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Metal-catalyzed and aryne-mediated multicomponent approaches to heterocycles

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by

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To my husband and my friend, Anton

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LIST OF ABBREVIATIONS

[O]	oxidation
°C	degrees Celsius
Ac	acetyl
Ada	adamantyl
APCI	atmospheric-pressure chemical ionization
aq.	aqueous
Ar	aryl
BHT	2,6-bis(1,1-dimethylethyl)-4-methylphenol
Bn	benzyl
bpy	2,2'-bipyridine
br	broad
calcd	calculated
cat.	catalytic amount
CMLD	center for methodology and library development
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
dba	dibenzylidene acetone
DBU	1,8-diazabicycloundec-7-ene

DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	*bis*(diphenylphosphino)ethane
dppf	(diphenylphosphino)ferrocene
dppp	*bis*(diphenylphosphino)propane
dt	doublet of triplets
EI	electron ionization
eq.	equation
equiv	equivalents
ESI	electron spray ionization
Et	ethyl
eV	electron-volt
FT-IR	Fourier transform infrared spectroscopy
g	gram
GC	gas chromatography

h	hour(s)
Hal	halogen
HetAr	heteroaryl
Hex	hexyl
HIV	human immunodeficiency virus
HMDS	hexamethyldisiloxane
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
i	*iso*
IR	infrared
J	coupling constant
KU	University of Kansas
LAH	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectrometry
M	molar
m	multiplet
mp	melting point
MCP	multicomponent process
MCR	multicomponent reaction
Me	methyl

Met	metal
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
MLSCN	molecular library screening center network
mmol	millimoles
mol	mole
MOM	methoxymethyl
Ms	mesyl
MS 4A	molecular sieves, 4 angstrom
MW	microwave
N	normal
NIH	National Institutes of Health
NIS	*N*-iodosuccinimide
nm	nanometer
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NSAID	non-steroidal anti-inflammatory drug

o	*ortho*
OPMCR	one-pot multicomponent reaction
p	*para*
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PS	polymer supported
q	quartet
QTOF	quadrupole time of flight
rt	room temperature
s	singlet
satd	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
T	temperature
t	time
t	triplet
t	*tert*
TBAF	tetrabutylammonium fluoride

TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDMS	*tert*-butyldimethylsilyl
td	triplet of doublets
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time of flight
Tol	tolyl
Ts	tosyl
US	ultrasound
UV	ultraviolet
W	watt
Δ	heat
δ	chemical shift in ppm
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

CHAPTER 1

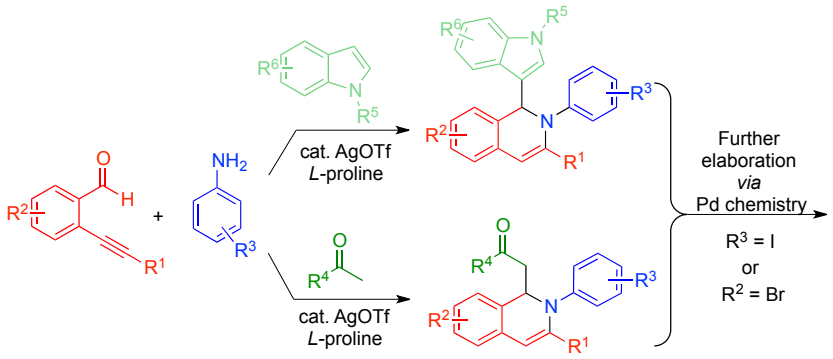
Dissertation organization

The eight chapters of this dissertation describe the importance of a number of novel approaches to chemical research and synthesis, such as combinatorial, multi-component, and aryne-mediated processes, as well as their combinations. The main focus of this thesis is the development of novel approaches towards medicinally-relevant heterocycles, such as 1,2-dihydroisoquinolines, indoles, benzofurans, 1*H*-indazoles and pyridoindoles, employing metal-catalyzed and aryne-mediated multicomponent strategies.

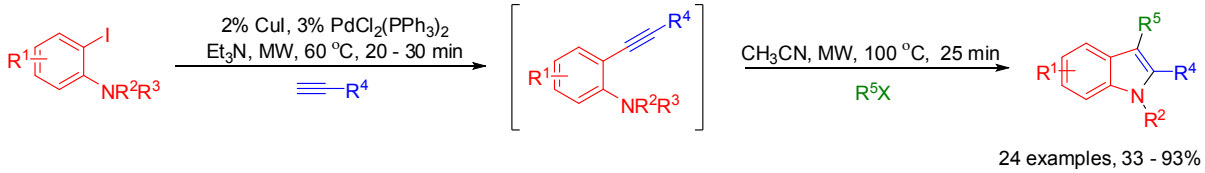
Chapter 2 is a review of recent advances in the development of multicomponent approaches to the synthesis of 5-membered ring fused aromatic heterocycles. It is meant to provide the reader with a general understanding of the importance of multicomponent synthetic strategies, as well as practical examples of their use in organic synthesis.

Chapter 3 is a paper that was published in the journal *ACS Combinatorial Science* in 2011.[1] This chapter describes the synthesis of a 105-membered library of medicinally promising 1,2-dihydroisoquinolines by a three-component reaction and their further elaboration using Pd-catalyzed couplings. While working on the library synthesis, a novel three-component reaction of 2-alkynylbenzaldehydes, anilines, and indoles has been discovered. This project was initiated together with a former postdoctoral fellow in our group, Dr. Raffaella Mancuso, in collaboration with the Kansas University NIH Center for Excellence in Chemical Methodology and Library Development (KU-CMLD). Dr. Mancuso

contributed to the initial library design and preparation of some of the library members. Researchers from the KU-CMLD carried out computational studies, LCMS purification of a portion of the library members and purity analysis for all of the compounds. These compounds have been added to the NIH library of compounds to be tested for an array of biological activities.

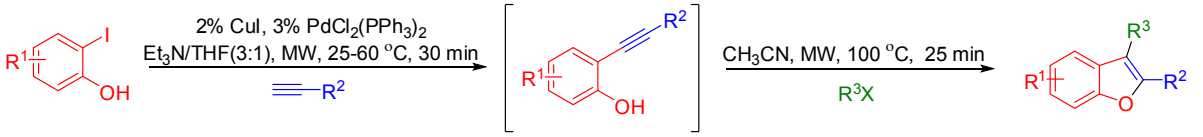


Chapter 4 is an article that was published in the journal *Tetrahedron* in 2009.[2] This chapter describes the scope and limitations of a methodology that allows the generation of 2,3-disubstituted indoles under Sonogashira reaction conditions in a one-pot, three-component fashion from readily available starting materials. A variety of medicinally-relevant indoles has been obtained in good to excellent yields using microwave-assisted reaction conditions. This project was initiated by a former postdoctoral fellow in our research group, Dr. Yu Chen, who also carried out the synthesis and characterization of the *N*-methyl-substituted indoles.

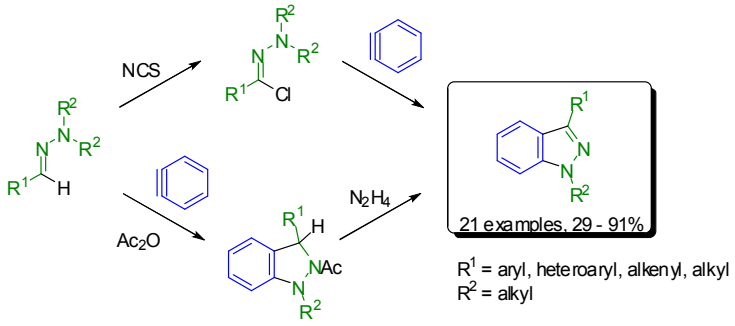


24 examples, 33 - 93%

Chapter 5 is a project soon to be published in the journal *Tetrahedron*. While working on the synthesis of indoles, we discovered that 2-iodophenols can participate in the same type of process, affording the corresponding 2,3-disubstituted benzofurans. This chapter describes the optimization process, scope, limitations and extensions of this one-pot, three-component methodology. Efforts in applying this method towards the total syntheses of the naturally-occurring oligostilbenes Amurensin H, Gnetuhainin B, and Gnetuhainin F are described.



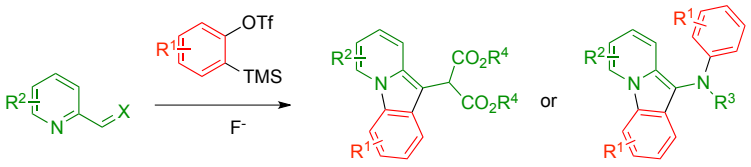
Chapter 6 is a paper that was published in the journal *Organic & Biomolecular Chemistry* in 2012.[3] This chapter describes the optimization process, scope and limitations of a methodology for the synthesis of *N*-alkylindazoles in a one-pot reaction of 1,1-dialkylhydrazones and arynes through two complimentary routes employing either NCS-chlorination or an Ac_2O-trapping/deprotection/aromatization sequence. For the NCS protocol, we found that in the case of cyclic hydrazones the succinimide molecule is incorporated into the final compounds, resulting in a one-pot, three-component reaction.



This project was carried out in collaboration with another group member, Anton

Dubrovskiy, who contributed by preparing the starting *N*,*N*-dialkylhydrazones, carrying out the optimization work on the process, and exploring the scope of the Ac_2O/deprotection/aromatization strategy.

Chapter 7 is a modification of a paper that was published in the *Journal of Organic Chemistry* in 2012.[4] It describes a methodology for the synthesis of various 10-substituted pyrido[1,2-*a*]indoles by the reaction of readily prepared 2-substituted pyridines and arynes under mild reaction conditions. The optimization of the process and examination of the scope of the reaction of *N*-(1-(pyridin-2-yl)ethylidene)amines with arynes is described. A one-pot, three-component version of this reaction employing 2-pyridine aldehydes, primary amines, and arynes was found to be successful. The reaction of 2-(pyridin-2-ylmethylene)malonates with benzyne was independently discovered at roughly the same time by the former Larock group members Dr. Donald C. Rogness and Dr. Jesse P. Waldo. Dr. Rogness carried out the optimization work and studies on the scope of the synthesis of pyrido[1,2-*a*]indolemalonates, as well as their characterization.



Lastly, chapter 8 summarizes the contributions described in the previous chapters and discusses future directions one might see in the areas of metal-catalyzed and aryne-mediated multicomponent strategies.

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2. Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908-8915.
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CHAPTER 2

Multicomponent Approaches to the Synthesis of 5-Membered Fused Aromatic Heterocycles. A Review.

2.1. INTRODUCTION

With increasing awareness of the environmental situation on our planet and the urge to improve it, the need for greener synthetic strategies and principles is becoming more and more obvious for chemical industries, as well as academic laboratories. Over the last couple of decades, significant progress in this direction has been made, introducing a plethora of novel approaches, such as combinatorial chemistry,[1] multicomponent processes,[2] microwave-[3] and ultrasound-assisted reactions,[4] solid phase syntheses,[5] *etc.* Among these, multicomponent processes (MCPs) have attracted the most attention due to their obvious synthetic utility and numerous advantages. Multicomponent processes include multicomponent reactions (MCRs), in which three or more different reactants are combined together in one reaction vessel to generate one major product. Another type of MCP is one-pot multi-component reactions (OPMCRs) - a sequential addition of three or more reactants to the same reaction vessel to generate the major product without isolation of the intermediate products after each step. The advantages of MCPs are minimization of the amounts of reagents, solvents, catalyst loadings, as well as no need for isolation and purification of the intermediate compounds, which dramatically decreases the amounts of

chemical waste and time invested. In addition, due to the fact that the intermediates are not isolated, losses of the material due to isolation are minimized and usually higher yields of the final products are obtained compared to the overall yields for traditional step-by-step approaches.

Since 1959, when Ugi reported the first four-component reaction,[6] interest in multicomponent reactions has grown immensely. The goal of this review is to give an overview of the developments in the applications of MCPs for the construction of 5-membered fused aromatic heterocyclic cores (*e.g.* indole, benzofuran, benzothiophene, indolizine, indazole, benzimidazole, benzoxazole, benzothiazole, and their close analogues). Methodologies that afford other types of heterocycles or employ heterocyclic compounds as one of the components will not be covered due to space limitations.

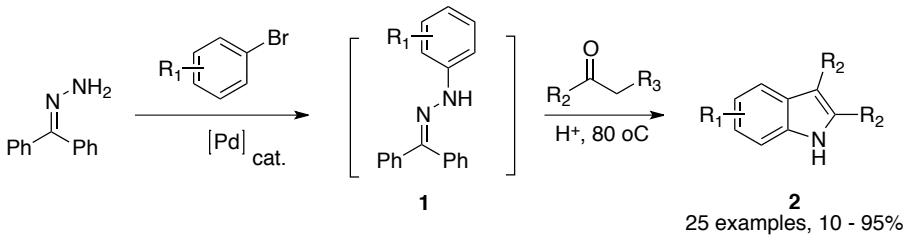
2.2. MCPs IN THE SYNTHESIS OF INDOLES

Compounds containing an indole core have been studied extensively due to their high biological and pharmaceutical activity, as well as utility as building blocks in organic synthesis.[7] Numerous methods to access the indole core have been developed, with a majority being multistep approaches. A number of MCPs for the synthesis of indoles have been successfully developed, providing a short and convenient route to these valuable structures.

2.2.1. Modifications of the Fischer indole synthesis

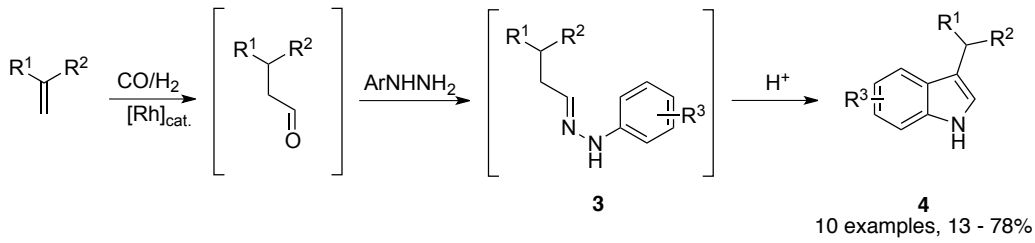
Attempts to transform the Fischer indole synthesis into a multicomponent process led to the discovery of several useful processes. In 1999, Buchwald described a three-component procedure that utilizes Pd-catalyzed amination for the one-pot formation of hydrazones **1**, which then can be cyclized *in situ* with enolizable ketones to form 2,3-disubstituted indoles **2** (Scheme 1).[8] Utilizing this method, the authors were also able to obtain *N*-aryl indoles when an additional equivalent of an aryl bromide was used in the first step.

Scheme 1. Synthesis of indoles *via* Pd-catalyzed amination/Fisher cyclization



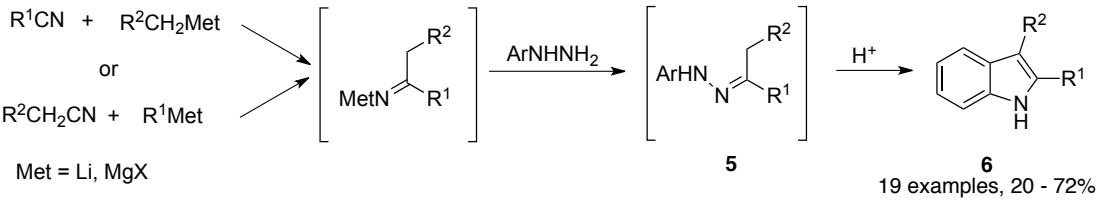
A method based on the Rh-catalyzed hydroformylation of alkenes, followed by coupling of the resulting aldehydes with hydrazines for the formation of alkyl analogues of **3** and subsequent Fischer cyclization to indoles **4**, has been developed by Elibracht (Scheme 2).[9] More recently, a similar method for the synthesis of 2,3-disubstituted indoles has been described based on a tandem hydroformylation–Fischer indolization protocol.[10]

Scheme 2. Rh-catalyzed hydroformylation of alkenes/Fischer indole synthesis



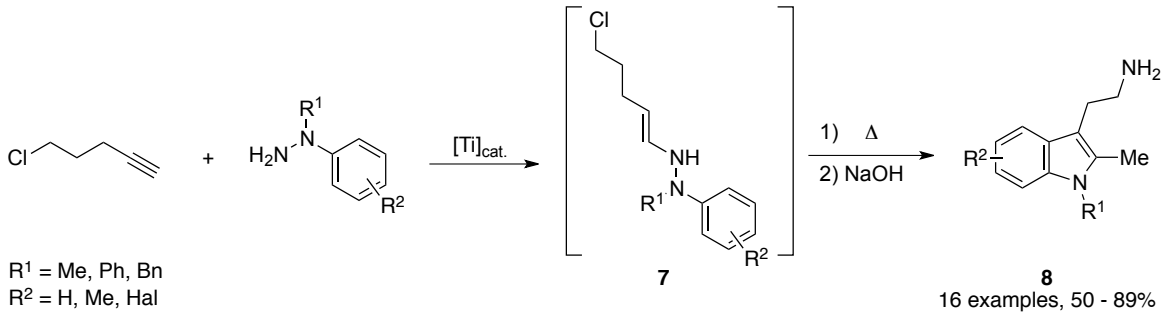
In a related method described by Simoneau and Ganem, arylhydrazones **5** are formed *in situ* from nitriles or carboxylic acids, organolithium or Grignard reagents and arylhydrazines (Scheme 3).[11] A number of pharmacologically useful 2,3-substituted indoles **6**, including a series of triptamines and tryptamides, has been prepared in good yields.

Scheme 3. Synthesis of indoles from nitriles, organometallic reagents and arylhydrazines



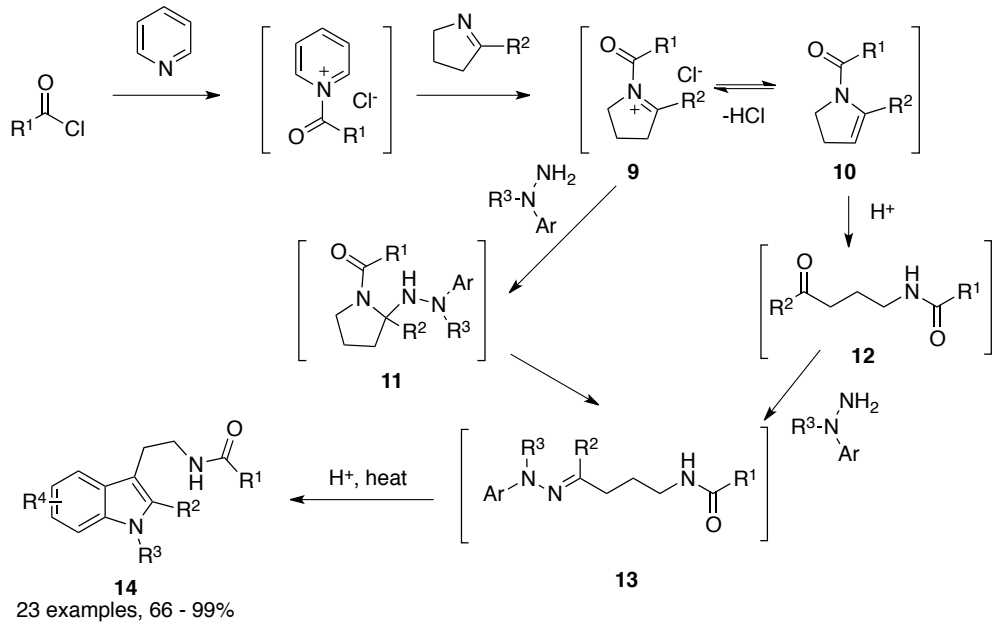
An alternative method for the synthesis of tryptamines and tryptamine homologues involving a Fischer indole synthesis and the titanium-catalyzed hydroamination of alkynes has been reported by Beller and co-workers (Scheme 4).[12] The Ti-catalyzed hydroamination of alkynes gives intermediate *N*-aryl-*N*-chloroalkylhydrazones **7**, which are transformed into the desired indoles **8** by a [3,3]-sigmatropic rearrangement. Finally, the chlorine atom is replaced by ammonia, generated in the reaction mixture during the previous step.

Scheme 4. Synthesis of tryptamines *via* Ti-catalzed hydroamination of alkynes



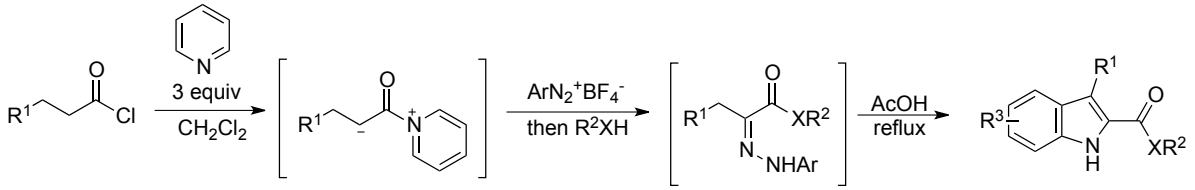
Very recently, one more three-component method for the formation of highly functionalized tryptamines has been reported, starting from acyl chlorides, 2-methyl-1-pyrroline, and arylhydrazines.[13] The proposed reaction pathway involves pyridine- or DMAP-catalyzed *N*-acylation of the 1-pyrroline to form the intermediate **9**, which co-exists in equilibrium with the enamine **10** (Scheme 5). Upon reaction of **9** or **10** with arylhydrazines, the Fisher indole precursor **13** is formed, which, upon heating under acidic conditions, provides the desired indoles **14** in good to excellent yields (66-99%).

Scheme 5. Plausible reaction pathway for the synthesis of highly functionalized triptamines



A similar pyridine-catalyzed, three-component coupling between acyl chlorides, diazonium salts, and alcohols or amines affords α-hydrazono carboxylic acid derivatives **15**, which after Fischer cyclization provide 2-(carboalkoxy)indoles **16** in good yields (Scheme 6).[14]

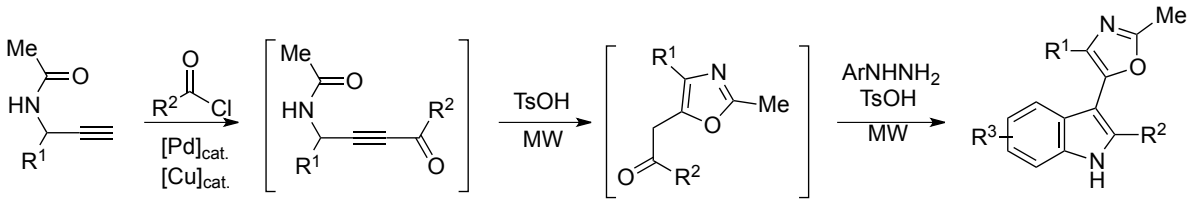
Scheme 6. Preparation of 2-(carboalkoxy)indoles *via* Fischer cyclization



R^1 = Me, Ph
XR^2 = OAlkyl, OBn, $NAlkyl_2$, NHCy, $NAllyl_2$
R^3 = Cl, F

Related 5-(3-indolyl)oxazoles **19** have been synthesized starting with the Sonogashira coupling of acyl chlorides with substituted propargylic amides, followed by cycloisomerization of the ynones **17** obtained to the corresponding oxazoles **18**. Subsequent coupling of **18** with arylhydrazines is followed by Fischer indole cyclization with the aid of microwave irradiation (Scheme 7).[15] As a result, a small library of highly luminescent compounds **19** was obtained.

Scheme 7. Synthesis of 5-(3-indolyl)oxazoles

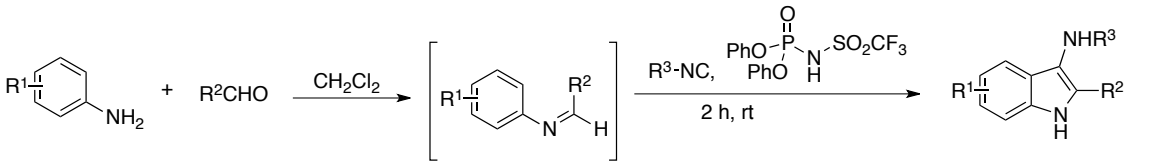


2.2.2. Modifications of the Ugi reaction

The three-component synthesis of 3-aminoindoles from aldehydes, anilines and isocyanides by an interrupted Ugi reaction has been reported by Sorensen *et al* (Scheme 8).[16] When carboxylic acids are omitted in the classical Ugi reaction, formation of the 3-

aminoindoles **21** is favored through the intermediate **20**. Addition of triflic phosphoramide was found to be critical to obtain high yields under mild reaction conditions. Although the *in situ* formation of the imine **20** is possible, the authors decided to focus on the precondensation of anilines and aldehydes in their studies of the scope of the process, and proceed then with the next step without purification of the imine, which greatly improved the yields of the desired products.

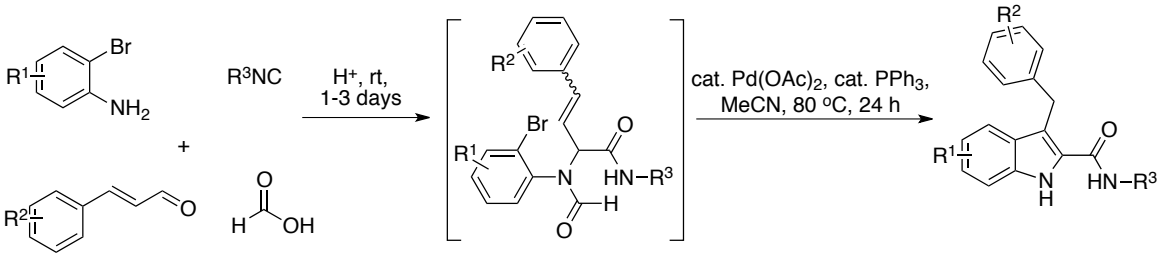
Scheme 8. Three-component synthesis of 3-aminoindoles



R1 = OMe, SMe, *etc.*
R2 = alkyl, Ar, CO_2Et
R3 = alkyl, Ar

A combination of the Ugi and Heck reactions provides a novel route to indoles (Scheme 9).[17] A two-step OPMCR of acrylic aldehydes, bromoanilines, formic acid and isocyanides affords the Ugi-Smiles adduct **22**, which under Heck reaction conditions leads to the polysubstituted indoles **23**, albeit in only 15-38% overall yields.

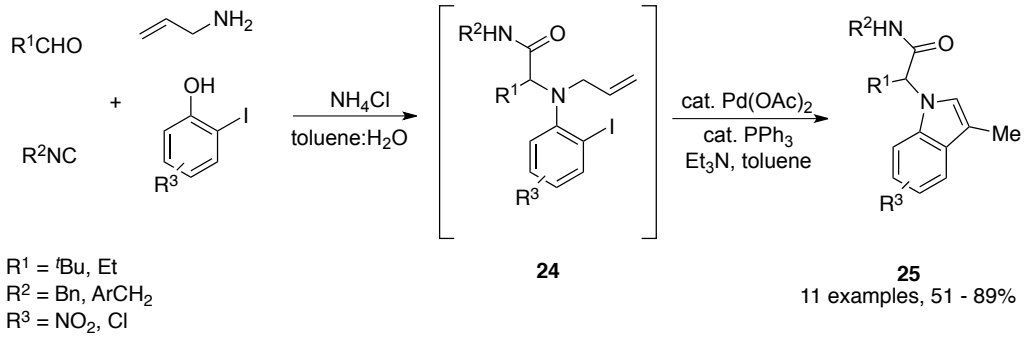
Scheme 9. Ugi/Heck reaction for the synthesis of indoles



R1 = H, F
R2 = H, OMe
R3 = alkyl, Bn, CH_2CO_2Me

The Ugi-Smiles reaction in combination with a Heck cyclization has also been reported for the synthesis of indole scaffolds.[18] 2-Iodo-4-nitrophenol, allylamine, aldehydes and isocyanides are combined in an Ugi-Smiles coupling to afford the intermediate **24**, which is converted in one-pot into the indoles **25** under Heck coupling conditions (Scheme 10). A one-pot reaction was possible if the residual isocyanide is neutralized prior to the addition of the palladium catalyst.

Scheme 10. Ugi-Smiles/Heck strategy for the synthesis of indoles



R^1 = ^{t}Bu, Et
R^2 = Bn, $ArCH_2$
R^3 = NO_2, Cl

24

25
11 examples, 51 - 89%

An Ugi coupling with intermediate preformation of the indole ring and its subsequent cleavage has been employed by several groups in the synthesis of other substrates, such as *N*-substituted diketopiperazines,[19] the natural product omuralide,[20] and others products.[21]

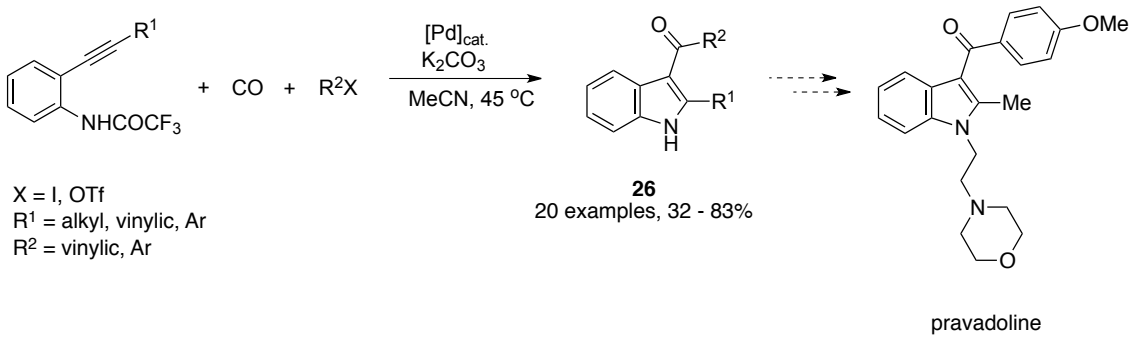
2.2.3. Pd, Cu or Pd/Cu-catalyzed MCPs for indole formation

A number of MCPs for the synthesis of indoles have been developed based on Pd- or Cu-catalyzed, or Pd/Cu-cocatalyzed reactions.

In addition to the Pd-catalyzed carboalkoxylation of 2-alkynyl anilines in the presence of CO and MeOH to afford 3-(carbomethoxy)indoles,[22] an analogous Pd-catalyzed three-component coupling between 2-alkynylacetanilides, aryl iodides and CO to afford indoles **26**

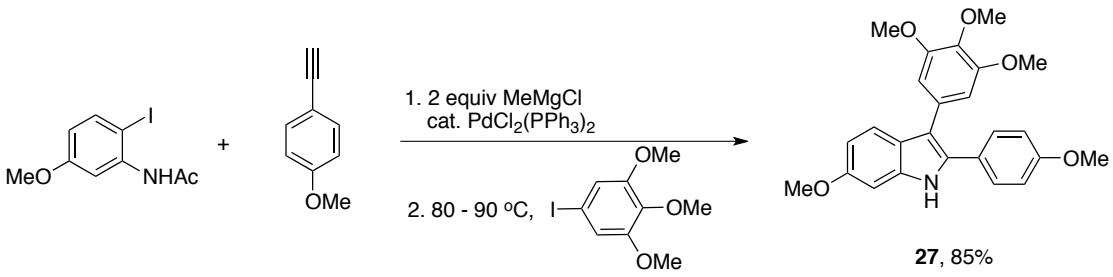
has been reported by Cacchi in 1994 (Scheme 11).[23] This methodology has been successfully applied to the synthesis of the NSAID pravadoline and later modified by other groups to provide a large variety of 2,3-disubstituted indoles and analogues.[24]

Scheme 11. Pd-catalyzed reaction between 2-alkynylacetanilides, aryl iodides and CO



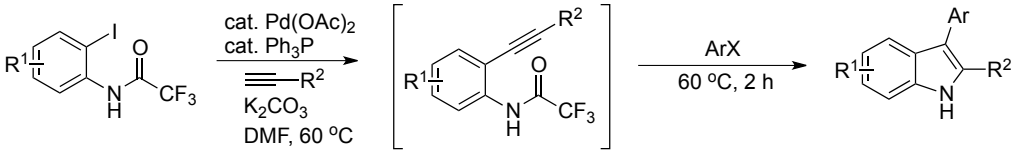
In 2001, Flynn reported a three-component synthesis of benzo[*b*]furans starting from *o*-iodophenols, alkynes and aryl iodides.[25] Over the course of this work, the authors found that 2-iodo-5-methoxyacetanilide can also be employed under the same reaction conditions to afford the indole **27** in an 85% yield (Scheme 12).

