of 2-{(4-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75nb') and 2-{(6-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75nb")

The general procedure B was followed using 2-(3-fluorophenoxy)pyridine (**73n**) (280 mg, 1.50 mmol), 4-bromoanisole (**18b**) (101 mg, 0.54 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 15/1) yielded **75nb'** (19 mg, 11%) and **75nb"** (64 mg, 40%) as colorless oils.

2-{(4-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75nb')



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.13 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.60 (tdd, *J* = 7.2, 2.0, 1.0 Hz, 1H), 7.43–7.31 (m, 3H), 7.03–6.74 (m, 6H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1 (C_q), 161.9 (C_q, J_{C-F} = 247 Hz), 158.7 (C_q), 151.5 (C_q, J_{C-F} = 11 Hz), 147.5 (CH), 139.3 (CH), 131.6 (C_q, J_{C-F} = 9 Hz), 130.3 (C_q, J_{C-F} = 4 Hz), 130.1 (CH), 129.4 (CH), 118.4 (CH), 113.5 (CH), 112.2 (CH, J_{C-F} = 21 Hz), 111.5 (CH), 109.9 (CH, J_{C-F} = 24 Hz), 55.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –(113.3–113.5) (m).

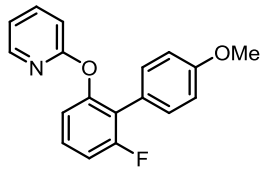
IR (film): 1587, 1487, 1465, 1422, 1236, 1177, 1140, 969, 808, 777, 537 cm^{-1}.

MS (EI) *m/z* (relative intensity) 295 (90) [M^+], 294 (100) [$M–H^+$], 278 (82), 235 (20).

HRMS (EI) *m/z* for $C_{18}H_{14}FNO_2^+$ [M^+] calcd. 295.1009

found 295.1011

2-{(6-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine (75nb")



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (ddd, *J* = 5.0, 2.0, 0.7 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.35–7.24 (m, 3H), 7.03 (ddd, *J* = 9.4, 8.3, 1.1 Hz, 1H), 6.98 (dt, *J* = 8.2, 1.1 Hz, 1H), 6.90 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.88–6.81 (m, 2H), 6.73 (dt, *J* = 8.3, 0.8 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4 (C_q), 160.5 (C_q, $J_{C–F}$ = 246 Hz), 158.9 (C_q), 152.3 (C_q, $J_{C–F}$ = 6 Hz), 147.4 (CH), 139.1 (CH), 131.3 (CH), 128.2 (C_q, $J_{C–F}$ = 10 Hz), 123.1 (C_q, $J_{C–F}$ = 17 Hz), 123.0 (CH), 118.2 (CH), 118.0 (CH, $J_{C–F}$ = 3 Hz), 113.3 (CH), 112.3 (CH, $J_{C–F}$ = 23 Hz), 111.4 (CH), 55.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –(114.5–114.6) (m).

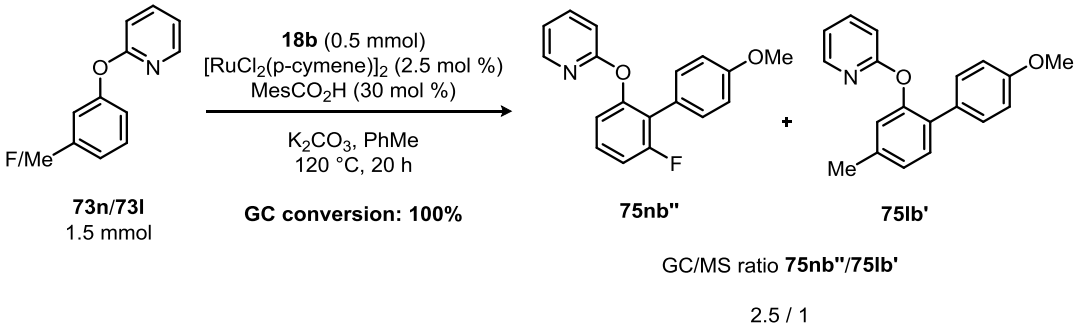
IR (film): 1518, 1455, 1425, 1237, 1177, 1037, 997, 831, 797, 737 cm^{-1}.

MS (EI) *m/z* (relative intensity): 295 (100) [M^+], 294 (98) [$M–H^+$], 278 (100), 235 (20).

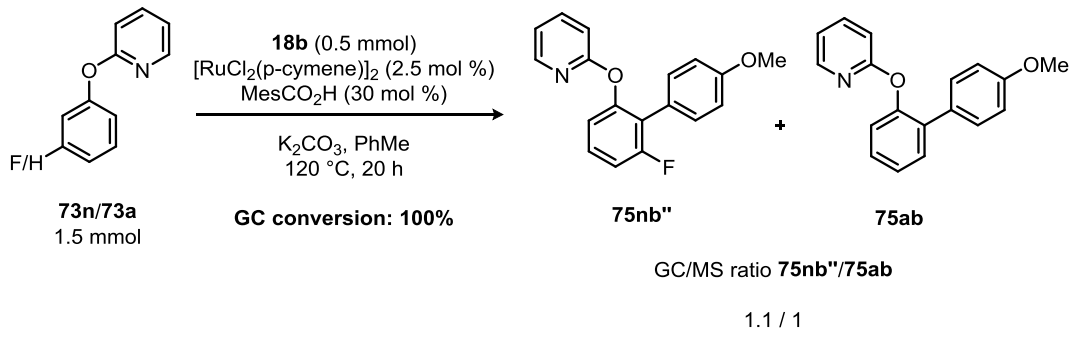
HRMS (EI) *m/z* for $C_{18}H_{14}FNO_2^+$ [M^+] calcd. 295.1009

found 295.1007

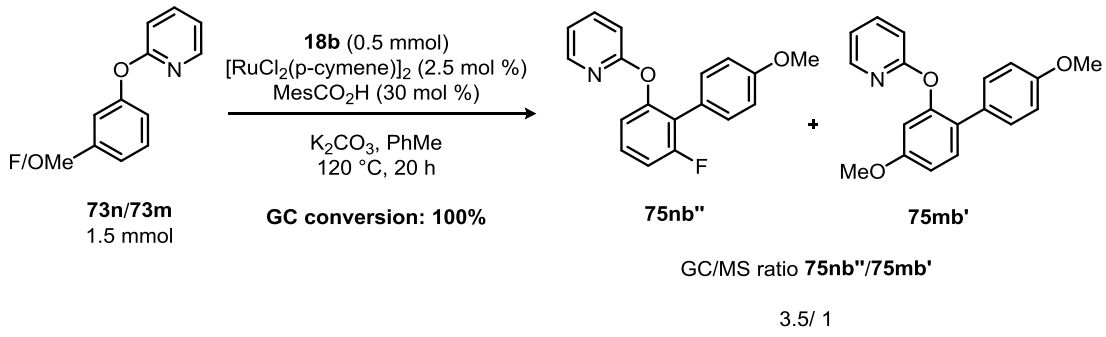
Intermolecular Competition experiments



A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.9 mg, 0.0125 mmol, 2.5 mol %), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), 2-(3-fluorophenoxy)pyridine (**73n**) (290 mg, 1.50 mmol), 2-(3-methylphenoxy)pyridine (**73l**) (275 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (110 mg, 0.58 mmol) in PhMe (2 mL) was stirred under N_2 at 120 °C for 20 h. Analysis of the crude mixture by GC/MS showed a full conversion of 4-bromoanisole, with a ratio 1/2.5 between **75lb**' and **75nb"**.

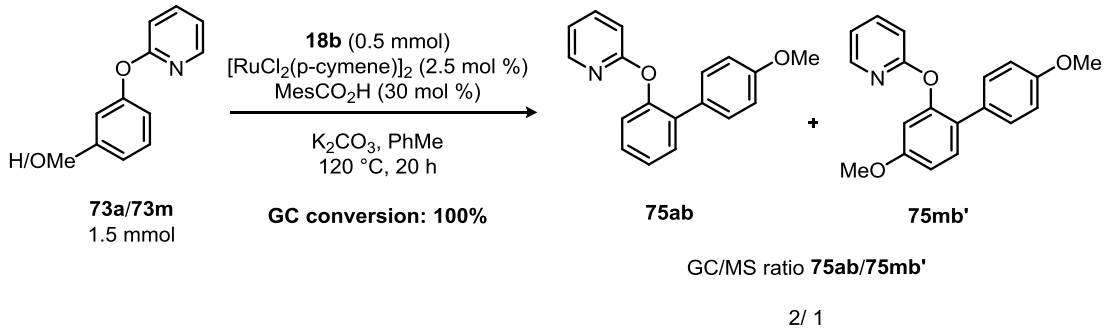


A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), 2-(3-fluorophenoxy)pyridine (**73n**) (288 mg, 1.50 mmol), 2-phenoxypyridine (**73a**) (260 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (96 mg, 0.51 mmol) in PhMe (2 mL) was stirred under N_2 at 120 °C for 20 h. Analysis of the crude mixture by GC/MS showed a full conversion of 4-bromoanisole, with a ratio 1/1.1 between **75ab** and **75nb"**.

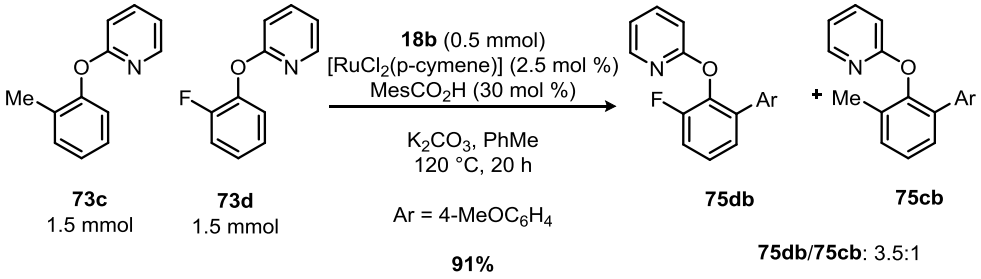


A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), 2-(3-fluorophenoxy)pyridine (**73n**) (293 mg, 1.55 mmol), 2-(3-methoxy)phenoxypyridine (**73m**) (302 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (103 mg, 0.55

mmol) in PhMe (2 mL) was stirred under N_2 at 120 °C for 20 h. Analysis of the crude mixture by GC/MS showed a full conversion of 4-bromoanisole, with a ratio 1/3.5 between **75mb'** and **75nb"**.

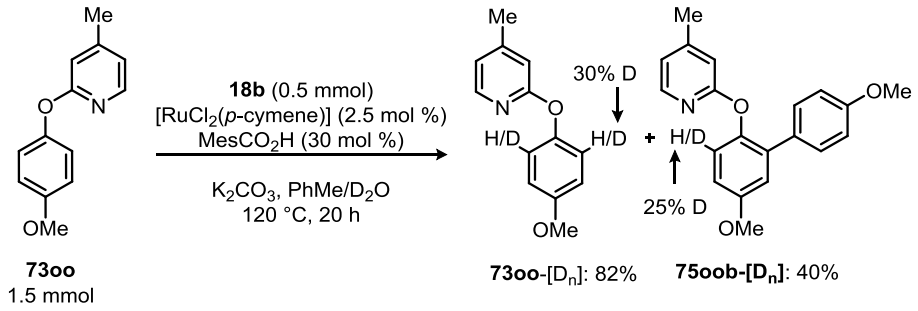


A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), 2-phenoxypyridine (**73a**) (259 mg, 1.50 mmol), 2-(3-methoxy)phenoxypyridine (**73m**) (301 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (96 mg, 0.51 mmol) in PhMe (2 mL) was stirred under N_2 at 120 °C for 20 h. Analysis of the crude mixture by GC/MS showed a full conversion of 4-bromoanisole, with a ratio 1/2 between **75ab** and **75mb'**.

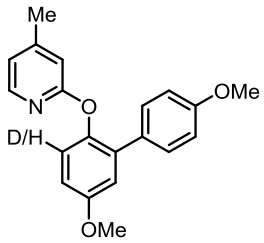


A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), 2-(2-fluorophenoxy)pyridine (**73d**) (284 mg, 1.50 mmol), 2-(2-methylphenoxy)pyridine (**73c**) (278 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (94 mg, 0.50 mmol) in PhMe (2 mL) was stirred under N_2 at 120 °C for 20 h. The reaction mixture was cooled to ambient temperature. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) to yield a mixture of **75db** and **75cb** (132 mg, 91%, combined yield) in a ratio of 3.5 : 1, as estimated by ^{1}H-NMR spectroscopy.

Isotopic labeling experiment



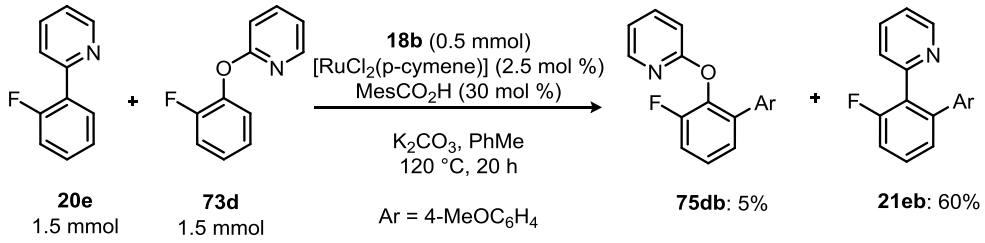
A mixture of phenoxypyridine **73oo** (323 mg, 1.5 mmol), 4-bromoanisole (**18b**) (99.8 mg, 0.53 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol, 2.5 mol %), $MesCO_2H$ (24.7 mg, 0.15 mmol) and K_2CO_3 (139 mg, 1.0 mmol)), D_2O (54 µL) and PhMe (2.0 mL) was stirred at 120 °C for 20 h under N_2. At ambient temperature, the reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) to yield **73oo**-[D_n] (266 mg, 82%) as a white solid and **75oob**-[D_n] (67.2 mg, 40%) as a colorless oil.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 5.2 Hz, 1H), 7.42 (dd, *J* = 8.9, 0.6 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 0.75 H), 6.96 (d, *J* = 3.1 Hz, 1H), 6.93–6.80 (m, 3H), 6.69 (ddd, *J* = 5.2, 1.4, 0.7 Hz, 1H), 6.53 (dt, *J* = 1.4, 0.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.26 (s, 3H).

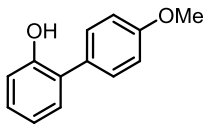
^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.4 (C_q), 158.8 (C_q), 156.7 (C_q), 150.6 (C_q), 147.0 (CH), 144.3 (C_q), 135.2 (C_q), 130.2 (C_q), 130.1 (CH), 123.7 (CH), 119.2 (CH), 115.7 (CH/CD), 113.5 (CH), 113.4 (CH), 111.0 (CH), 55.6 (CH_3), 55.2 (CH_3), 21.0 (CH_3).

Competition experiment between 2-flurophenoxypyridine (73d) and 2-fluorophenylpyridine (20e)



A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.012 mmol, 2.5 mol %), $MesCO_2H$ (**6**)(25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (139 mg, 1.00 mmol), 2-(2-fluorophenoxy)pyridine (**73d**) (285 mg, 1.50 mmol), 2-(2-fluorophenyl)pyridine (**20e**) (262 mg, 1.50 mmol) and 4-bromoanisole (**18b**) (94 mg, 0.50 mmol) in dry PhMe (2 mL) was stirred under N_2 at 120°C for 20 h. The reaction mixture was cooled to ambient temperature. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 15/1) yielding **75db** (8 mg, 5%) and **21eb** (83 mg, 60%).

Synthesis of 4'-methoxy-[1,1'-biphenyl]-2-ol (77ab)



To a solution of 2-{(4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine **75ab** (138.6 mg, 0.50 mmol) in PhMe (20 mL) under N_2 was added MeOTf (100 µL, 0.88 mmol). The reaction mixture was stirred under N_2 at 100 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature. Evaporation of the solvent *in vacuo* yielded 221 mg of a white solid. Quantitative conversion was checked with ^{1}H-NMR. The solid was dissolved in dry methanol (5.0 mL) and was added under N_2 to a solution of Na (294 mg, 12 mmol) in dry methanol (15.0 mL). The reaction mixture was heated at 80 °C for 15 min. The reaction mixture was allowed to cool to ambient temperature and the solvent was evaporated *in vacuo*. H_2O (75 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20/1 → 10/1) to yield **77ab** (81 mg, 81%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.6 Hz, 2H), 7.28–7.20 (m, 2H), 7.03 (d, J = 8.6 Hz, 2H), 7.00–6.94 (m, 2H), 5.18 (s, 1H), 3.86 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (C_q), 152.5 (C_q), 130.3 (CH), 130.2 (CH), 129.1 (C_q), 128.7 (CH), 127.8 (C_q), 120.8 (CH), 115.6 (CH), 114.7 (CH), 55.3 (CH_3).

IR (film): 3415, 1606, 1515, 1482, 1451, 1240, 1032, 826, 794, 749 cm^{-1}.

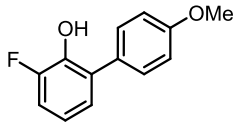
MS (EI) *m/z* (relative intensity): 200 (100) [M^+], 185 (55), 128 (42).

HRMS (EI) *m/z* for $C_{13}H_{12}O_2^+$ [M^+] calcd. 200.0837

found 200.0832

The spectral data were in accordance with those reported in the literature. [116]

Synthesis of 3-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-ol (77db)



To a solution of 2-{(3-fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)oxy}pyridine **75db** (153.1 mg, 0.50 mmol) in PhMe (20 mL) under N_2 was added MeOTf (100 µL, 0.88 mmol). The reaction mixture was stirred under N_2 at 100 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature. Evaporation of the solvent *in vacuo* yielded a yellow oil (229.7 mg). Quantitative conversion was checked with ^{1}H-NMR. The oil was dissolved in dry methanol (5.0 mL) and was added under N_2 to a solution of Na (294 mg, 12 mmol) in dry methanol (15.0 mL). The reaction mixture was heated at 80 °C for 15 min. The reaction mixture was allowed to cool to ambient temperature and the solvent was evaporated *in vacuo*. H_2O (75 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) to yield **77db** (102 mg, 90%) as a white solid.

M. p.: 104–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.44 (d, J = 8.7 Hz, 2H), 7.09–7.02 (m, 2H), 7.02–6.97 (d, J = 8.7 Hz, 2H), 6.94–6.84 (m, 1H), 5.24 (d, J = 4.6 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2 (C_q), 151.3 (C_q, J_{C-F} = 246 Hz), 140.7 (C_q, J_{C-F} = 18 Hz), 130.2 (CH), 130.1 (C_q), 128.7 (C_q, J_{C-F} = 3 Hz), 125.5 (CH, J_{C-F} = 3 Hz), 120.1 (CH, J_{C-F} = 7 Hz), 114.1 (CH), 114.1 (CH, J_{C-F} = 18 Hz), 55.3 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -139.8 (m).

IR (neat): 3390, 1514, 1462, 1235, 1181, 1023, 883, 828, 784, 562 cm^{-1}.

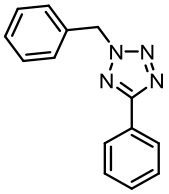
MS (EI) *m/z* (relative intensity): 218 (100) [M^+], 203 (45), 147 (25), 146 (45).

HR-MS (EI) *m/z* for $C_{13}H_{11}FO_2$ [M^+] calcd. 218.0743

found 218.0749

5.3.2 Ruthenium-Catalyzed Direct Arylation of Phenyltetrazoles

Synthesis of 2-Benzyl-5-phenyl-2*H*-tetrazole (100a)



5-Phenyl-1*H*-tetrazole (**98a**) (4.41 g, 30.0 mmol) was dissolved in DMSO (20 mL) and the reaction mixture was cooled to 0 °C. Powdered NaOH (2.03 g, 50.0 mmol) was added. The reaction was then allowed to warm up to ambient temperature. Benzyl bromide (**99a**) (5.23 g, 30.7 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 10/1) yielding **100a** (5.07 g, 71%) as a white solid.

M. p.: 70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.06 (m, 2H), 7.51–7.30 (m, 8H), 5.81 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4 (C_q), 133.3 (C_q), 130.3 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.3 (C_q), 126.8 (CH), 56.8 (CH_2).

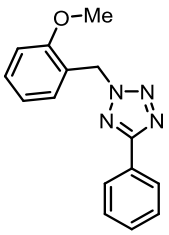
IR (ATR): 1467, 1448, 1197, 1072, 1045, 1026, 723, 689, 671 cm^{-1}.

MS (EI) *m/z* (relative intensity): 207 (22), 180 (100), 179 (90), 178 (42), 165 (36), 104 (27), 91 (85).

HRMS (ESI) *m/z* for $C_{14}H_{12}N_4Na^+$ [M+Na^+] calcd. 259.0965

found 259.0958

Synthesis of 2-(2-Methoxybenzyl)-5-phenyl-2*H*-tetrazole (100b)



5-Phenyl-1*H*-tetrazole (**98a**) (4.09 g, 28.0 mmol) was dissolved in DMSO (20 mL) and the reaction mixture was cooled to 0 °C. Powdered NaOH (2.03 g, 50.0 mmol) was added. The reaction was allowed to warm up to ambient temperature. 2-Methoxybenzyl bromide (**99b**) (6.48 g, 32.0 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielding **100b** (5.09 g, 68%) as a white solid.