Scheme 12. One-pot synthesis of indole **27** from 2-iodo-5-methoxyacetanilide



This methodology has been later extended by the authors to its carbonylative version for the synthesis of tubulin polymerization inhibitors.[26] Lu and co-workers reported a modification of this method for the synthesis of 2,3-disubstituted indoles **29**. The use of *o*-iodo-*N*-trifluoroacetanilides significantly expanded the reaction scope (Scheme 13).[27]

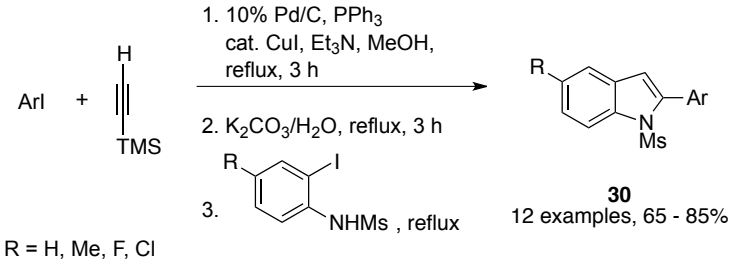
Scheme 13. Synthesis of 2,3-disubstituted indoles from the *o*-iodo-*N*-trifluoroacetanilides



The Larock group recently developed a microwave-assisted modification of this reaction, which allows the efficient synthesis of multisubstituted indoles and *N*-methylindoles under Sonogashira conditions.[28]

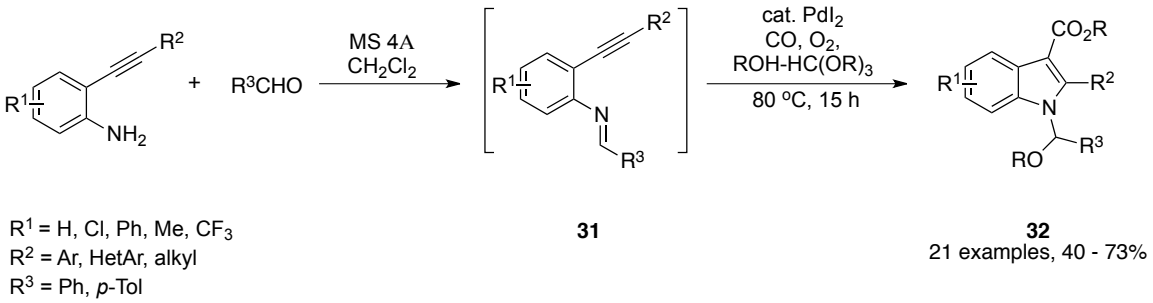
Recently, Rao *et al* reported a new method for the synthesis of indoles from (trimethylsilyl)acetylene and iodoarenes in the presence of 10% Pd/C−CuI, followed by treatment of the reaction mixture with potassium carbonate in aqueous MeOH, and then coupling with *o*-iodoanilides (Scheme 14).[29] The reaction sequence includes 2 consecutive Sonogashira couplings and Pd-catalyzed cyclization of intermediate 2-alkynylanilines to form the corresponding indoles **30**.

Scheme 14. Indoles from (trimethylsilyl)acetylene, iodoarenes and *o*-iodoanilines



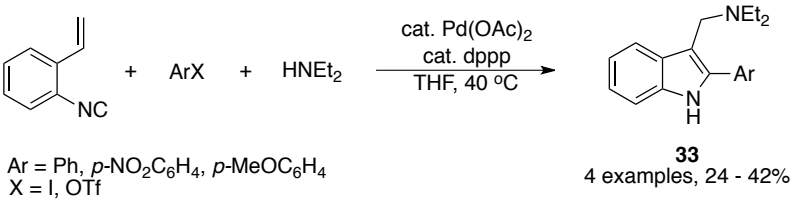
A multicomponent cascade process, based on the sequential nucleophilic attack of *in situ* preformed imines, followed by a palladium-catalyzed oxidative heterocyclization-alkoxycarbonylation process, leads to 1-(alkoxyarylmethyl)indole-3-carboxylic esters **32**, as has been reported by Gabriele in 2010 (Scheme 15).[30] Imines **31** are formed *in situ* from the reaction of 2-alkynylanilines and aldehydes and a further reaction with CO and O_2 in ROH-$HC(OR)_3$ as a solvent in the presence of catalytic amounts of PdI_2 to afford a wide variety of indoles **32** in 40-73% yields.

Scheme 15. Pd-catalyzed synthesis of 1-(alkoxyarylmethyl)indole-3-carboxylic esters



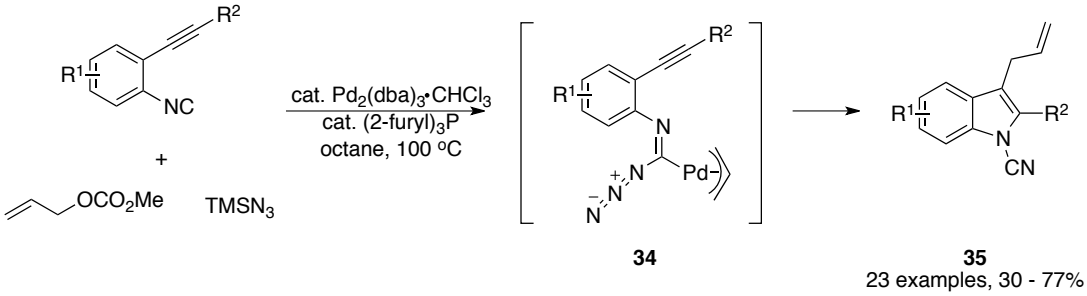
In 2002, a Pd-catalyzed three-component reaction for the synthesis of 2-aryl-3-(methylamino)indoles was reported (Scheme 16).[31] 2-Vinylphenylisocyanide, aryl iodides and secondary amines combine together to provide indoles **33** in low to moderate (24-42%) yields.

Scheme 16. Synthesis of 2-aryl-3-(methylamino)indoles



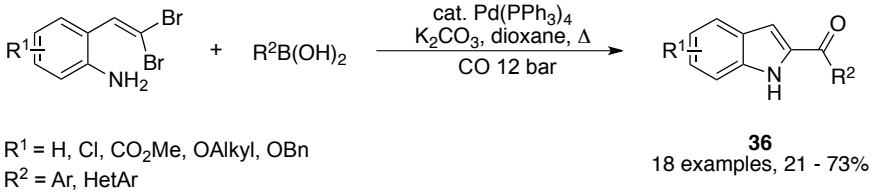
The same year, Yamamoto reported a Pd-catalyzed multicomponent process for the synthesis of *N*-cyanoindoles from isocyanides, allyl carbonates, and trimethylsilyl azide (Scheme 17).[32] The authors proposed that this transformation most likely proceeds through the intermediate **34**, which upon losing N_2 and cyclizing, affords 1-cyano-3-allylindoles **35** in 30-77% yields.

Scheme 17. Pd-catalyzed multicomponent reaction for the synthesis of *N*-cyanoindoles



A *C*,*N*-coupling/carbonylation/*C*,*C*-coupling sequence starting from 2-*gem*-dibromovinylanilines and boronic acids under an atmosphere of carbon monoxide has been reported to afford 2-aroylindoles **36** (Scheme 18).[33] The use of methanol, instead of boronic acids, also proved to be successful, affording 2-(carbomethoxy)indoles.[34]

Scheme 18. Pd-catalyzed multicomponent reaction for the synthesis of 2-aroylindoles

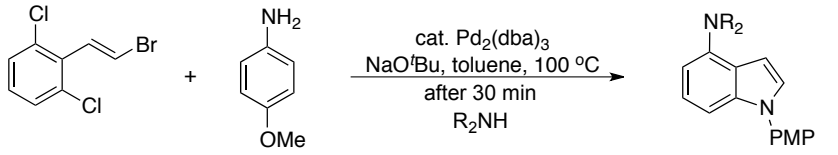


R^1 = H, Cl, CO_2Me, OAlkyl, OBn
R^2 = Ar, HetAr

36
18 examples, 21 - 73%

2-(2-Haloalkenyl)aryl halides have been shown to participate in sequential amination reactions to provide 1-substituted indoles **37** under Pd catalysis (Scheme 19).[35]

Scheme 19. Sequential amination reactions for the synthesis of 1-substituted indoles

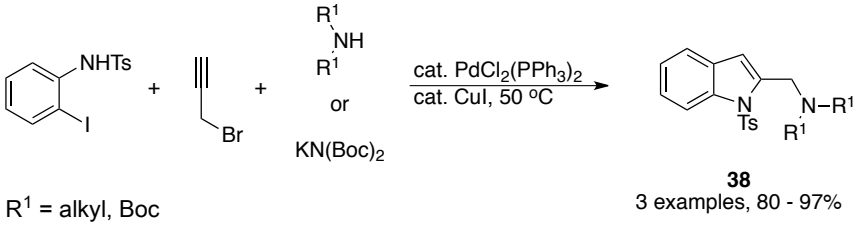


R_2NH = morpholine, PMPNHMe

37
2 examples, 55 - 57%

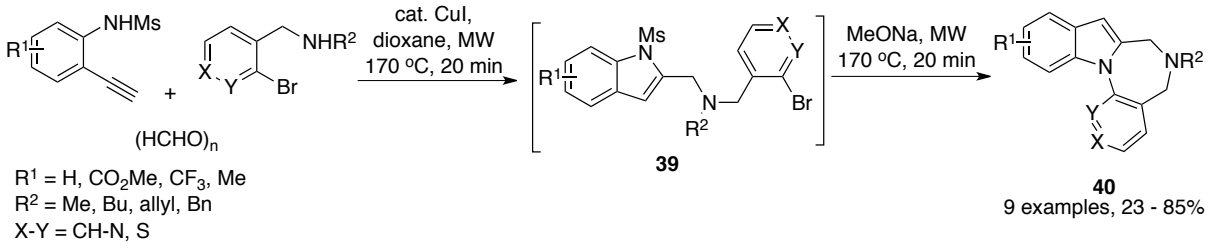
In their efforts to develop a new method for the synthesis of tertiary propargylic amines, Alami and co-workers found that when protected 2-iodoanilines are used as starting materials, good yields of the corresponding indole products **38** can be obtained (Scheme 20).[36] In this reaction, propargyl bromide and the amine form the corresponding propargylic amine, followed by an *in situ* Sonogashira reaction and intramolecular Pd-catalyzed cyclization, leading to the formation of the desired 2-(aminomethyl)indoles **38** in 80-97% yields. Examples of indoles bearing tertiary, as well as Boc-protected methylamino, groups were prepared successfully using this methodology.

Scheme 20. Three-component synthesis of 2-(methylamino)indoles



Copper was found to be a suitable catalyst for the formation of indole-fused benzo-1,4-diazepines **40** by a Mannich-type process starting from 2-alkynylanilines, formaldehyde, and amines (Scheme 21).[37] This domino three-component coupling-indole formation-*N*-arylation sequence proceeds through the formation of alkynylamines, which under CuI-catalyzed conditions provide indole intermediates **39**, which after deprotection and additional *N*-*C* bond formation result in the formation of benzo-1,4-diazepines **40** in 23-85% yields. Various modifications of this method were later reported to afford a wide array of indole analogues.[38]

Scheme 21. Formation of 2-methylaminoindoles *via* modified Mannich reaction

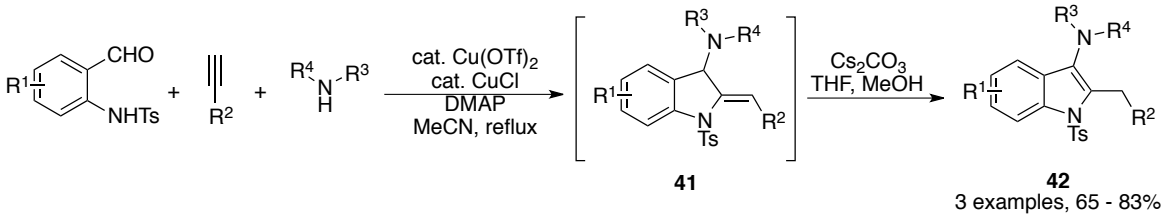


A similar method that involves a reaction between 2-ethynylaniline, sulfonyl azides, and nitroolefins, affords 2-amino-3-alkylindoles in good yields.[39]

Gevorgyan and co-workers developed an efficient Cu(I)-catalyzed MCR for the synthesis of 3-aminoindoles.[40] 2-Aminobenzaldehydes, secondary amines, and alkynes are combined to form the corresponding propargylamine intermediate, which then undergoes

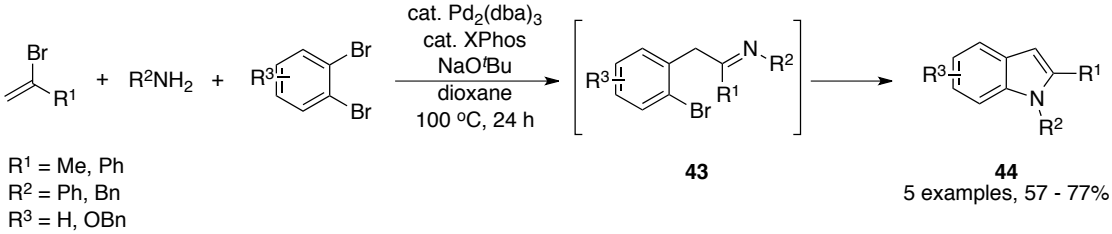
cyclization to the desired indolines **41**. The indolines **41** were synthesized in good to excellent yields. Alternatively these scaffolds can be isomerized *in situ* into the indoles **42** (Scheme 22).

Scheme 22. Cu(I)-catalyzed MCR for the synthesis of 3-aminoindoles



A Pd/Cu-catalyzed process that employs *ortho*-dihaloarenes together with primary amines and bromoalkenes was developed in 2007 by Barluenga and co-workers (Scheme 23).[41] The imine intermediate **43** is formed after the Pd-catalyzed coupling of the bromoalkene and the amine and subsequent *C-H* activation and coupling with dibromobenzenes. This intermediate then undergoes *C-N* coupling to afford the 1,2-disubstituted indole derivatives **44** in 57-77% yields. An alternative process employing terminal alkynes, instead of bromoalkenes, also proved to be successful.[42]

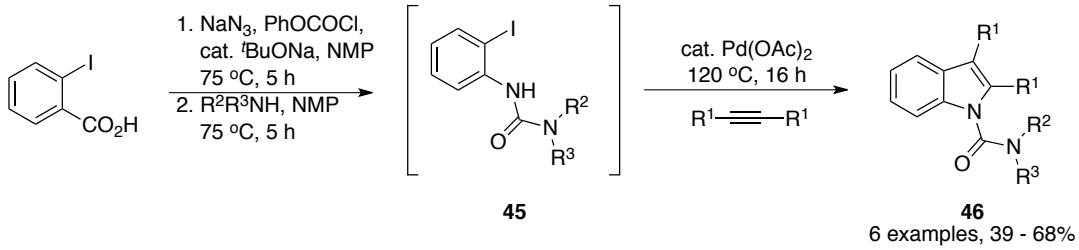
Scheme 23. Synthesis of indoles from *ortho*-dihaloarenes



Lebel and co-workers reported an OPMCR for the synthesis of indoles **45** from 2-iodobenzoic acid by a one-pot Curtius rearrangement, followed by a Pd-catalyzed

indolization (Scheme 24).[43] Various indoles and *N*-acylindoles were obtained following this method in good to excellent yields. The authors note that annulation of the aromatic ureas **45** had not been reported previously. The fact that intermediate 2-iodoindoles are not isolated is important, since the number of available 2-iodoanilines is limited.

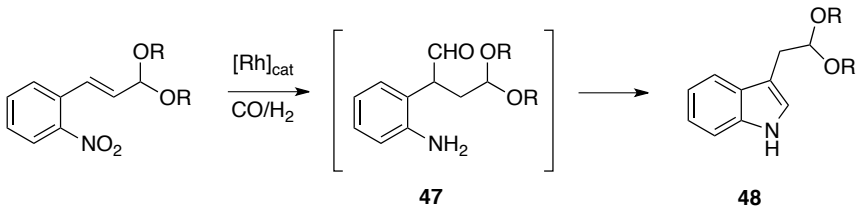
Scheme 24. Curtius rearrangement/Pd-catalyzed indolization of 2-iodoarenecarboxylic acids



2.2.4. Other MCPs for the synthesis of indoles

Del Ponte and co-workers reported a rhodium-catalyzed domino hydroformylation/ indolization of *m*-substituted-*o*-nitrocinnamaldehyde diethyl acetals for the synthesis of 3-substituted indoles **48** (Scheme 25).[44] The process most likely proceeds through the aniline intermediate **47** with attack of its amino group onto the aldehyde and subsequent aromatization to afford indoles **48**. Unfortunately, no studies of the scope of this process have been carried out.

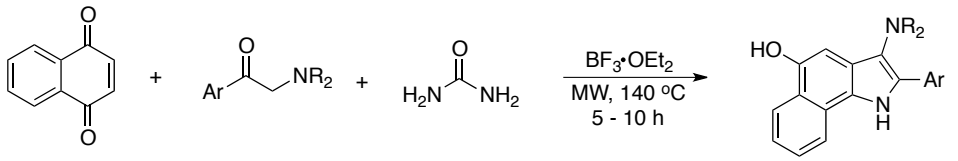
Scheme 25. Rhodium-catalyzed domino hydroformylation/indolization



A rapid synthesis of 5-hydroxybenzo[*g*]indole scaffolds by a modified Nenitzescu

reaction has been reported.[45] This fast, neat, microwave-assisted, Lewis acid-catalyzed, one-pot reaction efficiently produces various benzo[*g*]indoles **49** from aminoketones, naphthoquinones and urea as an environmentally friendly source of ammonia (Scheme 26).

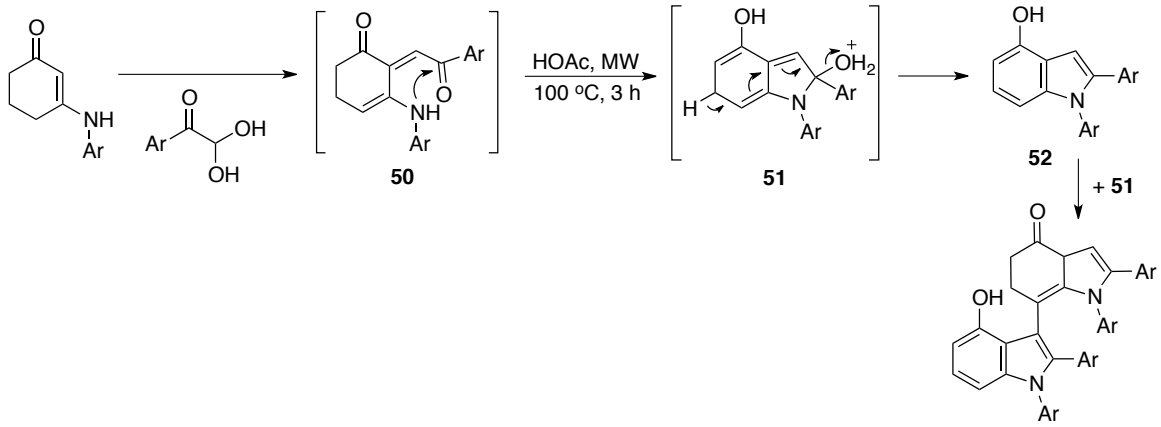
Scheme 26. Synthesis of 5-hydroxybenzo[*g*]indoles



49
12 examples, 50 - 88%

Recently, a multicomponent domino reaction that employs an intermolecular allylic esterification and indole formation has been described.[46] In this process, the formation of the dihydroindole core **51** through intermediate **50** and its subsequent dimerization provides the desired indoles **53** in moderate 40-54% yields (Scheme 27).

Scheme 27. Multicomponent domino reaction for the synthesis of indoles **53**

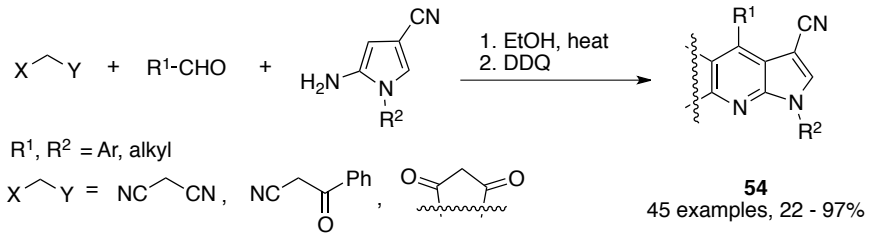


50 **51** **52** **53**
12 examples, 40 - 54%

Very recently, a one-pot, three-component synthesis of the 7-azaindole derivatives **54** from *N*-substituted 2-amino-4-cyanopyrroles, aldehydes, and active methylene compounds

has been reported (Scheme 28).[47] A small library of 7-azaindoles **54** has been prepared following the described methodology.

Scheme 28. One-pot, three-component synthesis of 7-azaindoles



It is noteworthy that indoles have been extensively studied as starting materials for MCPs. Recently, a review on the use of indoles in MCPs appeared in the literature that nicely summarizes the developments in this area, and provides a more detailed overview of the synthesis of indoles by the MCPs described above.[48]

2.3. MCPs IN THE SYNTHESIS OF BENZOFURANS

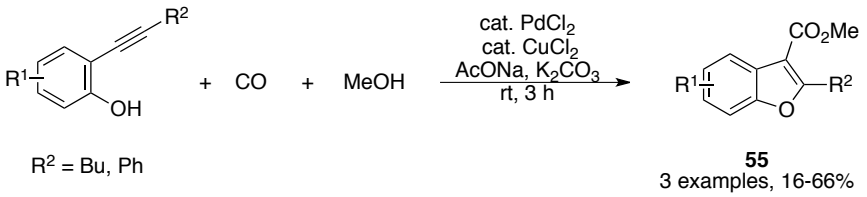
Similarly to indoles, interest in synthesizing benzofurans has been growing for many years due to their high biological potential.[49] A number of convenient methods have been developed that allow preparation of a variety of substituted benzofurans in few steps with good overall yields and from readily available starting materials. Several examples of MCPs for the synthesis of this valuable core have been developed.

2.3.1. MCPs for the synthesis of benzofurans from 2-halophenols

Several Pd-catalyzed methods involving the use of CO as one of the components have been reported. As early as 1989, the first carbonylative cyclization of 2-alkynylphenols was reported by Sakamoto (Scheme 29).[22] In this process, the methyl benzofuran-3-carboxylates

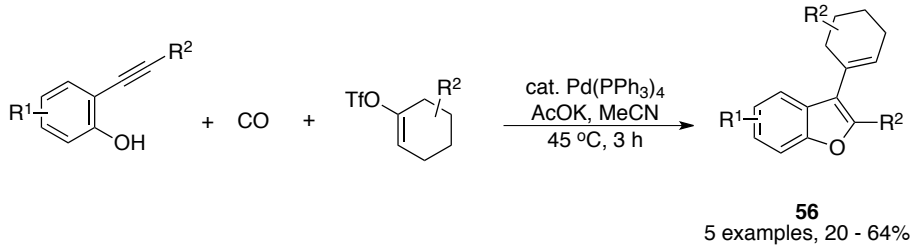
55 were obtained in good yields, although the scope of the process was rather limited. Later, this method was employed in the synthesis of XH-14 and its analogues,[50] and a modified catalytic system (PdI_2/thiourea/CBr_4) was reported, which significantly increased yields and expanded the scope of the initial process.[51] A related method was developed for the generation of benzo[*b*]furan-3-carboxylic acids.[52]

Scheme 29. Three-component carbonylative cyclization of 2-alkynylphenols



An analogous process reported in 1996 by Cacchi involves the Pd-catalyzed cyclization of 2-alkynylphenols in the presence of vinylic triflates and CO (Scheme 30).[53] In this case, the benzofurans **56** are obtained in 20-64% yields. Fathi and co-workers later successfully extended this process to the use of aryl iodides and prepared a number of highly substituted benzofurans.[54]

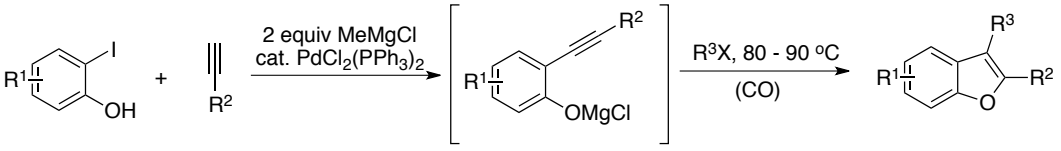
Scheme 30. Pd-catalyzed cyclization of 2-alkynylphenols with vinylic triflates and CO



Although these methods allow generation of the desired benzo[*b*]furan core in good yields, the possibilities for the synthesis of polyfunctionalized compounds is limited due to

the use of CO as an one of the components. In 2001, Flynn reported the first three-component synthesis of benzo[*b*]furans starting from iodophenols, alkynes and aryl iodides (Scheme 31).[25] In this Pd-catalyzed process, the first Sonogashira coupling was found to be inefficient when 2-iodophenols were employed. The authors turned to the use of MeMgCl as a reagent to mask the phenol group, which allowed a more efficient Sonogashira reaction to take place. The authors propose that after the intermediate **57** is formed, attack of the oxygen onto the triple bond in the second step of this OPMCR is promoted by the "R^3PdX" species formed *in situ* after the addition of R^3X to the reaction mixture. Despite the reactive nature of the MeMgCl reagent, a number of functional groups are tolerated under these reaction conditions and the process affords the highly substituted benzofurans **58** in good to excellent yields (45-88%). Examples of the coupling in the presence of CO results in the formation of the corresponding carbonylative coupling products.

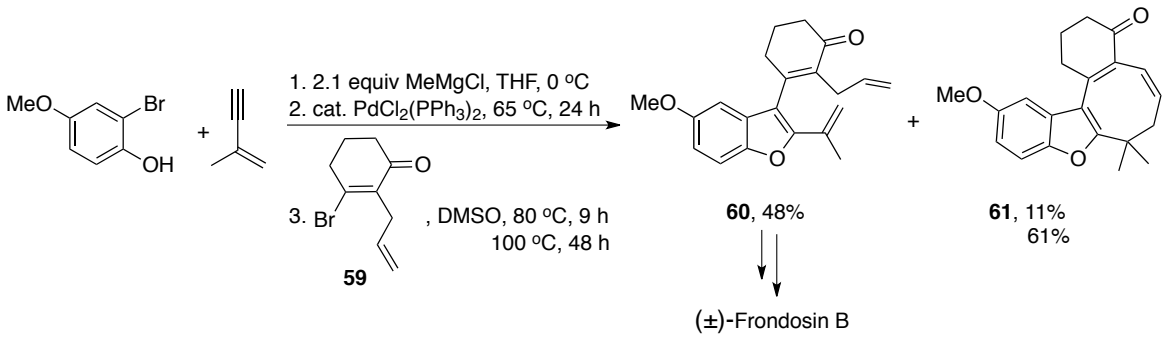
Scheme 31. Three-component synthesis of benzofurans



The authors later applied this method for the one-pot, three-component synthesis of (±)-Frondosin B.[55] The OPMCR between 2-bromo-4-methoxy-phenol, 3-methylbutenyne and vinylic bromide **59** was successful, affording the non-cyclized product **60** as a major product in a 48% yield, along with 11% of the ring-expanded product **61** (Scheme 32). The authors propose that the product **61** is likely formed from compound **60** by a 1,7-hydrogen shift. This

ring-expanded analogue **61** could be obtained as a sole product in a 61% yield if the cyclization step is carried out at 100 °C for 48 h. The product **60** was then successfully converted to (±)-Frondosin B in 3 additional steps.

Scheme 32. One-pot synthesis of a ring-expanded analogue of (±)-Frondosin B



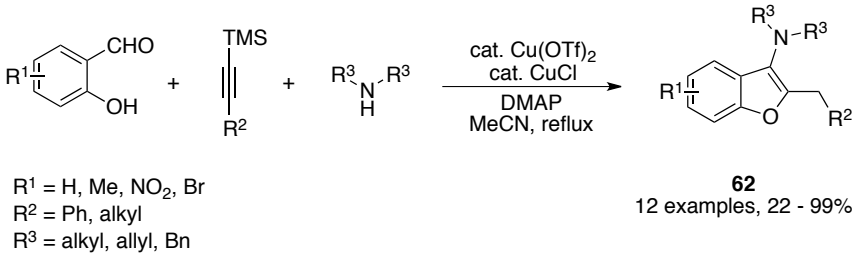
The Larock group developed a similar microwave-assisted one-pot method that does not require the use of the harsh MeMgCl reagent and allows one to obtain benzo[*b*]furans in excellent yields in a one-pot process under milder reaction conditions.[56] Also, a similar palladium-mediated, three-component process for the synthesis of furo[2,3-*b*]pyridones starting from 3-iodopyridones have been reported by the Balme group.[57]

The same OPMCR developed for the formation of indoles **38** has been successfully applied to the synthesis of 2-(methylamino)benzo[*b*]furans (Scheme 20).[36]

2.3.2. MCPs for the synthesis of benzofurans from phenols or 2-hydroxybenzaldehydes

An MCR analogous to the one developed for the synthesis of indoles **42**,[40] has been reported for the synthesis of 2-(alkylamino)substituted benzo[*b*]furans (Scheme 33).[58] Various alkynes and amines were well tolerated under the optimized reaction conditions and afforded the benzo[*b*]furans **62** in 22-99% yields.

Scheme 33. Three-component synthesis of 3-aminobenzofurans



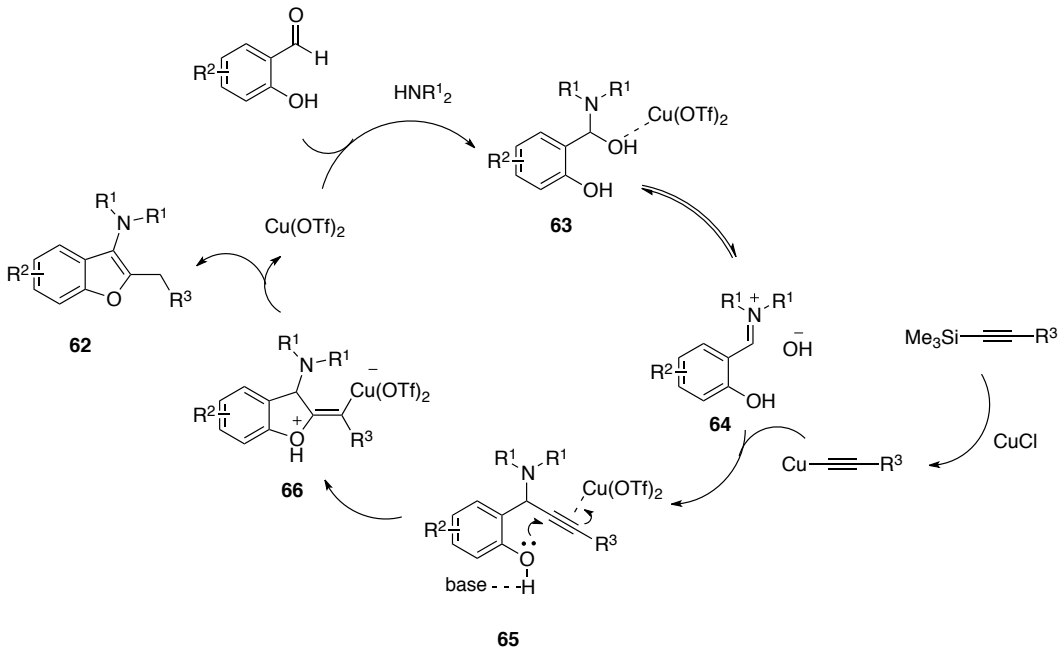
R^1 = H, Me, NO_2, Br
R^2 = Ph, alkyl
R^3 = alkyl, allyl, Bn

62
12 examples, 22 - 99%

In this three-component coupling of an alkynylsilane, *o*-hydroxybenzaldehydes and secondary amines, the best results were obtained when the CuCl/$Cu(OTf)_2$ catalytic system was employed. The authors propose that CuCl is required for transforming the TMS-alkyne into the corresponding copper acetylide. The $Cu(OTf)_2$ is responsible for: a) being a Lewis acid to facilitate formation of the iminium intermediate **64**, and b) activating the alkyne moiety to help with nucleophilic attack by the OH group in the intermediate **65** by a 5-exo-dig cyclization to produce compound **66**, which after losing $Cu(OTf)_2$, deprotonation and aromatization affords the desired 3-aminobenzo[*b*]furans **62** (Scheme 34).

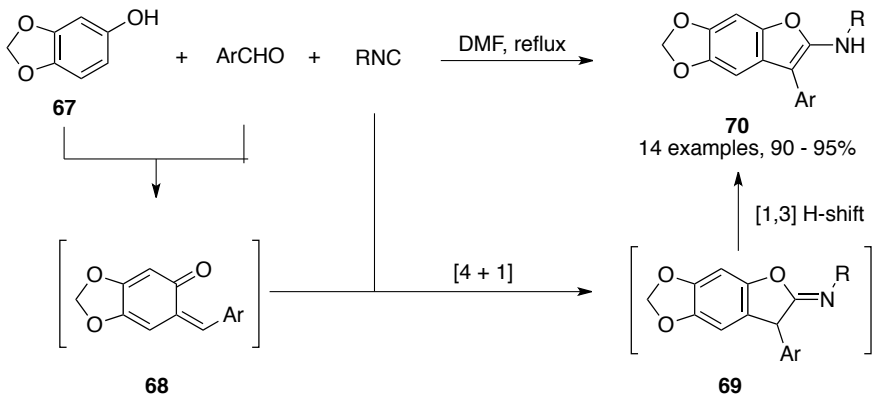
Analogous processes where terminal acetylenes[59] or isocyanides[60] are employed, instead of the silyl acetylenes, have been reported by other groups. In the case of isocyanides, 2,3-diaminobenzo[*b*]furans are obtained.

Scheme 34. Proposed reaction mechanism



Recently, a novel method has been reported for the synthesis of 2-amino-3-arylbenzo[*b*]furans starting from the phenol **67**, aldehydes and alkyl isocyanides (Scheme 35).[61] The reaction proceeds in DMF under reflux conditions and affords a variety of products **70** in excellent (90-95%) yields. The authors propose that the reaction between phenol and aldehyde most likely produces the oxoquinodimethane intermediate **68**, which can then add to the isocyanide molecule to form the [4+1] cycloaddition adduct **69**. A [1,3]-hydrogen shift in compound **69** results in the formation of the product **70**. 1-Naphthol was also shown to undergo an analogous transformation and afford naphtho[1,2-*b*]furan-2-amines in excellent 90-95% yields. A similar process was reported by Mosslemin *et al* for the synthesis of annulated furan heterocycles.[62]

Scheme 35. Three-component reaction between phenols, aldehydes and isocyanides

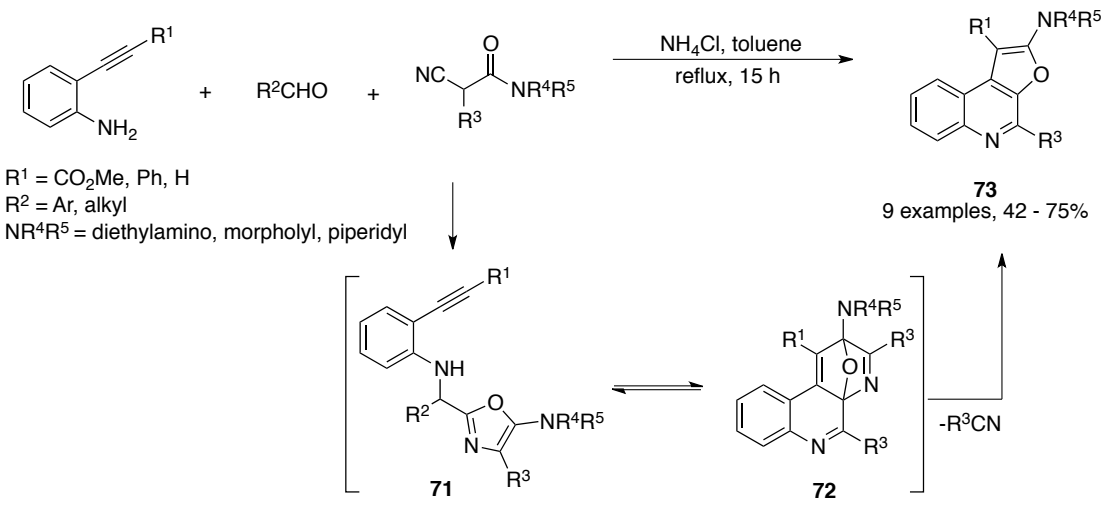


Very recently an analogous method for the synthesis of acenaphtho[1,2-*b*]furan derivatives has been reported by Damavandi and co-workers.[63]

2.3.3. MCPs for the synthesis of benzofuran analogues

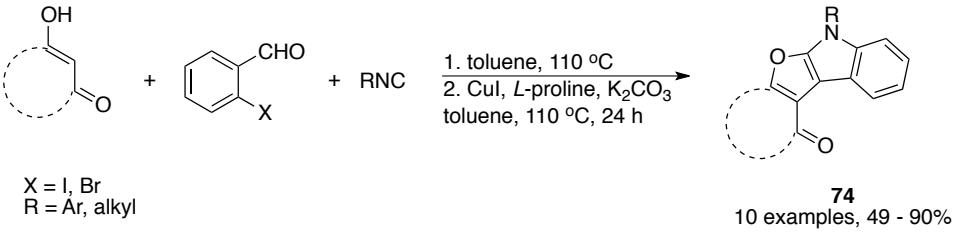
A three-component synthesis of furo[2,3-*c*]quinolones from 2-alkynylanilines, aldehydes, and isocyanoacetamides has been reported (Scheme 36).[64] Although no detailed mechanistic study has been carried out, the authors propose that this transformation proceeds through the oxazole intermediate **71**, which, followed by intramolecular cycloaddition to the triple bond, forms the oxa-bridged intermediate **72**. The latter, by a retro-Diels-Alder loss of the nitrile unit and *in situ* oxidation by atmospheric oxygen, furnishes the furo[2,3-*c*]quinolones **73** in moderate to good (42-75%) yields.

Scheme 36. A three-component synthesis of furo[2,3-*c*]quinolines



Very recently, an isocyanide-based multicomponent reaction in combination with an intramolecular Ullmann reaction for the synthesis of furo[2,3-*b*]indoles has been described.[65] The Cu-catalyzed reaction of 1,3-dicarbonyl compounds, 2-halobenzaldehydes and isocyanides afforded products **74** in 49-90% yields (Scheme 37).

Scheme 37. Multicomponent reaction for the synthesis of furo[2,3-*b*]indoles



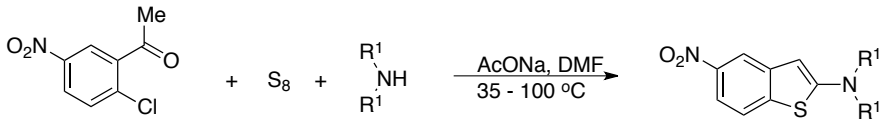
2.4. MCPs IN THE SYNTHESIS OF BENZOTHIOPHENES

Benzothiophenes and benzoselenophenes are compounds of interest to synthetic chemists due to their wide variety of useful applications.[66] Though a variety of methods have

been discovered for the synthesis of these compounds, there is only one reported example of MCP for their synthesis.

In 2007, an OPMCR for the synthesis of 2-aminobenzo[*b*]thiophenes was reported by Neckers and co-workers.[67] The authors discovered that the reaction between 1-(2-chloro-5-nitrophenyl)ethanone and secondary amines in the presence of elemental sulfur and NaOAc gives 2-aminobenzothiophenes **75**, albeit in only low to moderate (4-46%) yields (Scheme 38).

Scheme 38. One-pot three-component synthesis of 2-aminobenzo[*b*]thiophenes



R^1 = alkyl, allyl, Bn

75
11 examples, 4 - 46%

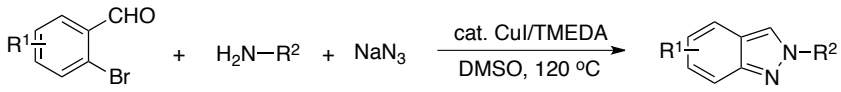
2.5. MCPs IN THE SINTHESIS OF INDAZOLES

1*H*- and 2*H*-Indazoles are important classes of compounds whose derivatives are widely used in the pharmaceutical industry.[68] There has been a lot of interest in the synthesis of these structures in the last few decades. Numerous synthetic pathways for the synthesis of 1*H*-indazoles have been developed, whereas methods for the synthesis of 2*H*-analogues are still relatively underexplored. Several MCPs for the synthesis of indazoles and analogues have been reported recently.

In 2011, a copper-catalyzed, one-pot, three-component synthesis of 2*H*-indazoles was reported (Scheme 39).[69] 2-Bromobenzaldehydes are reacted with primary amines and NaN_3

to afford good to excellent yields of a variety of 2*H*-indazoles **76**.

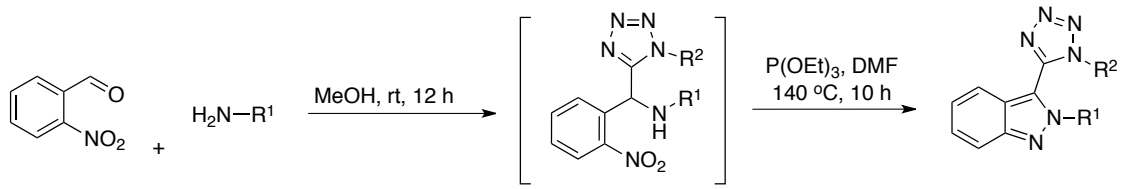
Scheme 39. Three-component synthesis of 2*H*-indazoles



76
25 examples, 20 - 98%

Very recently, another one-pot method for the synthesis of 2*H*-indazoles has been reported (Scheme 40).[70] This process is based on a four-component Ugi reaction of 2-nitrobenzaldehydes, amines, and isocyanides in the presence of $TMSN_3$. The preformed Ugi intermediates **77** are transformed into the 2*H*-indazoles **78** by heating with triethylphosphite in DMF. In most cases, moderate to good (24-65%) yields of indazoles **78** were obtained.

Scheme 40. Four-component synthesis of 2*H*-indazoles



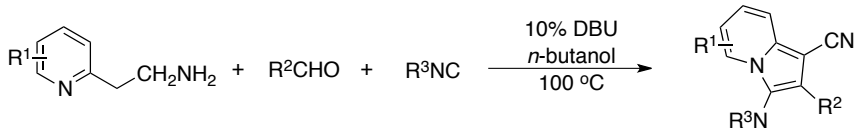
$TMSN_3$ R^2NC **77** **78**
12 examples, 24 - 65%

2.6. MCPs IN THE SYNTHESIS OF INDOLIZINES AND ANALOGUES

Indolizines, pyridoindoles, and their partially hydrogenated analogues are known for their pharmaceutical and biological activity. Although a lot of methods have been developed for their synthesis, many of them are either harsh or require multiple steps.[71] Recently, several multicomponent approaches have been reported that significantly improve the already existing methods and allow quick and easy generation of these valuable cores.

In 2005, an MCR for the synthesis of indolizines was reported (Scheme 41).[72] This method allows great possibilities for variation of the substituents in all three of the starting materials. The variously substituted indolizines **79** were obtained in 10-73% yields.

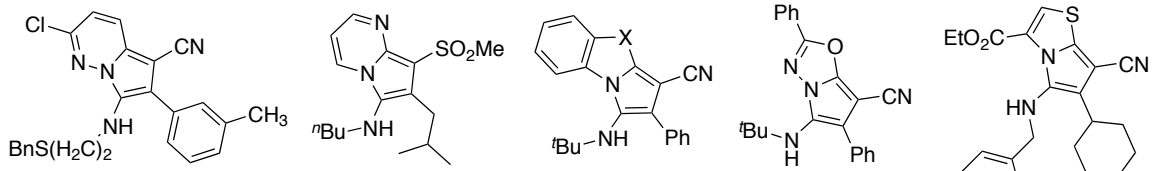
Scheme 41. Three-component synthesis of indolizines



79
11 examples, 10 - 73% yield

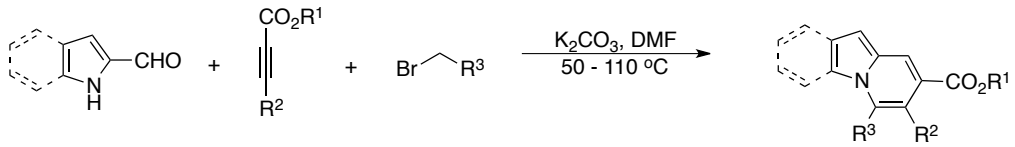
The authors demonstrated that other heterocyclic moieties can be used in place of the starting pyridines, leading to a great variety of mixed heterocyclic compounds (Scheme 42).

Scheme 42. Selected examples of the other heterocycles obtained



A convenient three-component reaction for the synthesis of indolizines and their annulated versions, pyridoindoles, has been reported by Zou and co-workers (Scheme 43).[73] The indolizines **80** were obtained in moderate to excellent (42-97%) yields by the reaction of pyrrole-2-carboxaldehyde with alkyl bromides and alkenes. Using an indole-2-carboxaldehyde afforded the pyrido[1,2-*a*]indoles **81** in moderate (40-58%) yields.

Scheme 43. MCR for the synthesis of indolizines and pyridoindoles

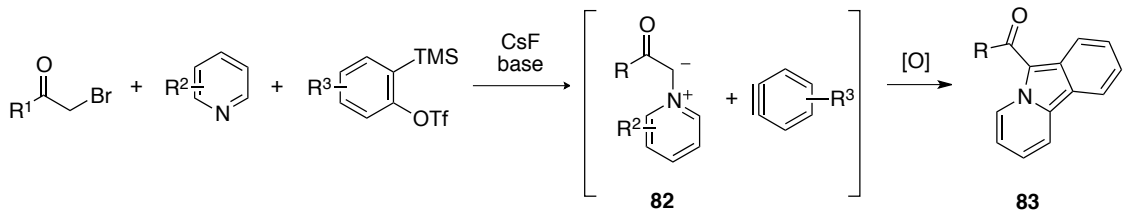


R^1 = Me, Et, Ph
R^2 = H, CO_2Me, Me, Ph
R^3 = COAr, COAlkyl, CO_2Et, CN

indolizines **80**: 31 examples, 42 - 97% yield
pyridoindoles **81**: 6 examples, 40 - 58% yield

An interesting MCR for the synthesis of pyrido[2,1-*a*]isoindoles involving aryne annulation has been independently reported by Huang and Zhang (Scheme 44).[74] In this process, a pyridinium salt, formed from the reaction of pyridine with α-bromoketones, most likely generates the azomethine ylide **82** by the elimination of HBr. A [3 + 2] cycloaddition of the ylide **82** with the aryne, followed by aromatization, affords the desired products **83**.

Scheme 44. MCR for the synthesis of pyrido[2,1-*a*]isoindoles



82

83
12 examples, 37 - 60% (Huang)
14 examples, 31 - 60% (Zhang)

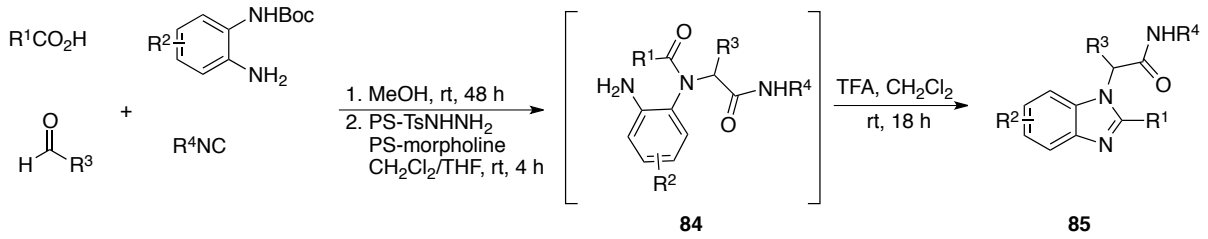
2.7. MCPs IN THE SYNTHESIS OF BENZIMIDAZOLES

Benzimidazole and its derivatives play a crucial role in the pharmaceutical industry and have a wide range of applications in material science.[75] Numerous processes for their synthesis have been developed. However, multicomponent approaches to this valuable core are still very limited.

Tempest and Hulme reported a synthesis of benzimidazoles by a four-component Ugi

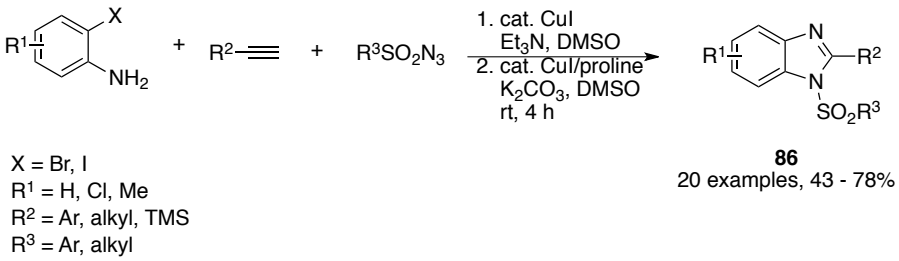
coupling.[76] Although this transformation was technically carried out in two steps, the isolation of the intermediate Ugi product after Boc-group cleavage was minimized and the product **84** was used crude in the cyclization step to afford a variety of benzimidazoles **85** (Scheme 45).

Scheme 45. Synthesis of benzimidazoles by a four-component Ugi coupling



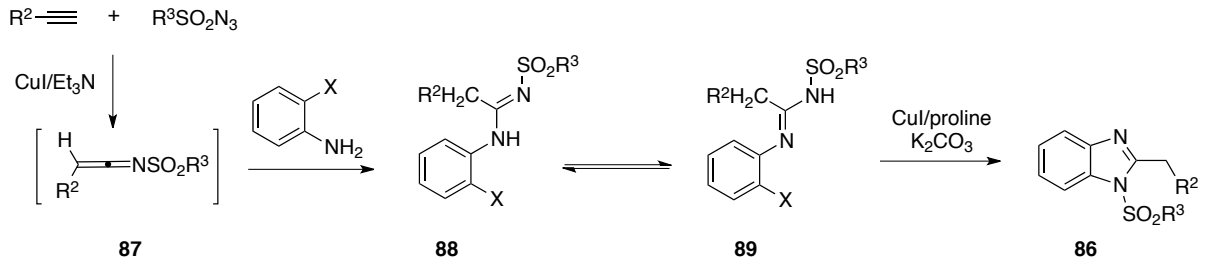
In 2010, Wang and co-workers reported a copper-catalyzed, three-component cascade reaction between sulfonyl azides, terminal alkynes and 2-bromoanilines for the synthesis of 1,2-disubstituted benzimidazoles **86** (Scheme 46).[77]

Scheme 46. Synthesis of 1,2-disubstituted benzimidazoles **86**



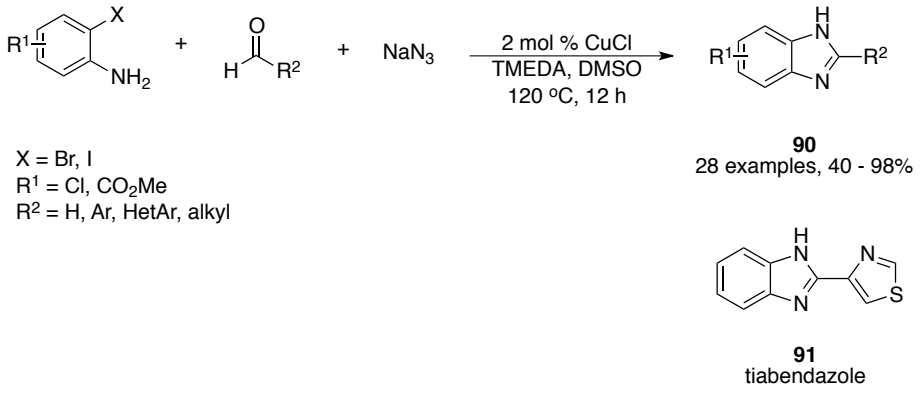
The authors propose that this transformation is most likely occurring through the ketamine intermediate **87**, formed from the reaction of an alkyne and a sulfonyl azide (Scheme 47). Intermediate **87** is then reacted with aniline to produce the *N*-sulfonylamide **88**, which is in equilibrium with its tautomer **89**. The Cu-catalyzed intramolecular *C*-*N* coupling of **89** affords the benzimidazoles **86**.

Scheme 47. Proposed reaction mechanism



In 2011, Lee and co-workers reported a three-component approach for the synthesis of benzimidazoles from 2-haloanilines, aldehydes, and NaN_3 under Cu(I)-catalyzed conditions (Scheme 48).[78] A total of 28 benzimidazoles **90** were prepared through this method in good to excellent yields. The authors also showed that the fungicide and parasiticide tiabendazole (**91**) (trade names Mintezol and Tesaderm) could be accessed through this method in a 97% yield starting from 2-iodoaniline.

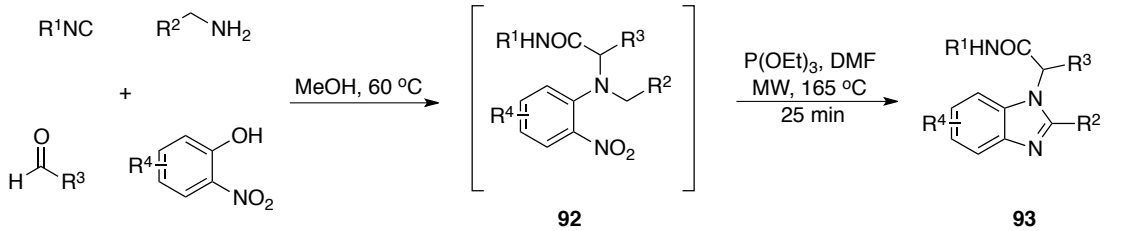
Scheme 48. MCR for the synthesis of benzimidazoles



The same year, El Kaïm and Grimaud reported a phosphite-mediated synthesis of benzimidazoles by a four-component Ugi-Smiles approach from 2-nitrophenols (Scheme

49).[79] After the Ugi-Smiles intermediate **92** is obtained, the reaction mixture is filtered and dried and then subjected to a second step to afford the desired benzimidazoles **93** in 23-83% yields. When aromatic aldehydes were employed, mixtures of isomers were obtained due to the formation of two competing benzylic positions in the corresponding intermediates **92**.

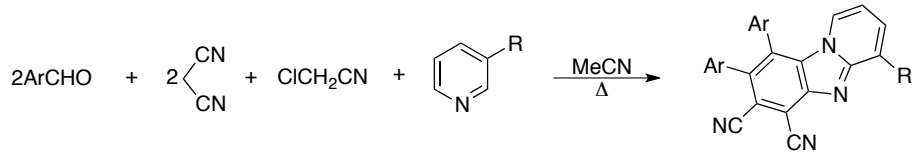
Scheme 49. Phosphite-mediated synthesis of benzimidazoles



R^1 = Ar, alkyl
R^2 = Ar, HetAr
R^3 = alkyl
R^4 = H, OMe, Me

The synthesis of a pyrido[1,2-*a*]benzimidazole by a novel multicomponent reaction of chloroacetonitrile, malononitrile, an aromatic aldehyde, and pyridine has been reported by Yan and co-workers (Scheme 50).[80] In this process, 6 molecules are combined in a one-pot process to create 21 examples of multifunctional pyrido[1,2-*a*]benzimidazoles **94** in 20-51% yields. In some cases, small amounts of polysubstituted benzenes or 2-amino-3-cyanoindoles were obtained as side products.

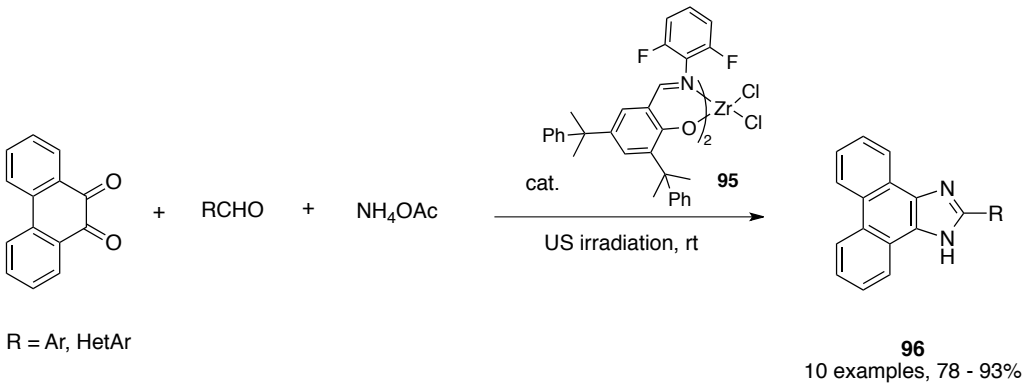
Scheme 50. MCR for the synthesis of pyrido[1,2-*a*]benzimidazoles



R = H or Me

A novel methodology for the synthesis of 1*H*-phenanthro[9,10-*d*]imidazoles under ultrasonic irradiation has been reported.[81] 9,10-Phenanthrenequinone, an aromatic aldehyde, and ammonium acetate were reacted in the presence of catalytic amounts of **95** and afforded the phenanthro[9,10-*d*]imidazoles **96** in good to excellent (78-93%) yields (Scheme 51)**.**

Scheme 51. Synthesis of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles

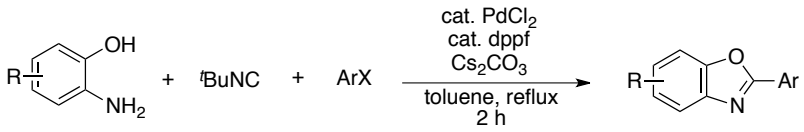


2.8. MCPs IN THE SYNTHESIS OF BENZOXAZOLES AND BENZISOXAZOLES

Benzoxazoles and isomeric benzisoxazoles represent pharmaceutically valuable compounds and approaches to their synthesis have been studied extensively.[82] While a few MCPs have been developed for the synthesis of benzoxazoles, no reports of MCPs for the synthesis of benzisoxazoles have been described in the literature.

A novel Pd-catalyzed multicomponent process has been developed for the synthesis of benzoxazoles and their non-fused analogues, oxazolines (Scheme 52).[83] Starting from 2-aminophenols, *tert*-butylisocyanide, and various aryl halides, the authors were able to obtain the benzoxazoles **97** in excellent (92-99%) yields. Oxazolines were obtained when 2-aminoethan-1-ol was used, instead of 2-aminophenols.

Scheme 52. Pd-catalyzed multicomponent process for the synthesis of benzoxazoles



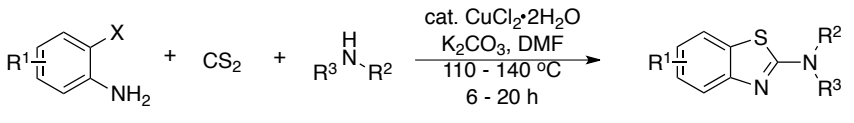
97
5 examples, 92 - 99%

2.9. MCPs IN THE SYNTHESIS OF BENZOTHIAZOLES

Benzothiazoles represent another class of compounds that play an important role as biologically and synthetically important scaffolds. To the best of our knowledge, only two examples of MCPs to access these compounds have been reported recently.

A Cu-catalyzed, cascade, three-component reaction for the synthesis of 2-*N*-substituted benzothiazoles from 2-haloanilines, carbon disulfide, and amines has been reported (Scheme 53).[84] Various amines were found to be efficient in this process, including primary, secondary aliphatic and aromatic amines, cyclic secondary amines, and aromatic *N*-containing heterocycles, such as pyrrole, indole, and imidazole. A small library of 49 unique compounds **98** has been generated employing this methodology.

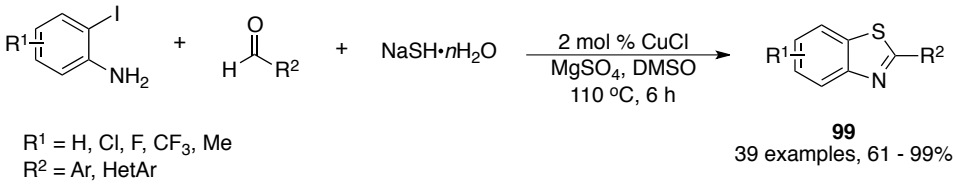
Scheme 53. Three-component reaction for the synthesis of 2-*N*-substituted benzothiazoles



98
49 examples, 40 - 97%

Very recently, a Cu-catalyzed OPMCR for the synthesis of benzothiazoles from 2-iodoanilines, aldehydes, and sodium hydrosulfide as a sulfur source has been reported (Scheme 54).[85] A small library of 39 benzothiazoles **99** has been synthesized in 61-99% yields. The authors note that NaSH·nH$_2$O functions both as a sulfur surrogate and as an oxidant in this transformation.

Scheme 54. Cu-catalyzed OPMCR for the synthesis of benzothiazoles



2.10. CONCLUSIONS

As can be seen from the methods described above, MCPs are becoming a convenient and efficient tool for easy access to 5-membered fused aromatic heterocycles. The obvious advantages of these one-pot methods motivate scientists to continue their work in this direction so that more methods can be developed. However, considering the demands of today's pharmaceutical industry, the field of multicomponent reactions is still under-exploited and more efficient MCPs for the synthesis of new heterocycles of pharmaceutical interest are waiting to be discovered.