M. p: 80 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.18–8.06 (m, 2H), 7.49–7.40 (m, 3H), 7.35–7.28 (m, 1H), 7.17 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.98–6.85 (m, 2H), 5.84 (s, 2H), 3.84 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.7 (C_q), 156.8 (C_q), 129.9 (CH), 129.8 (CH), 129.4 (CH), 128.4 (CH), 127.2 (C_q), 126.5 (CH), 121.5 (C_q), 120.3 (CH), 110.4 (CH), 55.2 (CH_3), 51.4 (CH_2).

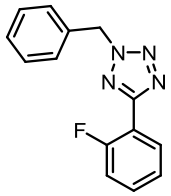
IR (ATR): 1527, 1496, 1463, 1448, 1332, 1255, 1102, 1022 cm^{-1}.

MS (EI) *m/z* (relative intensity): 266 (2) [M^+], 241 (5), 207 (100), 195 (28), 167 (25), 121 (85), 91 (90).

HRMS (ESI) *m/z* for $C_{15}H_{14}N_4ONa^+$ [M+Na^+] calcd. 289.1060

found 289.1066

Synthesis of 2-Benzyl-5-(2-fluorophenyl)-2*H*-tetrazole (100c)



5-(2-Fluorophenyl)-1*H*-tetrazole (**98c**) (826 mg, 5.00 mmol) was dissolved in DMSO (10 mL) and the reaction mixture was cooled to 0 °C. Powdered NaOH (366 mg, 9.10 mmol) was added. The reaction was allowed to warm up to ambient temperature. Benzylbromide (**99a**) (1.10 g, 6.20 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 20/1) yielding **100c** (524 mg, 41%) as a yellow solid.

M. p.: 72–73 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (td, J = 7.5, 1.8 Hz, 1H), 7.54–7.33 (m, 6H), 7.31–7.10 (m, 2H), 5.85 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q, J_{C-F} = 5.0 Hz), 160.0 (C_q, J_{C-F} = 256 Hz), 133.1 (C_q), 131.8 (CH, J_{C-F} = 8 Hz), 129.9 (CH, J_{C-F} = 2 Hz), 128.9 (CH), 128.9 (CH), 128.3 (CH), 124.3 (CH, J_{C-F} = 4 Hz), 116.6 (CH, J_{C-F} = 21 Hz), 115.5 (C_q, J_{C-F} = 12 Hz), 56.8 (CH_2).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –111.66 (ddd, J = 10.6, 7.3, 5.0 Hz).

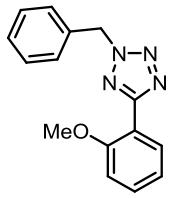
IR (ATR): 1621, 1584, 1480, 1456, 1435, 1226, 1100, 1032, 825, 795, 777, 753, 720 cm^{-1}.

MS (EI) *m/z* (relative intensity): 225 (10), 198 (65), 183 (20), 177 (159, 104 (15), 91 (100).

HRMS (ESI) *m/z* for $C_{14}H_{12}N_4F^+$ [M+H$^+$] calcd 255.1041

found 255.1041

Synthesis of 2-benzyl-5-(2-methoxyphenyl)-2*H*-tetrazole



5-(2-Methoxyphenyl)-1*H*-tetrazole (**98d**) (883 mg, 5.00 mmol) was dissolved in DMSO (10 mL) and the reaction mixture was cooled to 0 °C. Powdered NaOH (354 mg, 8.80 mmol) was added. The reaction was allowed to warm up to ambient temperature. Benzylbromide (**99a**) (874 mg, 5.10 mmol) was then added and the reaction mixture was stirred at ambient temperature overnight. EtOAc (50 mL) and H_2O (50 mL) were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude reaction mixture was purified by column chromatography on silica gel (*n*-hexane/EtOAc 10/1→5/1) yielding **100d** (368 mg, 27%) as a white solid.

M. p.: 59–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.89 (m, 1H), 7.49–7.31 (m, 6H), 7.12–6.99 (m, 2H), 5.84 (s, 2H), 3.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (C_q), 157.5 (C_q), 133.5 (C_q), 131.5 (CH), 130.8 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 120.7 (CH), 116.5 (C_q), 111.8 (CH), 56.6 (CH_2), 56.0 (CH_3).

IR (ATR): 1604, 1585, 1483, 1446, 1427, 1252, 1105, 1025, 750, 722, 698, 687 cm^{-1}.

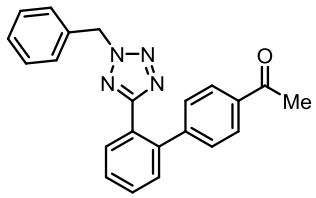
MS (EI) *m/z* (relative intensity): 266 (5) [M^+], 237 (10), 210 (75), 195 (25), 179 (35), 167 (28), 104 (32), 91 (100), 65 (35).

HRMS (EI) *m/z* for $C_{15}H_{14}N_4O^+$ [M^+] calcd. 266.1168

found 266.1169

Synthesis of 1-(2´-(2-Benzyl-2*H*-tetrazol-5-yl)-[1,1´-biphenyl]-4-yl)ethan-1-one (101ad) and of 1,1´-(2´-(2-Benzyl-2*H*-tetrazol-5-yl)-[1,1´:3´,1´´-terphenyl]-4,4´´-diyl)bis(ethan-1-one) (102ad)

Procedure D1 was followed using 2-benzyl-5-phenyl-2*H*-tetrazole (**100a**) (118 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (111 mg, 0.55 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (26 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (16.7 mg, 0.027 mmol, 5.4 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane / EtOAc 3/1) yielded **101ad** (24.3 mg, 14%) and **102ad** (86.1 mg, 37%) as white solids.



101ad:

M. p.: 106–107 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.87 (m, 1H), 7.83–7.73 (m, 2H), 7.53 (td, *J* = 6.8, 1.7 Hz, 2H), 7.42 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.36–7.27 (m, 3H), 7.25–7.18 (m, 2H), 7.18–7.13 (m, 1H), 5.61 (s, 2H), 2.60 (s, 3H).

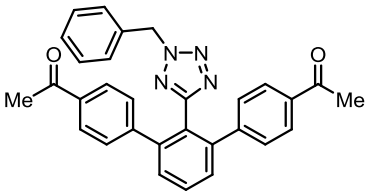
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7 (C_q), 165.2 (C_q), 145.8 (C_q), 140.9 (C_q), 135.5 (C_q), 133.1 (C_q), 130.4 (CH), 130.4 (CH), 130.1 (CH), 130.1 (CH), 129.4 (CH), 128.8 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 126.1 (C_q), 56.6 (CH_2), 26.6 (CH_3).

IR(ATR): 1669, 1602, 1357, 1265, 1185, 1033, 1003, 957, 854, 832, 795, 733 cm^{-1}.

MS (EI) *m/z* (relative intensity): 354 (12) [M^+], 326 (40), 235 (45), 207 (100), 192 (35), 179 (62), 164 (65), 91 (85).

HRMS (EI) *m/z* for $C_{22}H_{18}N_4O^+$ [M^+] calcd. 354.1481

found 354.1478



102ad:

M. p.: 171–172 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 4H), 7.65 (dd, J = 8.3, 7.1 Hz, 1H), 7.51–7.45 (m, 2H), 7.34–7.22 (m, 3H), 7.22–7.15 (m, 4H), 7.02–6.95 (m, 2H), 5.54 (s, 2H), 2.55 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6 (C_q), 163.6 (C_q), 145.0 (C_q), 142.7 (C_q), 135.5 (C_q), 133.2 (C_q), 130.0 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 125.4 (C_q), 56.5 (CH_2), 26.6 (CH_3).

IR (ATR): 1674, 1605, 1401, 1360, 1265, 1177, 960, 856, 827, 808, 727, 706 cm^{-1}.

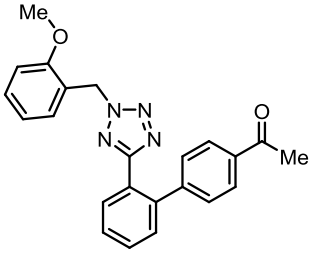
MS (EI) *m/z* (relative intensity): 472 (12) [M^+], 444 (40), 353 (14), 325 (15), 283 (22), 239 (73), 91 (100).

HRMS (EI) *m/z* for $C_{30}H_{24}N_4O_2^+$ [M^+] calcd. 472.1899

found 472.1892

Synthesis of 1-(2´-2-[2-Methoxybenzyl]-2*H*-tetrazol-5-yl)-[1,1´-biphenyl]-4-yl)ethan-1-one (101bd) and 1,1´-{2´-(2-[2-methoxybenzyl]-2*H*-tetrazol-5-yl)-[1,1´:3´,1´´-terphenyl]-4,4´´-diyl}bis(ethan-1-one) (102bd)

Procedure D1 was followed using 2-(2-methoxybenzyl)-5-phenyl-*2H*-tetrazole (**100b**) (134 mg, 0.50 mmol) and 4-bromoacetophenone (**18d**) (113 mg, 0.57 mmol) , K_2CO_3 (140 mg, 1.00 mmol), $MesCO_2H$ (26 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 5.2 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane / EtOAc 3/1) yielded **101bd** (23.5 mg, 12%) as a colorless oil and **102bd** (92.4 mg, 37%) as a white solid.



101bd:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.83–7.73 (m, 2H), 7.58–7.44 (m, 2H), 7.40 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.34–7.24 (m, 1H), 7.25–7.15 (m, 2H), 6.94–6.79 (m, 3H), 5.68 (s, 2H), 3.78 (s, 3H), 2.59 (s, 3H).

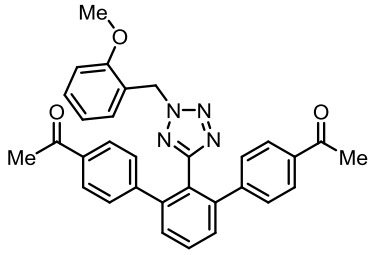
^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.7 (C_q), 164.9 (C_q), 157.0 (C_q), 145.9 (C_q), 140.8 (C_q), 135.5 (C_q), 130.4 (CH), 130.3 (CH), 130.2 (CH), 130.0 (CH), 129.7 (CH), 129.4 (CH), 128.1 (CH), 127.9 (CH), 121.6 (C_q), 121.6 (C_q), 120.5 (CH), 110.7 (CH), 55.5 (CH_3), 51.4 (CH_2), 26.6 (CH_3).

IR (ATR): 1678, 1603, 1495, 1356, 1250, 1026, 1005, 956, 837, 786, 753 cm^{-1}.

MS (EI) *m/z* (relative intensity): 384 (15) [M^+], 356 (18), 207 (55), 206 (52), 179 (35), 164 (32), 121 (100), 91 (85).

HRMS (EI) *m/z* for $C_{23}H_{20}N_4O_2^+$ [M^+] calcd. 384.1586

found 384.1580



102bd:

M. p: 141–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.70 (m, 4H), 7.64 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.30–7.16 (m, 5H), 6.81 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.74 (td, *J* = 7.5, 1.1 Hz, 1H), 6.57 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.60 (s, 2H), 3.74 (s, 3H), 2.56 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.6 (C_q), 163.2 (C_q), 156.7 (C_q), 145.1 (C_q), 142.7 (C_q), 135.5 (C_q), 130.0 (CH), 129.5 (CH), 129.4 (CH), 128.9 (CH), 127.9 (CH), 125.6 (C_q), 121.7 (C_q), 120.5 (CH), 110.6 (CH), 55.5 (CH_3), 51.2 (CH_2), 26.6 (CH_3).

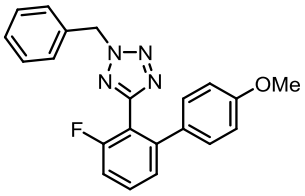
IR (ATR): 1676, 1603, 1495, 1358, 1251, 1111, 1050, 960, 838, 808, 788, 748, 706 cm^{-1}.

MS (EI) *m/z* (relative intensity): 502 (15), 474 (32), 283 (18), 239 (67), 121 (100), 91 (82).

HRMS (EI) *m/z* for $C_{31}H_{26}N_4O_3$ [M^+] calcd 502.2005

found 502.2005

Synthesis of 2-Benzyl-5-(3-fluoro-4´-methoxy-[1,1´-biphenyl]-2-yl)-2*H*-tetrazole (101cb)



General procedure D1 was followed using 2-benzyl-5-(2-fluorophenyl)-2*H*-tetrazole (**100c**) (128 mg, 0.50 mmol), 4-bromoanisole (**18b**) (109 mg, 0.58 mmol), K_2CO_3 (140 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (16.0 mg, 0.026 mmol, 5.2 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 10/1) yielded **101cb** (156 mg, 86%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (td, *J* = 8.1, 5.7 Hz, 1H), 7.32 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.24 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.20–7.11 (m, 3H), 7.01–6.93 (m, 2H), 6.72–6.59 (m, 2H), 5.73 (s, 2H), 3.76 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1 (C_q, J_{C-F} = 251 Hz), 160.3 (C_q), 158.8 (C_q), 144.7 (C_q, J_{C-F} = 4 Hz), 133.3 (C_q), 131.4 (CH, J_{C-F} = 9 Hz), 131.4 (C_q), 130.1 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 125.6 (CH, J_{C-F} = 3 Hz), 115.1 (C_q, J_{C-F} = 15 Hz), 114.1 (CH, J_{C-F} = 22 Hz), 113.5 (CH), 56.6 (CH_2), 55.1 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –112.9 (dd, *J* = 9.2, 5.7 Hz).

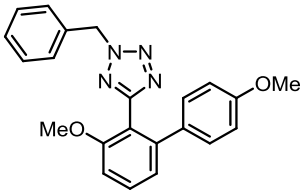
IR (ATR): 1610, 1512, 1462, 1430, 1290, 1237, 1179, 1093, 1032, 893, 834, 796, 732, 714 cm^{-1}.

MS (EI) *m/z* (relative intensity): 360 (20) [M^+], 332 (10), 241 (32), 213 (98), 198 (25), 170 (65), 91 (50).

HRMS (EI) *m/z* for $C_{21}H_{17}FN_4O^+$ [M^+] calcd. 360.1386

found 360.1376

Synthesis of 2-Benzyl-5-(3,4´-dimethoxy-[1,1´-biphenyl]-2-yl)-2*H*-tetrazole (101db)



General procedure D1 was followed using 2-benzyl-5-(2-methoxyphenyl)-2*H*-tetrazole (**100d**) (154 mg, 0.57 mmol), 4-bromoanisole (**18b**) (108 mg, 0.57 mmol), K_2CO_3 (140 mg, 1.00 mmol), $MesCO_2H$ (27 mg, 0.16 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (n-hexane/EtOAc 5/1) yielded **101db** (179.4 mg, 83%) as a yellow solid.

M. p.: 108–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.39 (td, *J* = 8.0, 1.1 Hz, 1H), 7.34–7.24 (m, 3H), 7.14–7.06 (m, 2H), 7.03 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.00–6.92 (m, 3H), 6.61 (dd, *J* = 8.8, 0.9 Hz, 2H), 5.71 (s, 2H), 3.79 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3 (C_q), 158.5 (C_q), 158.4 (C_q), 144.3 (C_q), 133.6 (C_q), 132.4 (C_q), 131.0 (CH), 130.1 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 122.1 (CH), 115.9 (C_q), 113.2 (CH), 109.4 (CH), 56.3 (CH_2), 55.9 (CH_3), 55.0 (CH_3).

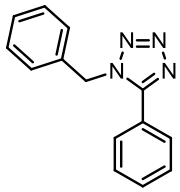
IR (ATR): 1605, 1569, 1526, 1465, 1441, 1429, 1261, 1235, 1117, 1034, 1018, 839, 790, 775 cm^{-1}.

MS (EI) *m/z* (relative intensity): 372 (35) [M^+], 344 (30), 253 (60), 239 (40), 225 (50), 210 (35), 195 (72), 182 (52), 165 (50), 152 (70), 139 (40), 91 (100).

HRMS (EI) *m/z* for $C_{22}H_{20}N_4O_2^+$ [M^+] calcd. 372.1586

found 372.1576

Synthesis of 1-Benzyl-5-phenyl-1*H*-tetrazole (60a)



General procedure C2 was followed using benzylamine (**105a**) (3.16 g, 29.4 mmol) and benzoyl chloride (**104a**) (3.97 g, 28.2 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **60a** (4.17 g, 63%) as a white solid.

M. p.: 94–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.44 (m, 5H), 7.35 (m, 3H), 7.20–7.10 (m, 2H), 5.62 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5 (C_q), 133.8 (C_q), 131.2 (CH), 129.0 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 127.0 (CH), 123.6 (C_q), 51.3 (CH_2).

IR (ATR): 1497, 1458, 1401, 1368, 1136, 1109, 1076, 774, 732, 720, 693, 671, 607 cm^{-1}.

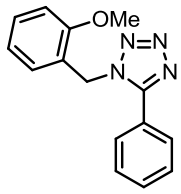
MS (EI) *m/z* (relative intensity): 236 (20) [M^+], 207 (8), 179 (25), 91 (100), 65 (15).

HRMS (EI) *m/z* for $C_{14}H_{12}N_4^+$ [M^+] calcd. 236.1062

found 236.1055

The spectral data were in accordance with those reported in the literature.[117]

Synthesis of 1-(2-Methoxybenzyl)-5-phenyl-1*H*-tetrazole (60b)



General procedure C2 was followed using 2-methoxybenzylamine (**105b**) (4.92 g, 35.8 mmol) and benzoyl chloride (**104a**) (4.80 g, 34.1 mmol). Recrystallization from EtOAc yielded **60b** (3.46 g, 38%) as a white powder.

M. p.: 100–101 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.61 (m, 2H), 7.60–7.44 (m, 3H), 7.31 (ddd, *J* = 8.3, 7.3, 2.0 Hz, 1H), 7.02–6.92 (m, 1H), 6.88 (ddd, *J* = 10.9, 7.9, 1.1 Hz, 2H), 5.63 (s, 2H), 3.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3 (C_q), 154.6 (C_q), 130.9 (CH), 129.9 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 124.0 (C_q), 122.1 (C_q), 120.8 (CH), 110.4 (CH), 55.2 (CH_3), 46.8 (CH_2).

IR (ATR): 1602, 1529, 1494, 1462, 1334, 1296, 1115, 1029, 761, 733, 712, 699 cm^{-1}.

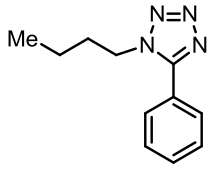
MS (EI) *m/z* (relative intensity): 266 (45) [M^+], 210 (15), 121 (100), 91 (95), 65 (35).

HRMS (EI) *m/z* for $C_{15}H_{14}N_4O^+$ [M^+] calcd. 266.1168

found 266.1174

The spectral data were in accordance with those reported in the literature.[78c]

Synthesis of 1-*n*-Butyl-5-phenyl-1*H*-tetrazole (60c)



General procedure C2 was followed using *n*-butylamine (**105c**) (1.0 mL, 10.1 mmol) and benzoyl chloride (**104a**) (1.3 mL, 11.2 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **60c** (405 mg, 20%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.50 (m, 5H), 4.41 (t, *J* = 7.5 Hz, 2H), 1.97–1.81 (m, 2H), 1.41–1.23 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1 (C_q), 131.1 (CH), 129.2 (CH), 129.6 (CH), 128.6 (CH), 128.6 (CH), 124.1 (C_q), 47.8 (CH_2), 31.7 (CH_2), 19.6 (CH_2), 13.4 (CH_3).

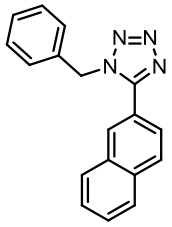
IR (film): 2961, 1536, 1463, 1405, 1112, 1077, 996, 778 cm^{-1}.

MS (EI) *m/z* (relative intensity): 203 (10), 174 (15), 173 (100), 159 (15), 131 (13), 118 (55), 104 (53), 103 (20), 91 (24), 90 (25), 89 (23), 77 (38), 41 (38).

HRMS (EI) *m/z* for $C_{11}H_{14}N_4^+$ [M^+] calcd 202.1218

found 202.1224.

Synthesis of 1-Benzyl-5-(naphtalen-2-yl)-1*H*-tetrazole (60d)



General procedure C1 was followed using benzylamine (**105a**) (1.26 g, 11.8 mmol) and 2-naphtoic acid (**103b**) (2.07 g, 12.0 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 6/1) yielded **60d** (1.87 g, 55%) as a yellow solid.

M. p.: 99–100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 1.7 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.91 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.81 (m, 1H), 7.68 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.64–7.52 (m, 2H), 7.43–7.33 (m, 3H), 7.25–7.17 (m, 2H), 5.69 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6 (C_q), 134.0 (C_q), 133.9 (C_q), 132.5 (C_q), 129.2 (CH), 129.0 (CH), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 124.8 (CH), 120.7 (C_q), 51.5 (CH_2).

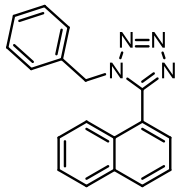
IR (ATR): 1587, 1528, 1264, 1234, 801, 775, 754, 718, 701, 658 cm^{-1}.

MS (EI) *m/z* (relative intensity): 286 (30) [M^+], 153 (12), 139 (15), 91 (100).

HRMS (EI) *m/z* for $C_{18}H_{14}N_4$ [M^+] calcd. 286.1218

found 286.1226

Synthesis of 1-Benzyl-5-(naphtalen-1-yl)-1*H*-tetrazole (60e)



General procedure C1 was followed using benzylamine (**105a**) (1.35 g, 12.6 mmol) and 1-naphtoic acid (**103c**) (2.15 g, 12.5 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 15/1) and recrystallization from *n*-hexane/$CHCl_3$ (v/v: 1/1) yielded **60e** (512 mg, 14%) as a white solid.

M. p.: 92–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.95 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.64–7.33 (m, 5H), 7.33–7.12 (m, 3H), 7.02–6.85 (m, 2H), 5.39 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7 (C_q), 133.4 (C_q), 133.3 (C_q), 131.6 (CH), 131.2 (C_q), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 126.9 (CH), 124.8 (CH), 124.3 (CH), 121.1 (C_q), 51.4 (CH_2).

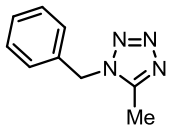
IR (ATR): 1587, 1528, 1497, 1397, 1114, 1073, 863, 801, 775, 755, 717, 701, 658 cm^{-1}.

MS (EI) *m/z* (relative intensity): 286 (18) [M^+], 257 (30), 153 (20), 139 (19), 91 (100), 65 (20).

HRMS (EI) *m/z* for $C_{18}H_{14}N_4$ [M^+] calcd. 286.1218

found 286. 1227

Synthesis of 1-Benzyl-5-methyl-1*H*-tetrazole (107a)



General procedure C2 was followed using benzylamine (**105a**) (3.4 mL, 31 mmol), and acetyl chloride (**104h**) (2.2 mL, 31 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 1/1) yielded **107a** (4.35 g, 83%) as a white solid.

M. p.: 51–53 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.33 (m, 3H), 7.20 (ddd, J = 5.3, 2.8, 0.8 Hz, 2H), 5.50 (s, 2H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ= 151.5 (C_q), 133.0 (C_q), 129.0 (CH), 128.7 (CH), 127.3 (CH), 50.6 (CH_2), 8.8 (CH_3).

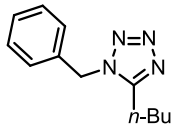
IR (ATR): 1530, 1407, 1241, 1120, 993, 786, 718, 698, 666, 578 cm^{-1}.

MS (EI) *m/z* (relative intensity): 174 (10) [M^+], 118 (15), 91 (100), 77 (10), 65 (15), 43 (15).

HRMS (EI) *m/z* for $C_9H_{10}N_4$ [M^+] calcd. 174.0905

found 174.0907

Synthesis of 1-Benzyl-5-*n*-butyl-1*H*-tetrazole (107b)



General procedure C2 was followed using benzylamine (**105a**) (1.1 mL, 10 mmol) and valeryl chloride (**104i**) (1.2 mL, 10 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **107b** (1.35 g, 62%) as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 3H), 7.22–7.13 (m, 2H), 5.49 (s, 2H), 2.77–2.65 (m, 2H), 1.70–1.58 (m, 2H), 1.39–1.24 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0 (C_q), 133.4 (C_q), 129.0 (CH), 128.7 (CH), 127.2 (CH), 50.5 (CH_2), 28.7 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 13.4 (CH_3).

IR (ATR): 2959, 1517, 1497, 1455, 1083, 721 cm^{-1}.

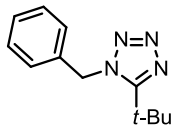
MS (EI) *m/z* (relative intensity): 216 (10) [M^+], 201 (10), 188 (20), 187 (100).

HRMS (ESI) *m/z* for $C_{12}H_{17}N_4$ [M+H^+] calcd. 217.1448

found 217.1450

The spectral data were in accordance with those reported in the literature.[118]

Synthesis of 1-Benzyl-5-(*tert*-butyl)-1*H*-tetrazole (107c)



General procedure C2 was followed using benzylamine (**105a**) (1.1 mL, 10 mmol) and pivaloyl chloride (**104j**) (1.3 mL, 10 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **107c** (1.64 g, 66%) as a white solid.

M. p.: 84–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 3H), 7.16–7.04 (m, 2H), 5.69 (s, 2H), 1.40 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (C_q), 134.3 (C_q), 128.9 (CH), 128.3 (CH), 126.6 (CH), 51.9 (CH_2), 31.3 (C_q), 28.9 (CH_3).

IR (ATR): 1499, 1455, 1263, 1208, 1171, 1113, 780, 723 cm^{-1}.

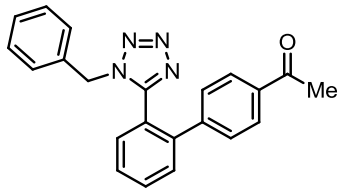
MS (EI) *m/z* (relative intensity): 216 (20) [M^+], 187 (20), 160 (15), 145 (15), 131 (35), 105 (35), 91 (100), 84 (27), 77 (18), 65 (31), 57 (39), 41 (32).

HRMS (EI) *m/z* for $C_{12}H_{16}N_4^+$ [M^+] calcd. 216.1375

found 216.1372

Synthesis of 1-{2'(1-Benzyl-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl}ethanone (62ad) and 1,1'-(1-benzyl-1*H*-tetrazol-5-yl)-[1,1'; 3', 1''-terphenyl]-4, 4''- diyl)diethanone (63ad)

General procedure D1 was followed using 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) (120 mg, 0.51 mmol), 4-bromoacetophenone (**18d**) (112 mg, 0.56 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (27.6 mg, 0.17 mmol, 30 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (16.1 mg, 0.026 mmol, 5.2 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded **62ad** (116 mg, 64%) and **63ad** (21 mg, 9%) as white solids.



62ad:

M. p.: 157–159 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.78 (m, 2H), 7.67 (td, *J* = 7.7, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (td, *J* = 7.7, 1.4 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.24–7.09 (m, 5H), 6.85–6.69 (m, 2H), 4.88 (s, 2H), 2.58 (s, 3H).

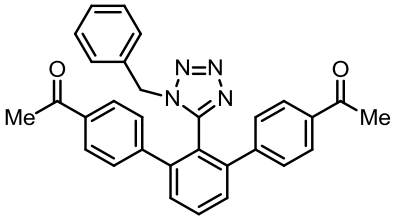
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4 (C_q), 154.2 (C_q), 143.3 (C_q), 140.7 (C_q), 136.3 (C_q), 132.8 (C_q), 131.7 (CH), 131.2 (CH), 130.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 122.7 (C_q), 51.0 (CH_2), 26.6 (CH_3).

IR (ATR): 1680, 1496, 1437, 1402, 1357, 1265, 959, 849, 721, 700 cm^{-1}.

MS (EI) *m/z* (relative intensity): 354 (12) [M^+], 353 (35), 325 (10), 206 (8), 192 (8), 179 (8), 164 (11), 151 (6), 91 (100), 65 (15), 43 (38).

HRMS (EI) *m/z* for $C_{22}H_{18}N_4O^+$ [M^+] calcd. 354.1481

found 354.1468.



63ad:

M. p.: 220–223 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.64 (m, 5H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.24 (ddt, *J* = 7.8, 7.4, 1.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.07–6.96 (m, 4H), 6.69 (dd, *J* = 7.1, 1.6 Hz, 2H), 4.72 (s, 2H), 2.55 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4 (C_q), 152.3 (C_q), 143.2 (C_q), 142.5 (C_q), 136.2 (C_q), 132.3 (C_q), 131.5 (CH), 129.9 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.1 (CH), 121.2 (C_q), 50.9 (CH_2), 26.6 (CH_3).

IR (ATR): 1683, 1604, 1424, 1394, 1354, 1264, 1111, 962, 825, 803, 726, 702, 596 cm^{-1}.

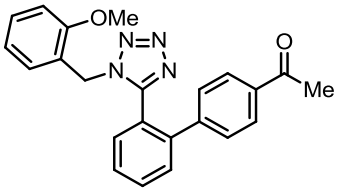
MS (EI) *m/z* (relative intensity): 473 (12), 472 (37) [M^+], 471 (35), 283 (12), 239 (19), 91 (100), 65 (10), 43 (74).

HRMS (EI) *m/z* for $C_{30}H_{24}N_4O_2^+$ [M^+] calcd. 472.1899

found 472.1902

Synthesis of 1-{2'-(1-[2-Methoxybenzyl]-1*H*-tetrazol-5-yl)-([1,1'-biphenyl]-4-yl)}ethanone (62bd) and 1,1'-{2'-(1-[2-Methoxybenzyl]-1*H*-tetrazol-5-yl)-[1,1':3', 1''-terphenyl]-4-4''-diyl}diethanone (63bd)

General procedure D1 was followed using **60b** (268 mg, 1.00 mmol), 4-bromoacetophenone (**18d**) (217 mg, 1.10 mmol), K_2CO_3 (278 mg, 2.00 mmol), $MesCO_2H$ (53.1 mg, 0.32 mmol, 32 mol %) and $[RuCl_2(p\text{-cymene})]_2$ (31.4 mg, 0.05 mmol, 5.0 mol %) in PhMe (3.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1 → 2:1) yielded **62bd** (250 mg, 65%) as a light yellow solid and **63bd** (56 mg, 11%) as a white solid.



62bd:

M. p.: 112–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.77 (m, 2H), 7.66 (ddd, *J* = 7.8, 7.1, 1.6 Hz, 1H), 7.57 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.51 (td, *J* = 7.4, 1.4 Hz, 1H), 7.45 (ddd, *J* = 7.8, 1.6, 0.6 Hz, 1H), 7.24–7.15 (m, 3H), 6.80 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.74 (td, *J* = 7.4, 1.0 Hz, 1H), 6.69 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.80 (s, 2H), 3.51 (s, 3H), 2.58 (s, 3H).

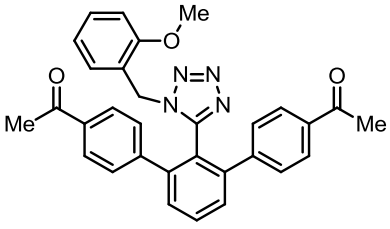
^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4 (C_q), 156.6 (C_q), 154.3 (C_q), 143.6 (C_q), 140.8 (C_q), 136.1 (C_q), 131.3 (CH), 131.3 (CH), 130.1 (CH), 130.1 (CH), 129.8 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 123.2 (C_q), 121.2 (C_q), 120.5 (CH), 110.3 (CH), 55.0 (CH_3), 46.0 (CH_2), 26.6 (CH_3).

IR (ATR): 1686, 1603, 1495, 1402, 1251, 1018, 844, 772, 760, 599 cm^{-1}.

MS (EI) *m/z* (relative intensity): 384 (24) [M^+], 383 (25), 356 (8), 235 (10), 207 (32), 206 (35), 179 (15), 164 (15), 121 (100), 91 (70).

HR-MS (EI) *m/z* for $C_{23}H_{19}N_4O_2^+$ [M-H^+] calcd. 383.1508

found 383.1510.



63bd:

M. p.: 155–156 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.81–7.66 (m, 5H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.30–7.16 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 4H), 6.76–6.67 (m, 2H), 6.62 (dd, *J* = 7.7, 1.8 Hz, 1H), 4.77 (s, 2H), 3.47 (s, 3H), 2.55 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.2 (C_q), 156.6 (C_q), 152.2 (C_q), 143.4 (C_q), 142.5 (C_q), 136.0 (C_q), 131.1 (CH), 130.3 (CH), 130.0 (CH), 129.7 (CH), 129.0 (CH), 128.1 (CH), 121.5 (C_q), 120.6 (CH), 120.5 (C_q), 110.4 (CH), 55.2 (CH_3), 46.1 (CH_2), 26.6 (CH_3).

IR (ATR): 1682, 1603, 1497, 1354, 1253, 1116, 1022, 804, 765 cm^{-1}.

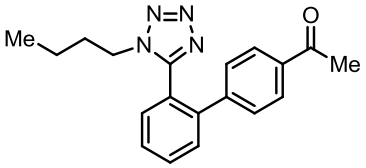
MS (EI) *m/z* (relative intensity): 502 (12) [M^+], 474 (20), 283 (10), 239 (22), 121 (100), 91 (75), 43 (24).

HRMS (EI) *m/z* for $C_{31}H_{26}N_4O_3^+$ [M^+] calcd. 502.2005

found 502.2012

Synthesis of 1-{2'-(*n*-Butyl-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl}ethanone (62cd) and 1,1'-{2'-(1-*n*-Butyl-1*H*-tetrazol-5-yl)[1,1':3',1''-terphenyl]-4-4''-diyl}diethanone (63cd)

General procedure D1 was followed using 1-*n*-butyl-5-phenyl-1*H*-tetrazole (**60c**) (102 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (111 mg, 0.55 mmol), K_2CO_3 (143 mg, 1.03 mmol), $MesCO_2H$ (26.9 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.026 mmol, 5.2 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **62cd** (85 mg, 53%) as a colorless oil and **63cd** (36 mg, 16%) as a white solid.



62cd:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.84 (m, 2H), 7.74–7.65 (m, 1H), 7.62–7.55 (m, 3H), 7.23 (d, *J* = 7.5 Hz, 2H), 3.55 (dd, *J* = 8.1, 6.8 Hz, 2H), 2.57 (s, 3H), 1.43–1.29 (m, 2H), 1.10–0.91 (m, 2H), 0.69 (t, *J* = 7.2 Hz, 3H).

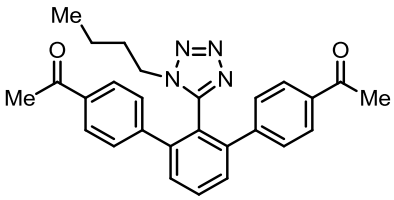
^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3 (C_q), 154.2 (C_q), 143.5 (C_q), 140.5 (C_q), 136.3 (C_q), 131.7 (CH), 131.5 (CH), 130.3 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 122.9 (C_q), 47.0 (CH_2), 30.6 (CH_2), 26.6 (CH_3), 19.4 (CH_2), 13.1 (CH_3).

IR (film): 2960, 1681, 1604, 1438, 1357, 1262, 1005, 841, 763, 596 cm^{-1}.

MS (EI) *m/z* (relative intensity): 319 (100) [M-H$^+$], 291 (45), 263 (8), 249 (18), 178 (14), 151 (10), 43 (30).

HRMS (ESI) *m/z* for $C_{19}H_{19}N_4O^+$ [M-H$^+$] calcd. 319.1559

found 319.1564.



63cd:

M. p.: 199–201 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.2 Hz, 4H), 7.76 (t, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 4H), 3.67–3.28 (m, 2H), 2.55 (s, 6H), 1.25 (ddd, *J* = 7.7, 6.0, 1.3 Hz, 2H), 1.06–0.76 (m, 2H), 0.68 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3 (C_q), 152.2 (C_q), 143.4 (C_q), 142.6 (C_q), 136.2 (C_q), 131.5 (CH), 130.0 (CH), 129.2 (CH), 128.3 (CH), 121.4 (C_q), 46.9 (CH_2), 30.3 (CH_2), 26.6 (CH_3), 19.5 (CH_2), 13.2 (CH_3).

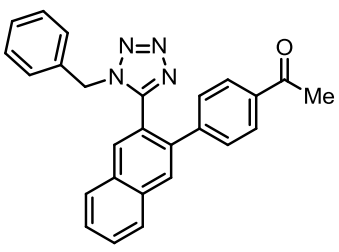
IR (ATR): 1681, 1602, 1405, 1358, 1260, 953, 846, 807, 604 cm^{-1}.

MS (EI) *m/z* (relative intensity): 438 (60) [M$^+$], 437 (100), 4096 (18), 381 (20), 325 (17), 311 (20), 269 (15).

HRMS (ESI) *m/z* for $C_{27}H_{25}N_4O_2^+$ [M-H$^+$] calcd. 437.1978

found 437.1976

Synthesis of 1-[4-{3‘-(1‘‘-Benzyl-1*H*-tetrazol-5-yl)naphtalen-2-yl}phenyl]ethanone (62dd)



General procedure D1 was followed using 1-benzyl-5-(naphtalen-2-yl)-1*H*-tetrazole (**60d**) (144 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (111 mg, 0.56 mmol), K_2CO_3 (141 mg, 1.02 mmol), $MesCO_2H$ (25.4 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.5 mg, 0.026 mmol, 5.2 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded **62dd** (97 mg, 48%) as a white solid.

General procedure D2 was followed using 1-benzyl-5-(naphtalen-2-yl)-1*H*-tetrazole (**60d**) (148 mg, 0.52 mmol), 4-bromoacetophenone (**18d**) (120 mg, 0.60 mmol), KOAc (100 mg, 1.0 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (16.2 mg, 0.026 mmol, 5.2 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4/1) yielded **62dd** (108.2 mg, 52%) as a white solid.

M. p.: 175–177 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.96 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.90 (s, 1H), 7.84 (dd, *J* = 8.5, 1.9 Hz, 3H), 7.69–7.56 (m, 2H), 7.25 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.19–7.03 (m, 3H), 6.76 (dd, *J* = 6.8, 1.6 Hz, 2H), 4.92 (s, 2H), 2.57 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.2 (C_q), 154.2 (C_q), 143.4 (C_q), 136.8 (C_q), 136.0 (C_q), 134.1 (C_q), 132.8 (C_q), 131.9 (C_q), 131.9 (CH), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.6 (CH), 120.3 (C_q), 51.0 (CH_2), 26.7 (CH_3).

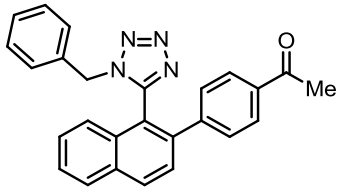
IR (ATR): 1675, 1597, 1492, 1430, 1356, 1264, 1118, 1099, 956, 836, 735, 603, 476 cm^{-1}.

MS (EI) *m/z* (relative intensity): 404 (38) [M^+], 403 (70), 375 (15), 257 (10), 227 (10) 214 (20), 91 (100) 65 (10), 43 (20).

HRMS (EI) *m/z* for $C_{26}H_{19}N_4O^+$ [M-H^+] calcd. 403.1559

found 403.1575

Synthesis of 1-{4-(1-[1-Benzyl-1*H*-tetrazol-5-yl]naphtalen-2-yl)phenyl}ethan-1-one (60e)



General procedure D1 was followed using 1-benzyl-5-(naphtalen-1-yl)-1*H*-tetrazole (**60e**) (146mg, 0.50 mmol), 4-bromacetophenone (**18d**) (109 mg, 0.55 mmol), K_2CO_3 (143 mg, 1.02 mmol), $MesCO_2H$ (26.6 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.7 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **62ed** (49.5 mg, 24%) as an orange solid.

M. p.: 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.88–7.78 (m, 2H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.40 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.32–7.24 (m, 2H), 7.14–7.01 (m, 2H), 6.95 (dd, *J* = 8.3, 6.8 Hz, 2H), 6.59 (dd, *J* = 7.4, 1.6 Hz, 2H), 4.94 (d, *J* = 14.8 Hz, 1H), 4.75 (d, *J* = 14.8 Hz, 1H), 2.59 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4 (C_q), 152.5 (C_q), 143.6 (C_q), 139.8 (C_q), 136.2 (C_q), 132.5 (C_q), 132.3 (C_q), 132.0 (C_q), 131.9 (CH), 129.4 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 126.9 (CH), 124.8 (CH), 119.3 (C_q), 51.1 (CH_2), 26.6 (CH_3).

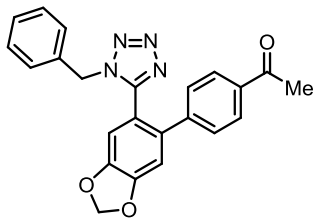
IR (ATR): 1677, 1605, 1355, 1265, 1240, 1119, 821, 781, 751, 730 cm^{-1}.

MS (EI) *m/z* (relative intensity): 404 (32) [M^+], 375 (10), 257 (11), 243 (15), 213 (19), 91 (100), 43 (36).

HRMS (EI) *m/z* for $C_{26}H_{19}N_4O^+$ [M-H^+] calcd. 403.1559

found 403.1565

Synthesis of 1-{4-(6-[1-Benzyl-1*H*-tetrazol-5-yl]benzo[d][1,3]dioxol-5-yl)phenyl}ethan-1-one (62hd)



General procedure D1 was followed using 5-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-1*H*-tetrazole (**60h**) (141 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (125 mg, 0.62 mmol), K_2CO_3 (141 mg, 1.00 mmol), $MesCO_2H$ (31.0 mg, 0.18 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (15.9 mg, 0.025 mmol, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **62hd** (53 mg, 26%) as a white solid.

General procedure D2 was followed using 5-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-1*H*-tetrazole (**60h**) (142 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (125 mg, 0.62 mmol), KOAc (99 mg, 1.0 mmol) and $[RuCl_2(p\text{-cymene})]_2$ (15.7 mg, 0.025 mmol, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **62hd** (12 mg, 6%) as a white solid.

M. p.: 228–230 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.5 Hz, 2H), 7.34–7.12 (m, 5H), 6.92 (s, 2H), 6.88–6.79 (m, 2H), 6.12 (s, 2H), 4.92 (s, 2H), 2.57 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.2 (C_q), 153.8 (C_q), 150.2 (C_q), 146.1 (C_q), 137.3 (C_q), 136.6 (C_q), 133.1 (C_q), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 125.9 (CH), 121.8 (C_q), 116.2 (C_q), 108.7 (CH), 102.2 (CH_2), 51.1 (CH_2), 26.9 (CH_3).

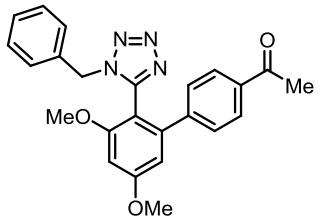
IR (ATR): 1674, 1495, 1254, 993, 985, 837 cm^{-1}.

MS (EI) *m/z* (relative intensity): 398 (16) [M^+], 369 (9), 208 (6), 150 (7), 98 (7), 91 (100), 69 (8), 43 (87).