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CHAPTER 3

Solution-Phase Parallel Synthesis of a Diverse Library of 1,2-Dihydroisoquinolines

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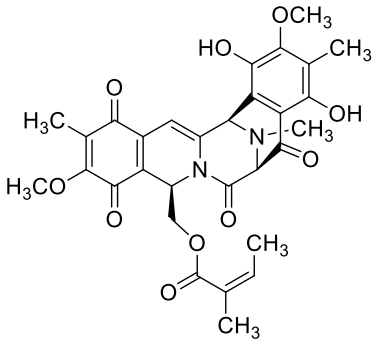
3.1. ABSTRACT

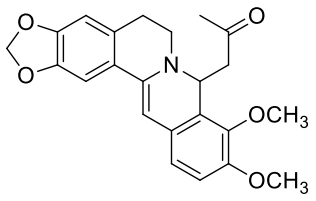
Synthesis of a 105 membered library of 1,2-dihydroisoquinolines is described. The 1,2-dihydroisoquinoline compounds have been prepared in good yields using a Lewis acid and organocatalyst-cocatalyzed multicomponent reaction of 2-(1-alkynyl)benzaldehydes, amines and ketones. Various indoles have also been employed as pronucleophiles, furnishing 1-(3-indolyl)-1,2-dihydroisoquinolines. The halogen functionality present in some of the synthesized compounds allows for further diversification by palladium-catalyzed Suzuki-Miyaura and Sonogashira cross-couplings to give more diversified 1,2-dihydroisoquinoline derivatives.

3.2. INTRODUCTION

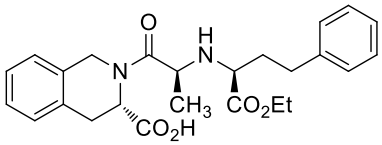
Structures containing a 1,2-dihydroisoquinoline fragment are valuable intermediates for the synthesis of biologically active compounds, *e.g.* alkaloids and pharmuticals.[1] For example, cribrostatin 4 and toneberbine IK-2 have been shown to possess cytotoxicity against some human cancer cells (Figure 1).[2,3] The hydrochloride salt of the tetrahydroisoquinoline quinapril (sold under the brand name Accupril) is used for the treatment of congestive heart failure and hypertension[4].



cribrostatin 4



acetoneberbine IK-2



quinapril

Figure 1. Examples of biologically active 1,2-dihydro- and tetrahydroisoquinolines

Among the numerous methods developed for synthesis of the 1,2-dihydroisoquinoline core, the most common strategies include functionalization of preformed isoquinoline units using various nucleophiles[5] or ring-forming reactions of 2-(1-alkynyl)arenecarboxaldehyde imines through transition metal-catalyzed processes.[6] The latter processes have also been extended to one-pot procedures that employ 2-(1-alkynyl)arenecarboxaldehydes and amines

to preform the required imines *in situ*.[7]

The solution-phase parallel synthesis of libraries of low molecular weight compounds is increasingly important in modern medicinal chemistry.[8] This approach facilitates the high throughput screening of larger and more diverse sets of compounds with less time spent on optimization of the reaction conditions. In continuation of our work in adapting proven methods for the synthesis of heterocycles to a high throughput synthesis format,[9] we herein report the solution phase synthesis of a library of 1,2-dihydroisoquinolines.

In order to synthesize a library with greater chances for biological activity, the multi-substituted 1,2-dihydroisoquinoline template **1** has been evaluated computationally for its drug-like properties on the basis of Lipinski's "rule of five"[10] (Scheme 1).

Calculations have been performed based on the commercial availability of aldehydes **4 (**Scheme 2), terminal alkynes **5** and **10**, ketones **6**, anilines **7**, indoles **9** and boronic acids **11** (Figures 2 and 4). This data has been used to populate a virtual library of all theoretically possible products, giving 24,888 [(8 x 2 x 6 x 40) + (8 x 50 x 6 x 3) + (8 x 50 x 6) + (8 x 53 x 9 x 3)] unique potential compounds. A small subset of this virtual library, namely 239 compounds, was shown to follow Lipinski's rules with ≤1 violation. The library synthesis of 1,2-dihydroisoquinolines described herein was primarily focused on the preparation of compounds that fall within these 239 examples.

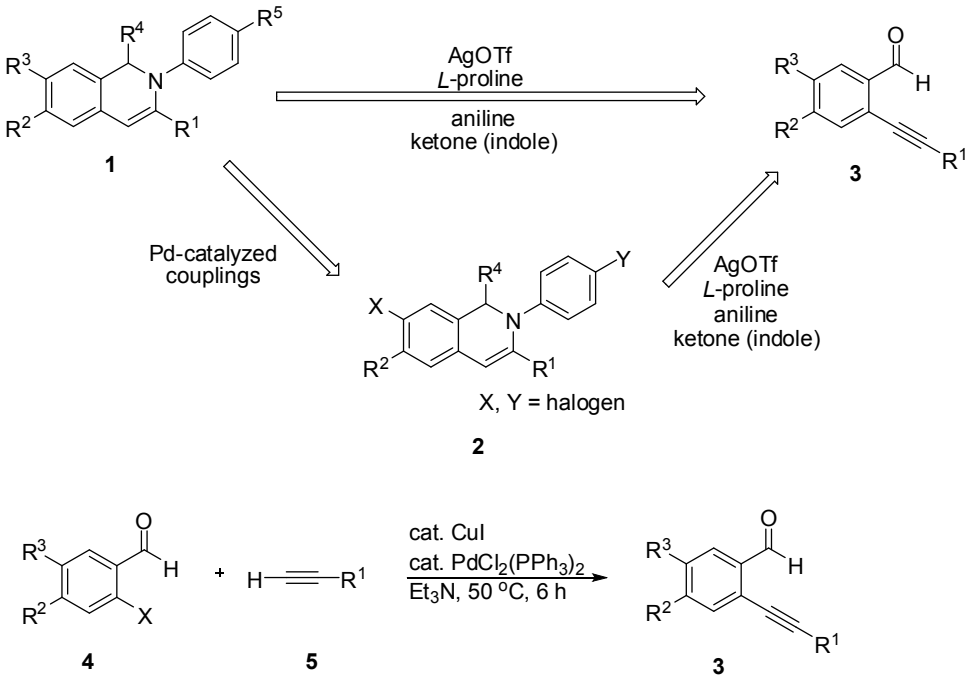
3.3. RESULTS AND DISCUSSION

3.3.1. Library construction

To study a wide variety of multisubstituted 1,2-dihydroisoquinolines, we developed

the strategy described in Scheme 1. The 1,2-Dihydroisoquinolines **1** can be prepared directly from the corresponding 2-(1-alkynyl)benzaldehydes **3** through reaction with anilines **7** and either ketones **6** or indoles **9**. More highly substituted 1,2-dihydroisoquinolines can be prepared via palladium-catalyzed couplings of the corresponding halogen-containing 1,2-dihydroisoquinolines **2**, prepared through the same three-component coupling reaction.

Scheme 1. Library outline and preparation of 2-(1-alkynyl)benzaldehydes **3**



The 2-(1-Alkynyl)benzaldehydes **3** are easily prepared by palladium/copper-catalyzed Sonogashira coupling[11] of the corresponding *o*-bromobenzaldehydes **4** (1.0 equiv of **4**, 1.05 equiv of terminal alkyne **5**, 2 mol % of $PdCl_2(PPh_3)_2$, 2 mol % of CuI, and Et_3N at 50 °C for 6 h) (Scheme 1)**.** The yields of this process range from 65% to 100% and this procedure readily accommodates various functional groups (Table 1).

Table 1. Data for Compounds **3**{*1-15*}

compound **3**	R^1	R^2	R^3	X	yield (%)[a]
3{*1*}	4-(MeO)C_6H_4	H	H	Br	99
3{*2*}	3,5-$(MeO)_2C_6H_3$	H	H	Br	96
3{*3*}	3,5-$(MeO)_2C_6H_3$	H	MeO	Br	85
3{*4*}	3,5-$(MeO)_2C_6H_3$	H	Br	I	68[b]
3{*5*}	3-(MeO)C_6H_4	H	H	Br	78
3{*6*}	3-(MeO)C_6H_4	H	F	Br	100
3{*7*}	4-$(O_2N)C_6H_4$	H	H	Br	65[c]
3{*8*}	3-thiophenyl	H	H	Br	68
3{*9*}	3-thiophenyl	H	MeO	Br	87
3{*10*}	3-thiophenyl	H	F	Br	89
3{*11*}	3-thiophenyl			Br	90
3{*12*}	3-MeC_6H_4	H	H	Br	81
3{*13*}	phenyl	H	NO_2	Cl	89
3{*14*}	4-(MeO)C_6H_4	H	Br	I	56
3{*15*}	Phenyl	H	F	Br	84

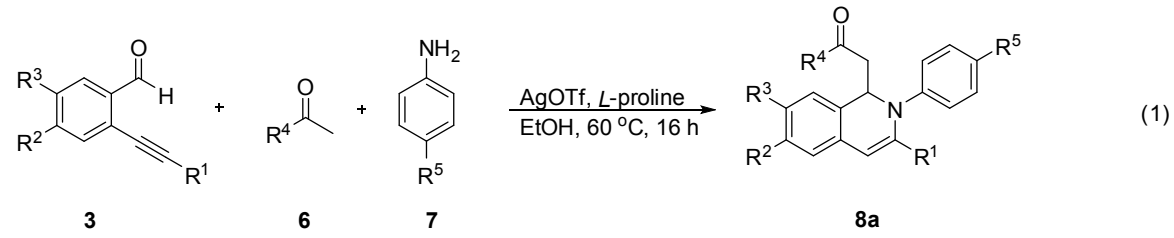
[a]Isolated yields after column chromatography. All compounds **3** were characterized by ^{1}H NMR spectroscopy. Those not described in the literature were additionally characterized by ^{13}C NMR and HRMS; [b]prepared from the corresponding methyl benzoate (1. LAH; 2. PCC); [c]this reaction used different reaction conditions: 3% $PdCl_2(PPh_3)_2$, 2% CuI, ^{i}Pr$_2$NH (4 equiv), DMF, 70 ° C, 2 h.

3.3.2. Preparation of the building blocks

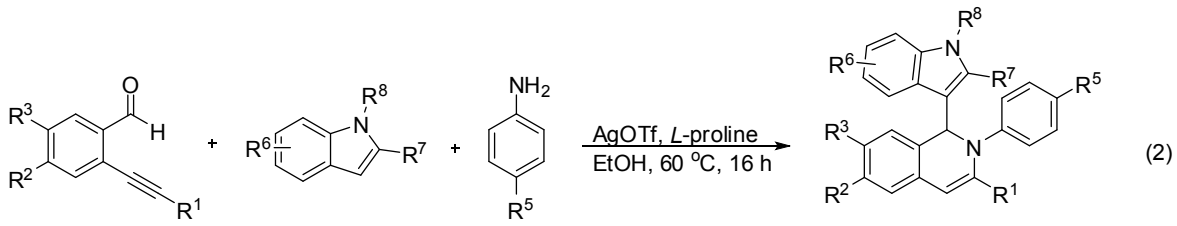
For the synthesis of the 1,2-dihydroisoquinoline core, we utilized the procedure described by Ding *et al*.[7a] (Scheme 2, eq. 1). The advantages of this three-component AgOTf and *L*-proline cocatalyzed process include the commercially availability of ketones **6** and amines **7**, three independent points of diversification and formation of the desired products in

one step.

Scheme 2. Synthesis of 1,2-dihydroisoquinolines and 1-(3-indolyl)-1,2-dihydroisoquinolines



3 **6** **7** **8a** (1)



3 **9** **7** **8b** (2)

Additionally, we are able to replace ketones with indoles in this process, which allows one to isolate 1-(3-indolyl)-1,2-dihydroisoquinolines in a single one-pot process (Scheme, eq. 2). Since initiation of this work, Yamamoto and Wu have independently reported the use of indoles in the same type of process under slightly modified reaction conditions.[12] By employing the reaction conditions optimized for ketones using a sublibrary of indoles **9**, we have been able to isolate 1-(3-indolyl)-1,2-dihydroisoquinolines in moderate to good yields in most cases, broadening the scope of the previously reported 1,2-dihydroisoquinoline synthesis.

The sublibraries of ketones, anilines and indoles used for the synthesis of 1,2-dihydroisoquinolines **8** are presented in Figure 2.

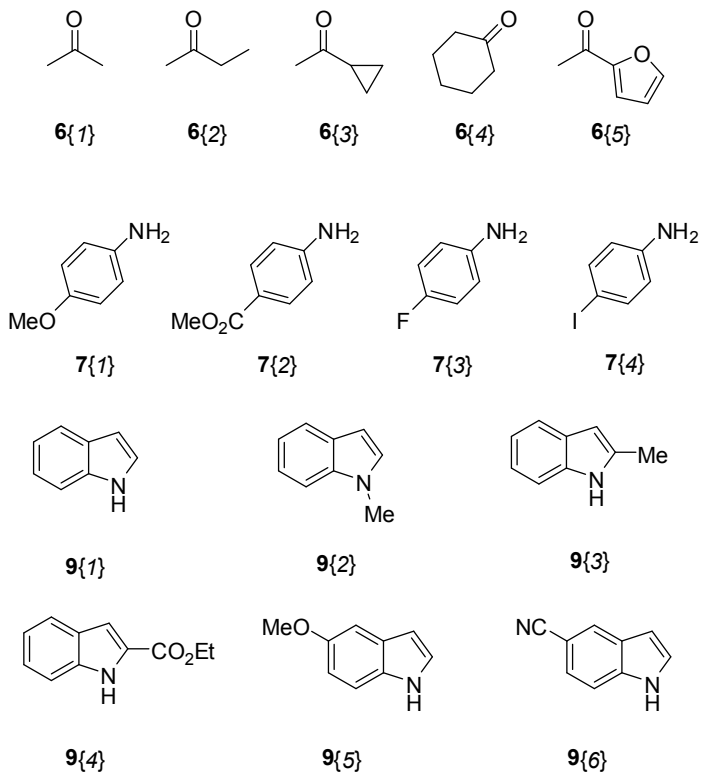


Figure 2. Ketone **6**{*1-5*}, aniline **7**{*1−4*} and indole **9**{*1−6*} sublibraries

The data for the 1,2-dihydroisoquinolines **8**{*1-30*} prepared, but not subjected to further diversification, is shown in Table 2.

Table 2. Library Data for Compounds **8**{*1-30*}

product	**3**	**6** or **9**	**7**	yield (%)[a]	purity (%)[c]
8{*1*}	**3**{*1*}	**6**{*4*}	**7**{1}	33	96
8{*2*}	**3**{*1*}	**9**{*1*}	**7**{1}	69	98
8{*3*}	**3**{*2*}	**6**{*1*}	**7**{1}	43	99
8{*4*}	**3**{*2*}	**9**{4}	**7**{1}	9	88
8{*5*}	**3**{3}	**6**{*5*}	**7**{2}	15	100
8{*6*}	**3**{5}	**9**{*1*}	**7**{2}	76	95
8{*7*}	**3**{6}	**9**{3}	**7**{2}	29	100

Table 2 continued.

8{8}	**3**{7}	**6**{*3*}	**7**{1}	0	-
8{*9*}	**3**{7}	**9**{*5*}	**7**{2}	0	-
8{*10*}	**3**{8}	**6**{*1*}	**7**{1}	56	96
8{*11*}	**3**{8}	**6**{*1*}	**7**{3}	56	99
8{*12*}	**3**{8}	**6**{*2*}	**7**{1}	56	93
8{*13*}	**3**{8}	**6**{*4*}	**7**{1}	72	42
8{*14*}	**3**{11}	**6**{*5*}	**7**{2}	15[b]	100
8{*15*}	**3**{11}	**9**{*1*}	**7**{1}	24	100
8{*16*}	**3**{12}	**6**{*1*}	**7**{1}	56	96
8{17}	**3**{12}	**6**{*1*}	**7**{3}	66	98
8{*18*}	**3**{12}	**6**{2}	**7**{1}	72	100
8{*19*}	**3**{12}	**6**{*4*}	**7**{1}	60	94
8{20}	**3**{12}	**9**{*2*}	**7**{1}	63	98
8{*21*}	**3**{12}	**9**{1}	**7**{1}	72	98
8{*22*}	**3**{13}	**6**{2}	**7**{1}	77	82
8{*23*}	**3**{14}	**6**{*1*}	**7**{1}	59	97
8{*24*}	**3**{14}	**6**{*1*}	**7**{3}	98	98
8{*25*}	**3**{14}	**6**{2}	**7**{1}	77	100
8{*26*}	**3**{14}	**6**{4}	**7**{1}	44	31
8{*27*}	**3**{15}	**6**{*1*}	**7**{1}	78	95
8{*28*}	**3**{15}	**6**{*1*}	**7**{3}	98	100
8{*29*}	**3**{15}	**6**{*2*}	**7**{1}	74	100
8{*30*}	**3**{15}	**6**{4}	**7**{1}	53	13

[a] Isolated yield after column chromatography. [b] Isolated yield after preparative HPLC. [c] UV purity determined at 214 nm after preparative HPLC.

1,2-Dihydroisoquinolines **8**{*31-51*}, containing halogen atoms that can be further subjected to palladium-catalyzed couplings, have been isolated and purified by column

chromatography. All of the 1,2-dihydroisoquinolines **8**{*31-51*}, except **8**{*39*} and **8**{*45*}, which were used crude in the next step, were fully characterized using HRMS, as well as ^{1}H and ^{13}C NMR spectroscopy (see the Supporting Information for the experimental details). In most cases, moderate to good yields of the 1,2-dihydroisoquinolines **8**{*31-51*} have been obtained. The results are summarized in Figure 3.

As can be seen from both Table 2 and Figure 3, this process is generally functional group tolerant and allows one to obtain diversely-substituted 1,2-dihydroisoquinolines in 9-98% yields. The major limitation of this procedure is that it does not tolerate strong electron-withdrawing groups in the alkyne portion of the 2-(1-alkynyl)benzaldehydes **3.** For example, in the reactions of compound **3**{*7*}, bearing a nitro group, compounds **8**{*8*} and **8**{*9*} were not detected in the crude reaction mixtures, and compound **8**{*39*} was obtained in only an 11% yield. By employing indoles **9** instead of ketones **6** in this process, good yields from the unsubstituted indole **9**{*1*} have been obtained. This process exhibits good tolerance of various functional groups in positions 1 and 5 of the indole; thus, compounds **8**{*20*}, **8**{*50*} and **8**{*51*} were obtained in 63, 46 and 75% yields, respectively. The presence of functional groups in position 2 of the indole significantly lowered the yields of the corresponding products; thus, compounds **8**{*4*} and **8**{*7*} were obtained in only 9 and 29% yields, respectively.

2.3.3. Diversification

Finally, the 1,2-dihydroisoquinolines **8**{*31-51*} can be further elaborated using well known palladium-mediated processes, such as Suzuki-Miyaura[13] and Sonogashira[11] couplings (Scheme 3).

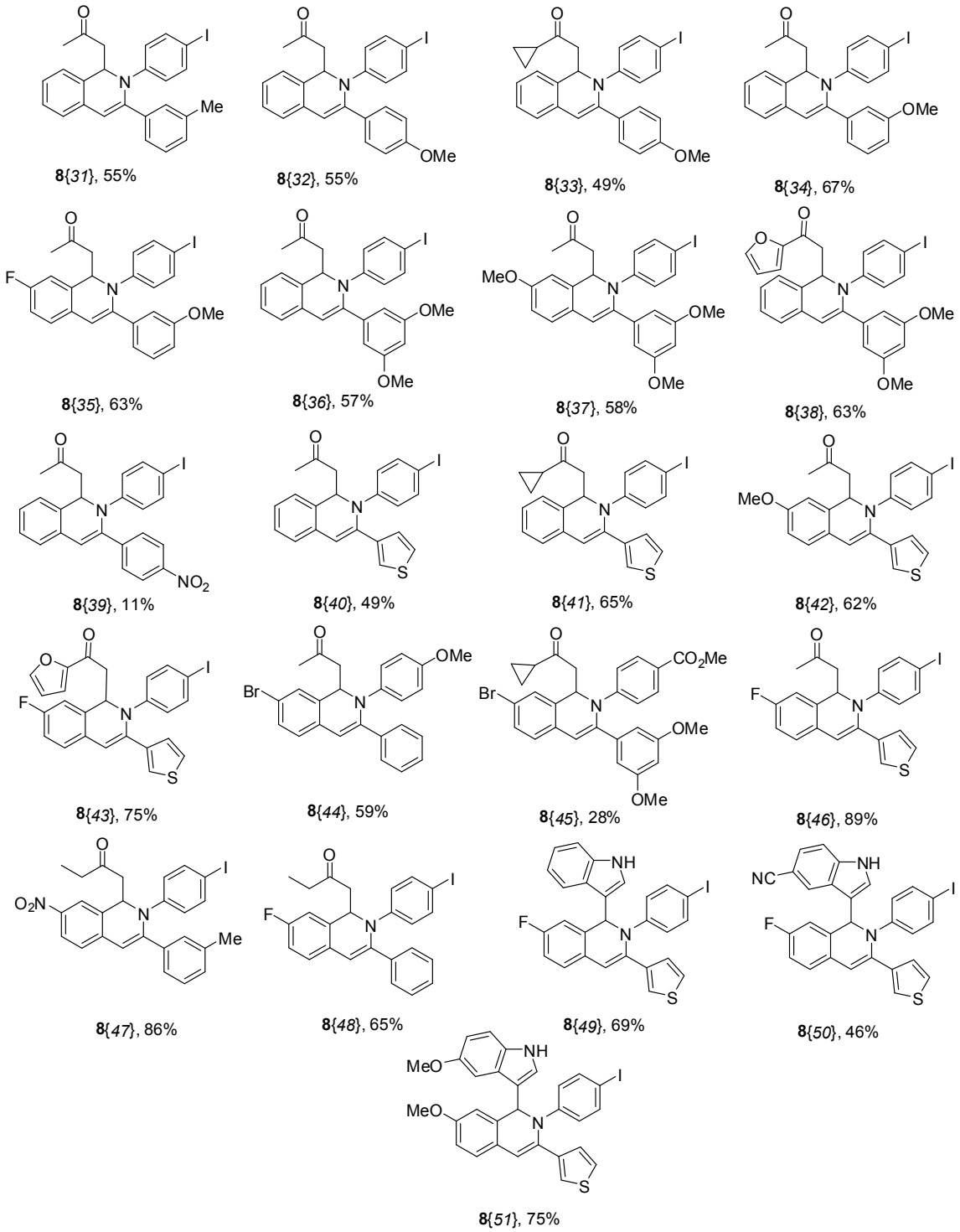
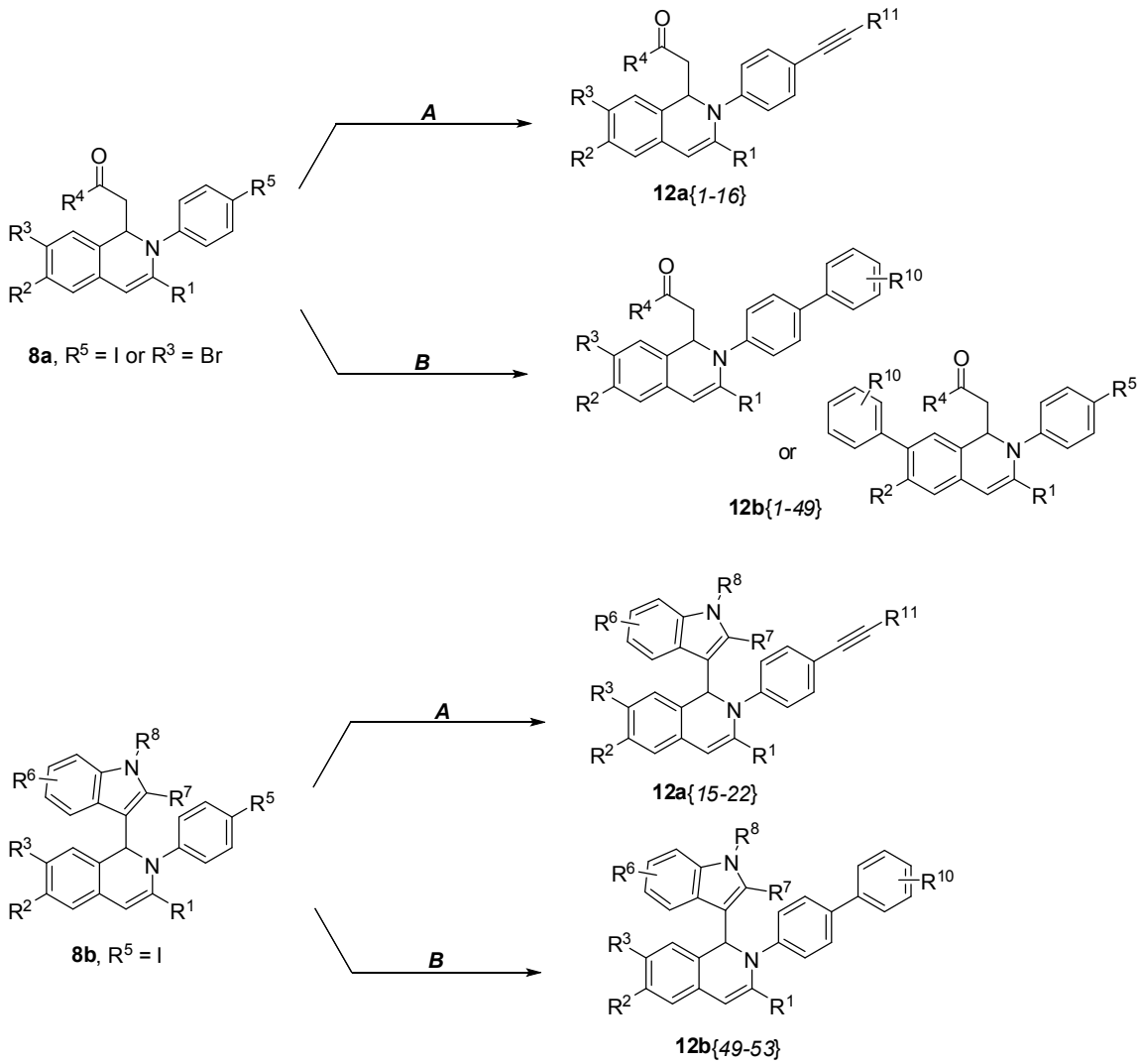


Figure 3. Halogen-containing 1,2-dihydroisoquinolines **8**{*31*−*51*}

Scheme 3. Diversification of 1,2-dihydroisoquinolines **8**{*31-51*}[a]



[a] Method **A** (Sonogashira coupling): 3 mol % $PdCl_2(PPh_3)_2$, 3 mol % CuI, Et_3N, alkyne **10** (1.2 equiv), 60 °C, 40 min under microwave irradiation. Method **B** (Suzuki-Miyaura coupling): 5 mol % $Pd(PPh_3)_4$, 1M Cs_2CO_3 (2 equiv), boronic acid **11** (1.2 equiv), 1:1 EtOH/DMF, 120 °C, 20 min under microwave irradiation.

Sonogashira coupling of the 1,2-dihydroisoquinolines **8**{*31-51*} with various terminal alkynes **10** nicely provides the corresponding alkyne products **12a**{*1-22*} using Et_3N as the solvent under microwave irradiation for 40 min at 60 °C (Scheme 3). The Suzuki-Miyaura coupling of the 1,2-dihydroisoquinolines **8**{*31−51*} with various arylboronic acids **11**

proceeded smoothly to give the desired products **12b**{*1-53*}. The reactions were carried out in a 1:1 ethanol/DMF mixture with the addition of 1M aqueous Cs_2CO_3 solution at 120 °C under microwave irradiation for 20 min. The sublibraries of commercially available terminal alkynes **10** and boronic acids **11**, containing heterocycles and polar functionality to incorporate drug-like moieties into the resulting coupling products were chosen based on their commercial availability and the Lipinski compliance calculations mentioned above (Figure 4).

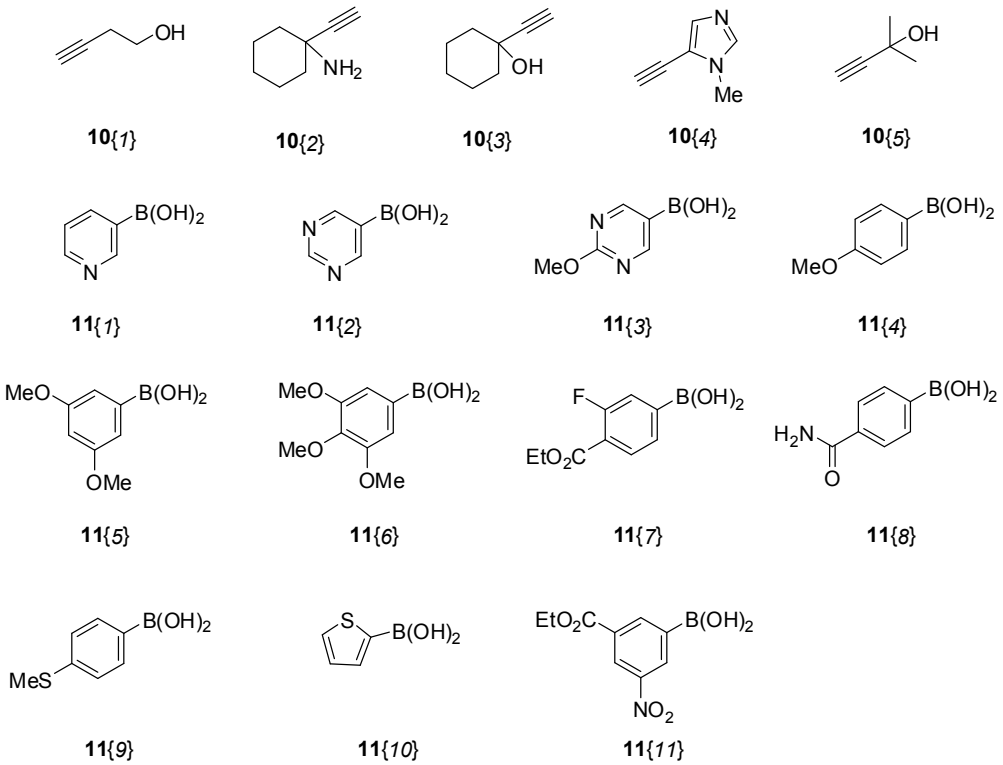


Figure 4. Terminal alkyne **10**{*1-5*} and boronic acid **11**{*1-11*} sublibraries

Fluorine atom-containing 2-(1-alkynyl)benzaldehydes **3**{*6*}, **3**{*10*}, **3**{*15*}, aniline **7**{*3*} and arylboronic acid **11**{*7*} have been chosen because the resulting fluorine-containing 1,2-dihydroisoquinolines and Suzuki-Miyaura coupling products are of considerable interest

due to the many versatile applications of fluorine-containing compounds in industry and medicine.[14] The results for the Sonogashira and Suzuki-Miyaura couplings performed on the 1,2-dihydroisoquinolines **8**{*31-51*} are summarized in Table 3.