HRMS (EI) *m/z* for $C_{23}H_{18}N_4O_3^+$ [M-H^+] calcd 397.1301

found 397.1307

Synthesis of 1-(2'-[1-Benzyl-1*H*-tetrazol-5-yl]-3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)ethan-1-one (62gd)



General procedure D2 was followed using 1-benzyl-5-(2,4-dimethoxyphenyl)-1*H*-tetrazole (**60g**) (149 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (118 mg, 0.59 mmol), KOAc (99 mg, 1.00 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1→1/1) yielded **62gd** (72.6 mg, 35%) as a white solid.

M. p.: 176–177 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 9.6 Hz, 2H), 7.20–7.11 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 7.1 Hz, 2H), 6.49 (dd, *J* = 9.9, 2.5 Hz, 2H), 5.05 (d, *J* = 3.4 Hz, 2H), 3.84 (s, 3H), 3.57 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5 (C_q), 162.4 (C_q), 158.8 (C_q), 151.7 (C_q), 144.3 (C_q), 143.5 (C_q), 136.2 (C_q), 133.4 (C_q), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 107.0 (CH), 104.3 (C_q), 98.1 (CH), 56.0 (CH_3), 55.9 (CH_3), 51.3 (CH_2), 26.9 (CH_3).

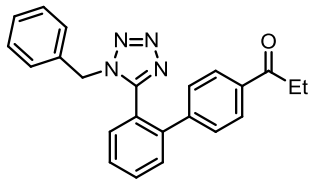
IR (ATR): 1681, 1496, 1394, 1208, 1147, 1012 cm^{-1}.

MS(EI) *m/z* (relative intensity): 414 (24) [M^+], 413 (49), 385 (11), 91 (100), 43 (98).

HRMS (EI) *m/z* for $C_{24}H_{22}N_4O_3^+$ [M^+] calcd. 414.1692

found 414.1684

Synthesis of 1-(2'-[1-Benzyl-1*H*-tetrazol-5-yl]-[1,1'-biphenyl]-4-yl) propan-1-one (62ap)



General procedure D1 was followed using 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) (122 mg, 0.51 mmol), 4'-bromopropiophenone (**18p**) (126 mg, 0.58 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25.6 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **62ap** (119 mg, 63%) as a white solid.

M. p.: 90–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dt, *J* = 8.5, 1.5 Hz, 2H), 7.67 (ddd, *J* = 8.8, 7.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 7.8, 1.3, 0.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 (ddd, *J* = 7.8, 1.3 Hz, 1H), 7.23–7.10 (m, 5H), 6.77 (d, *J* = 6.6 Hz, 2H), 4.86 (s, 2H), 2.97 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.0 (C_q), 154.2 (C_q), 143.1 (C_q), 140.7 (C_q), 136.1 (C_q), 132.8 (C_q), 131.6 (CH), 131.1 (CH), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH), 127.6 (CH), 122.7 (C_q), 50.9 (CH_2), 31.8 (CH_2), 8.0 (CH_3).

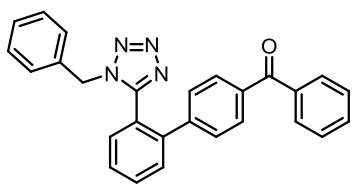
IR (ATR): 1682, 1400, 1223, 953, 804, 772, 759, 718, 705, 584 cm^{-1}.

MS (EI) *m/z* (relative intensity): 368 (30) [M^+], 367 (85), 339 (32), 206 (15), 192 (25), 178 (17), 164 (21), 151 (12), 91 (100), 65 (15).

HRMS (ESI) *m/z* for $C_{23}H_{19}N_4O^+$ [M-H^+] calcd. 367.1559

found 367.1557

Synthesis of 2'-(1-Benzyl-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl(phenyl)methanone (62af)



General procedure D1 was followed using 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) (119 mg, 0.50 mmol), 4-bromobenzophenone (**18f**) (149 mg, 0.57 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.4 mg, 0.026 mmol, 5.2 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1) yielded **62af** (174 mg, 70%) as a white solid.

M. p.: 123–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.65 (m, 5H), 7.66–7.56 (m, 2H), 7.54–7.45 (m, 3H), 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.25–7.12 (m, 5H), 6.80 (dt, *J* = 6.5, 1.6 Hz, 2H), 4.93 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.8 (C_q), 154.2 (C_q), 142.7 (C_q), 140.8 (C_q), 137.2 (C_q), 136.8 (C_q), 132.8 (C_q), 132.6 (CH), 131.6 (CH), 131.2 (CH), 130.5 (CH), 130.4 (CH), 129.9 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 126.6 (CH), 128.5 (CH), 128.3 (CH), 122.7 (C_q), 51.0 (CH_2).

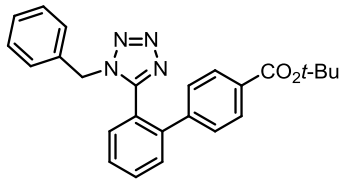
IR (ATR): 1653, 1600, 1446, 1402, 1276, 1098, 923, 794, 767, 697, 664, 633 cm^{-1}.

MS (EI) *m/z* (relative intensity): 416 (55) [M^+], 415 (100), 387 (26), 269 (8), 164 (8), 105 (30), 91 (60), 77 (22), 65 (10).

HRMS (ESI) *m/z* for $C_{27}H_{21}N_4O^+$ [M+H^+] calcd 417.1715

found 417.1710

Synthesis of *tert*-Butyl 2'-(1-benzyl-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl-carboxylate (62aw)



General procedure D1 was followed using 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) (120 mg, 0.51 mmol), *tert*-butyl 4-bromobenzoate (**18w**) (169 mg, 0.65 mmol), K_2CO_3 (140 mg, 1.00 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.6 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane 6:1) and recrystallization from EtOAc yielded **62aw** (121 mg, 58%) as a white solid.

M. p.: 190–192 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 7.1, 3.0 Hz, 2H), 7.66 (td, *J* = 7.6, 1.5 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.25–7.10 (m, 5H), 6.76 (dt, *J* = 6.9, 1.5 Hz, 2H), 4.83 (s, 2H), 1.59 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0 (C_q), 154.3 (C_q), 142.7 (C_q), 140.9 (C_q), 132.9 (C_q), 131.6 (CH), 131.5 (C_q), 131.2 (CH), 130.2 (CH), 129.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 122.7 (C_q), 81.4 (C_q), 50.9 (CH_2), 28.1 (CH_3).

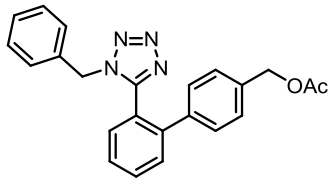
IR (ATR): 1699, 1470, 1457, 1438, 1401, 1363, 1295, 1161, 1121, 1106, 861, 848, 721, 556, 535 cm^{-1}.

MS (EI) *m/z* (relative intensity): 412 (55) [M^+], 411 (100), 355 (57), 339 (15), 327 (19), 209 (13), 164 (15), 91 (86), 57 (31).

HRMS (ESI) *m/z* for $C_{25}H_{25}N_4O_2^+$ [M+H^+] calcd. 413.1978

found 413.1972.

Synthesis of (2'-[1-Benzyl-1*H*-tetrazol-5-yl]-[1,1'-biphenyl]-4-yl)methylacetate (62al)



General procedure D1 was followed using 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) (119 mg, 0.50 mmol), 4-bromobenzyl acetate (**18l**) (134 mg, 0.58 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (30.2 mg, 0.18 mmol, 36 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.8 mg, 0.027 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1) yielded **62al** (114 mg, 59%) as a white solid.

M. p.: 72–73 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (dddd, *J* = 7.8, 7.1, 1.4, 0.7 Hz, 1H), 7.55 (ddd, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.44 (tdd, *J* = 7.3, 1.4, 0.7 Hz, 1H), 7.34 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.29–7.23 (m, 2H), 7.21–7.09 (m, 5H), 6.78–6.72 (m, 2H), 5.08 (s, 2H), 4.82 (s, 2H), 2.13 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7 (C_q), 154.5 (C_q), 141.2 (C_q), 138.6 (C_q), 135.9 (C_q), 133.0 (C_q), 131.6 (CH), 131.2 (CH), 130.3 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 122.6 (C_q), 65.5 (CH_2), 50.8 (CH_2), 20.9 (CH_3).

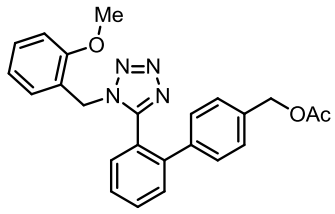
IR (ATR): 1724, 1498, 1469, 1248, 1108, 971, 926, 834, 824, 740, 716, 700, 666, 560, 528 cm^{-1}.

MS (EI) *m/z* (relative intensity): 384 (50) [M^+], 383 (100), 355 (17), 251 (20), 205 (20), 192 (8), 178 (20), 177 (28), 165 (12), 151 (10), 91 (86), 65 (14), 43 (21).

HRMS (EI) *m/z* for $C_{23}H_{19}N_4O_2^+$ [M-H^+] calcd. 383.1508

found 383.1503

Synthesis of 1-{(2'-(1-[2-Methoxybenzyl]-1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)}methyl acetate (62bl)



General procedure D1 was followed using 1'-(2-methoxybenzyl)-5-phenyl-1*H*-tetrazole (**60b**) (134 mg, 0.50 mmol), 4-bromobenzyl acetate (**18l**) (126 mg, 0.55 mmol), K_2CO_3 (140 mg, 1.01 mmol), $MesCO_2H$ (26.7 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded **62bl** (165 mg, 75%) as a white solid.

General procedure D1 was followed using 1'-(2-methoxybenzyl)-5-phenyl-1*H*-tetrazole (**60b**) (138 mg, 0.50 mmol), 4-bromobenzyl acetate (**18l**) (130 mg, 0.56 mmol), K_2CO_3 (144 mg, 1.01 mmol), $MesCO_2H$ (26.9 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (8.0 mg, 0.013 mmol, 2.5 mol %) were stirred in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4/1) yielded **62bl** (160.4 mg, 72%) as a white solid.

General procedure D1 was followed using 1'-(2-methoxybenzyl)-5-phenyl-1*H*-tetrazole (**60b**) (138 mg, 0.51 mmol), 4-bromobenzyl acetate (**18l**) (127 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.0 mmol), $MesCO_2H$ (26.3 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (3.9 mg, 0.005 mmol, 1.0 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4/1) yielded **62bl** (147.6 mg, 66%) as a white solid.

M. p.: 119–121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (ddd, *J* = 8.0, 6.5, 2.1 Hz, 1H), 7.55 (ddd, *J* = 7.7, 1.3, 0.7 Hz, 1H), 7.51–7.40 (m, 2H), 7.30–7. 24 (m, 2H), 7.20 (ddd, *J* = 8.5, 6.9, 2.3 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.83–6.72 (m, 2H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.08 (s, 2H), 4.75 (s, 2H), 3.51 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (C_q), 156.7 (C_q), 154.6 (C_q), 141.4 (C_q), 139.0 (C_q), 135.7 (C_q), 131.3 (CH), 131.2 (CH), 130.1 (CH), 130.1 (CH), 130.0 (CH), 128.8 (CH), 128.4 (CH), 127.7 (CH), 123.2 (C_q), 121.5 (C_q), 120.5 (CH), 110.3 (CH), 65.6 (CH_2), 55.0 (CH_3), 46.1 (CH_2), 21.0 (CH_3).

IR (ATR): 1733, 1538, 1495, 1278, 1099, 923, 838, 521 cm^{-1}.

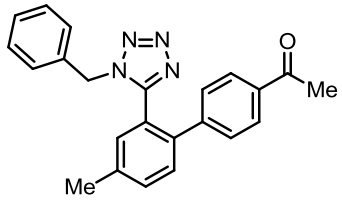
HRMS (ESI) *m/z* for $C_{24}H_{23}N_4O_3^+$ [M+H$^+$] calcd. 415.1770

found 415.1765.

The spectral data were in accordance with those reported in the literature.[78c]

Intramolecular competition experiments

Synthesis of 1-{2'-[1-Benzyl-1*H*-tetrazol-5-yl]-4'-methyl-[1,1'-biphenyl]-4-yl}ethanone (62kd')



General procedure D1 was followed using 1-benzyl-5-(3-tolyl)-1*H*-tetrazole (**60k**) (126 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (113 mg, 0.57 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (28.2 mg, 0.17 mmol, 34 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.4 mg, 0.026 mmol, 5.2 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded **62kd'** (121 mg, 65%) as a yellow solid.

General procedure D2 was followed using 1-benzyl-5-(3-tolyl)-1*H*-tetrazole (**60k**) (124 mg, 0.49 mmol), 4-bromoacetophenone (**18d**) (111 mg, 0.55 mmol), KOAc (100 mg, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.6 mg, 0.025 mmol, 5.0 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1) yielded **62kd'** (82.5 mg, 45%) as a yellow solid.

M. p.: 126–129 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.79 (ddd, *J* = 8.3, 2.0, 1.6 Hz, 2H), 7.44 (s, 1H), 7.44 (s, 1H), 7.18 (tdd, *J* = 7.4, 2.0, 1.3 Hz, 1H), 7.16–7.10 (m, 5H), 6.74 (d, *J* = 7.2 Hz, 2H), 4.83 (s, 2H), 2.54 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4 (C_q), 154.4 (C_q), 143.4 (C_q), 138.7 (C_q), 137.7 (C_q), 136.0 (C_q), 132.9 (C_q), 132.4 (CH), 131.7 (CH), 130.1 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 122.4 (C_q), 50.9 (CH_2), 26.6 (CH_3), 20.9 (CH_3).

IR (ATR): 2918, 1682, 1603, 1405, 1237, 1205, 1072, 955, 830, 717, 702, 601 cm^{-1}.

MS (EI) *m/z* (relative intensity): 368 (30) [M^+], 367 (77), 339 (22), 221 (8), 178 (17), 91 (100), 65 (10), 43 (27).

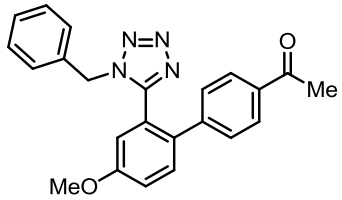
HRMS (EI) *m/z* for $C_{23}H_{19}N_4O^+$ [M-H^+] calcd. 367.1559

found 367.1560

Synthesis of 1-(2'-[1-Benzyl-1*H*-tetrazol-5-yl]-4'-methoxy-[1,1'-biphenyl]-4-yl)ethanone (62ld') and 1-(2'-[1-Benzyl-1*H*-tetrazol-5-yl]-6'-methoxy-[1,1'-biphenyl]-4-yl)ethanone (62ld")

General procedure D1 was followed using 1-benzyl-5-(3-methoxyphenyl)-1*H*-tetrazole (**60l**) (136 mg, 0.51 mmol), 4-bromoacetophenone (**18d**) (114 mg, 0.57 mmol), K_2CO_3 (141 mg, 1.02 mmol), $MesCO_2H$ (25.7 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.026 mmol, 5.2 mol %) in PhMe (2.0 mL). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1 → 4:1 → 3:1) yielded **62ld'** (67.6 mg, 35%) and **62ld"**(22.8 mg, 12%) as a yellow solid and a white solid respectively.

General procedure D2 was followed using 1-benzyl-5-(3-methoxyphenyl)-1*H*-tetrazole (**60l**) (132 mg, 0.49 mmol), 4-bromoacetophenone (**18d**) (117 mg, 0.58 mmol), KOAc (107 mg, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (16.4 mg, 0.026 mmol, 5.2 mol %). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 5/1→4/1→7/2) yielded **62ld'** (86.3 mg, 45%) as a yellow solid and **62ld"** (28.3 mg, 15%) as a white solid.



62ld':

M. p.: 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (dt, *J* = 8.1, 2.5 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.22–7.10 (m, 6H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.77 (dt, *J* = 6.8, 1.5 Hz, 2H), 4.84 (s, 2H), 3.77 (s, 3H), 2.56 (s, 3H).

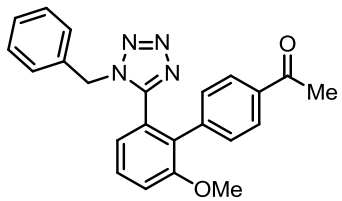
^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1 (C_q), 159.3 (C_q), 154.1 (C_q), 143.1 (C_q), 135.8 (C_q), 132.8 (C_q), 132.8 (C_q), 131.5 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 123.6 (C_q), 118.0 (CH), 115.7 (CH), 55.6 (CH_3), 51.0 (CH_2), 26.6 (CH_3).

IR (ATR): 1669, 1603, 1513, 1401, 1269, 1230, 1029, 850, 823, 731, 721, 706, 646, 599 cm^{-1}.

MS (EI) *m/z* (relative intensity): 384 (25) [M^+], 383 (65), 355 (20), 236 (10), 151 (12), 91 (100), 65 (14), 43 (19).

HRMS (EI) *m/z* $C_{23}H_{19}N_4O^+$ [M-H^+] calcd. 383.1508

found 383.1518



62ld":

M. p.: 59–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ =7.80 (dt, *J* = 8.5, 2.0 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.25–7.17 (m, 4H), 7.15 (dd, *J* = 8.5, 1.9 Hz, 2H), 6.95 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.86 (dt, *J* = 6.4, 1.3 Hz, 2H), 4.96 (s, 2H), 3.83 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5 (C_q), 156.9 (C_q), 153.8 (C_q), 139.3 (C_q), 136.0 (C_q), 133.1 (C_q), 130.5 (CH), 129.9 (C_q), 129.7 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 124.7 (C_q), 122.7 (CH), 113.8 (CH), 56.0 (CH_3), 50.9 (CH_2), 26.5 (CH_3).

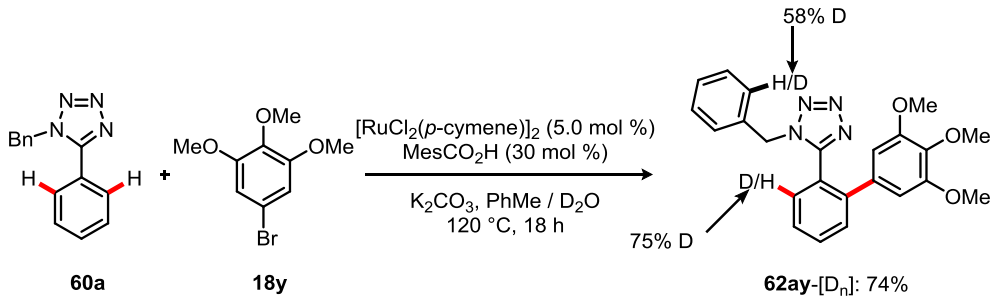
IR (ATR): 2931, 1679, 1606, 1498, 1435, 1401, 1260, 1080, 1024, 751, 721, 698, 602 cm^{-1}.

MS (EI) *m/z* (relative intensity): 384 (30) [M^+], 383 (60), 355 (15), 237 (11), 194 (13), 165 (8), 151 (8), 91 (100), 65 (13), 43 (15).

HRMS (ESI) *m/z* for $C_{23}H_{21}N_4O_2^+$ [M+H^+] calcd. 385.1665

found 385. 1659.

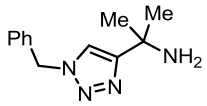
Labeling experiment with 60a and 18y



A mixture of 1-benzyl-5-phenyl-1*H*-tetrazole (**60a**) (121 mg, 0.51 mmol), 1-bromo-3,4,5-trimethoxybenzene (**18y**) (137 mg, 0.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (16.5 mg, 0.027 mmol, 5.4 mol %), $MesCO_2H$ (25.1 mg, 0.18 mmol) and K_2CO_3 (139 mg, 1.0 mmol), D_2O (0.2 mL) and *o*-xylene (1.8 mL) was stirred at 120 °C for 18 h under nitrogen. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1) yielded **62ay**-[D_n] (152.0 mg, 74%) as a yellow oil. The D-incorporation in **62ay**-[D_n] was estimated by ^{1}H NMR spectroscopy.

5.3.3 Ruthenium-Catalyzed Direct Arylation of Benzamides Bearing a Bidentate Directing Group

Synthesis of 2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (109a)



General procedure E1 was followed using benzylbromide (**99a**) (8.53 g, 50.0 mmol), and 2-methyl-2-aminobutyne (**108a**) (4.21 g, 50 mmol). Aqueous work up and Kugelrohrdistillation yielded **109a** (8.20 g, 76%) as a white solid.

M. p.: 66–68 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.22 (m, 6H), 5.49 (s, 2H), 2.14 (brs, 2H), 1.51 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ= 157.5 (C_q), 134.6 (C_q), 128.8 (CH), 128.4 (CH), 127.9 (CH), 118.3 (CH), 53.8 (CH_2), 48.4 (C_q), 31.2 (CH_3).

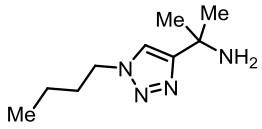
IR (ATR): 2966, 1497, 1456, 1198, 1053, 1015, 821, 716, 696 cm^{-1}.

MS (EI) *m/z* (relative intensity): 201 (85) [M^+], 156 (5), 91 (100), 65 (18), 58 (15).