Table 3. Library Data for Compounds **12a**{*1-22*}and **12b**{*1-53*}

product	**8**	**10 or 11**	yield (%)[a]	purity (%)[c]		product	**8**	**10 or 11**	yield (%)[a]	purity (%)[c]
12a{*1*}	**8**{*33*}	**10**{*1*}	65	100		**12b**{17}	**8**{*38*}	**11**{*1*}	15[b]	100
12a{*2*}	**8**{*34*}	**10**{*1*}	99	100		**12b**{*18*}	**8**{*38*}	**11**{2}	38[b]	100
12a{*3*}	**8**{*35*}	**10**{*2*}	69	-		**12b**{19}	**8**{*38*}	**11**{*3*}	34[b]	100
12a{4}	**8**{*35*}	**10**{*3*}	96	100		**12b**{*20*}	**8**{*38*}	**11**{*8*}	66	100
12a{*5*}	**8**{*35*}	**10**{*1*}	84	100		**12b**{21}	**8**{*39*}	**11**{*3*}	45	98
12a{*6*}	**8**{*36*}	**10**{*1*}	89	100		**12b**{22}	**8**{*40*}	**11**{*2*}	86	96
12a{7}	**8**{*36*}	**10**{2}	54	100		**12b**{*23*}	**8**{*40*}	**11**{*3*}	68	100
12a{8}	**8**{*36*}	**10**{3}	75	99		**12b**{*24*}	**8**{*40*}	**11**{*4*}	76	97
12a{*9*}	**8**{*37*}	**10**{*3*}	31[b]	100		**12b**{25}	**8**{*40*}	**11**{*6*}	75	100
12a{*10*}	**8**{*37*}	**10**{*1*}	62	100		**12b**{*26*}	**8**{*40*}	**11**{10}	52	98
12a{*11*}	**8**{*37*}	**10**{*2*}	58	100		**12b**{27}	**8**{*40*}	**11**{*11*}	20	100
12a{*12*}	**8**{*40*}	**10**{*1*}	84	98		**12b**{28}	**8**{*41*}	**11**{*1*}	41	99
12a{*13*}	**8**{*42*}	**10**{*1*}	69	98		**12b**{29}	**8**{*41*}	**11**{2}	84	94
12a{*14*}	**8**{*43*}	**10**{*1*}	75	100		**12b**{*30*}	**8**{*42*}	**11**{1}	26[b]	100
12a{*15*}	**8**{*46*}	**10**{*3*}	94	100		**12b**{*31*}	**8**{*42*}	**11**{3}	64	98
12a{*16*}	**8**{*46*}	**10**{*4*}	77	100		**12b**{*32*}	**8**{*42*}	**11**{*10*}	48[b]	100
12a{*17*}	**8**{49}	**10**{5}	100	98		**12b**{33}	**8**{*43*}	**11**{*3*}	58	100

Table 3 continued.

12a{*18*}	**8**{49}	**10**{*1*}	12[b]	100		**12b**{*34*}	**8**{*43*}	**11**{*8*}	42[b]	100
12a{*19*}	**8**{49}	**10**{*4*}	25	93		**12b**{*35*}	**8**{*43*}	**11**{11}	0	-
12a{*20*}	**8**{*50*}	**10**{1}	21[b]	100		**12b**{*36*}	**8**{*44*}	**11**{*2*}	36[b]	92
12a{*21*}	**8**{*50*}	**10**{5}	100	100		**12b**{37}	**8**{*44*}	**11**{*4*}	69	98
12a{*22*}	**8**{51}	**10**{*1*}	11[b]	100		**12b**{38}	**8**{*44*}	**11**{*5*}	71	98
12b{*1*}	**8**{*31*}	**11**{5}	70	95		**12b**{*39*}	**8**{*44*}	**11**{7}	13[b]	99
12b{*2*}	**8**{*32*}	**11**{10}	28[b]	98		**12b**{*40*}	**8**{*44*}	**11**{9}	16[b]	95
12b{*3*}	**8**{*32*}	**11**{7}	16[b]	93		**12b**{*41*}	**8**{*44}*	**11**{*10*}	27[b]	92
12b{*4*}	**8**{*32*}	**11**{*5*}	91	99		**12b**{*42*}	**8**{*45*}	**11**{*1*}	21[b]	100
12b{*5*}	**8**{*33*}	**11**{*2*}	100	100		**12b**{*43*}	**8**{*45*}	**11**{*3*}	43[b]	100
12b{*6*}	**8**{*33*}	**11**{*6*}	63	100		**12b**{*44*}	**8**{*45*}	**11**{*8*}	16[b]	>99
12b{*7*}	**8**{*34*}	**11**{2}	49[b]	97		**12b**{*45*}	**8**{*46*}	**11**{*1*}	63	100
12b{8}	**8**{35}	**11**{*2*}	89	100		**12b**{*46*}	**8**{*46*}	**11**{*3*}	75	100
12b{*9*}	**8**{35}	**11**{*6*}	91	100		**12b**{47}	**8**{*46*}	**11**{*8*}	58[b]	100
12b{10}	**8**{35}	**11**{*7*}	48	100		**12b**{*48*}	**8**{*47*}	**11**{*4*}	50	96
12b{11}	**8**{*36*}	**11**{*2*}	77	100		**12b**{*49*}	**8**{*48*}	**11**{*4*}	77	94
12b{*12*}	**8**{*36*}	**11**{*6*}	100	99		**12b**{*50*}	**8**{*49*}	**11**{4}	93	100
12b{*13*}	**8**{*36*}	**11**{*10*}	100	99		**12b**{*51*}	**8**{*50*}	**11**{*6*}	36[b]	100
12b{*14*}	**8**{*37*}	**11**{*2*}	42[b]	100		**12b**{*52*}	**8**{*50*}	**11**{*7*}	18[b]	100
12b{*15*}	**8**{*37*}	**11**{*4*}	55	100		**12b**{*53*}	**8**{*51*}	**11**{10}	40	85
12b{16}	**8**{*37*}	**11**{*10*}	22[b]	100						

[a] Isolated yield after column chromatography. [b] Isolated yield after preparative HPLC. [c] UV purity determined at 214 nm after preparative HPLC.

Under our reaction conditions, microwave irradiation has been shown not only to dramatically reduce the reaction times, but to provide higher yields of both the desired alkyne products **12a**{*1-22*} and the Suzuki-Miyaura coupling products **12b**{*1-53*} when compared to conventional heating methods. These processes have been performed in parallel on approximately a ~35-60 mg scale, starting from 1,2-dihydroisoquinolines **8**{*31-51*}. All of the crude products **12a** and **12b** were isolated by either column chromatography or preparative HPLC. The purity of the reaction mixtures has been analyzed by TLC, LC-MS, and HPLC. We have used Lipinski's rule of five[10] as a general guide for bioavailability, because compounds with poor bioavailability face more of a challenge in becoming successful clinical candidates. According to Lipinski's rules, the favorable drug candidates should have a molecular weight less than 500, clogP less than 5, the number of hydrogen bond donors less than 5 and acceptors less than 10, and the number of rotatable bonds less than 10. These parameters were calculated for each of the library members using the SYBYL[15] program. The majority of the 105 1,2-dihydroisoquinolines **8**{*1-30*}, **12a**{*1-22*} and **12b**{*1-53*} synthesized satisfy these requirements.

3.4. CONCLUSIONS

In summary, a simple and efficient method for the parallel synthesis of multi-substituted 1,2-dihydroisoquinolines **8** and **12** has been developed employing a one-pot, three-component AgOTf and *L*-proline-cocatalyzed reaction of 2-(1-alkynyl)benzaldehydes, amines and ketones or indoles. Palladium-catalyzed couplings, such as Suzuki-Miyaura and Sonogashira cross-couplings have been used to further diversify the 1,2-dihydroisoquinolines

8, providing pure 5+ mg samples of each library compound. The average purity of the 105 members of this library is 94.1% and the average yield is 55.7%. The elaborated, multi-substituted 1,2-dihydroisoquinolines **8***{1-30}*, **12a***{1-22}* and **12b***{1-53}* have been added to the collection of the Kansas University NIH Center for Chemical Methodologies and Library Development (KU CMLD) and will be submitted to the National Institutes of Health Molecular Library Screening Center Network (MLSCN) for evaluation by a broad range of assays.

3.5. ACKNOWLEDGEMENTS

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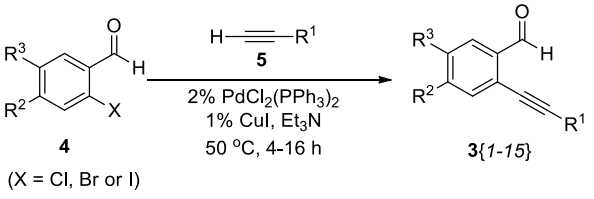
3.6. EXPERIMENTAL

3.6.1. General remarks.

The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ as the solvent using tetramethylsilane (TMS) as an internal standard, unless otherwise stated.

Chemical shifts are reported in δ units (ppm) by assigning the TMS resonance in the ^{1}H NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C NMR spectrum as 77.23 ppm. All coupling constants, *J*, are reported in Hertz (Hz). Analytical thin layer chromatography (TLC) was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. High resolution mass spectra (HRMS) were obtained using a Waters/Micromass LCT Premier TOF using EI at a voltage of 70 eV. Commercially available reagents were used without further purification, unless otherwise stated. The anhydrous organic solvents (*e.g.* Et_2O, EtOAc, $CHCl_3$, MeOH, EtOH, CH_3CN, DMF, hexane, toluene, *etc*.) were purchased from commercial sources and used as received. The palladium catalysts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. The boronic acids were donated by Frontier Scientific and Synthonix Co. Ltd. All microwave irradiation reactions were carried out on a Biotage-EXP Microwave synthesis system, operating at a frequency of 2450 MHz with continuous irradiation power from 0-300 W in 2 mL oven-dried Biotage microwave vials sealed with an aluminum/Teflon® crimp top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The reaction temperature was measured by an IR sensor on the outer surface of the process vial.

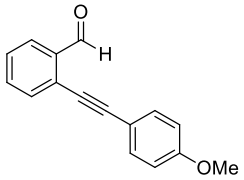
3.6.2. General procedure for preparation of the 2-(1-alkynyl)benzaldehydes 3.



(1)

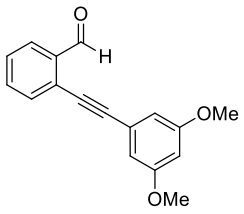
These compounds were prepared according to a procedure reported previously by our group.[1] To a solution of the corresponding 2-bromoarenecarboxaldehyde (0.54 mmol) and alkyne (0.65 mmol) in Et_3N (2.2 mL) was added $PdCl_2(PPh_3)_2$ (0.011 mmol, 2 mol %) and the mixture was stirred for 5 min. Then CuI (0.0054 mmol, 1 mol %) was added and the reaction mixture was heated to 50 °C under a nitrogen atmosphere for 4-16 h. After completion, the resulting mixture was concentrated under reduced pressure and subjected to column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

2-[(4-Methoxyphenyl)ethynyl]benzaldehyde (3{1})



This compound was obtained as a cream colored solid in a 99% yield: mp 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.91 (d, J = 8.7 Hz, 2H), 7.42 (dd, J = 7.7, 7.7 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.59 (m, 2H), 7.93 (d, J = 7.8 Hz, 1H), 10.65 (s, 1H). The ^{1}H NMR spectral data is in good agreement with the literature data.[16]

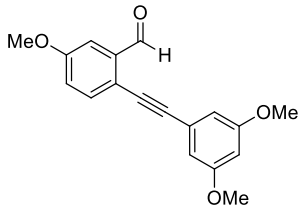
2-[(3,5-Dimethoxyphenyl)ethynyl]benzaldehyde (3{2})



This compound was obtained as a yellow solid in a 99% yield: mp 76-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 6H), 6.51 (d, J = 2.2 Hz, 1H), 6.71 (d, J = 2.2 Hz, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 84.6, 96.5, 102.8, 109.6,

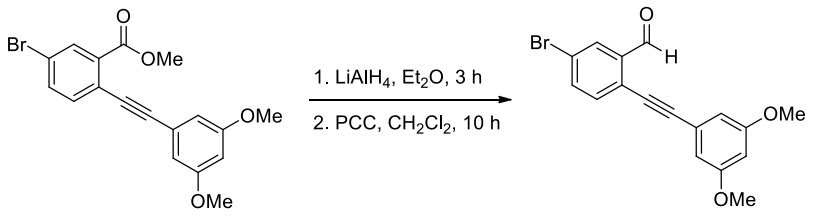
123.8, 126.9, 127.5, 128.9, 133.5, 133.9, 136.1, 160.9, 191.9; HRMS (EI) calcd for $C_{17}H_{14}O_3$ 266.09431, found 266.09490.

2-[(3,5-Dimethoxyphenyl)ethynyl]-5-methoxybenzaldehyde (3{3})



This compound was obtained as a yellow solid in a 85% yield: mp 118-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 6H), 3.89 (s, 3H), 6.49 (t, J = 2.2 Hz, 1H), 6.69 (d, J = 2.2 Hz, 2H), 7.15 (dd, J = 2.7, 8.6 Hz, 1H), 7.43 (d, J = 2.6, 1H), 7.57 (d, J = 8.6 Hz, 1H), 10.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 55.9, 84.6, 95.1, 102.5, 109.5, 110.1, 119.7, 121.9, 124.1, 134.8, 137.5, 160.0, 160.9, 191.8; HRMS (EI) calcd for $C_{18}H_{16}O_4$ 296.10491, found 296.10490.

5-Bromo-2-[(3,5-dimethoxyphenyl)ethynyl]benzaldehyde (3{4})

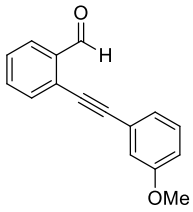


(2)

This compound was prepared from the corresponding methyl ester by $LiAlH_4$ reduction to the alcohol and PCC oxidation. To a solution of 1.02 g (2.72 mmol) of the starting material in ethyl ether (30 mL) was slowly added 1.25 g (3.26 mmol) of $LiAlH_4$ and the reaction mixture was allowed to stir at room temperature for 3 h. Then brine was added and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and

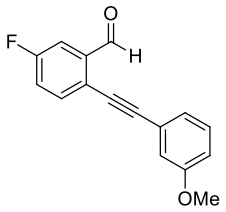
concentrated *in vacuo*. The crude product was dissolved in methylene chloride (14 mL) and 0.70 g (3.26 mmol) of pyridinium chlorochromate (PCC) was added. The reaction mixture was stirred for 10 h. After a standard work-up procedure, aldehyde **3**{*4*} was obtained as a colorless solid in a 68% yield: mp 126-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 6H), 6.51 (s, 1H), 6.69 (d, *J* = 2.1 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.69 (dd, *J* = 1.9, 8.2 Hz, 1H), 8.05 (d, *J* = 1.8 Hz, 1H), 10.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 83.7, 97.6, 102.9, 109.6, 117.7, 123.4, 125.6, 130.5, 134.8, 136.9, 137.1, 160.9, 190.4; HRMS (EI) calcd for $C_{17}H_{13}O_3Br$ 344.00480, found 344.00569.

2-[(3-Methoxyphenyl)ethynyl]benzaldehyde (3{5})



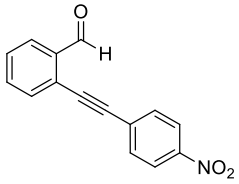
This compound was obtained as a colorless oil in a 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.95 (dd, *J* = 1.5, 8.3 Hz, 1H), 7.08 (s, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 84.9, 96.5, 115.9, 116.6, 123.5, 124.4, 126.9, 127.5, 128.8, 129.8, 133.4, 136.1, 159.7, 191.9; HRMS (EI) calcd for $C_{16}H_{12}O_2$ 236.08373, found 236.08409.

5-Fluoro-2-[(3-methoxyphenyl)ethynyl]benzaldehyde (3{6})



This compound was obtained as a yellow solid in a 100% yield: mp 81-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 3H), 6.95 (dd, J = 2.2, 8.2 Hz, 1H), 7.07 (s, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.27-7.33 (m, 2H), 7.60-7.67 (m, 2H), 10.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 83.8, 96.2, 113.8, 114.1, 115.9, 116.6, 121.5, 121.7, 123.1, 123.3, 124.4, 129.9, 135.4, 135.5, 137.9, 138.1, 159.7, 161.4, 163.9, 190.6 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{16}H_{11}O_2F$ 254.07433, found 254.07509.

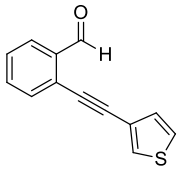
2-[(4-Nitrophenyl)ethynyl]benzaldehyde (3{7})



This compound was obtained under slightly modified reaction conditions. To a solution of 2-bromobenzaldehyde (0.25 mmol) in DMF (4 mL) was added $PdCl_2(PPh_3)_2$ (0.0075 mmol, 3 mol %) and CuI (0.0050 mmol, 2 mol %) and the reaction mixture stirred for 2 min. Then the vial was sealed, flushed with argon and $^{i}Pr_2NH$ (0.14 mL) was added and the reaction mixture was heated to 70 °C. Then the alkyne (0.3 mmol) in 1 mL of DMF was added dropwise over 5 min and the solution was stirred at 70 °C for 2 h. After completion of the reaction, the resulting mixture was concentrated under reduced pressure and subjected to column chromatography on silica gel using ethyl acetate/hexanes as the eluent. The product was obtained as an orange solid in a 65% yield: mp 129-131 °C; ^{1}H

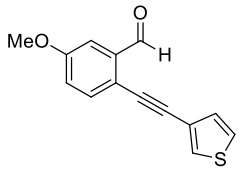
NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.5 Hz, 1H), 7.62-7.73 (m, 4H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 2H), 10.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 90.1, 93.9, 123.9, 125.3, 128.1, 129.3, 129.8, 132.6, 133.7, 134.1, 136.2, 147.6, 191.1; HRMS (EI) calcd for $C_{15}H_9NO_3$ 251.05824, found 251.05877.

2-[(3-Thiophenyl)ethynyl]benzaldehyde (3{8})



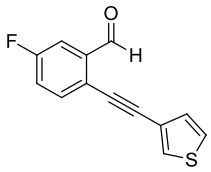
This compound was obtained as a yellow oil in a 68% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 4.9 Hz, 1H), 7.32 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.53-7.62 (m, 2H), 7.93 (d, *J* = 7.8 Hz, 1H), 10.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.7, 91.7, 121.6, 125.9, 127.0, 127.4, 128.7, 129.9, 133.3, 133.9, 135.9, 191.8; HRMS (EI) calcd for $C_{13}H_9OS$ 212.02958, found 212.03001.

5-Methoxy-2-[(3-thiophenyl)ethynyl]benzaldehyde (3{9})



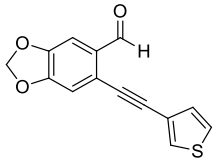
This compound was obtained as an off-white solid in an 87% yield: mp 74-76 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.12 (dd, *J* = 2.7, 8.6 Hz, 1H), 7.20 (d, *J* = 4.9 Hz, 1H), 7.33 (dd, *J* = 3.1, 4.8 Hz, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.54 (t, *J* = 6.3 Hz, 2H), 10.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 84.6, 90.2, 109.9, 119.7, 121.9, 125.9, 129.3, 128.9, 129.8, 134.6, 137.3, 159.9, 191.7; HRMS (EI) calcd for $C_{14}H_{10}O_2S$ 242.04015, found 242.04058.

5-Fluoro-2-[(3-thiophenyl)ethynyl]benzaldehyde (3{10})



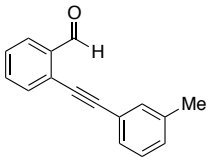
This compound was obtained as a yellow solid in an 89% yield: mp 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 1.0, 4.9 Hz, 1H), 7.28 (td, *J* = 2.8, 8.3 Hz, 1H), 7.34 (dd, *J* = 3.0, 4.9 Hz, 1H), 7.58-7.63 (m, 3H), 10.55 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6, 91.4, 113.7, 113.9, 121.3, 121.4, 121.6, 123.1, 126.0, 129.8, 129.9, 135.2, 135.3, 137.8, 137.9, 161.2, 163.7, 190.6 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{13}H_7OSF$ 230.02016, found 230.02063.

4,5-Dioxolyl-2-[(3-thiophenyl)ethynyl]benzaldehyde (3{11})



This compound was obtained as a colorless solid in a 90% yield: mp 118-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 2H), 6.94 (s, 1H), 7.17 (d, *J* = 4.9 Hz, 1H), 7.31 (m, 2H), 7.54 (br s, 1H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.5, 90.4, 102.4, 105.9, 111.8, 121.4, 123.5, 125.8, 129.5, 129.6, 132.4, 148.6, 152.3, 189.9; HRMS (EI) calcd for $C_{14}H_8O_3S$ 256.01941, found 256.02003.

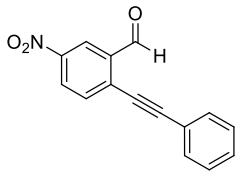
2-[(3-Tolyl)ethynyl]benzaldehyde (3{12})



This compound was obtained as a yellow solid in an 81% yield: mp 36-37 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.19-7.65 (m, 8H), 7.95 (d, *J* = 6.0 Hz,

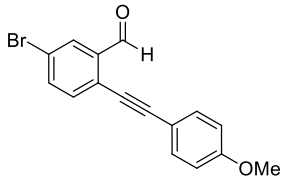
1H), 10.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 84.8, 96.8, 122.4, 127.5, 128.6, 128.7, 128.9, 130.2, 132.5, 133.4, 133.9, 166.6, 191.9; HRMS (EI) calcd for $C_{16}H_{12}O$ 220.08880, found 221.09611.

5-Nitro-2-(phenylethynyl)benzaldehyde (3{13})



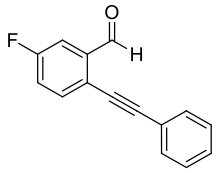
This compound was obtained as a yellow solid in an 89% yield: mp 111-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.46 (m, 3H), 7.61 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 8.40 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.8, 101.9, 121.4, 122.9, 127.9, 128.9, 130.3, 132.2, 132.6, 134.6, 136.7, 147.5, 189.5; HRMS (EI) calcd for $C_{15}H_{19}NO_3$ 251.05821, found 252.06553.

5-Bromo-2-[(4-methoxyphenyl)ethynyl]benzaldehyde (3{14})



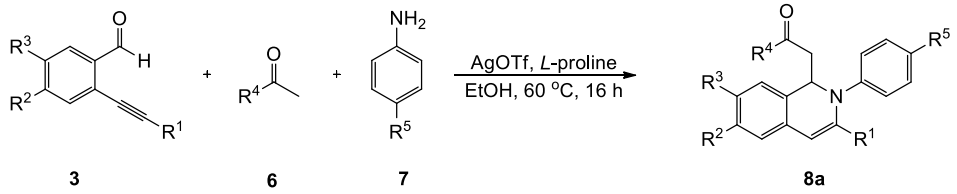
This compound was obtained as a white solid in a 56% yield: mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.49-7.45 (m, 3H), 7.65 (dd, *J* = 2.3, 8.2 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 10.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 82.5, 97.9, 114.1, 114.2, 124.2, 126.2, 130.2, 133.2, 134.0, 134.3, 136.6, 160.4, 190.4; HRMS calcd for $C_{16}H_{11}BrO_2$ 315.1613, found 315.1633.

5-Fluoro-2-(phenylethynyl)benzaldehyde (3{15})



This compound was obtained as a yellow solid in an 84% yield: mp 51-52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (td, J = 6.3, 2.1 Hz, 1H), 7.37-7.40 (m, 3H), 7.54-7.66 (m, 4H), 10.60 (d, J = 2.4 Hz, 1H); the ^{1}H NMR spectral data is in good agreement with the literature data.[17]

3.6.3. General procedure for preparation of the 1,2-dihydroisoquinolines 8a

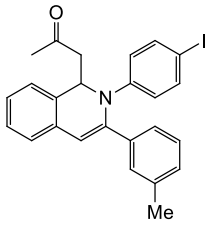


3 6 7 8a (3)

These compounds were prepared according to a procedure reported previously by Wu and co-workers.[18] To a solution of the corresponding 2-(1-alkynyl)benzaldehyde **3** (1.08 mmol), aniline **7** (1.08 mmol) and ketone **6** (5.38 mmol) in EtOH (5.4 mL) were added AgOTf (0.108 mmol, 10 mol %) and *L*-proline (0.108 mmol, 10 mol %) and the mixture was stirred at 50-60 °C under a nitrogen atmosphere for 16 h. After completion of the reaction, the resulting mixture was concentrated under reduced pressure, quenched with water (30 mL), extracted with EtOAc (2 × 30 mL) and dried over Na_2SO_4 (anhydrous). The solvent was evaporated and the reaction mixture was subjected to column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

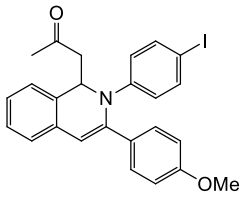
3.6.4. Data for the 1,2-dihydroisoquinolines subjected to further elaboration

Compound 8{31}



This compound was obtained as a yellow oil in a 55% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.21 (s, 3H), 2.41 (dd, J = 4.7, 16.9 Hz, 1H), 3.15 (dd, J = 8.9, 17.0 Hz, 1H), 5.40 (dd, J = 4.7, 8.9 Hz, 1H), 6.69 (s, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.94 (t, J = 6.8 Hz, 2H), 7.04 (t, J = 7.3 Hz, 2H), 7.10-7.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 31.9, 47.2, 60.7, 85.4, 113.4, 124.4, 124.5, 124.9, 125.3, 127.2, 127.7, 127.8, 128.7, 129.3, 131.6, 132.4, 137.1, 137.6, 138.4, 140.1, 147.0, 207.3; HRMS (EI) calcd for $C_{25}H_{20}INO$ 477.05900, found 478.06620.

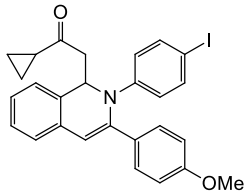
Compound 8{32}



This compound was obtained as a yellow solid in a 55% yield: mp 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.48 (dd, J = 4.6, 17.0 Hz, 1H), 3.24 (dd, J = 9.2, 16.9 Hz, 1H), 3.73 (s, 3H), 5.47 (dd, J = 4.6, 9.1 Hz, 1H), 6.70 (s, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 7.4 Hz, 1H), 7.10 (td, J = 1.6, 7.2 Hz, 1H), 7.18-7.24 (m, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 47.1, 55.4, 60.8, 85.4, 111.8, 114.2, 124.5, 124.6, 126.2, 126.9,

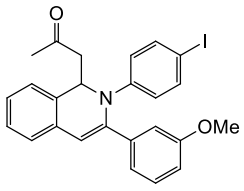
127.7, 128.4, 129.5, 131.8, 132.2, 137.5, 139.7, 147.1, 159.8, 207.3; HRMS (EI) calcd for $C_{25}H_{22}INO_2$ 495.06952, found 495.07023.

Compound 8{33}



This compound was obtained as a yellow solid in a 49% yield: mp 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dd, *J* = 2.9, 7.8 Hz, 2H), 1.10 (dd, *J* = 2.8, 4.4 Hz, 2H), 1.84 (m, 1H), 2.54 (dd, *J* = 4.3, 16.4 Hz, 1H), 3.38 (dd, *J* = 9.6, 16.4 Hz, 1H), 3.77 (s, 3H), 5.50 (dd, *J* = 4.2, 9.6 Hz, 1H), 6.70 (s, 1H), 6.81 (dd, *J* = 8.9, 10.9 Hz, 4H), 7.02 (d, *J* = 7.4 Hz, 1H), 7.13 (td, *J* = 10.0, 7.5 Hz, 1H), 7.22-7.27 (m, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 11.7, 22.3, 46.7, 55.5, 61.2, 85.3, 111.9, 114.1, 124.6, 124.7, 125.3, 126.9, 127.8, 128.6, 129.6, 131.9, 132.4, 137.6, 139.8, 147.2, 159.9, 209.7; HRMS (EI) calcd for $C_{27}H_{24}INO_2$ 521.08517, found 521.08653.

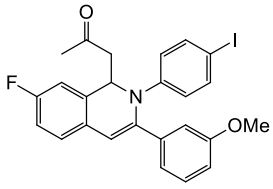
Compound 8{34}



This compound was obtained as a yellow solid in a 67% yield: mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.51 (dd, *J* = 4.6, 17.0 Hz, 1H), 3.24 (dd, *J* = 9.1, 16.9 Hz, 1H), 3.74 (s, 3H), 5.49 (dd, *J* = 4.6, 9.0 Hz, 1H), 6.76-6.80 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.02-7.07 (m, 3H), 7.13-7.28 (m, 4H), 7.35 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 47.3, 55.4, 60.7, 85.6, 112.8, 113.6, 114.0, 119.7, 124.4,

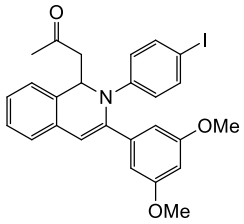
124.9, 125.4, 127.4, 127.8, 129.8, 131.5, 132.5, 137.7, 138.7, 139.9, 147.0, 159.9, 207.3; HRMS (EI) calcd for $C_{25}H_{22}INO_2$ 495.06952, found 495.07074.

Compound 8{35}



This compound was obtained as a yellow solid in a 63% yield: mp 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.50 (dd, *J* = 4.5, 17.3 Hz, 1H), 3.23 (dd, *J* = 8.9, 17.3 Hz, 1H), 3.72 (s, 3H), 5.45 (dd, *J* = 4.6, 8.8 Hz, 1H), 6.74-6.77 (m, 3H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.92 (t, *J* = 8.5 Hz, 1H), 7.00 (s, 1H), 7.05 (d, *J* = 7.7 Hz, 2H), 7.14-7.23 (m, 2H), 7.35 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 46.9, 55.3, 60.3, 85.8, 112.3, 112.5, 112.6, 113.9, 114.6, 114.8, 119.5, 124.3, 126.4, 126.5, 127.7, 129.8, 134.3, 134.4, 137.7, 138.4, 139.3, 146.8, 159.9, 160.8, 163.3, 206.8 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{25}H_{21}FINO_2$ 513.06010, found 513.06164.

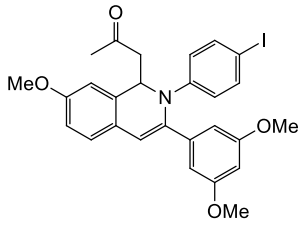
Compound 8{36}



This compound was obtained as a yellow solid in a 57% yield: mp 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.49 (dd, *J* = 4.5, 17.0 Hz, 1H), 3.23 (dd, *J* = 9.2, 16.9 Hz, 1H), 3.71 (s, 6H), 5.47 (dd, *J* = 4.5, 9.1 Hz, 1H), 6.35 (t, *J* = 2.1 Hz, 1H), 6.63 (d, *J* = 2.2 Hz, 2H), 6.79 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 7.3 Hz, 1H),

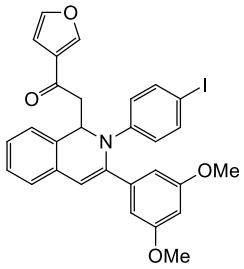
7.14 (td, J = 1.5, 7.2 Hz, 1H), 7.20-7.27 (m, 2H), 7.35 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 47.2, 55.5, 60.7, 85.6, 100.6, 105.4, 113.6, 124.3, 124.9, 125.3, 127.4, 127.8, 131.4, 132.5, 137.7, 139.4, 139.9, 147.1, 161.0, 207.2; HRMS (EI) calcd for $C_{26}H_{24}INO_3$ 525.08009, found 525.08176.

Compound 8{37}



This compound was obtained as a yellow oil in a 45% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.47 (dd, J = 3.9, 17.1 Hz, 1H), 3.23 (dd, J = 9.3, 17.0 Hz, 1H), 3.70 (s, 6H), 3.73 (s, 3H), 5.42 (dd, J = 4.1, 8.9 Hz, 1H), 6.33 (s, 1H), 6.43 (d, J = 8.1 Hz, 1H), 6.59 (s, 1H), 6.62 (s, 2H), 6.78 (br s, 2H), 6.87 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.3 Hz, 1H), 7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 47.1, 55.4, 55.5, 60.7, 85.3, 100.2, 104.9, 110.6, 113.6, 117.4, 123.9, 124.5, 126.4, 134.3, 137.6, 137.9, 139.5, 147.3, 159.4, 160.9, 207.2; HRMS (EI) calcd for $C_{27}H_{26}INO_4$ 555.09065, found 555.09221.