HRMS (ESI) *m/z* for $C_{12}H_{16}N_4Na^+$ [M+Na^+] calcd. 239.1267

found 239.1263

Synthesis of 2-(1-*n*-Butyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (109b)



General procedure E1 was followed using *n*-butylbromide (**95b**) (1.44 g, 10.0 mmol), and 2-methyl-2-aminobutyne (**108a**) (858 mg, 10.0 mmol). Aqueous work up yielded **109b** (1.46 g, 76%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 4.30 (ddd, *J* = 7.4, 4.5, 1.5 Hz, 2H), 2.60 (brs, 2H), 2.01–1.71 (m, 2H), 1.53 (s, 6H), 1.36 (ddd, *J* = 12.2, 5.5, 3.2 Hz, 2H), 0.95 (ddd, *J* = 7.7, 4.8, 2.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8 (C_q), 118.4 (CH), 49.9 (CH_2), 48.7 (C_q), 32.3 (CH_2), 31.2 (CH_3), 19.7 (CH_2), 13.4 (CH_3).

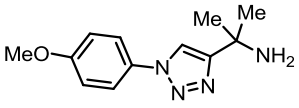
IR(ATR): 3359, 2962, 2873, 1599, 1462, 1381, 1219, 1127 cm^{-1}.

MS (EI) *m/z* (relative intensity): 182 (10) [M^+], 167 (100), 155 (40), 138 (15), 84 (31), 57 (66), 41 (35).

HRMS (ESI) *m/z* for $C_9H_{19}N_4^+$ [$M+H^+$] calcd 183.1604

found 183.1607

Synthesis of 2-{1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl}propan-2-amine (109c)



General procedure E2 was followed using 4-iodoanisole (**66a**) (2.41 g, 10.3 mmol) and 2-methyl-2-aminobutyne (**108a**) (829 mg, 10.0 mmol). Aqueous work up yielded **109c** (1.91 g, 82%) as an orange solid.

M. p.: 90–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 7.61 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 2.67 (brs, 2H), 1.63 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7 (C_q), 157.2 (C_q), 130.7 (C_q), 122.2 (CH), 117.3 (CH), 114.7 (CH), 55.6 (CH_3), 49.0 (C_q), 69.4 (CH_3).

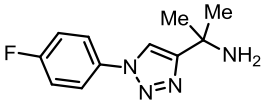
IR(ATR): 2964, 1515, 1300, 1250, 1215, 1053, 1027, 998, 873, 823, 807 cm^{-1}.

MS (EI) *m/z* (relative intensity): 232 (10) [M^+], 204 (52), 189 (100), 172 (34), 147 (80), 132 (50), 82 (44), 77 (60).

HRMS (EI) *m/z* for $C_{12}H_{16}N_4O$ [M^+] calcd. 232.1324

found 232.1334

Synthesis of 2-{1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl}propan-2-amine (109d)



General procedure E2 was followed using 4-fluoroiodobenzene (**66c**) (2.68 g, 12.0 mmol), and 2-methyl-2-aminobutyne (**108a**) (877 mg, 10.5 mmol). Aqueous work up yielded **109d** (2.00 g, 86%) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.69 (ddd, *J* = 9.1, 4.7, 1.0 Hz, 2H), 7.31–7.08 (m, 2H), 2.09 (s, 2H), 1.60 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.3 (C_q, J_{C-F} = 249 Hz), 157.7 (C_q), 133.5 (C_q, J_{C-F} = 3 Hz), 122.4 (CH, J_{C-F} = 9 Hz), 117.2 (CH), 116.6 (CH, J_{C-F} = 23 Hz), 48.9 (C_q), 31.2 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –112.5 (s).

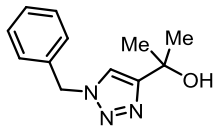
IR (ATR): 2969, 1515, 1381, 1229, 1157, 1098, 1043, 837 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 221 (16) [M^+], 204 (7), 176 (100), 161 (11), 122 (33).

HRMS (ESI) *m/z* for $C_{11}H_{14}N_4F^+$ [$M+H^+$] calcd. 221.1197

found 221.1198

Synthesis of 2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (109e)



General procedure E1 was followed using benzylbromide (**99a**) (1.87 g, 10.8 mmol), and 2-methyl-but-3-yn-2-ol (**108b**) (699 mg, 10.7 mmol). Aqueous work up yielded **109e** (2.0 g, 98%) as a white solid.

M. p.: 79–81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–6.66 (m, 6H), 5.50 (s, 2H), 2.49 (s, 1H), 1.61 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (C_q), 134.6 (C_q), 129.0 (CH), 128.6 (CH), 128.1 (CH), 119.0 (CH), 68.4 (C_q), 54.0 (CH_2), 30.4 (CH_3).

IR (ATR): 3300, 2976, 1457, 1372, 1220, 1172, 1078, 961, 794, 729, 719, 697 cm^{-1}.

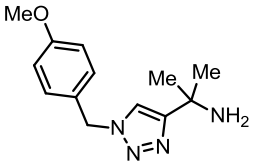
MS (ESI) *m/z* (relative intensity): 240 (60) [$M+Na^+$], 218 (100), 172 (20).

HR-MS (ESI) *m/z* for $C_{12}H_{14}N_3O^+$ [$M-H^+$] calcd. 216.1142

found 216.1142

The spectral data were in accordance with those reported in the literature.[119]

Synthesis of 2-{1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl}propan-2-amine (109f)



General procedure E1 was followed using 4-methoxybenzylbromide (**99a**) (2.12 g, 10.5 mmol) and 2-methyl-2-aminobutyne (**108a**) (877 mg, 10.5 mmol). Aqueous work up yielded **109f** (1.90 g, 73%) as a yellow solid.

M. p.: 58–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.11 (m, 3H), 6.89 (dd, J = 8.3, 1.2 Hz, 2H), 5.41 (s, 2H), 3.80 (s, 3H), 2.15 (s, 2H), 1.50 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5 (C_q), 157.2 (C_q), 129.4 (CH), 126.5 (C_q), 118.0 (CH), 114.2 (CH), 55.2 (CH_3), 53.4 (CH_2), 48.5 (C_q), 31.2 (CH_3).

IR (ATR): 2963, 1611, 1513, 1458, 1250, 1173, 1052, 1024, 880, 818, 767 cm^{-1}.

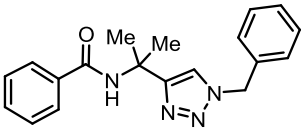
MS (ESI) *m/z* (relative intensity): 247 (34), 230 (42), 202 (100), 121 (64).

HRMS (ESI) *m/z* for $C_{13}H_{19}N_4O^+$ [M+H$^+$] calcd 247.1553

found 247.1556

Synthesis of Benzamides 78

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)benzamide (78a)



General procedure F1 was followed using benzoyl chloride (**104a**) (1.6 mL, 13.7 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (2.7 g, 12.5mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 1/1) yielded **78a** (3.4 g, 85%) as a white solid.

M. p.: 152–155 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.67 (m, 2H), 7.54–7.32 (m, 7H), 7.32–7.22 (m, 2H), 7.04 (s, 1H), 5.51 (s, 2H), 1.85 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7 (C_q), 153.9 (C_q), 135.2 (C_q), 134.5 (C_q), 131.2 (CH), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 126.8 (CH), 120.3 (CH), 54.1 (CH_2), 51.7 (C_q), 27.9 (CH_3).

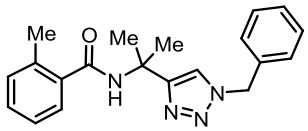
IR (ATR): 3285, 3118, 1648, 1578, 1299, 1219, 851, 727, 711, 689, 664 cm^{-1}.

MS (EI) *m/z* (relative intensity): 305 (15), 292 (32), 277 (90), 171 (15), 105 (85), 98 (15), 91 (100), 77 (55).

HR-MS (EI) *m/z* for $C_{19}H_{20}N_4O^+$ [M^+] calcd. 320.1637

found 320.1645

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (78b)



General procedure F1 was followed using 2-toluoyl chloride (**104b**) (1.6 mL, 12.2 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (2.45 g, 11.3 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 3/2 → 1/1) yielded **78b** (2.56 g, 68%) as a white solid.

M. p.: 120–121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.45–7.03 (m, 9H), 6.44 (s, 1H), 5.52 (s, 2H), 2.37 (s, 3H), 1.85 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 153.7 (C_q), 137.1 (C_q), 135.7 (C_q), 134.6 (C_q), 130.8 (CH), 129.6 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 126.6 (CH), 125.6 (CH), 120.4 (CH), 54.1 (CH_2), 51.8 (C_q), 27.9 (CH_3), 19.6 (CH_3).

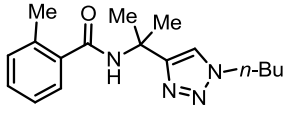
IR (ATR): 3241, 1639, 1532, 1192, 1049, 721, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 334 (10) [M^+], 306 (10), 291 (55), 200 (10), 119 (65), 91 (100).

HRMS (EI) *m/z* for $C_{20}H_{22}N_4O^+$ [M^+] calcd. 334.1794

found 334.1798

Synthesis of *N*-{2-[1-Butyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-2-methylbenzamide (78c)



General Procedure F1 was followed using 2-toluoyl chloride (**104b**) (1.1 mL, 8.4 mmol), and 2-(1-butyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109b**) (1.46 g, 8.0 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 1/1) yielded **78c** (1.70 g, 70%) as a white solid.

M. p.: 80–81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 7.36 (dd, J = 7.9, 1.5 Hz, 1H), 7.30–7.20 (m, 1H), 7.22–7.10 (m, 2H), 6.48 (s, 1H), 4.34 (t, J = 7.3 Hz, 2H), 2.40 (s, 3H), 2.02–1.71 (m, 8H), 1.50–1.25 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (C_q), 153.1 (C_q), 137.1 (C_q), 135.6 (C_q), 130.7 (CH), 129.5 (CH), 126.5 (CH), 125.5 (CH), 120.2 (CH), 51.8 (C_q), 49.9 (CH_2), 32.1 (CH_2), 27.9 (CH_3), 19.6 (CH_2), 19.5 (CH_3), 13.3 (CH_3).

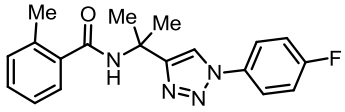
IR (ATR): 3259, 2965, 2935, 1645, 1531, 1317, 1193, 1046, 801, 747, 722 cm^{-1}.

MS (EI) *m/z* (relative intensity): 300 (55) [M^+], 272 (25), 257 (90), 229 (32), 201 (15), 166 (34), 119 (100), 91 (73), 84 (37), 57 (38).

HRMS (EI) *m/z* for $C_{17}H_{24}N_4O^+$ [M^+] calcd. 300.1950

found 300.1946

Synthesis of *N*-{2-(1-[4-Fluorophenyl]-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-2-methylbenzamide (78d)



General procedure F1 was followed using 2-toluoyl chloride (**104b**) (1.3 mL, 9.9 mmol), and 2-(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109d**) (2.0 g, 9.1 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 5/1) and recrystallization from EtOAc (10 mL) yielded **78d** (1.9 g, 62%) as a white solid.

M. p.: 157–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1H), 7.84–7.64 (m, 2H), 7.48–7.28 (m, 1H), 7.32–7.08 (m, 5H), 6.41 (s, 1H), 2.42 (s, 3H), 1.93 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 162.2 (C_q, J_{C-F} = 249 Hz), 153.7 (C_q), 136.8 (C_q), 135.7 (C_q), 133.3 (C_q, J_{C-F}= 3 Hz), 130.8 (CH), 129.6 (CH), 126.6 (CH), 125.6 (CH), 122.4 (CH, J_{C-F}= 9 Hz), 119.1 (CH), 116.5 (CH, J_{C-F}= 23 Hz), 51.6 (C_q), 28.0 (CH_3), 19.6 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -112.40 (d, J = 4.5 Hz).

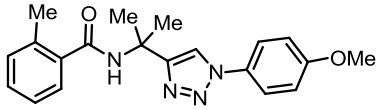
IR (ATR): 3244, 3128, 1660, 1538, 1309, 1228, 1205, 1095, 840, 820 cm^{-1}.

MS (EI) *m/z* (relative intensity): 338 (2) [M^+], 310 (43), 295 (70), 175 (40), 160 (25), 119 (100), 91 (70).

HRMS (EI) *m/z* for $C_{19}H_{19}FN_4O^+$ [M^+] calcd. 338.1543

found 338.1537

Synthesis of *N*-{2-(1-[4-Methoxyphenyl]-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-2-methylbenzamide (78e)



General procedure F1 was followed using 2-toluoyl chloride (**104b**) (1.1 mL, 8.4 mmol), and 2-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109c**) (1.9 g, 8.2 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 1/1) yielded **78e** (1.76 g, 61%) as a light yellow solid.

M. p.: 171–172 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.39 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.27 (ddd, *J* = 7.7, 7.3, 1.6 Hz, 1H), 7.24–7.10 (m, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.48 (s, 1H), 3.86 (s, 3H), 2.43 (s, 3H), 1.94 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 159.7 (C_q), 153.6 (C_q), 137.0 (C_q), 135.7 (C_q), 130.8 (CH), 130.5 (C_q), 129.6 (CH), 126.6 (CH), 125.6 (CH), 122.1 (CH), 119.0 (CH), 114.6 (CH), 55.5 (CH_3), 51.8 (C_q), 28.0 (CH_3), 19.6 (CH_3).

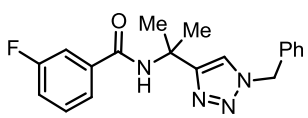
IR (ATR): 3239, 3142, 1652, 1516, 1309, 1260, 1057, 823, 652 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 373 (30) [M+Na^+], 351 (100), 188 (25).

HRMS (ESI) *m/z* for $C_{20}H_{23}N_4O_2^+$ [M+H^+] calcd. 351.1816

found 351.1816

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-3-fluorobenzamide (78f)



General Procedure F1 was followed using 3-fluorobenzoyl chloride (**104c**) (1.3 mL, 10.7 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (2.19 g, 10.1 mmol). Recrystallization from EtOAc (20 mL) yielded **78f** (2.51 g, 73%) as a white solid.

M. p.: 151–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.23 (m, 9H), 7.24–7.10 (m, 1H), 7.07 (br s, 1H), 5.52 (s, 2H), 1.84 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3 (C_q, J_{C-F} = 3 Hz), 162.6 (C_q, J_{C-F} = 248 Hz), 153.7 (C_q), 137.5 (C_q, J_{C-F} = 7 Hz), 134.5 (C_q), 130.0 (CH, J_{C-F} = 8 Hz), 129.0 (CH), 128.7 (CH), 128.0 (CH, J_{C-F} = 2 Hz), 122.3 (CH, J_{C-F} = 3 Hz), 120.2 (CH), 118.1 (CH, J_{C-F} = 21 Hz), 114.2 (CH, J_{C-F} = 23 Hz), 54.1 (CH_2), 52.0 (C_q), 27.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -(111.9–112.2) (m).

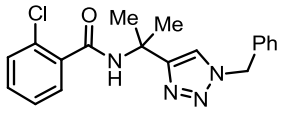
IR (ATR): 3252, 3116, 1653, 1586, 1481, 1269, 1188, 756, 722, 695 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 361 (35) [M+Na$^+$], 339 (100) [M+H$^+$].

HRMS (ESI) *m/z* for $C_{19}H_{19}N_4OFNa^+$ [M+Na$^+$] calcd. 361.1435

found 361.1434

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-chlorobenzamide (78g)



General procedure F1 was followed using 2-chlorobenzoyl chloride (**104d**) (0.82 mL, 6.5 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (1.33 g, 6.1 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1→1/1) yielded **78g** (1.85 g, 85 %) as a white solid.

M. p.: 125–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 1H), 7.50 (s, 1H), 7.40–7.34 (m, 3H), 7.33 (t, *J* = 2.1 Hz, 1H), 7.31–7.24 (m, 4H), 6.72 (brs, 1H), 5.52 (s, 2H), 1.86 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7 (C_q), 153.2 (C_q), 135.8 (C_q), 134.4 (C_q), 130.7 (CH), 130.4 (C_q), 129.9 (CH), 129.3 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 126.7 (CH), 120.3 (CH), 54.0 (CH_2), 52.3 (C_q), 27.9 (CH_3).

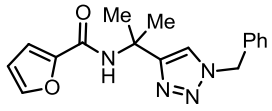
IR (ATR): 3249, 3058, 1647, 1536, 1320, 1193, 1036, 758, 726, 713, 680, 464 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 377 (42) [M+Na$^+$], 355 (100) [M+H$^+$].

HRMS (ESI) *m/z* for $C_{19}H_{20}N_4OCl^+$ [M+H$^+$] calcd. 355.1320

found 355.1321

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)furan-2-carboxamide (78h)



General procedure F1 was followed using 2-furoyl chloride (**104e**) (0.70 mL, 7.1 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (1.37 g, 6.3 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1→1/1) yielded **78h** (1.26 g, 64%) as a white solid.

M. p.: 95–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H), 7.43–7.32 (m, 4H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.01 (d, *J* = 4.1 Hz, 2H), 6.49–6.41 (m, 1H), 5.50 (s, 2H), 1.83 (d, *J* = 1.6 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4 (C_q), 153.3 (C_q), 148.1 (C_q), 143.5 (CH), 134.5 (C_q), 128.8 (CH), 128.4 (CH), 127.8 (CH), 120.3 (CH), 113.5 (CH), 111.8 (CH), 54.0 (CH_2), 51.5 (C_q), 28.0 (CH_3).

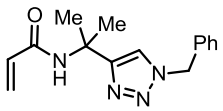
IR (ATR): 3237, 3116, 1654, 1568, 1531, 1302, 1054, 741, 720, 695 cm^{-1}.

MS (EI) *m/z* (relative intensity): 310 (8) [M$^+$], 295 (10), 282 (30), 267 (55), 171 (10), 98 (12), 95 (75), 91 (100), 65 (15).

HRMS (EI) *m/z* for $C_{17}H_{18}N_4O_2^+$ [M$^+$] calcd. 310.1430

found 310.1430

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)acrylamide (78i)



General procedure F1 was followed using acroyl chloride (**104f**) (0.55 mL, 6.8 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (1.34 g, 6.2 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 1/1→EtOAc) yielded **78i** (1.32 g, 79%) as a white solid.

M. p.: 150–151 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.40–7.33 (m, 3H), 7.31–7.21 (m, 2H), 6.45 (brs, 1H), 6.21 (dt, *J* = 16.9, 1.6 Hz, 1H), 6.06 (ddd, *J* = 16.9, 9.9, 1.3 Hz, 1H), 5.57 (dd, *J* = 9.9, 1.6 Hz, 1H), 5.49 (s, 2H), 1.77 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6 (C_q), 153.5 (C_q), 134.5 (C_q), 131.5 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 125.7 (CH_2), 120.3 (CH), 54.1 (CH_2), 51.4 (C_q), 27.8 (CH_3).

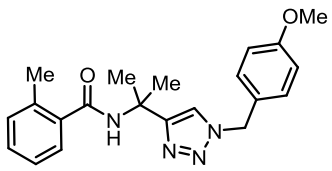
IR (ATR): 3246, 3114, 2981, 1674, 1551, 1400, 1241, 1216, 1056, 714, 694 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 293 (66) [M+Na$^+$], 271 (100) [M+H$^+$], 200 (5), 172 (12).

HRMS (ESI) *m/z* for $C_{15}H_{19}N_4O^+$ [M+H$^+$] calcd. 271.1553

found 271.1554

Synthesis of *N*-{2-[1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-2-methylbenzamide (78j)



General procedure F1 was followed using *o*-toluoyl chloride (**104b**) (0.70 mL, 5.3 mmol) and 2-(1-[4-methoxybenzyl]-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109f**) (1.01 g, 4.1 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 1/1) yielded **78j** (1 18 g, 79%) as a white solid.

M. p.: 142–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 0.8 Hz, 1H), 7.37–7.31 (m, 1H), 7.30–7.20 (m, 3H), 7.19–7.12 (m, 2H), 6.94–6.85 (m, 2H), 6.47 (s, 1H), 5.43 (s, 2H), 3.80 (s, 3H), 2.37 (s, 3H), 1.83 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5 (C_q), 159.8 (C_q), 153.6 (C_q), 137.1 (C_q), 135.6 (C_q), 130.8 (CH), 129.6 (CH), 129.5 (CH), 126.6 (CH), 126.5 (C_q), 125.6 (CH), 120.1 (CH), 114.4 (CH), 55.2 (CH_3), 53.6 (CH_2), 51.8 (C_q), 27.9 (CH_3), 19.5 (CH_3).

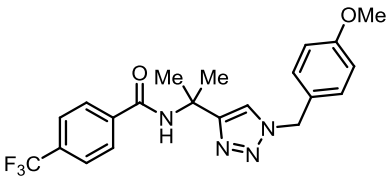
IR (ATR): 3137, 2978, 1655, 1535, 1252, 1057, 1033, 735 cm^{-1}.

MS (EI) *m/z* (relative intensity): 364 (11) [M$^+$], 336 (10), 321 (46), 121 (100), 119 (42), 91 (28).

HRMS (EI) *m/z* for $C_{21}H_{24}N_4O_2^+$ [M$^+$] calcd. 364.1899

found 364.1901

Synthesis of N-{2-(1-[4-Methoxybenzyl]-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-4-(trifluoromethyl)benzamide (78k)



General procedure F1 was followed using 4-trifluoromethylbenzoyl chloride (**104g**) (0.35 mL, 2.4 mmol) and 2-(1-[4-methoxybenzyl]-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109f**) (561 mg, 2.3 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 3/2→1/1) yielded **78k** (810 mg, 85%) as a white solid.