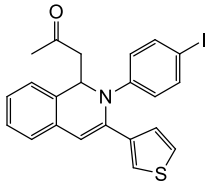
Compound 8{38}



This compound was obtained as a yellow solid in a 63% yield: mp 177-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (dd, J = 4.2, 15.6 Hz, 1H), 3.57 (s, 6H),

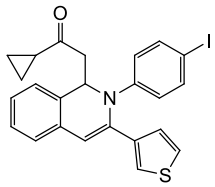
3.72 (dd, J = 10.1, 15.6 Hz, 1H), 5.64 (dd, J = 4.2, 10.1 Hz, 1H), 6.27 (t, J = 2.2 Hz, 1H), 6.40 (dd, J = 1.7, 3.6 Hz, 1H), 6.51 (d, J = 2.2 Hz, 2H), 6.82 (m, 3H), 7.05-7.35 (m, 7H), 7.49 (d, J = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.4, 55.3, 61.8, 85.8, 100.8, 105.3, 112.6, 113.3, 118.5, 124.3, 124.9, 125.3, 127.4, 127.9, 131.5, 132.1, 137.6, 139.1, 140.0, 147.0, 147.1, 152.9, 160.7, 187.4; HRMS (EI) calcd for $C_{29}H_{24}INO_4$ 577.07500, found 577.07660.

Compound 8{40}



This compound was obtained as a yellow solid in a 49% yield: mp 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.45 (dd, J = 4.6, 16.7 Hz, 1H), 3.23 (dd, J = 9.3, 16.7 Hz, 1H), 5.41 (dd, J = 4.6, 9.3 Hz, 1H), 6.78 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 7.4 Hz, 1H), 7.10-7.24 (m, 6H), 7.36 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 47.2, 61.0, 85.6, 112.6, 123.4, 124.2, 124.9, 125.4, 126.1, 127.2, 127.8, 131.3, 132.2, 135.4, 137.6, 139.2, 147.2, 207.4; HRMS (EI) calcd for $C_{22}H_{18}INOS$ 471.01538, found 471.01680.

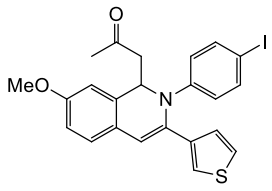
Compound 8{41}



This compound was obtained as a colorless solid in a 65% yield: mp 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (dd, J = 3.9, 7.7 Hz, 2H), 1.08 (t, J = 4.0 Hz,

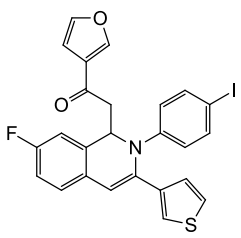
2H), 1.84 (m, 1H), 2.52 (dd, J = 4.3, 16.1 Hz, 1H), 3.36 (dd, J = 9.7, 16.1 Hz, 1H), 5.44 (dd, J = 4.3, 9.7 Hz, 1H), 6.77 (s, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 7.4 Hz, 1H), 7.12-7.27 (m, 6H), 7.37 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 11.7, 22.4, 46.8, 61.4, 85.5, 112.6, 123.6, 124.2, 124.8, 125.4, 125.9, 126.3, 127.2, 127.8, 131.4, 132.3, 135.5, 137.6, 139.3, 147.2, 209.6; HRMS (EI) calcd for $C_{24}H_{20}INOS$ 497.03103, found 497.03223.

Compound 8{42}



This compound was obtained as a yellow oil in a 47% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.45 (dd, J = 4.4, 16.8 Hz, 1H), 3.25 (dd, J = 9.5, 16.7 Hz, 1H), 3.74 (s, 3H), 5.37 (dd, J = 4.4, 9.5 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 6.76-6.80 (m, 2H), 6.85 (d, J = 8.8, Hz, 2H), 7.08 (s, 1H), 7.15-7.20 (m, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 47.2, 55.6, 61.2, 85.4, 110.6, 112.7, 113.8, 122.7, 124.0, 124.5, 125.9, 126.1, 126.3, 133.4, 134.0, 137.7, 139.4, 147.4, 159.3, 207.5; HRMS (EI) calcd for $C_{25}H_{22}INO_2$ 501.02595, found 501.02726.

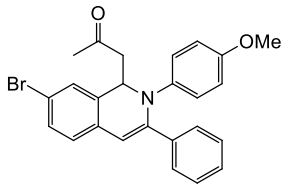
Compound 8{43}



This compound was obtained as a colorless solid in a 75% yield: mp 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (dd, J = 4.3, 15.2 Hz, 1H), 3.72 (dd, J =

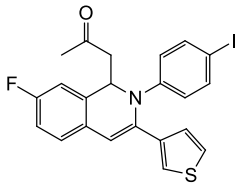
10.1, 15.2 Hz, 1H), 5.53 (dd, *J* = 4.3, 9.9 Hz, 1H), 6.42 (m, 1H), 6.75-6.82 (m, 4H), 6.88 (d, *J* = 1.4 Hz, 1H), 6.94 (td, *J* = 1.3, 8.3 Hz, 1H), 7.04 (d, *J* = 5.0 Hz, 1H), 7.10-7.12 (m, 2H), 7.20-7.25 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.1, 61.9, 85.9, 111.5, 112.4, 112.6, 114.7, 114.9, 118.6, 123.6, 124.2, 125.7, 126.1, 126.3, 126.4, 127.7, 133.7, 133.8, 135.0, 137.7, 138.7, 146.9, 147.2, 152.9, 160.7, 163.2, 187.3 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{25}H_{17}FINO_2S$ 541.00087, found 541.00204.

Compound 8{44}



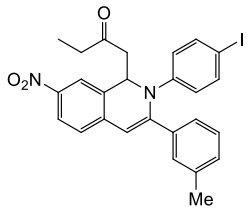
This compound was obtained as a yellow oil in a 59% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.49 (dd, *J* = 4.7, 16.9 Hz, 1H), 3.24 (dd, *J* = 9.1, 16.9 Hz, 1H), 3.65 (s, 3H), 5.39 (dd, *J* = 4.7, 9.0 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 2H), 6.68 (s, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 7.20-7.27 (m, 3H), 7.34 (dd, *J* = 1.9, 8.1 Hz, 1H), 7.49 (dd, *J* = 1.4, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 47.5, 55.5, 61.3, 110.6, 114.2, 119.9, 124.5, 126.0, 127.6, 128.4, 128.5, 128.7, 130.6, 130.9, 133.4, 137.3, 140.5, 141.9, 155.7, 207.1; HRMS (EI) calcd for $C_{25}H_{22}BrNO_2$ 447.08338, found 447.08396.

Compound 8{46}



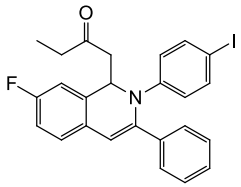
This compound was obtained as a yellow solid in a 73% yield: mp 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.49 (dd, *J* = 4.6, 16.9 Hz, 1H), 3.24 (dd, *J* = 9.1, 16.9 Hz, 1H), 5.39 (dd, *J* = 4.6, 9.1 Hz, 1H), 6.76 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.93 (t, *J* = 8.5 Hz, 1H), 7.14 (m, 1H), 7.18-7.24 (m, 3H), 7.40 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 47.0, 60.7, 85.9, 111.8, 112.5, 112.7, 113.7, 114.7, 114.9, 117.6, 123.5, 124.2, 126.0, 126.2, 126.3, 126.4, 127.7, 134.1, 134.2, 135.0, 137.8, 139.1, 147.1, 160.8, 163.3, 206.9 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{22}H_{17}FINOS$ 489.00596, found 489.00696.

Compound 8{47}



This compound was obtained as a yellow oil in an 86% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.3 Hz, 3H), 1.25 (s, 3H), 2.35-2.41 (m, 2H), 2.55 (dd, *J* = 4.8, 17.1 Hz, 1H), 3.28 (dd, *J* = 8.9, 17.1 Hz, 1H), 5.62 (dd, *J* = 4.8, 8.9 Hz, 1H), 6.77 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.28-7.40 (m, 5H), 7.45 (dd, *J* = 2.9, 6.5 Hz, 2H), 7.95 (d, *J* = 1.9 Hz, 1H), 8.12 (dd, *J* = 2.2, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 29.7, 37.8, 45.7, 60.8, 87.1, 111.0, 121.2, 123.4, 124.8, 125.2, 127.8, 129.0, 129.6, 132.1, 136.2, 137.9, 138.0, 144.7, 146.2, 146.3, 146.4, 150.7, 209.0.

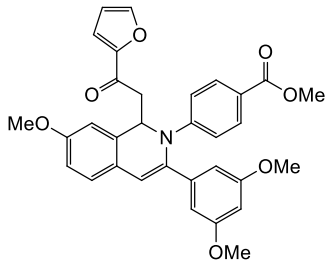
Compound 8{48}



This compound was obtained as a yellow oil in a 65% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.2 Hz, 3H), 2.35-2.38(m, 2H), 2.49 (dd, *J* = 4.7, 16.9 Hz, 1H), 3.23 (dd, *J* = 9.2, 16.9 Hz, 1H), 5.50 (dd, *J* = 4.6, 9.1 Hz, 1H), 6.78 (br s, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.90 (td, *J* = 2.2, 8.6 Hz, 1H), 7.21-7.29 (m, 4H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 37.9, 45.8, 56.9, 60.5, 85.7, 112.3, 112.5, 112.6, 114.6, 114.8, 124.4, 124.5, 126.4, 126.5, 127.0, 127.9, 128.8, 128.9, 134.4, 134.5, 136.8, 137.7, 139.3, 139.4, 146.8, 160.9, 163.3, 209.7 (extra peaks due to the ^{13}C-^{19}F coupling).

3.6.5. Data for selected 1,2-dihydroisoquinolines 8

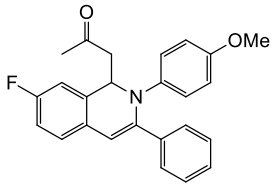
Compound 8{5}



This compound was obtained as a yellow oil in a 15% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (dd, *J* = 4.3, 15.8 Hz, 1H), 3.57 (s, 6H), 3.75 (m, 4H), 3.80 (s, 3H), 5.76 (dd, *J* = 4.2, 9.7 Hz, 1H), 6.26 (s, 1H), 6.46 (dd, *J* = 1.6, 3.4 Hz, 1H), 6.49 (s, 2H), 6.69 (s, 1H), 6.82 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.85 (s, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 3.3 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 42.2, 51.9, 55.3, 55.6, 60.9, 100.6, 104.9, 110.6, 113.7, 113.9, 114.2, 118.6, 120.7, 123.0, 124.5, 126.6, 130.6, 134.6, 137.5, 139.3, 147.2, 151.3, 153.0, 159.5, 160.9, 167.1, 187.3; HRMS (EI) calcd for $C_{32}H_{29}NO_7$ 539.19439, found 539.19565.

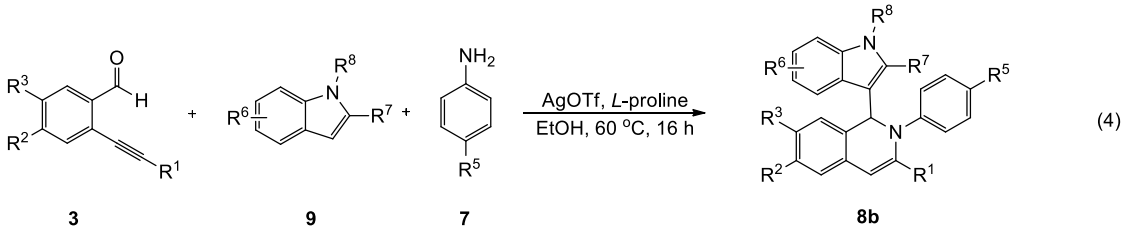
Compound 8{27}



This compound was obtained as a yellow oil in a 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.44 (dd, *J* = 4.9, 16.9 Hz, 1H), 3.17 (dd, *J* = 8.9, 16.9 Hz, 1H), 3.57 (s, 3H), 5.32 (dd, *J* = 4.9, 8.9 Hz, 1H), 6.54-6.56 (m, 2H), 6.63 (s, 1H), 6.69 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.86 (td, *J* = 2.6, 8.6 Hz, 1H), 6.89-6.92 (m, 2H), 7.12-7.19 (m, 4H), 7.43 (dd, *J* = 1.3, 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 47.4, 55.5, 61.4, 110.8, 112.5, 112.7, 114.2, 114.4, 114.6, 124.2, 124.4, 125.9, 126.0, 127.4, 127.5, 128.3, 128.6, 133.6, 133.7, 137.4, 140.6, 155.5, 160.6, 163.1, 207.3 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{25}H_{22}FNO_2$ 388.17130, found 388.17033.

3.6.6. General procedure for preparation of the 1-(3-indolyl)-1,2-dihydroisoquinolines 8b

To a solution of the corresponding 2-(1-alkynyl)benzaldehyde **3** (1.08 mmol), aniline **7** (1.08 mmol) and indole **9** (1.08 mmol) in EtOH (5.4 mL) were added AgOTf (0.108 mmol, 10 mol %) and *L*-proline (0.108 mmol, 10 mol %) and the mixture was stirred at 50-60 °C under a nitrogen atmosphere for 16 h.

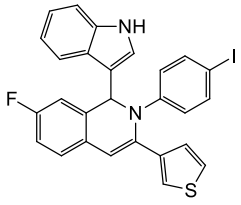


3 9 7 8b (4)

After completion of the reaction, the resulting mixture was concentrated under reduced pressure, quenched with water (30 mL), extracted with EtOAc (2 × 30 mL) and dried over Na_2SO_4 (anhydrous). The solvent was evaporated and the reaction mixture was subjected to column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

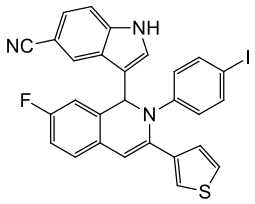
3.6.7. Data for 1-(3-indolyl)-1,2-dihydroisoquinolines subjected to further elaboration

Compound 8{49}



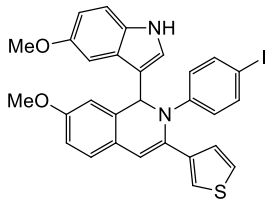
This compound was obtained as an orange solid in a 69% yield: mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 6.85 (d, *J* = 7.7 Hz, 2H), 6.91-6.96 (m, 2H), 7.09-7.20 (m, 7H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.77 (s, 1H), 8.01 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.4, 84.9, 111.8, 113.1, 113.3, 114.5, 114.8, 117.2, 119.2, 120.1, 122.5, 123.5, 123.7, 125.7, 125.9, 126.2, 126.3, 126.5, 128.2, 133.9, 134.1, 135.7, 136.7, 137.8, 139.2, 147.1, 160.5, 162.9 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{27}H_{18}FIN_2S$ 548.02194, found 548.02312.

Compound 8{50}



This compound was obtained as a yellow solid in a 46% yield: mp 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H), 6.75 (s, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.97-7.05 (m, 2H), 7.11-7.19 (m, 3H), 7.29 (dd, J = 5.5, 8.3 Hz, 1H), 7.35-7.50 (m, 5H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.3, 84.4, 101.8, 111.8, 111.9, 112.4, 112.5, 112.6, 114.1, 114.3, 116.4, 116.7, 120.4, 122.9, 123.0, 123.8, 124.2, 124.9, 125.6, 125.7, 125.8, 126.0, 126.1, 126.7, 127.7, 127.8, 132.9, 134.9, 137.3, 138.1, 138.4, 146.4, 159.9, 162.4 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{28}H_{17}FIN_3S$ 573.01719, found 573.01856.

Compound 8{51}

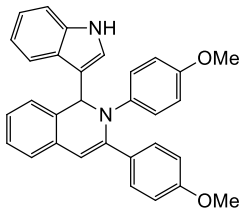


This compound was obtained as a yellow oil in a 75% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.81 (s, 3H), 6.18 (s, 1H), 6.55 (s, 1H), 6.61 (s, 1H), 6.74 (s, 1H), 6.79 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 7.11-7.21 (m, 5H), 7.42-7.47 (m, 3H), 7.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 56.1, 61.8, 84.3, 101.7, 111.7, 112.3, 112.4, 112.8, 113.5, 117.4, 122.9, 123.3, 124.3, 125.2, 125.7, 126.2, 126.3, 126.5,

131.9, 133.9, 134.3, 137.8, 139.6, 147.5, 154.2, 158.9; HRMS (EI) calcd for $C_{29}H_{23}IN_2O_2S$ 590.05249, found 590.05457.

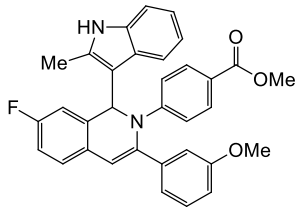
3.6.8. Data for selected 1-(3-indolyl)-1,2-dihydroisoquinolines

Compound 8{2}



This compound was obtained as an orange oil in a 69% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.71 (s, 3H), 6.29 (s, 1H), 6.51 (s, 1H), 6.67-6.74 (m, 5H), 7.04 (d, J = 8.7 Hz, 2H), 7.14-7.28 (m, 7H), 7.44 (d, J = 8.5 Hz, 2H), 7.93 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.6, 62.3, 110.1, 111.6, 113.8, 114.2, 118.9, 119.5, 119.8, 122.1, 123.3, 123.9, 124.3, 125.9, 126.0, 126.1, 127.3, 129.1, 130.7, 131.8, 132.6, 136.6, 141.4, 141.9, 154.9, 159.4; HRMS (EI) calcd for $C_{31}H_{26}N_2O_2$ 458.19942, found 458.20049.

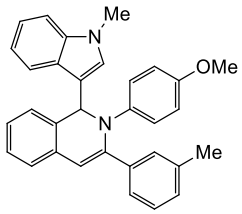
Compound 8{7}



This compound was obtained as a yellow oil in a 29% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.55 (s, 3H), 3.81 (s, 3H), 6.50 (s, 1H), 6.63 (s, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 6.85 (s, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 7.01-7.11 (m, 5H), 7.20 (dd, J = 5.6, 8.2 Hz, 1H), 7.28 (d, J = 10.2 Hz,

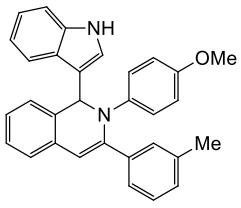
1H), 7.76 (d, J = 8.5 Hz, 3H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 51.9, 55.3, 60.8, 110.6, 112.4, 112.7, 113.3, 113.5, 113.9, 114.6, 114.8, 115.6, 119.5, 119.8, 120.2, 120.8, 121.7, 122.8, 126.3, 126.4, 127.2, 127.9, 129.6, 130.4, 131.8, 135.1, 135.2, 135.4, 139.5, 141.1, 152.4, 159.8, 160.8, 163.3, 167.1 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{33}H_{27}N_2FO_3$ 518.20056, found 518.20193.

Compound 8{20}



This compound was obtained as a yellow oil in a 63% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.55 (s, 3H), 3.66 (s, 3H), 6.29 (s, 1H), 6.58 (s, 2H), 6.66 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 7.02-7.06 (m, 3H), 7.13-7.28 (m, 8H), 7.36 (s, 1H), 8.13 (d, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 32.9, 55.6, 62.2, 109.7, 111.3, 111.4, 114.2, 117.6, 119.3, 119.6, 121.7, 123.8, 124.5, 125.2, 126.1, 127.3, 127.9, 128.0, 128.2, 128.6, 128.7, 132.2, 132.4, 137.4, 137.9, 138.3, 141.5, 142.3, 154.9; HRMS (EI) calcd for $C_{32}H_{28}N_2O$ 456.22015, found 456.22151.

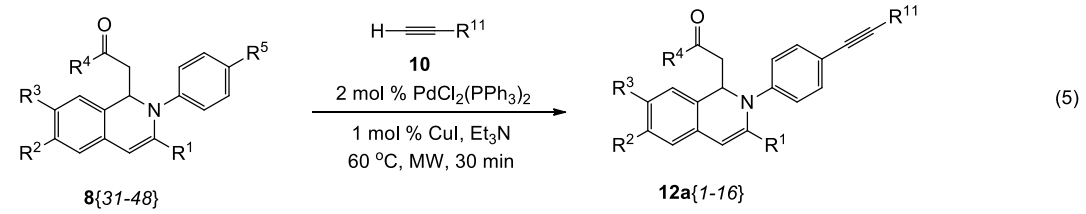
Compound 8{21}



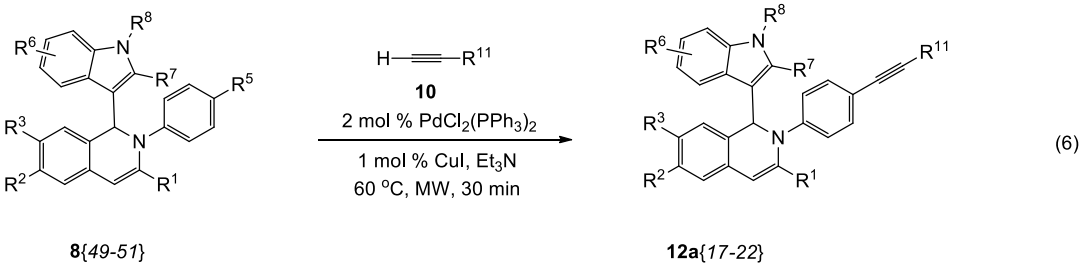
This compound was obtained as a yellow oil in a 72% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.66 (s, 3H), 6.29 (s, 1H), 6.56 (s, 1H), 6.66 (d, J = 8.9

Hz, 2H), 6.73 (s, 1H), 6.95 (d, J = 7.5 Hz, 1H), 7.01-7.05 (m, 3H), 7.12-7.29 (m, 8H), 7.36 (s, 1H), 7.85 (s, 1H), 8.11 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 55.6, 62.2, 111.4, 111.5, 111.6, 114.2, 119.1, 119.6, 119.8, 122.1, 123.3, 123.4, 123.8, 124.5, 125.2, 125.8, 126.1, 126.3, 127.4, 128.3, 128.5, 128.7, 131.9, 132.4, 141.4, 142.3, 154.9; HRMS (EI) calcd for $C_{31}H_{26}N_2O$ 442.20450, found 442.20575.

3.6.9. General procedure for the microwave-assisted Sonogashira coupling to prepare 1,2-dihydroisoquinolines 12a{*1-22*}



(5)



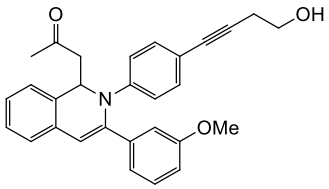
(6)

The 1,2-dihydroisoquinolines **8** (0.8-1.2 mmol), the alkyne **10** (1.2 equiv), 2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI and Et_3N (1.0-2.0 mL) were mixed in a 0.5-2.0 mL Biotage microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave reactor and irradiated so as to ramp the temperature up from room temperature to 60 °C and then held at that temperature for 30 min. The mixture was then cooled down and the solvent

was evaporated. The reaction mixture was purified by either column chromatography or preparative HPLC to afford the corresponding products **12a**{*1-22*}.

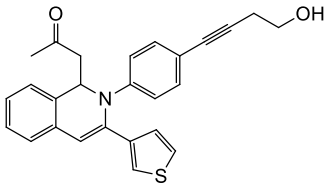
3.6.10. Data for selected 1,2-dihydroisoquinolines prepared via Sonogashira coupling

Compound 12a{2}



This compound was obtained as a yellow oil in a 99% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.54-2.59 (m, 3H), 3.23 (dd, *J* = 8.7, 16.8 Hz, 1H), 3.73-3.75 (m, 5H), 5.55 (dd, *J* = 5.0, 8.6 Hz, 1H), 6.76-6.78 (m, 2H), 6.98 (d, *J* = 8.7 Hz, 3H), 7.04-7.07 (m, 2H), 7.12-7.28 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 31.9, 47.4, 55.4, 60.5, 61.4, 82.7, 85.4, 112.8, 113.3, 114.0, 116.6, 119.7, 121.9, 124.9, 125.4, 127.3, 127.8, 129.7, 131.6, 132.2, 132.6, 138.9, 139.9, 146.9, 159.9, 207.3; HRMS (EI) calcd for $C_{29}H_{27}NO_3$ 437.19908, found 437.20032.

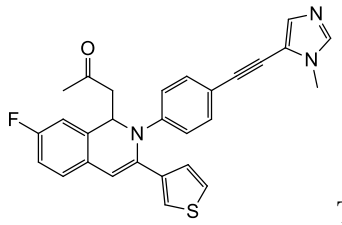
Compound 12a{12}



This compound was obtained as a yellow oil in an 84% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.53 (dd, *J* = 4.9, 16.5 Hz, 1H), 2.62 (t, *J* = 6.2 Hz, 2H), 3.22 (dd, *J* = 8.9, 16.6 Hz, 1H), 3.4 (t, *J* = 6.2 Hz, 2H), 5.48 (dd, *J* = 5.0, 8.9 Hz, 1H), 6.77 (s, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.12-7.23 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 32.1, 47.3, 60.9, 61.4, 82.7, 85.5, 112.4, 116.8, 121.8, 123.4,

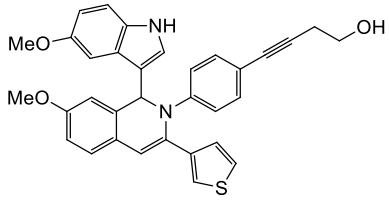
124.9, 125.5, 126.0, 126.2, 127.2, 127.8, 131.5, 132.3, 132.4, 135.6, 139.4, 147.1, 207.5; HRMS (EI) calcd for $C_{26}H_{23}NO_2S$ 413.14501, found 413.14440.

Compound 12a{16}



This compound was obtained as a yellow oil in a 77% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.55 (dd, *J* = 4.7, 16.9 Hz, 1H), 3.26 (dd, *J* = 8.9, 16.9 Hz, 1H), 3.66 (br s, 3H), 5.48 (dd, *J* = 4.8, 8.7 Hz, 1H), 6.78-6.81 (m, 2H), 6.95 (t, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 7.15 (s, 1H), 7.21-7.27 (m, 5H), 7.47-7.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 31.9, 46.9, 60.3, 111.9, 112.5, 112.7, 114.7, 114.9, 115.7, 121.7, 123.4, 126.0, 126.3, 126.4, 127.6, 127.7, 128.6, 128.7, 132.1, 132.2, 132.3, 134.4, 134.5, 134.8, 139.1, 147.6, 160.8, 163.3, 206.9 (extra peaks due to ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{28}H_{22}FN_3OS$ 467.14675, found 467.14783.

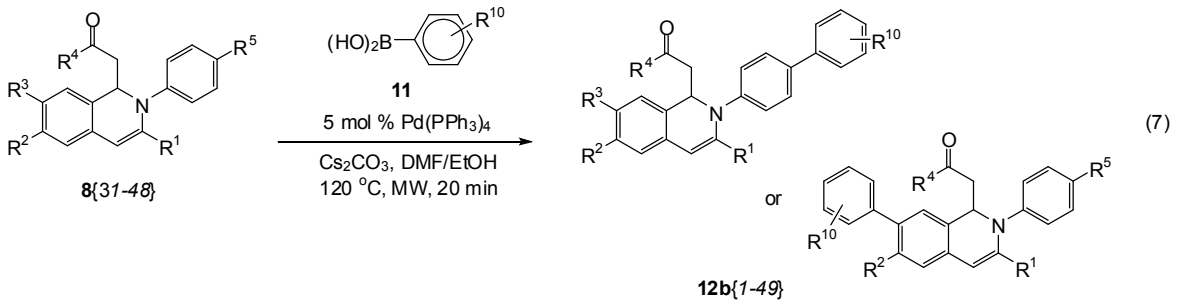
Compound 12a{22}



This compound was obtained as a yellow oil in a 42% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 1H), 2.65 (t, *J* = 6.2 Hz, 2H), 3.78 (br s, 5H), 3.84 (s, 3H), 6.28 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.80 (s, 1H), 6.84 (dt, *J* = 2.4, 8.3 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 1H), 7.05-7.12 (m, 3H), 7.19-7.23 (m, 4H), 7.47 (s, 1H), 7.83 (s, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 24.1, 55.6, 56.1, 61.4, 61.5, 82.8, 85.3, 101.6, 111.8 112.3, 112.6, 113.3, 115.7, 117.6, 120.8, 122.8, 124.2, 124.3, 125.2, 126.1, 126.3, 125.5, 131.9, 132.4, 133.9, 134.3, 139.7, 144.8, 147.3, 154.2, 158.9; HRMS (EI) calcd for $C_{33}H_{28}N_2O_3S$ 532.18210, found 532.18323.

3.6.11. General procedure for the microwave-assisted Suzuki-Miyaura coupling to prepare 1,2-dihydroisoquinolines 12b{*1-51*}.

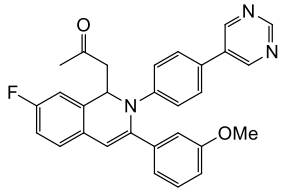


To a 2 mL microwave vial was added the appropriate 1,2-dihydroisoquinoline **8** (0.8-1.2 mmol), boronic acid **11** (1.2 equiv), 1M Cs_2CO_3 (0.2-0.4 mL) and 5 mol % $Pd(PPh_3)_4$ in 1:1 DMF/ethanol. The solution was vigorous stirred for 5 min at room temperature, flushed with argon, and then heated to 120°C under microwave irradiation for 20 min. Upon cooling to room temperature, the resulting reaction mixture was diluted with satd aq Na_2SO_4 and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated,

and purified by either column chromatography or preparative HPLC to afford the corresponding product.

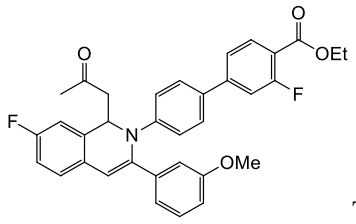
3.6.12. Data for selected 1,2-dihydroisoquinolines prepared via Suzuki-Miyaura coupling

Compound 12b{8}



This compound was obtained as a yellow oil in an 89% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.58 (dd, J = 4.6, 17.3 Hz, 1H), 3.30 (dd, J = 8.9, 17.3 Hz, 1H), 3.75 (s, 3H), 5.59 (dd, J = 4.6, 8.9 Hz, 1H), 6.79-6.82 (m, 3H), 6.96 (td, J = 2.4, 8.6 Hz, 1H), 7.06 (s, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.19-7.27 (m, 4H), 7.33 (d, J = 8.6 Hz, 2H), 8.81 (s, 2H), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 47.0, 55.4, 60.2, 112.4, 112.5, 112.7, 113.1, 114.1, 114.7, 119.6, 122.7, 126.5, 126.6, 127.5, 127.7, 127.8, 129.9, 133.9, 134.6, 134.7, 138.7, 139.3, 147.9, 154.5, 157.0, 160.1, 160.9, 163.4, 206.8 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{29}H_{24}FN_3O_2$ 465.18525, found 465.18637.