M. p.: 127–129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.81 (m, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.40 (s, 1H), 7.32–7.21 (m, 2H), 7.19 (s, 1H), 6.98–6.84 (m, 2H), 5.46 (s, 2H), 3.81 (s 3H), 1.84 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3 (C_q), 160.0 (C_q), 153.7 (C_q), 138.5 (C_q), 132.9 (C_q, m), 129.7 (CH), 127.4 (CH), 126.4 (C_q), 125.4 (CH, J_{C-F} = 4 Hz), 123.7 (C_q, J_{C-F} = 273 Hz), 119.8 (CH), 114.5 (CH), 55.3 (CH_3), 53.8 (CH_2), 52.1 (C_q), 27.8 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.9 (s).

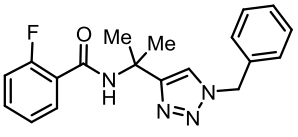
IR (ATR): 3227, 3146, 2978, 1652, 1614, 1515, 1327, 1305, 1229, 1159, 1116, 1066, 1058, 857, 836, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 390 (15), 375 (28), 173 (20), 145 (18), 121 (100).

HRMS (EI) *m/z* for $C_{21}H_{21}F_3N_4O_2^+$ [M^+] calcd. 418.1617

found 418.1624

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-fluorobenzamide (78l)



General procedure F2 was followed using 2-fluorobenzoic acid (**103f**) (884 mg, 6.3 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (1.35 g, 6.3 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 3/1) yielded **78l** (1.45 g, 68%) as a white solid.

M. p.: 127–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (tt, J = 7.9, 1.5 Hz, 1H), 7.47 (d, J = 1.1 Hz, 1H), 7.46–7.33 (m, 5H), 7.32–7.25 (m, 2H), 7.21 (tt, J = 7.6, 1.2 Hz, 1H), 7.09 (ddt, J = 8.3, 8.3, 1.2 Hz, 1H), 5.51 (s, 2H), 1.85 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (C_q, $J_{C–F}$ = 3 Hz), 160.4 (C_q, $J_{C–F}$ = 247 Hz), 159.5 (C_q), 134.6 (C_q), 133.0 (CH, $J_{C–F}$ = 9 Hz), 131.5 (CH, $J_{C–F}$ = 2 Hz), 128.9 (CH), 128.5 (CH), 127.9 (CH), 124.5 (CH, $J_{C–F}$ = 3 Hz), 121.8 (C_q, $J_{C–F}$ = 12 Hz), 120.4 (CH), 115.9 (CH, $J_{C–F}$ = 25 Hz), 54.0 (CH_2), 51.8 (C_q), 28.0 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = -112.91 (dddd, J = 13.4, 12.1, 8.0, 5.2 Hz).

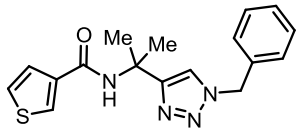
IR (ATR): 3312, 1641, 1551, 1319, 1220, 1013, 762, 721, 699 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 361 (50), 339 (100) [M^+], 200 (10), 172 (10).

HRMS (ESI) *m/z* for $C_{19}H_{20}N_4OF^+$ [M+H^+] calcd. 339.1616

found 339.1617

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)thiophene-3-carboxamide (78m)



General procedure F2 was followed using thiophen-3-carboxylic acid (**103h**) (810 mg, 6.3 mmol), and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (1.29 g, 6.0 mmol). Recrystallization from EtOAc (5 mL) yielded **78m** (1.07 g, 55%) as a white solid.

M. p.: 142–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (dd, J = 3.1, 1.3 Hz, 1H), 7.45 (s, 1H), 7.43–7.33 (m, 4H), 7.33–7.24 (m, 3H), 6.87 (s, 1H), 5.51 (s, 2H), 1.83 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3 (C_q), 153.8 (C_q), 138.2 (C_q), 134.5 (C_q), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 126.1 (CH), 126.1 (CH), 120.3 (CH), 54.1 (CH_2), 51.6 (C_q), 28.0 (CH_3).

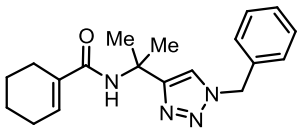
IR (ATR): 3116, 1637, 1532, 1291, 1221, 1055, 820, 748, 727, 698 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 349 (30), 327 (100) [M+H^+], 200 (10), 172 (10).

HRMS (ESI) *m/z* for $C_{17}H_{19}N_4OS^+$ [M+H^+] calcd. 327.1274

found 327.1274

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)cyclohex-1-ene carboxamide (78n)



General procedure F2 was followed using cyclohex-1-ene carboxylic acid (**103i**) (756 mg, 6.0 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**109a**) (1.30 g, 5.9 mmol). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 1/1) yielded **78n** (1.26 g, 65%) as a white solid.

M. p.: 116–117 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.40–7.31 (m, 3H), 7.30–7.22 (m, 2H), 6.73–6.45 (m, 1H), 6.48 (brs, 1H), 5.49 (s, 2H), 2.55–1.86 (m, 4H), 1.75 (s, 6H), 1.71–1.25 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7 (C_q), 153.8 (C_q), 134.5 (C_q), 133.7 (C_q), 132.9 (CH), 128.9 (CH), 128.4 (CH), 127.9 (CH), 120.1 (CH), 54.0 (CH_2), 51.2 (C_q), 27.9 (CH_3), 25.3 (CH_2), 24.2 (CH_2), 22.1 (CH_2), 21.5 (CH_2).

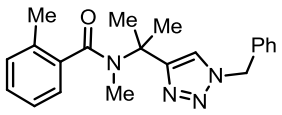
IR(ATR): 3289, 2940, 1625, 1533, 1293, 1199, 1076, 719 cm^{-1}.

MS(EI) *m/z* (relative intensity): 324 (5) [M^+], 296 (25), 281 (100), 201 (12), 109 (38), 91 (90), 81 (35).

HRMS (EI) *m/z* for $C_{19}H_{24}N_4O^+$ [M^+] calcd. 324.1950

found 324.1951

Synthesis of *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-*N*,2-dimethylbenzamide (78b-Me)



N-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (**78b**) (1.73 g, 5.20 mmol) was dissolved in THF (15 mL), and cooled to 0 °C. NaH (0.31 g, 60% in paraffin oil, 7.60 mmol) was added portionwise at 0 °C. The reaction mixture was then stirred for one hour at ambient temperature. Iodomethane (1.0 mL, 16.0 mmol) was then added, and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The collected organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc 1/1) yielded **78b-Me** (1.45 g, 80%) as a white solid.

M. p.: 94–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.36 (tdd, *J* = 4.7, 2.8, 2.0 Hz, 3H), 7.26 (dq, *J* = 3.2, 2.1, 1.6 Hz, 2H), 7.22–7.06 (m, 4H), 5.51 (s, 2H), 2.88 (s, 3H), 2.20 (s, 3H), 1.87 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C_q), 153.7 (C_q), 138.5 (C_q), 134.9 (C_q), 133.8 (C_q), 130.2 (CH), 129.0 (CH), 128.5 (CH), 128.3 (CH), 127.9 (CH), 125.8 (CH), 125.6 (CH), 120.8 (CH), 55.9 (C_q), 53.9 (CH_2), 34.3 (CH_3), 27.1 (CH_3), 18.6 (CH_3).

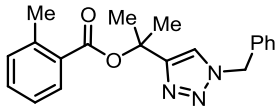
IR (ATR): 1624, 1379, 1058, 1048, 727, 709, 641 cm^{-1}.

MS (EI) *m/z* (relative intensity): 347 (5) [M^+], 305 (35), 201 (30), 132 (24), 119 (45), 91 (100).

HRMS (EI) *m/z* for $C_{21}H_{23}N_4O^+$ [M-H^+] calcd. 347.1872

found 347.1877

Synthesis of 2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl 2-methylbenzoate (111)



Benzylbromide (**99a**) (1.60 g, 9.3 mmol) was added to a suspension of NaN_3 (574 mg, 8.80 mmol) in degassed DMSO (15 mL). The mixture was stirred overnight at ambient temperature. Degassed water (30 mL) was then added at ambient temperature followed by sodium ascorbate (188 mg, 0.90 mmol), copper (II) sulfate hydrate (474 mg, 1.90 mmol) and 2-methylbut-3-yn-2-yl 2-methylbenzoate (**110**) (1.70 g, 8.60 mmol) and the mixture was stirred at ambient temperature overnight. The reaction mixture was then diluted with EtOAc (50 mL) and a solution of NH_4Cl/NH_3 (v/v 1:1, 50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The organic phases were then washed with a 1/1 solution of NH_4Cl/NH_3 (3 x 30 mL) until disappearance of the blue color, then with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue on silica gel (*n*-hexane/EtOAc 10/1) yielded **111** (1.60 g, 58%) as a white solid.

M. p.: 62–65 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.52 (s, 1H), 7.42–7.30 (m, 4H), 7.30–7.15 (m, 4H), 5.52 (s, 2H), 2.51 (s, 3H), 1.97 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4 (C_q), 151.6 (C_q), 139.3 (C_q), 134.6 (C_q), 131.4 (CH), 131.3 (CH), 130.8 (C_q), 130.2 (CH), 128.9 (CH), 128.4 (CH), 127.8 (CH), 125.5 (CH), 121.1 (CH), 77.4 (C_q), 54.0 (CH_2), 27.6 (CH_3), 21.6 (CH_3).

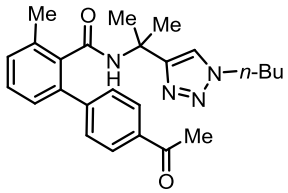
IR (ATR): 3135, 1697, 1455, 1362, 1257, 1224, 1125, 1072, 1046, 720 cm^{-1}.

MS (EI) *m/z* (relative intensity): 336 (100) [M^+], 200 (68), 172 (81), 123 (19), 91 (20).

HRMS (ESI) *m/z* for $C_{20}H_{22}N_3O_2$ [M+H$^+$] calcd. 336.1707

found 336.1706

Synthesis of 4'-Acetyl-*N*-(2-[1-*n*-butyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-3-methyl-[1,1'-biphenyl]-2-carboxamide (80cd)



General procedure G was followed using *N*-(2-[1-*n*-butyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (**78c**) (151 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (123 mg, 0.61 mmol), $RuCl_2(PPh_3)_3$ (24.8 mg, 0.025 mmol, 5.0 mol %), and Na_2CO_3 (82.9 mg, 0.77 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 3/2) yielded **80cd** (85.8 mg, 41%) as a white solid.

M. p.: 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.83 (m, 2H), 7.60–7.45 (m, 2H), 7.35–7.13 (m, 4H), 6.12 (s, 1H), 4.27 (dd, *J* = 8.0, 6.4 Hz, 2H), 2.62 (s, 3H), 2.37 (s, 3H), 1.84 (dd, *J* = 8.0, 6.4 Hz, 2H), 1.56 (s, 6H), 1.44–1.19 (m, 2H), 0.94 (td, *J* = 7.4, 1.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.6 (C_q), 168.2 (C_q), 152.5 (C_q), 145.2 (C_q), 137.8 (C_q), 136.8 (C_q), 135.7 (C_q), 135.3 (C_q), 129.8 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 126.8 (CH), 120.0 (CH), 51.7 (C_q), 50.0 (CH_2), 32.2 (CH_2), 27.4 (CH_3), 26.7 (CH_3), 19.7 (CH_2), 19.2 (CH_2), 13.5 (CH_3).

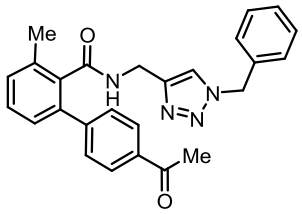
IR (ATR): 3304, 2975, 1681, 1641, 1536, 1363, 1312, 1269, 1220, 1185, 1015, 792, 604 cm^{-1}.

MS (EI) *m/z* (relative intensity): 418 (38) [M$^+$], 390 (15), 375 (100), 347 (18), 237 (22), 195 (65), 166 (30), 84 (16), 43 (50).

HRMS (EI) *m/z* for $C_{25}H_{30}N_4O_2^+$ [M$^+$] calcd. 418.2369

found 418.2371

Synthesis of 4'-Acetyl-*N*-([1-benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-3-methyl-[1,1'-biphenyl]-2-carboxamide (80od)



General procedure G was followed using *N*-([1-benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-methylbenzamide (**78o**) (155 mg, 0.50 mmol) 4-bromoacetophenone (**18d**) (121 mg, 0.60 mmol), $RuCl_2(PPh_3)_3$ (25.6 mg, 0.025 mmol, 5.0 mol %), and Na_2CO_3 (82.6 mg, 0.77 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1 →1/1) yielded **80od** (114.6 mg, 54%) as a white solid.

M. p.: 132–135 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.45–7.38 (m, 2H), 7.38–7.28 (m, 3H), 7.28–7.18 (m, 3H), 7.18–7.11 (m, 2H), 6.02 (t, *J* = 5.3 Hz, 1H), 5.42 (s, 2H), 4.37 (d, *J* = 5.8 Hz, 2H), 2.60 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8 (C_q), 169.2 (C_q), 145.0 (C_q), 143.9 (C_q), 138.0 (C_q), 135.8 (C_q), 135.7 (C_q), 135.6 (C_q), 134.5 (C_q), 129.9 (CH), 129.0 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 126.9 (CH), 122.1 (CH), 53.9 (CH_2), 34.7 (CH_2), 26.6 (CH_3), 19.3 (CH_3).

IR (ATR): 3260, 1678, 1633, 1542, 1357, 1268, 1226, 1046, 961, 846, 799, 743 cm^{-1}.

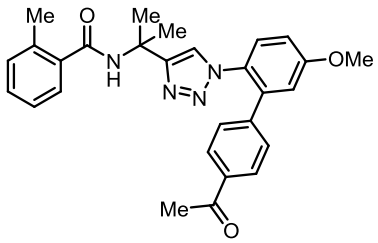
MS (EI) *m/z* (relative intensity): 424 (55) [M^+], 305 (10), 236 (12), 195 (32), 187 (20), 165 (20), 91 (100), 43 (25).

HRMS (ESI) *m/z* for $C_{26}H_{25}N_4O_2^+$ [M+H^+] calcd. 425.1972

found 425.1973

Carboxylate-assisted direct arylation of *N*-{2-(1-[4-Methoxyphenyl]-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-2-methylbenzamide (78e)

A mixture of *N*-{2-(1-[4-methoxyphenyl]-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-2-methylbenzamide (**78e**) (291 mg, 0.83 mmol), 4-bromoacetophenone (**18d**) (87.5 mg, 0.44 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.2 mg, 0.011 mmol, 2.5 mol %), $MesCO_2H$ (24.2 mg, 0.14 mmol, 30 mol %) and K_2CO_3 (120 mg, 0.87 mmol) in PhMe (2.0 mL) was stirred at 120 °C for 22 h under N_2.At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1 →5/2→2/1→3/2) yielded **112ed** (148 mg, 70%) as a white solid.



M. p.: 110–111 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.4 Hz, 2H), 7.52 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.29 (d, *J* = 0.9 Hz, 1H), 7.24 (dt, *J* = 7.1, 1.1 Hz, 2H), 7.19–7.10 (m, 4H), 7.02 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.98 (d, *J* = 2.8 Hz 1H), 6.38 (s, 1H), 3.89 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H), 1.73 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4 (C_q), 169.2 (C_q), 160.4 (C_q), 152.8 (C_q), 141.9 (C_q), 137.8 (C_q), 137.0 (C_q), 136.2 (C_q), 135.5 (C_q), 130.8 (CH), 129.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (C_q), 128.0 (CH), 126.5 (CH), 125.6 (CH), 123.2 (CH), 115.8 (CH), 114.0 (CH), 55.7 (CH_3), 51.5 (C_q), 27.9 (CH_3), 26.4 (CH_3), 19.5 (CH_3).

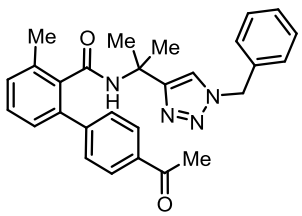
IR (ATR): 3240, 1683, 1665, 1634, 1603, 1517, 1301, 1267, 1214, 1041, 1026, 883, 746 cm^{-1}.

MS (EI) *m/z* (relative intensity): 439 (15), 425 (20), 305 (20), 241 (18), 200 (17), 119 (100), 91 (50), 43 (40).

HRMS (EI) *m/z* for $C_{28}H_{28}N_4O_3^+$ [M^+] calcd 468.2161

found 468.2163

Synthesis of 4'-Acetyl-*N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-3-methyl-[1,1'-biphenyl]-2-carboxamide (80bd)



General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (**78b**) (170 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (127 mg, 0.63 mmol), Na_2CO_3 (84.0 mg, 0.79 mmol) $RuCl_2(PPh_3)_3$ (24.5 mg, 0.025 mmol) in H_2O (0.2 mL) and *o*-xylene (1.8 mL). Column chromatography on silica gel (*n*-hexane/EtOAc 2/1→1/1) yielded **80bd** (153 mg, 66%) as a white solid.

M. p.: 123–125 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.75 (m, 2H), 7.57–7.43 (m, 2H), 7.43–7.08 (m, 9H), 6.06 (s, 1H), 5.46 (s, 2H), 2.59 (s, 3H), 2.34 (s, 3H), 1.53 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9 (C_q), 168.5 (C_q), 153.0 (C_q), 145.3 (C_q), 138.0 (C_q), 136.8 (C_q), 135.9 (C_q), 135.6 (C_q), 134.6 (C_q), 130.0 (CH), 129.1 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.0 (CH), 120.5 (CH), 54.1 (CH_2), 51.7 (C_q), 27.3 (CH_3), 26.7 (CH_3), 19.2 (CH_3).

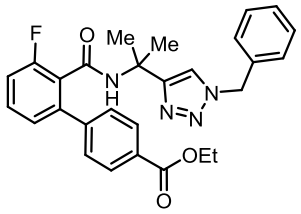
IR (ATR): 3294, 1775, 1677, 1637, 1538, 1360, 1308, 1271, 1184, 1051, 958, 804, 725, 605 cm^{-1}.

MS (EI) *m/z* (relative intensity): 452 (35) [M^+], 424 (18), 409 (100), 237 (20), 195 (57), 165 (20), 91 (81), 43 (32).

HRMS (EI) *m/z* for $C_{28}H_{28}N_4O_2^+$ [M^+] calcd. 452.2212

found 452.2215

Synthesis of Ethyl 2´-{(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)carbamoyl}-3´-fluoro-[1,1´-biphenyl]-4-carboxylate (80le)



General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-fluorobenzamide (**78l**) (179 mg, 0.52 mmol), 4-ethylbromobenzoate (**18e**) (153 mg, 0.66 mmol), $RuCl_2(PPh_3)_3$ (24.6 mg, 0.025 mmol, 5.0 mol %), and Na_2CO_3 (82.6 mg, 0.77 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1 → 1/1) yielded **80le** (244 mg, 95%) as a white solid.

M. p.: 156–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.3, 1.9 Hz, 2H), 7.53–7.43 (m, 2H), 7.43–7.31 (m, 4H), 7.29 (s, 1H), 7.28–7.19 (m, 2H), 7.19–7.05 (m, 2H), 6.38 (s, 1H), 5.47 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.64 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0 (C_q), 163.3 (C_q), 159.1 (C_q, J_{C-F} = 248 Hz), 152.8 (C_q), 143.3 (C_q, J_{C-F} = 2 Hz), 140.7 (C_q, J_{C-F} = 4 Hz), 134.5 (C_q), 130.4 (CH, J_{C-F} = 9 Hz), 129.6 (C_q), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 125.3 (CH, J_{C-F} = 3 Hz), 125.0 (C_q, J_{C-F} = 18 Hz), 120.2 (CH), 115.0 (CH, J_{C-F} = 22 Hz), 60.9 (CH_2), 53.9 (CH_2), 52.3 (C_q), 27.5 (CH_3), 14.3 (CH_3).

^{19}F NMR (283 MHz, $CDCl_3$): δ = –116.0 (dd, *J* = 9.0, 5.6 Hz).

IR (ATR): 3251, 1710, 1658, 1530, 1272, 1106, 1087, 766, 717 cm^{-1}.

MS (EI) *m/z* (relative intensity): 486 (2) [M^+], 458 (25), 444 (30), 443 (100), 199 (27), 170 (22), 91 (88).

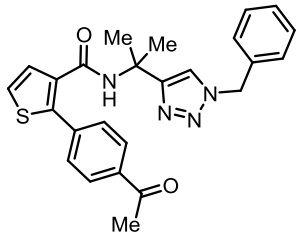
HRMS (ESI) *m/z* for $C_{28}H_{28}N_4O_3F^+$ [$M+H^+$] calcd. 487.2140

found 487.2139

Synthesis of 2-(4-Acetylphenyl)-*N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)thiophene-3-carboxamide (80md) and 2,4-Bis(4-acetylphenyl)-*N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)thiophene-3-carboxamide (81md)

General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)thiophene-3-carboxamide (**78m**) (169 mg, 0.52 mmol), 4-bromoacetophenone (**18d**) (122 mg, 0.61 mmol), $RuCl_2(PPh_3)_3$ (24.1 mg, 0.025 mmol, 5.0 mol %) and Na_2CO_3 (83.6 mg, 0.78 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1→3/2→1/1) yielded **80md** (90.2 mg, 39%) as a white solid and **81md** (70.5 mg, 24%) as a white solid.

General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)thiophene-3-carboxamide (**78m**) (327 mg, 1.0 mmol), 4-bromoacetophenone (**18d**) (108 mg, 0.54 mmol), $RuCl_2(PPh_3)_3$ (25.1 mg, 0.026 mmol, 5.2 mol %), and Na_2CO_3 (80.7 mg, 0.76 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1→3/2→1/1) yielded **80md** (104 mg, 43%) as a white solid and **81md** (66.1 mg, 43%) as a white solid.