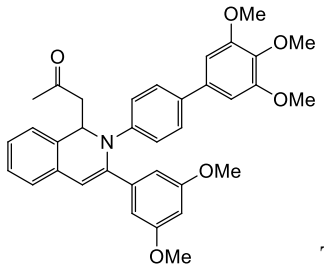
Compound 12b{10}



This compound was obtained as a yellow oil in a 48% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H), 2.17 (s, 3H), 2.59 (dd, J = 4.7, 17.3 Hz,

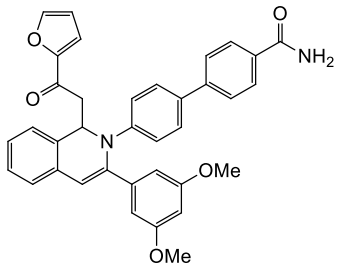
1H), 3.28 (dd, *J* = 8.8, 17.3 Hz, 1H), 3.75 (s, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 5.59 (dd, *J* = 4.9, 8.5 Hz, 1H), 6.78-6.83 (m, 3H), 6.95 (t, *J* = 7.3 Hz, 1H), 7.05 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.10-7.29 (m, 6H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.90 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 31.9, 47.1, 55.4, 60.2, 61.4, 112.5, 112.7, 112.8, 114.0, 114.6, 114.7, 114.8, 114.9,116.8, 116.9, 117.6, 119.6, 121.9, 122.4, 123.9, 126.5, 126.6, 127.7, 127.8, 127.9, 129.9, 132.1, 132.6, 134.6, 134.7, 147.2, 147.3, 147.7, 160.0, 160.9, 161.2, 163.4, 163.8, 164.5, 164.6, 206.9 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{34}H_{29}F_2NO_4$ 553.20645, found 553.20818.

Compound 12b{12}



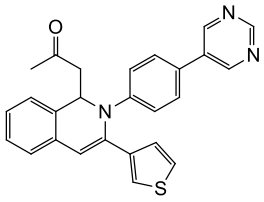
This compound was obtained as a yellow oil in a 100% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.57 (dd, *J* = 4.7, 16.7 Hz, 1H), 3.27 (dd, *J* = 8.9, 16.8 Hz, 1H), 3.73 (s, 6H), 3.85 (s, 3H), 3.87 (s, 6H), 5.58 (dd, *J* = 4.8, 8.9 Hz, 1H), 6.36 (s, 1H), 6.64 (s, 2H), 6.71 (d, *J* = 2.1 Hz, 2H), 6.80 (s, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.12-7.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 47.5, 55.5, 56.3, 60.9, 61.1, 100.6, 104.2, 105.5, 113.1, 113.2, 122.4, 124.9, 125.5, 127.3, 127.5, 127.7, 131.6, 132.6, 135.1, 136.9, 139.9, 140.4, 146.7, 153.5, 160.9, 207.4; HRMS (EI) calcd for $C_{35}H_{35}NO_6$ 565.24643, found 565.24819.

Compound 12b{20}



This compound was obtained as a yellow oil in a 66 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (dd, *J* = 4.0, 15.4 Hz, 1H), 3.60 (s, 6H), 3.77 (dd, *J* = 10.0, 15.4 Hz, 1H), 5.76 (dd, *J* = 4.0, 9.8 Hz, 1H), 6.29 (s, 1H), 6.46 (s, 1H), 6.57 (s, 2H), 6.85 (s, 1H), 7.11-7.19 (m, 5H), 7.25-7.32 (m, 4H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.55 (s, 1H), 7.79 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.6, 55.4, 61.8, 100.8, 105.5, 112.7, 113.3, 118.6, 122.6, 125.0, 125.4, 126.8, 127.4, 127.6, 127.9, 128.0, 131.4, 131.7, 132.4, 133.5, 139.6, 140.3, 144.4, 147.2, 147.4, 153.2, 160.8, 169.3, 187.6; HRMS (EI) calcd for $C_{36}H_{30}N_2O_5$ 570.21546, found 570.121675.

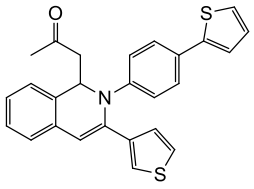
Compound 12b{22}



This compound was obtained as a colorless solid in an 86% yield: mp 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.53 (dd, *J* = 4.6, 16.8 Hz, 1H), 3.31 (dd, *J* = 9.3, 16.8 Hz, 1H), 5.56 (dd, *J* = 4.6, 9.2 Hz, 1H), 6.83 (s, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.16 (td, *J* = 1.9, 7.2 Hz, 1H), 7.17-7.28 (m, 7H), 7.35 (d, *J* = 8.7 Hz, 2H), 8.83 (s, 2H), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 47.3, 60.9, 112.9, 122.7, 123.5,

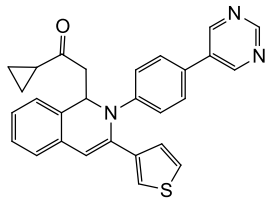
125.0, 125.4, 126.1, 126.2, 127.4, 127.6, 127.9, 131.4, 132.5, 134.0, 135.5, 139.4, 148.3, 154.5, 157.0, 207.4; HRMS (EI) calcd for $C_{26}H_{21}N_3OS$ 423.13965, found 423.14054

Compound 12b{26}



This compound was obtained as a yellow solid in a 52% yield: mp 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.54 (dd, *J* = 4.9, 16.4 Hz, 1H), 3.26 (dd, *J* = 9.1, 16.5 Hz, 1H), 5.50 (dd, *J* = 4.9, 8.9, 1H), 6.78 (s, 1H), 6.99 (t, *J* = 3.8 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 3H), 7.13-7.24 (m, 8H), 7.36 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 47.5, 61.1, 112.1, 115.5, 117.6, 122.4, 122.5, 123.5, 124.1, 124.8, 125.5, 125.9, 126.5, 127.2, 127.8, 128.6, 131.6, 132.3, 135.9, 139.6, 144.5, 146.8, 207.6; HRMS (EI) calcd for $C_{26}H_{21}NOS_2$ 427.10645, found 427.10748.

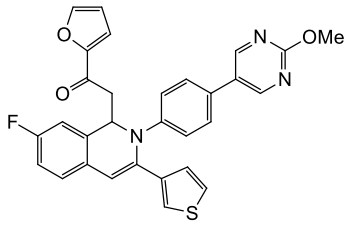
Compound 12b{29}



This compound was obtained as a colorless oil in an 84% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (dt, *J* = 2.9, 7.2 Hz, 2H), 1.10 (t, *J* = 4.2 Hz, 2H), 1.87 (m, 1H), 2.58 (dd, *J* = 4.2, 16.2 Hz, 1H), 3.42 (dd, *J* = 9.7, 16.2 Hz, 1H), 5.58 (dd, *J* = 4.2, 9.7 Hz, 1H), 6.82 (s, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 7.15 (td, *J* = 1.9, 7.0 Hz, 1H), 7.13-7.27 (m, 7H), 7.32 (d, *J* = 8.6 Hz, 2H), 8.81 (s, 2H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 11.7, 22.4, 46.8, 61.2, 112.9, 122.6, 123.6, 124.9, 125.4, 126.1, 127.3, 127.4, 127.5,

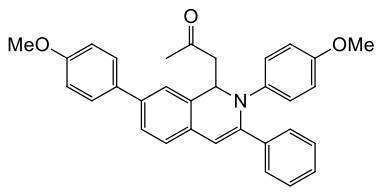
127.9, 131.5, 132.6, 134.0, 135.5, 139.5, 148.3, 154.4, 156.9, 209.6; HRMS (EI) calcd for $C_{28}H_{23}N_3OS$ 449.15532, found 449.15623.

Compound 12b{33}



This compound was obtained as a yellow oil in a 58% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (dd, J = 4.5, 15.2 Hz, 1H), 3.78 (dd, J = 10.0, 15.2 Hz, 1H), 4.03 (s, 3H), 5.66 (dd, J = 4.5, 10.0 Hz, 1H), 6.46 (dd, J = 1.7, 3.6 Hz, 1H), 6.83 (s, 1H), 6.86 (dd, J = 2.5, 8.6 Hz, 1H), 6.94-7.00 (m, 2H), 7.09-7.17 (m, 5H), 7.24-7.28 (m, 3H), 7.52 (d, J = 1.0 Hz, 1H), 8.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.3, 55.2, 61.9, 111.6, 112.5, 112.7, 114.8, 115.0, 118.6, 122.7, 123.6, 125.8, 126.2, 126.4, 126.5, 127.0, 127.8, 127.9, 128.0, 128.4, 133.9, 134.0, 135.3, 139.0, 147.2, 147.3, 153.1, 157.0, 160.9, 163.3, 164.9, 187.4, 112.0, 122.4, 122.5, 123.5, 125.0, 126.2, 127.4, 127.7, 131.1, 131.4, 132.5, 139.5, 143.0, 148.2, 148.9, 164.8, 187.4 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{30}H_{22}FN_3O_3S$ 523.13658, found 523.13767.

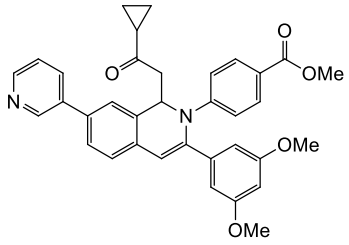
Compound 12b{37}



This compound was obtained as a yellow solid in a 69% yield: mp 91-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.56 (dd, J = 4.7, 16.7 Hz, 1H),

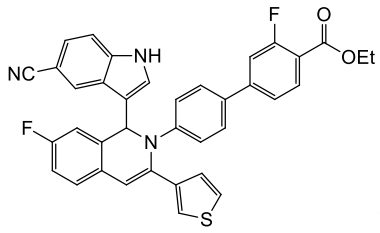
3.29 (dd, *J* = 9.1, 16.6 Hz, 1H), 3.65 (s, 3H), 3.83 (s, 3H), 5.48 (dd, *J* = 4.7, 8.9 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.76 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.20-7.32 (m, 5H), 7.43-7.48 (m, 3H), 7.53 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 47.9, 55.5, 61.9, 111.4, 114.2, 114.4, 123.7, 124.3, 125.0, 125.8, 127.5, 127.9, 128.2, 128.6, 130.5, 132.4, 133.5, 137.7, 139.5, 140.9, 141.1, 155.4, 159.2, 207.7; HRMS (EI) calcd for $C_{32}H_{29}NO_3$ 477.23038, found 477.23188.

Compound 12b{42}



This compound was obtained as a yellow oil in a 61 % yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.8 Hz, 2H), 1.1 (d, *J* = 3.9 Hz, 2H), 1.88 (br s, 1H), 2.75 (dd, *J* = 4.2, 16.7 Hz, 1H), 3.43 (dd, *J* = 8.8, 16.6 Hz, 1H), 3.72 (s, 6H), 3.81 (s, 3H), 5.75 (dd, *J* = 4.6, 8.4 Hz, 1H), 6.36 (s, 1H), 6.66 (s, 2H), 6.87 (s, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.32-7.35 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 8.55 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 11.8, 22.2, 46.8, 51.9, 55.5, 60.2, 100.7, 105.6, 113.6, 115.5, 120.9, 123.3, 123.7, 123.9, 124.1, 125.8, 126.6, 130.7, 131.3, 133.9, 134.2, 136.2, 136.9, 139.2, 140.4, 148.2, 148.6, 151.0, 161.1, 167.1, 208.9; HRMS (EI) calcd for $C_{37}H_{32}N_2O_5$ 560.23111, found 560.23277.

Compound 12b{52}



This compound was obtained as a yellow solid in a 42% yield: mp 136-138 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.39 (t, J = 6.0 Hz, 3H), 4.39 (m, 2H), 6.36 (s, 1H), 6.72 (d, J = 9.4 Hz, 2H), 6.95 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 8.5 Hz, 1H), 7.16-7.47 (m, 12H), 8.40 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 15.1, 61.8, 62.2, 103.7, 113.8, 113.9, 114.3, 114.5, 114.6, 115.4, 115.7, 115.8, 115.9, 118.2, 118.3, 118.9, 121.8, 123.0, 123.1, 123.2, 124.7, 125.7, 126.2, 127.2, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 129.1, 130.0, 130.1, 132.8, 133.2, 133.3, 133.8, 135.7, 135.8, 137.2, 137.3, 140.2, 140.9, 148.2, 148.3, 149.4, 161.9, 162.3, 164.4, 164.8, 164.9, 165.0 112.2, 115.5, 117.6, 114.0, 116.6, 119.7, 121.9, 127.2, 128.3, 128.8, 128.9, 130.6, 130.8, 134.1, 136.8, 137.8, 140.6, 135.9, 139.6, 144.5, 207.6 (extra peaks due to the ^{13}C-^{19}F coupling); HRMS (EI) calcd for $C_{37}H_{25}F_2N_3O_2S$ 613.16355, found 613.16556.

3.7. REFERENCES

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CHAPTER 4

Efficient Microwave-assisted One-pot Three-component Synthesis of Indoles under Sonogashira Conditions

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4.1. ABSTRACT

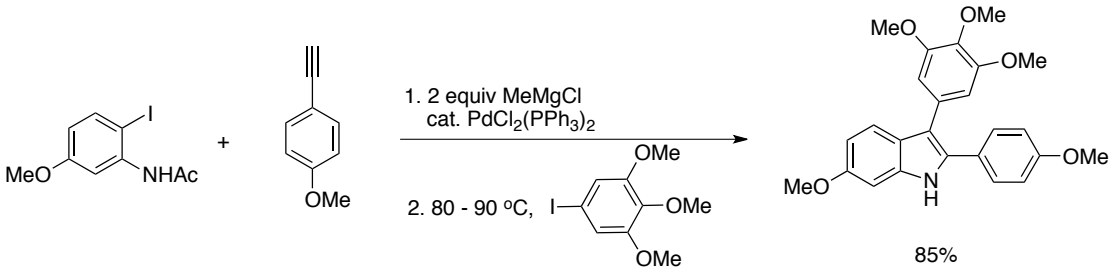
A microwave-assisted, one-pot, three-component coupling reaction for the synthesis of indoles has been developed. The reaction is carried out in two steps under standard Sonogashira coupling conditions from an *N*-substituted/*N,N*-disubstituted 2-iodoaniline and a terminal alkyne, followed by the addition of acetonitrile and an aryl iodide. A variety of polysubstituted indoles have been prepared in moderate to excellent yields using the present method.

4.2. INTRODUCTION

The indole nucleus is a ubiquitous heterocyclic structure found in numerous natural and synthetic compounds with a wide variety of biological activities and considerable pharmaceutical importance.[1] The synthesis of indoles, therefore, has attracted enormous

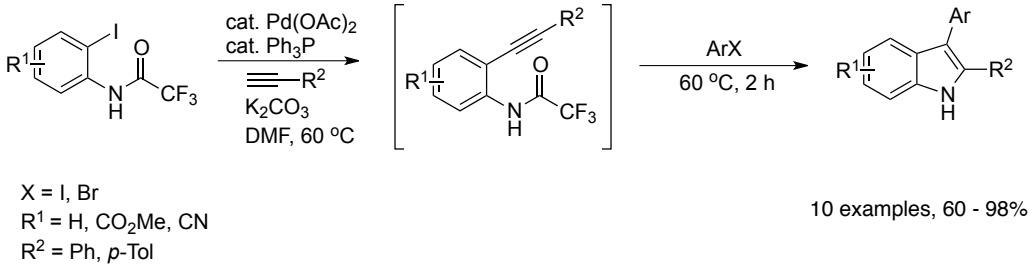
attention from synthetic organic chemists and a substantial number of methods for the preparation of indoles have been developed.[2] Among the methods developed so far, palladium-catalyzed indole syntheses have received extraordinary attention due to the relatively mild reaction conditions employed in these processes and the fact that they usually tolerate a wide variety of functional groups, thus avoiding protecting group chemistry. High regioselectivities and chemical yields are also generally achieved.[2b-d,3] Flynn previously demonstrated a one-pot, two-step synthesis of indoles by consecutive Sonogashira[4] and Cacchi[5] reactions (Scheme 1).[6] However, only one example of this process was reported.

Scheme 1. One-pot synthesis of indoles by Flynn



Lu and co-workers later on reported a one-pot, three-component synthesis of indoles by the same Sonogashira/Cacchi process in which they replaced the aryl iodide in the Cacchi cyclization with an aryl bromide (Scheme 2).[7] However, a significant substituent effect in the three starting components was observed on the rate of reaction. Sluggish reactions were observed, especially when an electron-withdrawing group was present at the *para*-position of either the iodide or the amide moiety of the starting material as in 2'-iodo-trifluoroacetanilide.

Scheme 2. One-pot synthesis of indoles by Lu



It is noteworthy that microwave technology has recently attracted more and more attention from synthetic organic chemists due to the many advantages microwave irradiation affords over conventional heating in chemical transformations, particularly the enormous acceleration of the reaction rate, significant energy savings, as well as high chemical yields and cleaner reactions.[8] Our group has been interested in developing new methodologies for the synthesis of functionalized indoles for almost two decades. We have previously developed a palladium-catalyzed heteroannulation reaction of internal alkynes and 2-iodoanilines known as the Larock indole synthesis;[9] and the electrophilic cyclization of *N,N*-dialkyl-2-(1-alkynyl)anilines induced by halide,[10] sulfur or selenium electrophiles to generate indoles.[11] As a continuation of our long-term interest in indole synthesis, we hereby report a microwave-assisted, one-pot, three-component reaction to synthesize 2,3-disubstituted indoles under Sonogashira coupling conditions.

4.3. RESULTS AND DISCUSSION

Our group previously developed synthetic protocols for the preparation of 3-iodo-,[10] 3-sulfenyl-, and 3-selenylindoles[11] by the electrophilic cyclization of *N,N*-dialkyl-2-(1-alkynyl)anilines by iodine or sulfenyl/selenyl chlorides. While preparing the starting *N,N*-

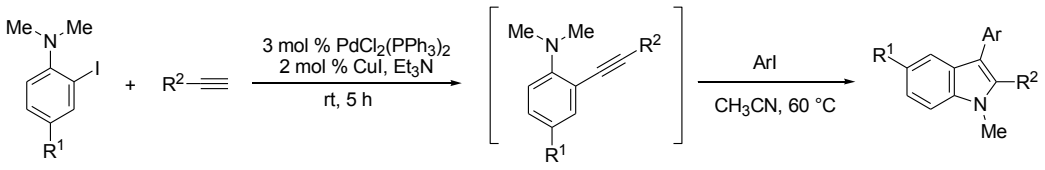
dialkyl-2-(1-alkynyl)anilines for this process, we discovered an interesting solvent effect during the Sonogashira coupling process. When the coupling of *N,N*-dialkyl-2-iodoanilines and terminal alkynes was carried out in Et_3N, the corresponding internal alkynes were generally obtained as a single product in high chemical yield. On the other hand, in the presence of a polar solvent, such as CH_3CN or DMF, with only 10 equiv of Et_3N present, a significant amount of an indole was obtained, alongside the desired *N,N*-dialkyl-2-(1-alkynyl)anilines. The indole is apparently generated by the palladium-catalyzed cyclization of the Sonogashira coupling product and any unreacted *N,N*-dialkyl-2-iodoaniline.

Cacchi has previously developed a similar cyclization between 2-(1-alkynyl)trifluoroacetanilides and aryl iodides in the presence of inorganic bases, such as K_2CO_3 or Cs_2CO_3.[5a,d,e,g] In the Cacchi reaction, the reaction outcome was influenced by both the base and the nature of the nitrogen nucleophile. Employing Et_3N as the base gave only low yields. On the other hand, a trifluoroacetamido group plays a key role in this cyclization. When a free amino or acetamido group is used, no cyclization occurs and only the starting alkynes are recovered. In our case, due to the high nucleophilicity of the *N,N*-dialkylamino moiety, intramolecular cyclization takes place more readily.

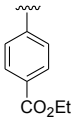
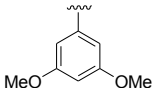
In our view, this one-pot cyclization approach provides an ideal protocol for parallel library synthesis. Thus, a one-pot, three-component coupling reaction was carried out using *N,N*-dimethyl-2-iodoaniline, phenylacetylene and ethyl 4-iodobenzoate (Table 1, entry 1). The Sonogashira coupling took place smoothly in Et_3N at room temperature, while efficient further cyclization required a higher reaction temperature (60 °C) and the addition of a polar solvent, such as CH_3CN. When a more bulky alkyne, such as 3,5-dimethoxyphenylacetylene,

and an electron-rich aryl iodide, such as 2-iodothiophene, were employed in this coupling, a considerably longer reaction time was needed for complete cyclization (Table 1, entry 2).

Table 1. One-pot synthesis of indoles under Sonogashira coupling conditions[a]



1 **2** **3**

entry	**1**	R^1	R^2	Ar	time (h)		**3**	% yield[b]
					Step 1	Step 2		
1	**1a**	H	C_6H_5		5	4	**3a**	82
2	**1b**	Br			5	12	**3j**	83

[a] Representative procedure: Step 1) 2-Iodoaniline **1** (0.500 mmol), terminal alkyne **2** (0.525 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), CuI (0.010 mmol), and 3 mL of Et_3N were mixed in a sealed 4-dram vial. The reaction was stirred at room temperature for the indicated time. Step 2) Aryl iodide (0.550 mmol) and 3 mL of CH_3CN were added to the reaction mixture of Step 1. The resulting mixture was stirred at 60 °C for the indicated time. [b] Isolated yields of indole product after column chromatography.

In order to enhance the reaction rate of this one-pot coupling/cyclization process for the purpose of developing a high-throughput parallel synthetic protocol, microwave technology has been employed. To our delight, the entire process was dramatically accelerated by

microwave irradiation. Both of the reactions were completed in less than an hour in yields comparable to those obtained previously.

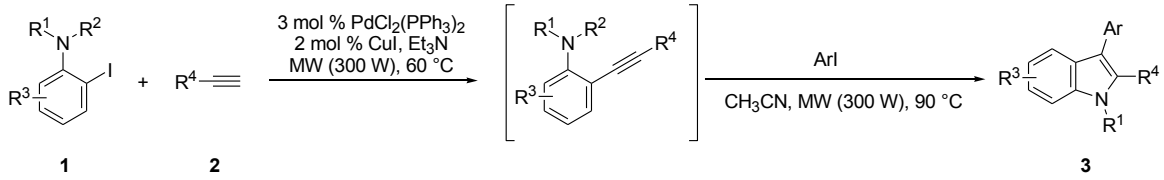
Encouraged by these results, we next explored the scope of this one-pot, two-step approach to substituted indoles. Both the Sonogashira coupling and cyclization take place smoothly when electron-rich aryl acetylenes are used (Table 2; entries 2, 4 and 6). A longer reaction time is necessary for complete conversion for both the Sonogashira and cyclization steps, when an electron-deficient aryl acetylene is employed (Table 2, entry 3). Smooth couplings were also observed when aliphatic acetylenes are employed (Table 2; entries 5, 7 and 8). When 2-methoxyphenylacetylene is used, the steric bulkiness induced by the 2-methoxy group requires a longer reaction time for cyclization (Table 2, entry 9). A free hydroxyl group in the alkyne is not well accommodated by this coupling process as only a 33% yield of the desired indole product was obtained (Table 2, entry 16).

No significant electronic effect has been observed in either the 2-iodoanilines or the aryl iodides employed. Both electron-withdrawing and electron-releasing groups are readily accommodated in these two components. An extra equivalent of aryl iodide was employed in the coupling processes utilizing *N,N*-dimethyl-4-bromo-2-iodoaniline in order to suppress any interference by the bromo moiety in the cyclization step (Table 2, entries 10-13). Both benzyl bromide and allyl acetate have been examined in this coupling process in place of the aryl iodide. However, none of the desired cyclization product was obtained in either case. The two alkyl groups present on the aniline nitrogen play a crucial role in the success of the overall process. Only Sonogashira coupling product was obtained when either 2-iodoaniline

or *N*-methyl-2-iodoaniline were employed, which is in good agreement with our previous experience with such Sonogashira processes.[10,11]

Besides *N,N*-dialkyl-2-iodoanilines, 2'-iodo-trifluoroacetanilides can also be employed in the current microwave-irradiated process (Table 2, entries 18-24). As described earlier using conventional heating, the addition of an inorganic base is necessary for the success of this cyclization. In addition, a slightly higher reaction temperature is needed for efficient cyclization.

Table 2. Microwave-assisted, one-pot synthesis of indoles under Sonogashira coupling conditions[a]



1 **2** **3**

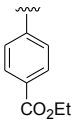
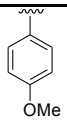
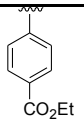
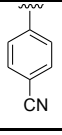
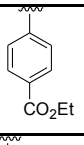
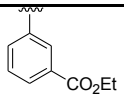
entry	**1**	R^1	R^2	R^3	R^4	Ar	time (min)		**3**	% yield[b]
							Step 1	Step 2		
1	**1a**	Me	Me	H	C_6H_5		20	30	**3a**	86
2	**1a**	Me	Me	H			20	20	**3b**	86
3	**1a**	Me	Me	H			30	50	**3c**	77
4	**1a**	Me	Me	H			20	30	**3d**	78

Table 2 continued.

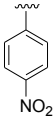
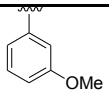
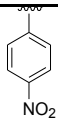
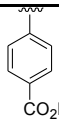
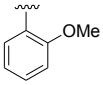
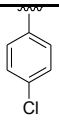
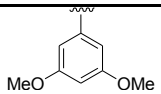
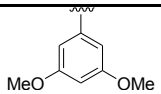
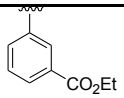
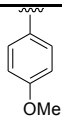
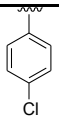
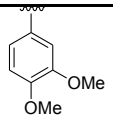
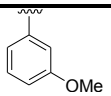
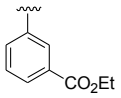
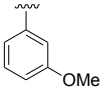
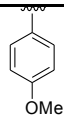
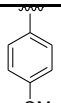
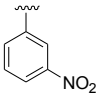
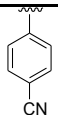
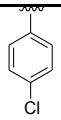
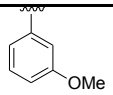
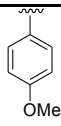
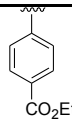
5	**1a**	Me	Me	H			20	30	**3e**	91
6	**1a**	Me	Me	H		C_6H_5	20	30	**3f**	91
7	**1a**	Me	Me	H			20	30	**3g**	72
8	**1a**	Me	Me	H			20	30	**3h**	63
9	**1a**	Me	Me	H			20	50	**3i**	87
10[c]	**1b**	Me	Me	4-Br			20	30	**3j**	74
11[c]	**1b**	Me	Me	4-Br			20	30	**3k**	76
12[c]	**1b**	Me	Me	4-Br			20	30	**3l**	85
13[c]	**1b**	Me	Me	4-Br	C_6H_5		20	30	**3m**	79
14	**1c**	Me	Me	4-Me	C_6H_5		30	30	**3n**	68
15	**1c**	Me	Me	4-Me			30	30	**3o**	94
16	**1c**	Me	Me	4-Me			30	30	**3p**	33

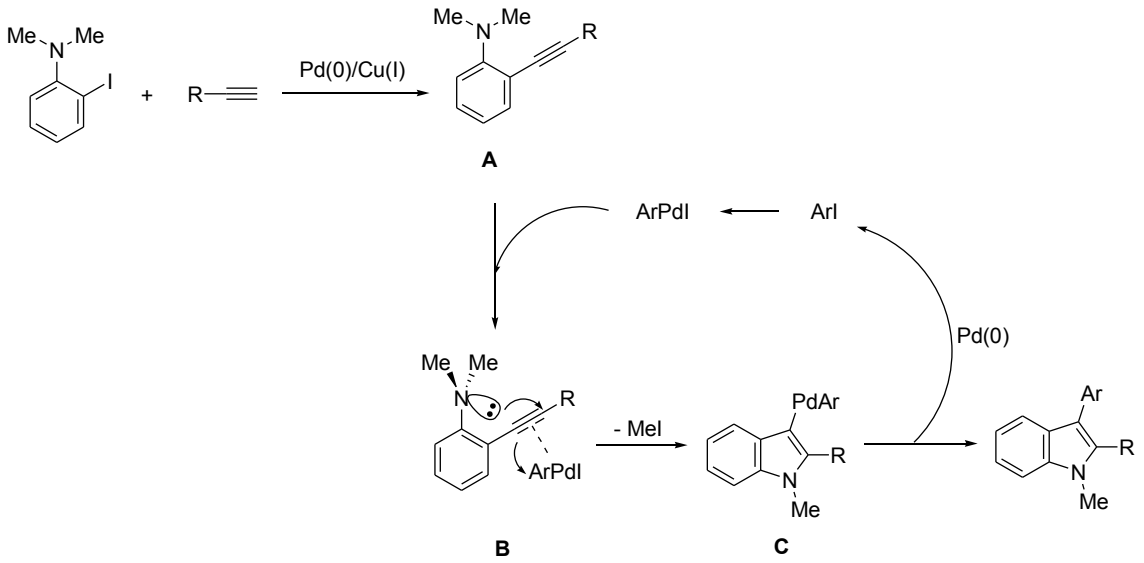
Table 2 continued.

17	**1d**	Me	Me	4-CO_2Me			30	30	**3q**	70
18	**1e**	H		H	C_6H_5		30	30 [d]	**3r**	93
19	**1e**	H		H			30	30 [d]	**3s**	82
20	**1f**	H		4-Me			30	30 [d]	**3t**	88
21	**1f**	H		4-Me		C_6H_5	30	30 [d]	**3u**	66
22	**1f**	H		4-Me			30	30 [d]	**3v**	67
23	**1g**	H		4-CO_2Me	C_6H_5		30	30 [d]	**3w**	76
24	**1g**	H		4-CO_2Me			30	30 [d]	**3x**	60

[a] Representative procedure: Step 1) 2-Iodoaniline **1** (0.500 mmol), terminal alkyne **2** (0.525 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), CuI (0.010 mmol), and 3 mL of Et_3N were mixed in a sealed 20 mL microwave vial. The reaction was stirred at 60 °C under microwave (300 W) irradiation for the indicated time. Step 2) Aryl iodide (0.550 mmol) and 3 mL of CH_3CN were added to the reaction mixture of Step 1. The resulting mixture was stirred at 90 °C under microwave irradiation (300 W) for the indicated time. [b] Isolated yields of indole product after column chromatography. [c] An extra equivalent of aryl iodide was employed in Step 2). [d] Step 2) was carried out at 100 °C with the addition of Cs_2CO_3 (3 equiv).

As mentioned above, this overall process involves two steps (Scheme 3). The first step is a Sonogashira coupling to generate the *N,N*-dialkyl-2-(1-alkynyl)aniline **A**. The aryl iodide is added upon completion of the Sonogashira coupling. Oxidative addition of the aryl iodide to Pd(0) affords an electrophilic ArPdI species, which activates the alkyne triple bond of **A** by coordination to form a π-palladium complex **B**, which subsequently undergoes intramolecular *trans*-aminopalladation by a 5-*endo-dig* cyclization, affording the indole-containing Pd(II) intermediate **C**. The 2,3-disubstituted indole is generated after reductive elimination.

Scheme 3. A proposed mechanism for the one-pot, two-step indole synthesis.



4.4. CONCLUSIONS

In summary, an efficient, microwave-assisted, one-pot, three-component reaction for the synthesis of polysubstituted indoles has been developed. A variety of functionalities, such as nitro, ester, hydroxyl, cyano, and halide groups are tolerated in this

coupling/cyclization process. The desired indoles have been obtained in moderate to excellent overall yields. This protocol provides an ideal synthetic approach for the parallel synthesis of an indole library. Further examination of the current reaction conditions for a one-pot, four-component synthesis of indoles, as well as other biologically interesting heterocycles, is underway in our laboratory.