80md:

M. p.: 165–166 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.93–7.89 (m, 2H), 7.56–7.52 (m, 2H), 7.38–7.32 (m, 4H), 7.30 (d, *J* = 5.3 Hz, 1H), 7.27 (d, *J* = 5.3 Hz, 1H), 7.25–7.20 (m, 2H), 6.19 (s, 1H), 5.45 (s, 2H), 2.59 (s, 3H), 1.64 (s, 6H).

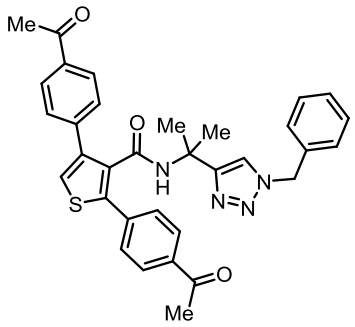
^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1 (C_q), 163.4 (C_q), 152.9 (C_q), 142.2 (C_q), 137.2 (C_q), 136.5 (C_q), 135.0 (C_q), 134.5 (C_q), 129.3 (CH), 128.9 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 125.4 (CH), 120.3 (CH), 54.0 (CH_2), 51.6 (C_q), 27.5 (CH_3), 26.6 (CH_3).

IR (ATR): 3278, 1678, 1633, 1602, 1542, 1297, 1271, 1200, 1188, 1053, 962, 713, 595 cm^{-1}.

MS (EI) *m/z* (relative intensity): 444 (8) [M^+], 416 (35), 401 (100), 229 (38), 187 (38), 91 (85).

HRMS (EI) *m/z* for $C_{25}H_{24}N_4O_2S^+$ [M^+] calcd. 444.1620

found 444.1626



81md:

M. p.: 151–154 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.85 (m, 4H), 7.72–7.58 (m, 2H), 7.59–7.50 (m, 2H), 7.37–7.28 (m, 5H), 7.23–7.16 (m, 2H), 6.33 (s, 1H), 5.47 (s, 2H), 2.59 (s, 6H), 1.60 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 197.4 (C_q), 197.2 (C_q), 164.7 (C_q), 152.4 (C_q), 142.2 (C_q), 141.5 (C_q), 139.8 (C_q), 137.2 (C_q), 136.5 (C_q), 136.0 (C_q), 135.0 (C_q), 134.5 (C_q), 129.0 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 124.1 (CH), 120.7 (CH), 54.1 (CH_2), 51.9 (C_q), 27.2 (CH_3), 26.7 (CH_3), 26.7 (CH_3).

IR (ATR): 3296, 1680, 1644, 1603, 1531, 1496, 1356, 1266, 1184, 1118, 955, 832, 720 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 585 (68) [M+Na^+], 563 (100) [M+H^+], 467 (17), 445 (32).

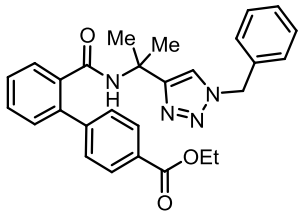
HRMS (ESI) *m/z* for $C_{33}H_{31}N_4O_3S^+$ [M+H^+] calcd. 563.2111

found 563.2112

Synthesis of Ethyl 2'-{(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)carbamoyl}1[1,1'-biphenyl]-4-carboxylate (80ae) and Diethyl 2'-{(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)carbamoyl}-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate (81ae)

General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)benzamide (**78a**) (166 mg, 0.52 mmol), 4-bromoethylbenzoate (**18e**) (136 mg, 0.59 mmol), $RuCl_2(PPh_3)_3$ (24.0 mg, 0.025 mmol, 5.0 mol %) and Na_2CO_3 (82.0 mg, 0.77 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1 → 2/1) yielded **80ae** (130 mg, 54%) as a white solid and **81ae** (69.1 mg, 24%) as a white solid.

General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)benzamide (**78a**) (321 mg, 1.00 mmol), 4-bromoethylbenzoate (**18e**) (115 mg, 0.50 mmol), $RuCl_2(PPh_3)_3$ (25.8 mg, 0.026 mmol, 5.0 mol %), and Na_2CO_3 (86.5 mg, 0.81 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1 → 2/1) yielded **80ae** (164 mg, 70%) as a white solid and **81ae** (33.1 mg, 22%) as a white solid.



80ae:

M. p.: 170–171 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.2 Hz, 2H), 7.60 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.52–7.40 (m, 3H), 7.41–7.30 (m, 4H), 7.30–7.20 (m, 4H), 6.08 (s, 1H), 5.47 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.60 (s, 6H), 1.46–1.24 (t, *J* = 7.1 Hz, 3H).

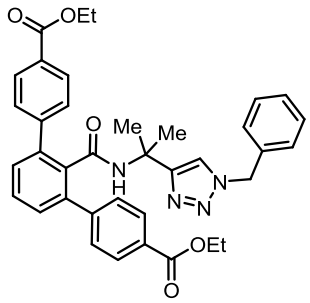
^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2 (C_q), 166.2 (C_q), 153 (C_q), 144.9 (C_q), 138.7 (C_q), 136.5 (C_q), 134.6 (C_q), 129.9 (CH), 129.8 (CH), 129.4 (CH), 129.4 (C_q), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 120.3 (CH), 60.9 (CH_2), 53.9 (CH_2), 51.6 (C_q), 27.3 (CH_3), 14.2 (CH_3).

IR (ATR): 3336, 1708, 1658, 1539, 1525, 1269, 1183, 1109, 1097, 1053, 757, 720, 701 cm^{-1}.

MS (EI) *m/z* (relative intensity): 468 (5) [M^+], 440 (25), 425 (100), 181 (30), 91 (62).

HRMS (ESI) *m/z* for $C_{28}H_{29}N_4O_3^+$ [$M+H^+$] calcd. 469.2234

found 469.2235



81ae:

M. p.: 182–183 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09–7.89 (m, 4H), 7.49 (m, 5H), 7.39–7.25 (m, 5H), 7.17 (dd, *J* = 6.2, 2.6 Hz, 2H), 7.02 (d, *J* = 1.1 Hz, 1H), 6.05 (s, 1H), 5.39 (s, 2H), 4.37 (qd, *J* = 7.1, 1.1 Hz, 4H), 1.39 (td, *J* = 7.1, 1.1 Hz, 6H), 1.31 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0 (C_q), 166.4 (C_q), 152.7 (C_q), 144.8 (C_q), 139.3 (C_q), 136.0 (C_q), 134.6 (C_q), 129.5 (C_q), 129.5 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 120.4 (CH), 61.0 (CH_2), 53.9 (CH_2), 51.8 (C_q), 26.9 (CH_3), 14.3 (CH_3).

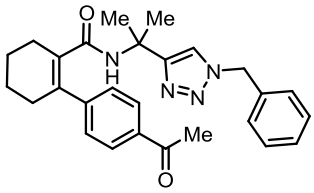
IR (ATR): 3288, 2983, 1714, 1640, 1530, 1363, 1270, 1179, 1099, 1018, 811, 769, 730 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 639 (90), 617 (100) [$M+H^+$].

HRMS (ESI) *m/z* for $C_{37}H_{36}N_4O_5Na^+$ [$M+Na^+$] calcd. 639.2578

found 639.2578

Synthesis of 4'-Acetyl-*N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxamide (80nd)



General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)cyclohex-1-ene carboxamide (**78n**) (163 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (124 mg, 0.62 mmol), $RuCl_2(PPh_3)_3$ (24.3 mg, 0.025 mmol, 5.0 mol %) and Na_2CO_3 (85.5 mg, 0.80 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1→1/1→1/2) yielded **80nd** (75.4 mg, 34%) as a white solid.

General procedure G was followed using *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)cyclohex-1-ene carboxamide (**78n**) (165 mg, 0.50 mmol), 4-bromoacetophenone (**18d**) (120 mg, 0.60 mmol), $RuCl_2(PPh_3)_3$ (53 mg, 0.05 mmol, 10.0 mol %) and Na_2CO_3 (82.3 mg, 0.77 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2/1→1/1→1/2) yielded **80nd** (107.7 mg, 48%) as a white solid.

M. p.: 134–136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.2 Hz, 2H), 7.40–7.32 (m, 3H), 7.32–7.15 (m, 5H), 5.64 (s, 1H), 5.43 (s, 2H), 2.55 (s, 3H), 2.46–2.22 (m, 4H), 1.83–1.62 (m, 4H), 1.38 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4 (C_q), 169.6 (C_q), 153.0 (C_q), 147.1 (C_q), 137.3 (C_q), 135.7 (C_q), 134.7 (C_q), 134.5 (C_q), 128.9 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 120.1 (CH), 54.0 (CH_2), 51.1 (C_q), 31.0 (CH_2), 27.1 (CH_3), 26.9 (CH_2), 26.6 (CH_3), 22.5 (CH_2), 21.8 (CH_2).

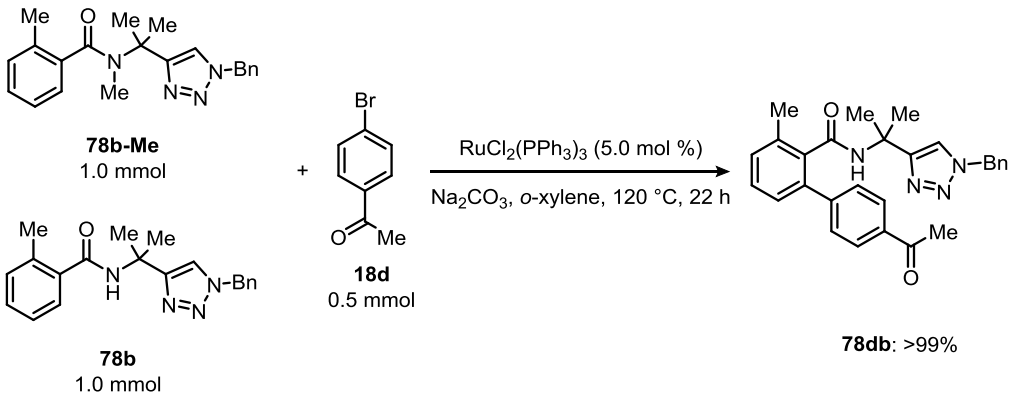
IR (ATR): 3281, 2932, 1681, 1652, 1604, 1523, 1225, 1213, 1193, 1054, 849, 820, 715 cm^{-1}.

MS (EI) *m/z* (relative intensity): 442 (40) [M^+], 399 (80), 227 (21), 200 (45), 185 (25), 172 (16), 91 (100), 43 (48).

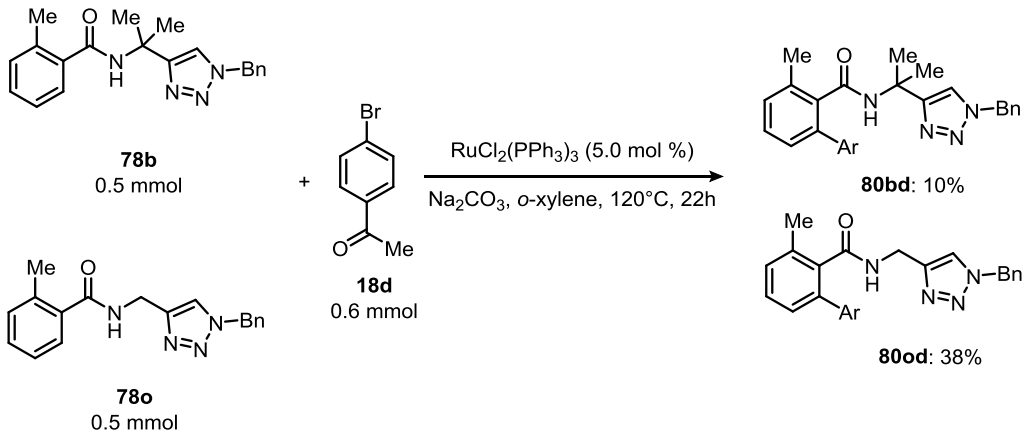
HRMS (EI) *m/z* for $C_{27}H_{30}N_4O_2^+$ [M^+] calcd. 442.2369

found 442.2373

Competition Experiments



A suspension of $RuCl_2(PPh_3)_3$ (25.4 mg, 0.026 mmol, 5.2 mol %), Na_2CO_3 (94.8 mg, 0.89 mmol), *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-*N*,2-dimethylbenzamide (**78b-Me**) (353 mg, 1.00 mmol), *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (**78b**) (340 mg, 1.00 mmol) and 4-bromoacetophenone (**18d**) (103.0 mg, 0.51 mmol) in *o*-xylene (2 mL) was stirred under N_2 at 120 °C for 22 h. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3/1). The crude mixture was analyzed by ^{1}H-NMR spectroscopy, and showed full conversion of the 4-bromoacetophenone to **78bd**.

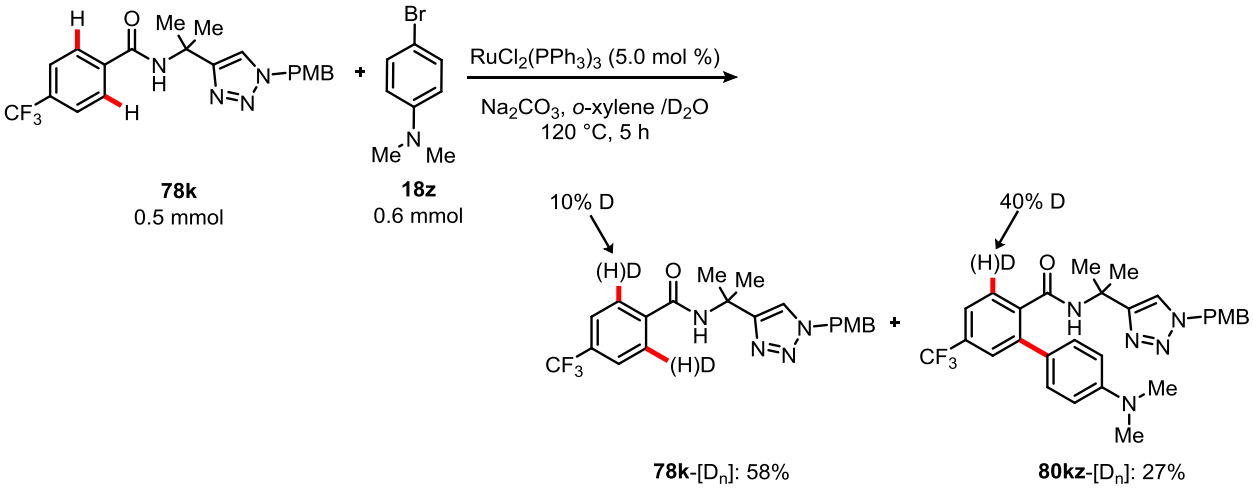


A suspension of $RuCl_2(PPh_3)_3$ (25.0 mg, 0.026 mmol, 5.2 mol %), Na_2CO_3 (81.6 mg, 0.76 mmol), *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (**78b**) (171 mg, 0.51 mmol), *N*-([1-benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-methylbenzamide (**78o**) (154 mg, 0.50 mmol) and 4-bromoacetophenone (**18d**) (124 mg, 0.62 mmol) in *o*-xylene (2 mL) was stirred under N_2 at 120 °C for 22 h. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 2/1→3/2→1/1→0/1) yielding **78b** (143 mg, 83%), **80bd** (27.7 mg, 10%), **78o** (58 mg, 38%) and **80od** (102 mg, 38%).

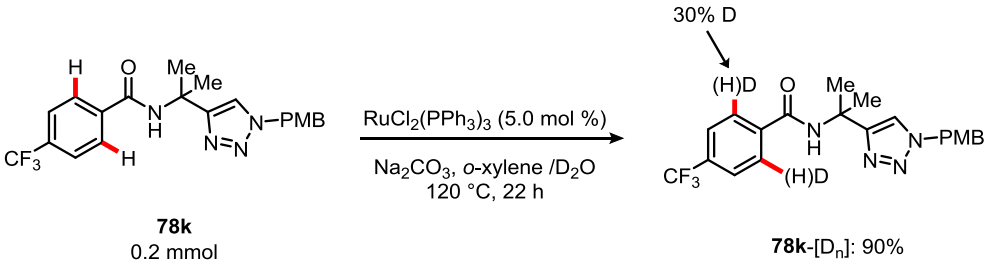
A suspension of $RuCl_2(PPh_3)_3$ (24.5 mg, 0.025 mmol, 5.0 mol %), Na_2CO_3 (87.5 mg, 0.82 mmol), *N*-{2-(1-[4-methoxyphenyl]-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-2-methylbenzamide (**78e**) (363 mg, 1.0 mmol), N-{2-[1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-2-methylbenzamide (**78j**) (368 mg, 1.00 mmol) and 4-bromoacetophenone (**18d**) (109 mg, 0.54 mmol) in *o*-xylene (2 mL) was stirred under N_2 at 120 °C for 22 h. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3/1) yielding **78j** (343 mg, 93%) and **78e** (330 mg, 91%).

A suspension of $RuCl_2(PPh_3)_3$ (25.1 mg, 0.026 mmol, 5.2 mol %), Na_2CO_3 (82.7 mg, 0.78 mmol), 2-methyl-*N*-(quinolin-8-yl)benzamide (**71b**) (262 mg, 1.0 mmol), *N*-(2-[1-benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-methylbenzamide (**78b**) (336 mg, 1.0 mmol) and 4-bromoacetophenone (**18d**) (97.1 mg, 0.48 mmol) in *o*-xylene (2 mL) was stirred under N_2 at 120 °C for 22 h. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3/1) yielding **71b** (238 mg, 90%) and **78b** (330 mg, 98%).

Deuterium experiments

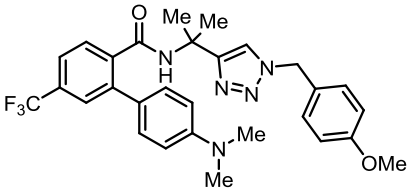


A mixture of *N*-{2-(1-[4-methoxybenzyl]-1H-1,2,3-triazol-4-yl)propan-2-yl-4-(trifluoromethyl)benzamide (**78k**) (210 mg, 0.50 mmol), 4-bromo-*N*,*N*-dimethylaniline (**18z**) (129 mg, 0.64 mmol), $RuCl_2(PPh_3)_3$ (24.3 mg, 0.025 mmol, 5.0 mol %) and Na_2CO_3 (82.6 mg, 0.77 mmol), D_2O (0.2 mL) and *o*-xylene (1.8 mL) was stirred at 120 °C for 22 h under N_2. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3/1→5/2→2/1→ 3/2) yielding **78k**-[D_n] (123 mg, 58%) as a white solid and **80kz**-[D_n] (72 mg, 27%) as a beige solid. The D-incorporation in **78k**-[D_n] and **80kz**-[D_n] was estimated by ^{1}H NMR spectroscopy.



A mixture of *N*-{2-(1-[4-methoxybenzyl]-1H-1,2,3-triazol-4-yl)propan-2-yl-4-(trifluoromethyl)benzamide (**78k**) (86 mg, 0.20 mmol), $RuCl_2(PPh_3)_3$ (10.5 mg, 0.01 mmol, 5.0 mol %) and Na_2CO_3 (36 mg, 0.33 mmol), D_2O (0.1 mL) and *o*-xylene (1.0mL) was stirred at 120 °C for 22 h under N_2. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3/1) recovering **78k**-[D_n] (78 mg, 90%) as a white solid. The D-incorporation in **78k**-[D_n] was estimated by ^{1}H NMR spectroscopy.

Synthesis of 4'-(dimethylamino)-*N*-{2-(1-[4-methoxybenzyl]-1H-1,2,3-triazol-4-yl)propan-2-yl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (80kz)



General procedure G was followed using *N*-{2-(1-[4-methoxybenzyl]-1H-1,2,3-triazol-4-yl)propan-2-yl-4-(trifluoromethyl)benzamide (**78k**)(333 mg, 0.79 mmol), 4-bromo-*N*,*N*-dimethylaniline (**18z**) (96 mg, 0.47 mmol), $RuCl_2(PPh_3)_3$ (20 mg, 0.02 mmol, 5.0 mol %) and Na_2CO_3 (72 mg, 0.67 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3/1→5/2→2/1) and filtration over Celite yielded **80kz** (58.8 mg, 23%) as a white solid.

M. p.: 111–112 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.68 (d, J = 8.0 Hz, 1H), 7.55 (m, 2H), 7.31 (s, 1H), 7.28–7.16 (m, 4H), 6.94–6.82 (m, 2H), 5.92 (s, 1H), 5.40 (s, 2H), 3.80 (s, 3H), 2.98 (s, 6H), 1.57 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C_q), 159.9 (C_q), 153.0 (C_q), 150.2 (C_q), 140.5 (C_q), 139.0 (C_q), 136.4 (C_q), 131.8 (C_q, m), 129.8 (CH), 129.6 (CH), 129.3 (CH), 126.9 (CH, J_{C-F} = 4 Hz), 126.8 (C_q), 125.8 (CH), 124.6 (C_q, J_{C-F} = 272 Hz), 123.3 (CH), 122.0 (C_q), 120.4 (CH), 114.4 (CH), 55.2 (CH_3), 53.5 (CH_2), 51.7 (C_q), 40.6 (CH_3), 27.4 (CH_3)

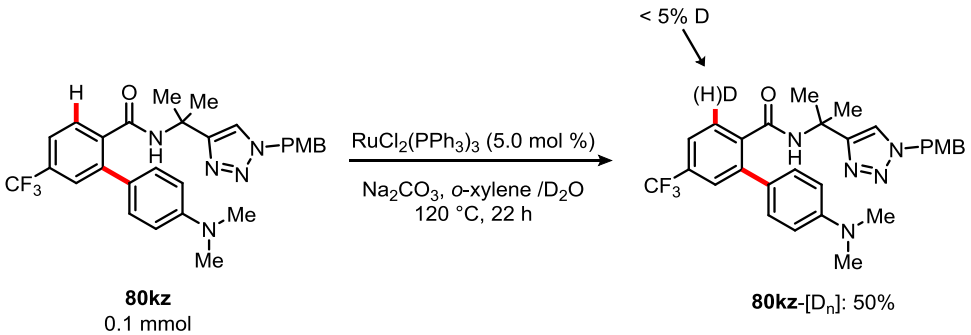
^{19}F NMR (282 MHz, $CDCl_3$) δ = –62.8 (s).

IR (ATR): 3321, 1651, 1611, 1514, 1334, 1249, 1167, 1117, 1035, 813 cm^{-1}.

MS (ESI) *m/z* (relative intensity): 560 (45) [M+Na$^+$], 538 (100) [M+H$^+$], 524 (5), 472 (5).

HRMS (ESI) *m/z* for $C_{29}H_{31}N_5O_2F_3^+$ [M+H$^+$] calcd 538.2424

found 538.2425



A mixture of 4'-(dimethylamino)-*N*-{2-(1-[4-methoxybenzyl]-1H-1,2,3-triazol-4-yl)propan-2-yl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (**80kz**) (50 mg, 0.10 mmol), $RuCl_2(PPh_3)_3$ (5.2 mg, 0.005 mmol, 5.0 mol %) and Na_2CO_3 (16 mg, 0.15 mmol), D_2O (0.1 mL) and *o*-xylene (1.0 mL) was

stirred at 120 °C for 22 h under N_2. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3/1) recovering **80kz**-[D_n] (25 mg, 50%) as a white solid. The D-incorporation in **80kz**-[D_n] was estimated by ^{1}H NMR spectroscopy.

5.3.4 Cristallographic details

Suitable crystals for X-ray diffractometry were obtained by dissolving **62ad** in a mixture of $CHCl_3$ (0.5 mL) and *n*-octane (0.5 mL), and by subsequent slow evaporation at ambient temperature.

Table 23: Crystal data and structure refinement for 62ad

Empirical formula	$C_{22}H_{18}N_4O$
Formula weight [g/mol]	354.40
Temperature [K]	120
Crystal system	monoclinic
Space group	$P2_1/n$
A[Å]	9.3312(3)
b [Å]	12.1915(4)
c [Å]	15.7406(6)
α [°]	90.00
β [°]	96.8370(10)
γ [°]	90.00
Volume [$Å^3$]	1777.94(11)
Z	4
ρ_{calc} [mg/mm^3]	1.324
m [mm^{-1}]	0.084
F(000)	744.0
Crystal size (mm^3)	0.34 × 0.14 × 0.05
2Θ range for data collection	4.24 to 58°
Index ranges	$-12 \leq h \leq 12$, $-16 \leq k \leq 16$, $-21 \leq l \leq 21$
Reflections collected	28278
Independent reflections	4723[R(int) = 0.0403]
Data/restraints/parameters	4723/0/316
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0431, wR_2 = 0.1050
Final R indexes [all data]	R_1 = 0.0645, wR_2 = 0.1230
Largest diff. peak/hole / e $Å^{-3}$	0.34/-0.23

More detailed illustrations of the molecular structure of **62ad** in the crystals including fragments of molecular packings and H-bondings are presented below.

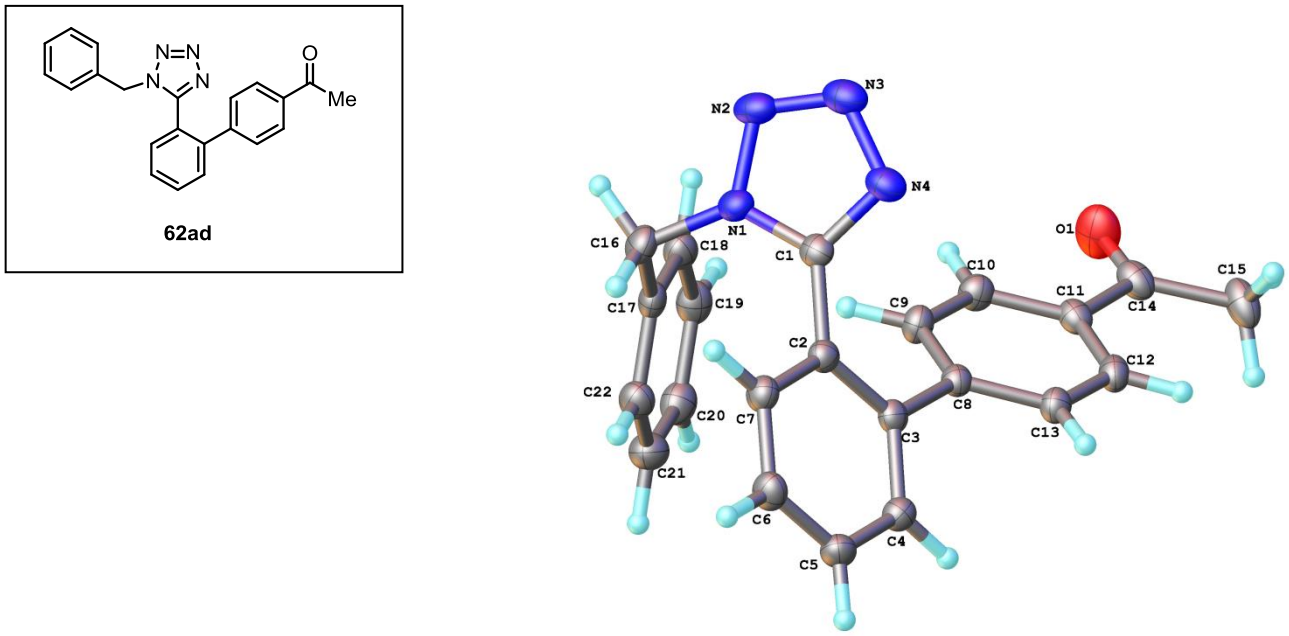


Figure 23: Molecular structure of 62ad in the crystals. Thermal ellipsoids are shown at 50% probability.

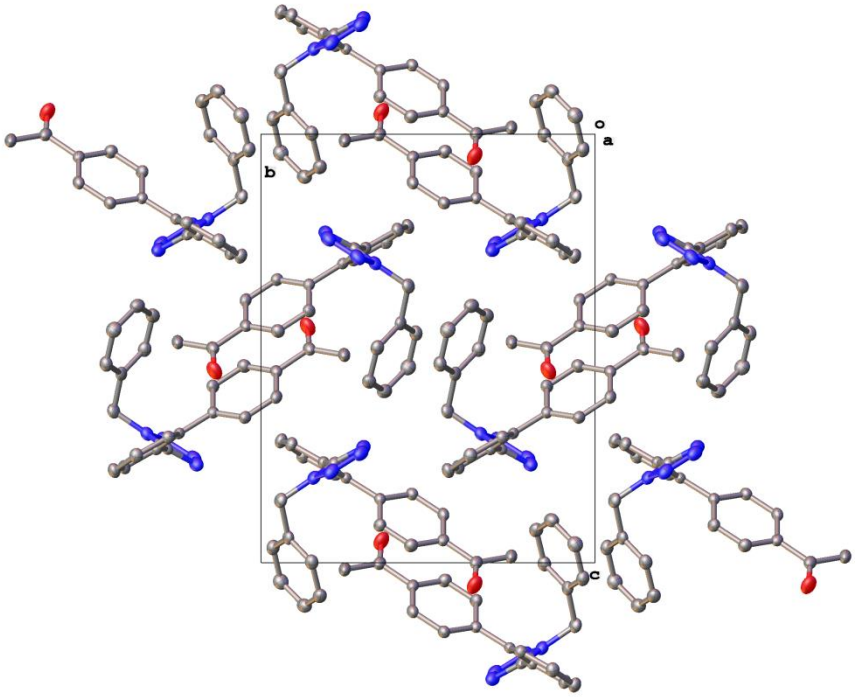


Figure 24: Fragment of the molecular packing in extended unit cell of 62ad; space group $P2_1/n$.

Table 24: Fractional Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for 62ad. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	8146.7(14)	11396.7(10)	5513.3(8)	45.6(3)
N1	8972.4(12)	6587.4(10)	3012.3(7)	24.8(2)
N2	10199.8(13)	7109.8(11)	2870.6(8)	30.6(3)
N3	9809.6(14)	7987.0(11)	2440.5(8)	33.0(3)
N4	8340.5(13)	8066.1(10)	2298.4(8)	29.2(3)
C1	7843.3(15)	7187.6(11)	2664.0(8)	22.8(3)
C2	6316.5(14)	6874.1(11)	2655.6(8)	21.8(3)
C3	5324.7(14)	7549.4(10)	3018.9(8)	20.7(3)
C4	3878.2(15)	7226.7(11)	2932.7(9)	23.9(3)
C5	3430.7(15)	6264.0(12)	2506.4(9)	27.1(3)
C6	4412.2(16)	5601.1(12)	2153.9(10)	28.1(3)
C7	5856.1(15)	5906.7(11)	2229.7(9)	25.5(3)
C8	5777.8(14)	8562.5(10)	3508.0(8)	21.0(3)
C9	6994.7(15)	8560.5(11)	4120.3(9)	25.2(3)
C10	7399.6(15)	9493.4(12)	4591.6(9)	26.7(3)
C11	6594.4(15)	10455.3(11)	4468.5(8)	24.2(3)
C12	5372.9(16)	10458.7(11)	3869.3(9)	25.5(3)
C13	4962.9(15)	9522.6(11)	3393.2(9)	23.8(3)
C14	7079.5(17)	11446.6(12)	4990.4(9)	29.2(3)
C15	6244(2)	12491.3(13)	4850.6(11)	36.0(4)
C16	9033.4(16)	5588.8(12)	3541.7(10)	28.1(3)
C17	8569.7(15)	5818.9(11)	4411.3(9)	24.8(3)
C18	9390.4(16)	6517.2(12)	4981.1(10)	28.3(3)
C19	8934.4(17)	6760.7(13)	5767.4(10)	30.9(3)
C20	7671.8(17)	6299.6(13)	5994.5(10)	32.4(3)
C21	6874.9(17)	5593.2(13)	5436.1(10)	33.8(3)
C22	7314.0(16)	5361.6(12)	4640.1(10)	29.2(3)

Table 25: Anisotropic displacement parameters ($Å^2x10^3$) for 62ad. The anisotropic displacement factor exponent takes the form $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	51.5(8)	34.8(6)	46.9(7)	-12.2(5)	-9.2(6)	-3.1(5)
N1	22.2(5)	25.2(6)	27.9(6)	-4.8(5)	6.8(4)	0.2(4)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N2	24.3(6)	33.5(7)	35.7(7)	-9.9(5)	10.2(5)	-4.7(5)
N3	32.6(7)	34.2(7)	34.0(7)	-7.4(5)	11.9(5)	-8.0(5)
N4	31.3(6)	29.3(6)	28.4(6)	-1.7(5)	9.5(5)	-5.7(5)
C1	25.3(6)	22.2(6)	21.5(6)	-4.0(5)	5.9(5)	-0.3(5)
C2	22.8(6)	21.0(6)	21.5(6)	1.6(5)	2.5(5)	0.8(5)
C3	23.7(6)	19.4(6)	18.7(6)	1.8(5)	1.4(5)	1.3(5)
C4	23.3(6)	24.8(6)	23.6(6)	0.0(5)	3.0(5)	1.4(5)
C5	22.1(6)	26.9(7)	31.8(7)	0.6(6)	1.7(5)	-1.2(5)
C6	29.7(7)	22.3(7)	31.7(7)	-4.6(5)	0.5(6)	-1.0(5)
C7	26.8(7)	22.1(6)	27.9(7)	-2.4(5)	4.4(5)	2.7(5)
C8	23.1(6)	19.7(6)	20.5(6)	0.4(5)	4.5(5)	0.7(5)
C9	27.0(7)	23.0(6)	25.1(6)	-1.1(5)	0.6(5)	4.3(5)
C10	26.0(7)	27.3(7)	26.2(7)	-1.2(5)	0.6(5)	0.2(5)
C11	30.7(7)	21.3(6)	21.6(6)	-1.0(5)	7.3(5)	-1.7(5)
C12	30.9(7)	20.3(6)	26.1(6)	2.2(5)	7.0(5)	3.8(5)
C13	26.1(6)	22.4(6)	22.9(6)	1.6(5)	2.5(5)	2.9(5)
C14	39.6(8)	24.0(7)	25.2(7)	-2.1(5)	8.5(6)	-5.3(6)
C15	60.2(11)	20.9(7)	28.1(7)	-1.5(6)	9.9(7)	-0.4(7)
C16	27.9(7)	24.2(7)	32.4(7)	-2.6(6)	4.3(6)	6.4(5)
C17	25.8(7)	19.2(6)	28.8(7)	0.7(5)	0.9(5)	5.5(5)
C18	24.7(7)	26.1(7)	32.9(7)	1.6(6)	-1.2(6)	1.1(5)
C19	33.3(8)	28.0(7)	29.4(7)	-1.3(6)	-4.8(6)	2.4(6)
C20	36.4(8)	32.4(8)	28.1(7)	1.9(6)	2.9(6)	7.0(6)
C21	30.2(8)	34.6(8)	37.1(8)	2.8(6)	6.0(6)	0.0(6)
C22	28.0(7)	24.7(7)	34.1(7)	-1.8(6)	0.5(6)	-1.4(5)

Table 26: Bond lengths for 62ad

Atom	Atom	Length/Å		Atom	Atom	Length/Å
O1	C14	1.2156(19)		C8	C9	1.3992(19)
N1	N2	1.3519(16)		C8	C13	1.3958(18)
N1	C1	1.3448(18)		C9	C10	1.3856(19)
N1	C16	1.4726(19)		C10	C11	1.3938(19)
N2	N3	1.2946(19)		C11	C12	1.390(2)
N3	N4	1.3658(18)		C11	C14	1.5006(19)

Atom	Atom	Length/Å		Atom	Atom	Length/Å
N4	C1	1.3255(18)		C12	C13	1.3936(19)
C1	C2	1.4736(18)		C14	C15	1.496(2)
C2	C3	1.4098(18)		C16	C17	1.510(2)
C2	C7	1.3987(19)		C17	C18	1.397(2)
C3	C4	1.3969(19)		C17	C22	1.383(2)
C3	C8	1.4898(18)		C18	C19	1.388(2)
C4	C5	1.3912(19)		C19	C20	1.390(2)
C5	C6	1.386(2)		C20	C21	1.383(2)
C6	C7	1.389(2)		C21	C22	1.393(2)

Table 27: Bond angles for 62ad

Atom	Atom	Atom	Angle/˚		Atom	Atom	Atom	Angle/˚
N2	N1	C16	120.42(12)		C13	C8	C9	118.40(12)
C1	N1	N2	108.33(12)		C10	C9	C8	120.97(13)
C1	N1	C16	131.00(12)		C9	C10	C11	120.54(13)
N3	N2	N1	106.53(12)		C10	C11	C14	118.62(13)
N2	N3	N4	110.99(12)		C12	C11	C10	118.80(12)
C1	N4	N3	105.56(12)		C12	C11	C14	122.58(13)
N1	C1	C2	124.91(12)		C11	C12	C13	120.85(13)
N4	C1	N1	108.59(12)		C12	C13	C8	120.45(13)
N4	C1	C2	126.42(13)		O1	C14	C11	119.98(14)
C3	C2	C1	121.70(12)		O1	C14	C15	120.86(14)
C7	C2	C1	117.68(12)		C15	C14	C11	119.15(14)
C7	C2	C3	120.52(12)		N1	C16	C17	111.31(11)
C2	C3	C8	122.29(12)		C18	C17	C16	120.05(13)
C4	C3	C2	118.00(12)		C22	C17	C16	120.26(13)
C4	C3	C8	119.68(12)		C22	C17	C18	119.66(13)
C5	C4	C3	121.03(13)		C19	C18	C17	120.00(14)
C6	C5	C4	120.69(13)		C18	C19	C20	120.13(14)
C5	C6	C7	119.31(13)		C21	C20	C19	119.77(15)
C6	C7	C2	120.44(13)		C20	C21	C22	120.31(15)
C9	C8	C3	120.77(11)		C17	C22	C21	120.10(14)
C13	C8	C3	120.77(12)					

Table 28: Selected torsion angles for 62ad

A	B	C	D	Angle/˚
N1	C1	C2	C3	122.22(15)
N1	C1	C2	C7	-61.35(18)
N1	C16	C17	C18	-64.97(17)

A	B	C	D	Angle/˚
N1	C16	C17	C22	113.47(15)
N2	N1	C16	C17	105.72(14)
N4	C1	C2	C3	-61.46(19)
N4	C1	C2	C7	114.98(15)
C1	N1	C16	C17	-67.85(18)
C2	C3	C8	C9	-45.06(18)
C2	C3	C8	C13	137.76(14)
C4	C3	C8	C9	132.95(14)
C4	C3	C8	C13	-44.23(18)
C10	C11	C14	O1	-0.7(2)
C10	C11	C14	C15	178.65(14)
C12	C11	C14	O1	179.15(14)
C12	C11	C14	C15	-1.5(2)
C16	N1	C1	N4	174.96(13)
C16	N1	C1	C2	-8.2(2)

Table 29: Hydrogen atom coordinates (Åx10^4) and isotropic displacement patrameters (Å^{2}x10^3) for 62ad.

Atom	*x*	*y*	*z*	U(eq)
H4	3163(18)	7691(14)	3193(11)	28(4)
H5	2413(18)	6066(14)	2473(11)	27(4)
H6	4100(20)	4922(16)	1846(12)	38(5)
H7	6559(18)	5436(14)	1972(11)	28(4)
H9	7582(18)	7884(14)	4243(11)	29(4)
H10	8256(19)	9478(14)	4999(11)	31(4)
H12	4791(19)	11106(15)	3779(11)	33(4)
H13	4099(18)	9549(14)	2960(11)	30(4)
H15A	5190(20)	12371(18)	4917(14)	53(6)
H15B	6310(20)	12735(17)	4278(14)	51(6)
H15C	6660(20)	13052(17)	5257(14)	49(6)
H16A	8408(18)	5042(14)	3227(11)	30(4)
H16B	10060(20)	5361(15)	3587(12)	39(5)
H18	10285(19)	6835(15)	4799(11)	34(5)
H19	9490(20)	7268(15)	6147(12)	39(5)
H20	7320(20)	6475(16)	6556(13)	44(5)
H21	5970(20)	5269(17)	5607(13)	48(5)
H22	6739(19)	4876(15)	4245(12)	36(5)

6 References

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7 Resume

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Education

2010-2013	PhD studies at the Georg-August Universitaet, Goettingen, under the supervision of Prof. Dr. Lutz Ackermann, on the research topic : « Ruthenium-catalyzed Direct C–H Bond Functionalizations »
November 2009	Diplome D´Ingénieur Chimiste, and Master en sciences, technologies, santé, à finalité recherche, mention chimie, spécialité chimie biomoléculaire (Diploma equivalent to a Honours Master's Degree) awarded by the Ecole Nationale Superieure de Chimie de Montpellier
	(Final grade 15.4 / 20, ECTS Grade A)
2007-2009	Postgraduate studies at the Ecole Nationale Supérieure de Chimie, Montpellier, France
	Main field of studies: Organic Chemistry
2006-2007	B Sc in Chemistry awarded by the Ecole Nationale Superieure de Chimie de Montpellier
2004-2006	Classes Préparatoires PCSI/PC*, Lycée Henri Wallon, Valenciennes, France

Industrial experience

March-Aug.2009	Hoffmann La Roche, Basel, Switzerland
	Discovery of a new and convenient synthesis of the benzophenone part of a natural substance: Balanol
June-Sept. 2008	Sanofi Aventis, Frankfurt am Main, Germany
	Chemical development of therapeutic molecules
July-Aug. 2007	Centre Nationale de la Recherche Scientifique (CNRS), Lille, France
	Synthesis of lignine derivatives

Teaching experience

In the context of obligatory teaching at the Georg August University, Goettingen:

Supervision of Bachelor thesis, supervision of the basic and advanced practical courses in organic chemistry, supervision of the “Analysenkurs”, communication with the students exclusively in german.

Languages

German	fluent
English	fluent
French	mother tongue

Publications

L. Ackermann, E. Diers, A. Manvar: "Ruthenium-catalyzed C–H Bond Arylations of Arenes Bearing Directing Groups via Six-Membered Ruthenacycles." *Org. Lett*. **2012**, *14*, 1154–1157.

E. Diers, N. Y. P. Kumar, T. Mejuch, I. Marek, L. Ackermann: "Carboxylate-assisted ruthenium (II)-catalyzed C–H arylations of 5-aryl tetrazoles: Step-economical access to Valsartan." *Tetrahedron* **2013**, 69, 4445–4453.

Poster presentations

Poster presentation at the Forum of Molecular Catalysis, Heidelberg, 28.06.2013

Poster presentation at the second Niedersachsiches Katalyse Symposium, Universität Gottingen, 10.2012

Poster presentation at the 4th EuCheMS, Prag, 08.2012

Poster presentation at the IRTG Symposium, Münster University, 02.2011

Poster presentation at the first Niedersachsiches Katalyse Symposium, Universität Gottingen, 10.2010