4.5. ACKNOWLEDGEMENTS

We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Center of Excellence for Chemical Methodologies and Library Development (P50 GM069663) for financial support of this project. We also thank Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts.

4.6. EXPERIMENTAL

4.6.1. General remarks

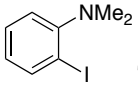
All reactions were carried out in sealed 20 mL oven-dried Biotage microwave vials. All commercially obtained chemicals were used as received without further purification unless otherwise indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively, using $CDCl_3$, acetone-d_6 or DMSO-d_6 as solvents. The chemical shifts of the ^{1}H NMR and ^{13}C NMR spectra are reported relative to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^{1}H NMR and δ 77.23 ppm for the ^{13}C NMR), acetone-d_6 (2.05 ppm for the ^{1}H NMR and δ 29.92 ppm for the ^{13}C NMR) or DMSO-d_6 (2.50 ppm for the ^{1}H

NMR and δ 39.51 ppm for the ^{13}C NMR). The high resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at a voltage of 70 eV. The melting points are uncorrected.

4.6.2. General procedure for preparation of the *N,N*-dimethyl-2-iodoanilines

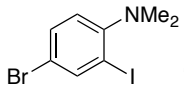
These compounds were prepared according to a procedure reported by Cadogan.[12] To a solution of the corresponding 2-iodoaniline (2.0 mmol) and iodomethane (0.85 g, 6.0 mmol) in DMF (10 mL) was added K_2CO_3 (0.55 g, 4.0 mmol). The resulting mixture was stirred at room temperature for 48 h. Water (10 mL) was added to the reaction mixture and the resulting solution was extracted with diethyl ether (3 × 10 mL). The organic layers were combined and washed with water to remove any remaining DMF and dried over anhydrous $MgSO_4$. The solvent was removed under vaccum and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

***N,N*-Dimethyl-2-iodoaniline (1a)**



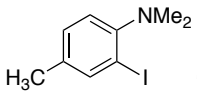
This compound was obtained as a yellow oil in an 81% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 2.76 (s, 6H), 6.77 (dt, J = 7.6, 1.5 Hz, 1H), 7.09 (dd, J = 7.8, 1.5 Hz, 1H), 7.31 (dt, J = 7.6, 1.5 Hz, 1H), 7.84 (dd, J = 7.8, 1.5 Hz, 1H). The ^1H NMR spectral data are in good agreement with the literature data.[10a]

***N,N*-Dimethyl-4-bromo-2-iodoaniline (1b)**



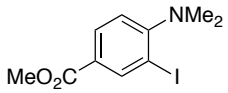
This compound was obtained as a light red oil in an 81% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 6H), 6.92 (d, J = 8.5 Hz, 1H), 7.40 (dd, J = 8.5, 2.4 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[11]

***N,N*,4-Trimethyl-2-iodoaniline (1c)**



This product was obtained as an orange liquid in a 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.72 (s, 6H), 6.99 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature.[10b]

4.6.3. Preparation of methyl 4-dimethylamino-3-iodobenzoate (1d)



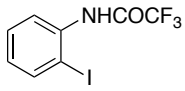
This compound was prepared according to a procedure reported by Larock.[13] The product was obtained as a colorless oil in a 44% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 6H), 3.85 (s, 3H), 6.98 (d, J = 8.4 Hz, 1H), 7.92 (dd, J = 8.4, 2.0 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[13]

4.6.4. General procedure for preparation of the *N*-trifluoroacetyl-2-iodoanilines

These compounds were prepared according to a procedure reported by Srinivasan.[14] To a solution of the corresponding 2-iodoaniline (4.3 mmol) and triethylamine (0.63 mL, 4.55 mmol) in THF (11 mL) at -15 ºC was slowly added trifluoroacetic anhydride (0.6 mL, 4.3 mmol) in 6.5 mL of THF. The resulting mixture was stirred for 1 h and then allowed to

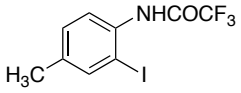
warm to room temperature and stirred for 16 h. The reaction mixture was then poured into a separatory funnel containing water (115 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

_N_-Trifluoroacetyl-2-iodoaniline (1e)



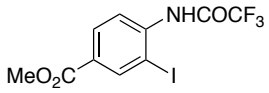
This product was obtained as a white solid in a 96% yield: mp 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (t, J = 7.0 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.29 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[15]

_N_-Trifluoroacetyl-2-iodo-4-methylaniline (1f)



This product was obtained as a pink solid in a 95% yield: mp 84-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 7.19 (d, J = 8.1 Hz , 1H), 7.66 (s, 1H), 8.01 (d, J = 8.3 Hz , 1H), 8.21 (s, 1H).

Methyl 4-(_N_-trifluoroacetamino)-3-iodobenzoate (1g)

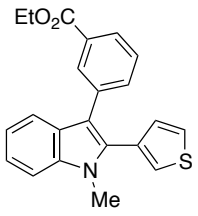


This product was obtained as a white solid in an 88% yield: mp 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 8.06 (dd, J = 1.9, 8.6 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.50 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[16]

4.6.5. General procedure for the microwave-assisted, one-pot synthesis of 1-methylindoles

The 2-iodoaniline **1** (0.500 mmol), a terminal alkyne **2** (0.525 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), CuI (0.010 mmol), and 3 mL of Et_3N were mixed in a sealed 20 mL microwave vial. The reaction mixture was stirred at 60 °C under microwave (300 W) irradiation for 20 min or until disappearance of the starting material as monitored by thin layer chromatography. To the reaction mixture was added the aryl iodide (0.550 mmol) and 3 mL of CH_3CN at room temperature. The resulting mixture was then stirred at 90 °C under microwave irradiation for 30 min or until disappearance of the starting material as monitored by thin layer chromatography. The reaction mixture was diluted by 10 mL of diethyl ether and washed with brine (10 mL). The aqueous phase was extracted with diethyl ether (2 × 5 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

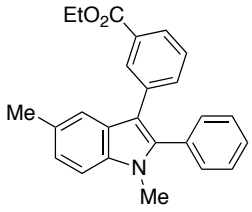
Ethyl 3-[1-methyl-2-(thiophen-3-yl)-1*H*-indol-3-yl]benzoate (3d)



This product was obtained as a yellow oil in a 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.69 (s, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 7.00 (dd, *J* = 1.2, 4.9 Hz, 1H), 7.17-7.22 (m, 2H), 7.28-7.35 (m, 3H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.45 (dd, *J* = 6.2, 1.4 Hz, 1H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR

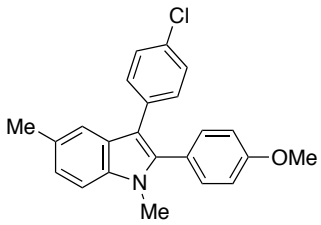
(100 MHz, $CDCl_3$) δ 14.5, 31.1, 60.9, 109.8, 114.8, 119.4, 120.6, 122.6, 126.0, 126.3, 126.8, 126.9, 128.4, 129.6, 130.7, 130.9, 131.76, 133.2, 134.1, 135.8, 137.4, 166.9; HRMS (EI) calcd for $C_{22}H_{19}NO_2S$ 361.11370, found 361.11422.

Ethyl 3-(1,5-dimethyl-2-phenyl-1*H*-indol-3-yl)benzoate (3n)



This product was obtained as a yellow oil in a 68% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.48 (s, 3H), 3.63 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 7.13 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 4H), 7.36 (m, 3H), 7.40 (dt, *J* = 7.7, 1.3 Hz, 1H) 7.56 (s, 1H), 7.84 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.07 (t, *J* = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 21.8, 31.1, 60.9, 109.5, 113.8, 119.0, 124.1, 126.7, 127.1, 128.30, 128.33, 128.6, 129.9, 130.6, 131.0, 131.2, 131.9, 134.3, 135.9, 138.4, 166.9; HRMS (EI) calcd for $C_{25}H_{23}NO_2$ 369.1729, found 369.1732.

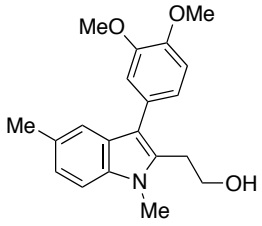
3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1,5-dimethyl-1*H*-indole (3o)



This product was obtained as a colorless solid in a 94% yield: mp 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.61 (s, 3H), 3.82 (s, 3H), 6.90 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.19-7.22 (m, 6H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 31.1, 55.5, 109.5, 113.3, 114.2, 118.9, 123.9,

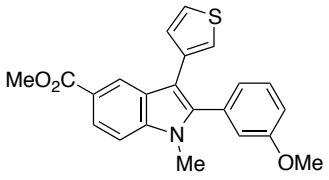
124.0, 127.1, 128.5, 129.8, 131.0, 131.1, 132.4, 134.3, 135.9, 138.1, 159.7; HRMS (EI) calcd for $C_{23}H_{20}ClNO$ 361.1233, found 361.1241.

2-([3-(3,4-Dimethoxyphenyl)]-1,5-dimethyl-1*H*-indol-2-yl)ethanol (3p)



This product was obtained as a light brown oil in a 33% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (br s, 1H), 2.42 (s, 3H), 3.11 (t, *J* = 6.8 Hz, 2H), 3.74 (s, 3H), 3.81 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 6.96 (d, *J* = 8.2 Hz, 1H), 7.01 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.5, 30.2, 56.1, 62.4, 108.9, 111.6, 113.6, 115.4, 118.8, 122.2, 123.3, 127.7, 128.3, 129.2, 133.4, 135.4, 147.7, 149.0; HRMS (EI) calcd for $C_{20}H_{23}NO_3$ 325.1678, found 325.1685.

Methyl 2-(3-methoxyphenyl)-1-methyl-3-(thiophen-3-yl)-1*H*-indole-5-carboxylate (3q)

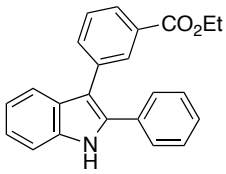


This product was obtained as a yellow oil in a 70% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.75 (s, 3H), 3.94 (s, 3H), 6.87 (s, 1H), 6.86 (m, 3H), 7.18-7.27 (m, 1H), 7.30-7.42 (m, 3H), 8.00 (d, *J* = 8.6 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.3, 52.0, 55.4, 109.4, 111.8, 114.5, 116.5, 121.8, 122.3, 122.8, 123.4, 123.8, 124.9, 126.6, 128.8, 129.8, 132.8, 134.5, 138.9, 139.7, 159.7, 168.2; HRMS (EI) calcd for $C_{22}H_{19}NO_3S$ 377.1086, found 377.1095.

4.6.6. General procedure for the microwave-assisted, one-pot synthesis of 1*H*-indoles

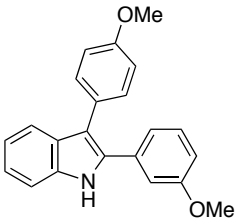
In an oven-dried 20 mL microwave vial, *N*-trifluoroacetyl-2-iodoaniline (0.6 mmol) was dissolved in Et_3N (4 mL), then $PdCl_2(PPh_3)_2$ (12.6 mg, 0.018 mmol, 3 mol %), CuI (2.3 mg, 0.012 mmol, 2 mol %) and the alkyne (0.63 mmol) were added. The vial was flushed with Ar, sealed and stirred at 60 ºC under microwave irradiation for 20-30 min. The resulting mixture was dissolved in CH_3CN (4 mL), ArI (0.66 mmol) and Cs_2CO_3 (586 mg, 1.8 mmol) were added, and the vial was flushed with Ar, sealed and stirred at 100 ºC under microwave irradiation for 30 min. To the reaction mixture were added ethyl acetate (10 mL) and brine (10 mL) and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as eluent.

Ethyl 3-(2-phenyl-1*H*-indol-3-yl)benzoate (3r)



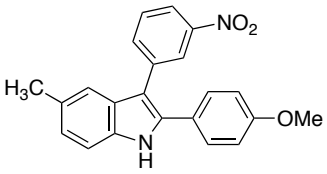
This product was obtained as a yellow solid in a 93% yield: mp 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.22-7.29 (m, 4H), 7.37-7.43 (m, 4H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 8.21 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 61.1, 111.2, 114.1, 119.6, 120.8, 123.0, 127.6, 128.0, 128.4, 128.7, 128.8, 128.9, 131.0, 131.3, 132.5, 134.8, 134.9, 135.7, 136.1, 167.0; HRMS (EI) calcd for $C_{23}H_{19}NO_2$ 341.1416, found 341.1426.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-1*H*-indole (3s)



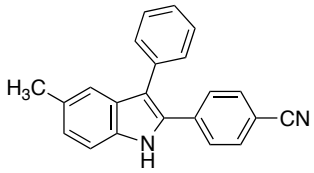
This product was obtained as a yellow oil in an 82% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.79 (s, 3H), 6.79 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.89-6.99 (m, 4H), 7.09-7.22 (m, 3H), 7.32-7.37 (m, 3H), 7.62 (d, *J* = 7.9 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.4, 111.1, 113.5, 113.6, 114.2, 115.0, 119.8, 120.5, 122.8, 127.5, 129.1, 129.9, 131.4, 133.7, 134.2, 135.9, 158.3, 159.7; HRMS (EI) calcd for $C_{22}H_{19}NO_2$ 329.1416, found 329.1425.

2-(4-Methoxyphenyl)-5-methyl-3-(3-nitrophenyl)-1*H*-indole (3t)



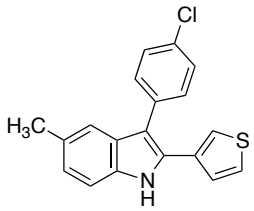
This product was obtained as an orange oil in an 88% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.77 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.20-7.28 (m, 3H), 7.40-7.46 (m, 2H), 7.65 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 8.23 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 55.4, 110.9, 111.3, 114.6, 118.3, 120.9, 124.5, 124.6, 124.7 128.4, 129.4, 129.7, 130.4, 134.2, 135.6, 136.4, 137.7, 148.7, 159.7; HRMS (EI) calcd for $C_{22}H_{18}N_2O_3$ 358.1317, found 358.1325.

4-(5-Methyl-3-phenyl-1*H*-indol-2-yl)benzonitrile (3u)



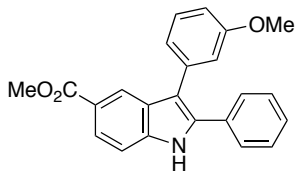
This product was obtained as a yellow solid in a 66% yield: mp 219-221 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 2.37 (s, 3H), 7.02 (d, J = 8.2 Hz, 1H), 7.29-7.39 (m, 7H), 7.59 (s, 4H), 10.53 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 21.6, 110.7, 111.8, 116.7, 117.9, 119.0, 119.5, 125.5, 127.1, 128.9, 129.2, 129.4, 130.6, 132.5, 132.6, 135.6, 135.8, 138.0; HRMS (EI) calcd for $C_{22}H_{16}N_2$ 308.1313, found 308.1323.

3-(4-Chlorophenyl)-5-methyl-2-(thiophen-3-yl)-1*H*-indole (3v)



This product was obtained as a light brown oil in a 67% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.00 (d, J = 4.7 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.22-7.27 (m, 3H), 7.34 (s, 1H), 7.37 (s, 4H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 110.7, 113.5, 119.0, 122.1, 124.6, 126.3, 127.1, 128.9, 130.1, 130.4, 130.5, 131.7, 132.3, 133.5, 133.9, 134.1; HRMS (EI) calcd for $C_{19}H_{14}ClNS$ 323.0535, found 323.0542.

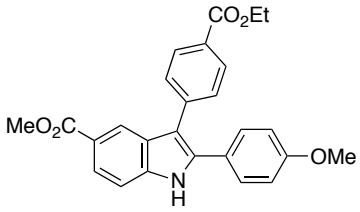
Methyl 3-(3-methoxyphenyl)-2-phenyl-1*H*-indole-5-carboxylate (3w)



This product was obtained as an ivory solid in a 76% yield: mp 211-213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (s, 3H), 3.83 (s, 3H), 6.87 (s, 1H), 6.93 (d, J

= 7.9 Hz, 2H), 7.34-7.42 (m, 4H), 7.49 (d, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 8.15 (s, 1H), 12.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.7, 54.9, 111.5, 111.9, 114.2, 114.8, 115.4, 121.1, 122.1, 122.9, 127.6, 127.9, 128.2, 128.5, 129.9, 131.7, 135.7, 135.8, 138.5, 159.4, 167.0; HRMS (EI) calcd for $C_{23}H_{19}NO_3$ 357.1365, found 357.1374.

Methyl 3-[4-(ethoxycarbonyl)phenyl]-2-(4-methoxyphenyl)-1*H*-indole-5-carboxylate (3x)



This product was obtained as an ivory solid in a 60% yield: mp 264-266 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (t, *J* = 7.0 Hz , 3H), 3.78 (s, 3H), 3.83 (s, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 8.16 (s, 1H), 12.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 51.7, 55.2, 60.6, 111.4, 112.3, 114.2, 114.8, 120.5, 121.3, 122.9, 127.2, 127.5, 129.6, 129.7, 136.8, 138.6, 139.9, 159.3, 165.6, 166.9; HRMS (EI) calcd for $C_{26}H_{23}NO_5$ 429.1576, found 429.1588.

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CHAPTER 5

Efficient Microwave-assisted One-pot Three-component Synthesis of 2,3-Disubstituted Benzofurans under Sonogashira Conditions. Approaches Towards Total Syntheses Amurensin H, Gnetuhainin B, and Gnetuhainin F

Manuscript to be submitted to *Tetrahedron*

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5.1. ABSTRACT

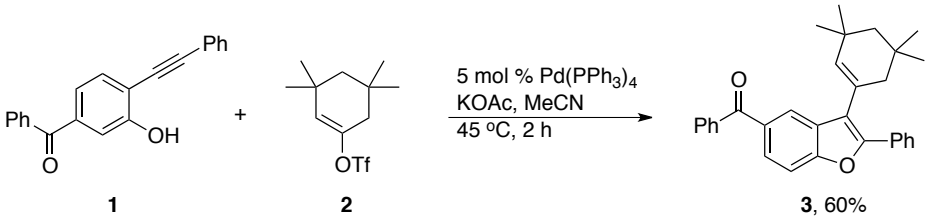
An efficient one-pot method for the synthesis of 2,3-disubstituted benzo[*b*]furans from commercially available 2-iodophenols, terminal acetylenes and aryl iodides has been developed utilizing Sonogashira reaction conditions. After an initial Sonogashira coupling of the 2-iodophenol with a terminal alkyne, cyclization involving the aryl iodide provides the 2,3-disubstituted benzo[*b*]furan in good to excellent yields. The use of microwave irradiation shortens the reaction times and minimizes the side products. This methodology is especially useful for the construction of libraries of highly substituted benzo[*b*]furans and their analogues.

5.2. INTRODUCTION

Benzo[*b*]furans have been studied extensively due to the high potential biological and pharmaceutical activity of this ring system.[1] Thus, numerous synthetic methods to access this

important scaffold have been developed.[2] Among others, Pd-catalyzed reactions have proven to be highly efficient and convenient for the synthesis and functionalization of benzo[*b*]furans. Several review articles and books have been published that summarize previous and recent developments in this area.[3] In 1996, while developing a method for the synthesis of 2-substituted benzo[*b*]furans, Cacchi and co-workers reported that 2-alkynylphenol **1** in the presence of vinylic triflate **2** and a palladium catalyst can undergo a cyclization to the corresponding 2,3-disubstituted benzo[*b*]furan **3** in a 60% yield (Scheme 1).[4]

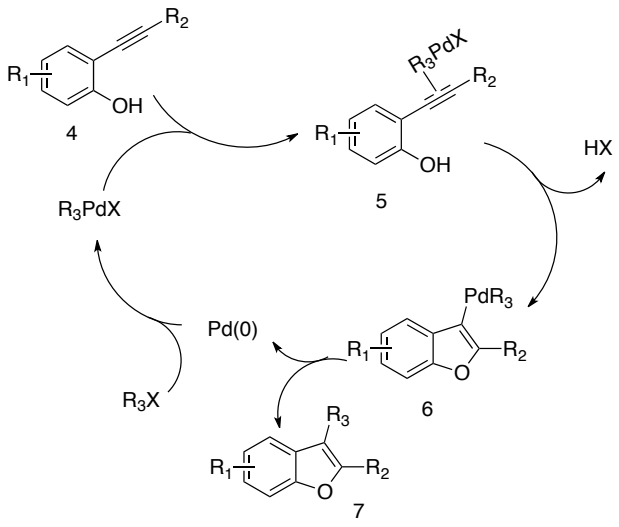
Scheme 1. Synthesis of a 2,3-disubstituted benzofuran from a 2-alkynylphenol



1 **2** **3**, 60%

Cacchi and co-workers proposed that this process most likely proceeds through a vinylic palladium intermediate, generated *in situ* from the vinylic triflate *via* oxidative addition to Pd(0) (Scheme 2). This "R^3PdX" species can act as a Lewis acid and coordinate with the triple bond of the 2-alkynylphenol **4** to form an alkyne-organopalladium complex **5**, which thus facilitates nucleophilic attack of the oxygen atom across the activated carbon-carbon triple bond to form the oxypalladation adduct **6**, which, after reductive elimination, forms the 2,3-disubstituted benzo[*b*]furan **7** and regenerates the Pd(0) catalyst.

Scheme 2. Proposed reaction mechanism

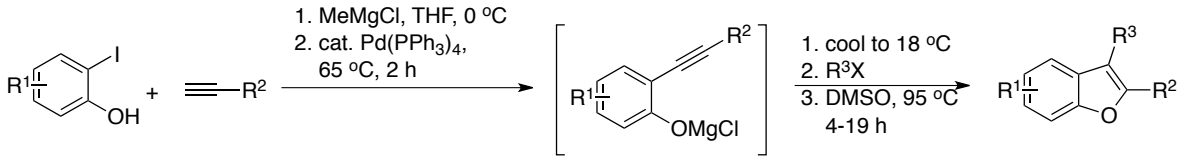


To access the starting 2-alkynylphenols, a 3-step route has been employed in most cases. First, the OH group is protected with an appropriate protecting group (*e.g.* acetyl), then the Sonogashira coupling is conducted, and, following deprotection of the phenol, the desired 2-alkynylphenol is obtained, generally in moderate yields. The major problem with the direct Sonogashira reaction between a 2-iodophenol and a terminal alkyne is that the coupling is often inefficient. In addition, if basic reaction conditions are employed, 3*H*-benzofurans are often formed as products, instead of the desired 2-alkynylphenol.

In order to transform the Cacchi's process into a three-component process, Flynn and co-workers employed MeMgCl as an additive to mask the phenol oxygen of the iodophenol (**8**). They were then able to conduct an efficient Sonogashira coupling and subsequent cyclization to a benzofuran (**10**) without isolating the corresponding 2-alkynylphenol (**9**) (Scheme 4).[5] A number of highly substituted benzofurans **10** have been obtained in moderate to good yields using this approach. The authors applied their methodology to the

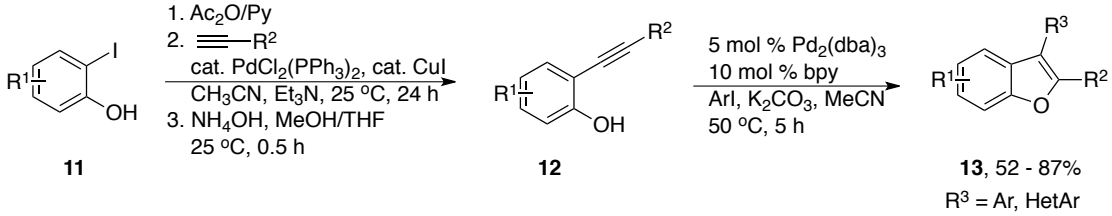
synthesis of (±)-frondosin B and its analogues, and benzo[*b*]furan-containing inhibitors of tubulin polymerization.[6] However, this method has not been found suitable for the construction of libraries of 2,3-substituted benzofurans, due to the highly reactive nature of the MeMgCl reagent and its incompatibility with a large number of functional groups.

Scheme 4. A one-pot approach to benzofurans using MeMgCl



In 2004, Hu, Fathi, and Yang, in order to access a 210 member library of 2,3-disubstituted benzofurans **13**, optimized the method developed by Cacchi starting from 2-alkynylphenols **11**, and, after their optimization studies, found more efficient conditions for the formation of 2,3-diarylsubstituted benzo[*b*]furans from 2-alkynylphenols (**12**) and aryl iodides (Scheme 5).[7] However, considering the 3-step route required for synthesis of the 2-alkynylphenols **12**, the average yields of the final benzofurans **13** (over 4 steps) were only moderate.

Scheme 5. Library of 2,3-disubstituted benzofurans



During the course of our own investigations into methodology for the synthesis of 2,3-disubstituted indoles under Sonogashira conditions,[8] we have found that 2-iodophenols can also participate in an analogous process, providing an efficient and convenient new route to 2,3-disubstituted benzofurans. This finding encouraged us to proceed with our own optimization studies of this process.

5.3. RESULTS AND DISCUSSION

5.3.1. Optimization of the reaction conditions

The 2-iodophenol **14**, phenyl acetylene (**15**), and ethyl 4-iodobenzoate (**17**) have been employed as starting materials under the reaction conditions we developed for the synthesis of indoles,[8] providing the benzofuran **18** in a 51% yield (Scheme 6). In order to improve the yield, optimization of the reaction conditions has been carried out as reported in Table 1.

Scheme 6. Model reaction

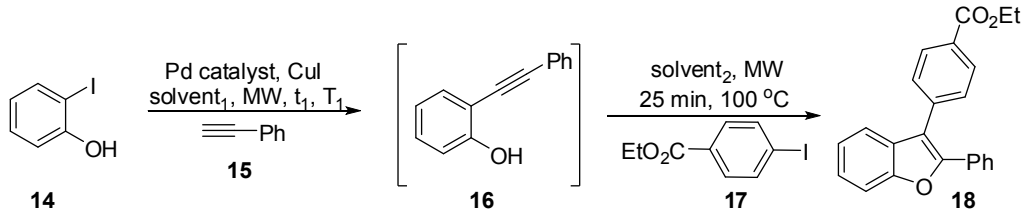


Table 1. Optimization of the reaction conditions[a]

entry	time (min)	temp. (°C)	solvent		ratio **14**:**15**:**17**	catalyst	yield **18**[b] (%)
	step 1	step 1	step 1	step 2			
1	15	60	Et_3N	MeCN	1:1.05:1.1	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	51
2	15	60	Et_3N	MeCN	1:1.05:1.1	2 mol % $Pd(PPh_3)_4$ 1 mol % CuI	23

Table 1 continued.

3	15	60	Et_3N	MeCN	1:1.05:1.1	2 mol % $Pd(dppe)_2$ 1 mol % CuI	10
4	15	60	Et_3N	MeCN	1:1.05:1.1	2 mol % $Pd(OAc)_2$ 4 mol % PPh_3 1 mol % CuI	6
5	15	60	Et_3N	MeCN	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	53
6	15	60	$^iPr_2NH$	MeCN	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	50
7	15	60	Et_3N	DMF	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	34
8	15	60	Et_3N	THF	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	29
9	15	60	Et_3N	Toluene	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	15
10	25	80	Et_3N	MeCN	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	20
11[c]	15	25	Et_3N	MeCN	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	53
12	30	25	Et_3N	MeCN	1:1.05:1.0	2 mol % $PdCl_2(PPh_3)_2$ 1 mol % CuI	73
13	30	25	Et_3N	MeCN	1:1.05:1.0	3 mol % $PdCl_2(PPh_3)_2$ 2 mol % CuI	86
14[d]	30	25	NMM/ Et_3N	MeCN	1:1.2:1.0	3 mol % $PdCl_2(PPh_3)_2$ 2 mol % CuI	89
15[e]	30	25	THF/ Et_3N	MeCN	1:1.2:1.0	3 mol % $PdCl_2(PPh_3)_2$ 2 mol % CuI	96

[a] Unless otherwise noted, all of the reactions were carried out under microwave irradiation on a 1.0 mmol scale in microwave-resistant vials. [b] Isolated yields after column chromatography. [c] When the first step of the reaction was carried out at 25 °C, much cleaner reaction mixtures were obtained than at 60 °C. [d] 0.5 ML of *N*-methylmorpholine (NMM)/1.5 mL of Et_3N using anhydrous solvents under argon. [e] 0.5 ML of THF/1.0 mL of Et_3N, and CuI were added as a solution in 0.5 mL of Et_3N using anhydrous solvents under argon.

Our initial examination of a number of palladium catalysts (Table 1, entries 1-4) indicated that bis(triphenylphosphine)palladium dichloride provided the best results. Changing the base from triethylamine to diisopropylamine (entries 5 vs 6) did not improve the yield of the desired benzofuran **18**. A study of the effect of various solvents on the second cyclization step revealed that DMF afforded product **18** in a 34% yield (entry 7), whereas THF and toluene were less efficient, providing only 29% and 15% yields, respectively (entries 8 and 9). Thus, acetonitrile proved to be the best solvent for this transformation. An increase in the temperature of the first step of the reaction to 80 ^{o}C decreased the yield of the desired product to 20% (entry 10), whereas conducting the first step at room temperature did not affect the yield of the product and the reaction was found to be cleaner based on TLC analysis when compared to the same reaction at 60 ^{o}C. Increasing the reaction time of the first step at room temperature to 30 minutes improved the yield of benzofuran **18** to 73% (entry 12). Furthermore, slightly increasing the catalyst loading and finding the best Pd/Cu catalyst ratio (3 mol % and 2 mol % respectively) improved the yield of benzofuran **18** to 86% (entry 13).

After the initial evaluation of the scope had been performed, the solubility of many iodophenols in triethylamine was found to be insufficient. The first step of the process was inefficient, leading to the exclusive formation of coupling products of the aryl iodides with the terminal alkyne and affording only low yields of the cyclized benzofurans. Thus, additional evaluation of the solvents for the first step has been performed.

In this methodology, the choice of solvents plays a crucial role. For the first step, the ideal solvent needs to be suitable for an efficient Sonogashira reaction, but should not

promote cyclization of the 2-alkynylphenol, which will result in formation of the undesired 3*H*-benzofuran. The second step, on the other hand, requires a solvent, which will promote the cyclization. We therefore tried to add additional reagents to the triethylamine to improve the solubility of the iodophenols, but retain reaction conditions favorable for the Sonogashira coupling. Solvents, like acetonitrile and DMF, solubilized the iodophenols well, but were not suitable for the first step, since they promote the cyclization pathway. The best additives were found to be *N*-methylmorpholine (NMM) (entry 14) and THF. Eventually, the ratio of 3/1 triethylamine/THF afforded the best results and was chosen as our optimized conditions. After we discovered that the reaction was sensitive to the palladium/copper ratio, we again looked at this factor. We subsequently found that due to the very low amounts of CuI needed, it was better to add the exact amount of CuI desired as a 7.5M solution in Et_3N. When running the reaction under an inert atmosphere and anhydrous conditions, this allowed us to increase the yield of the desired benzofuran product **18** to 96% (entry 15).

4.3.3. Evaluation of the reaction scope and limitations

After "optimal" conditions for the formation of benzo[*b*]furan **18** were found, an evaluation of the reaction scope was performed (Table 2).

Table 2. Scope of the reaction

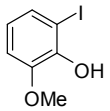
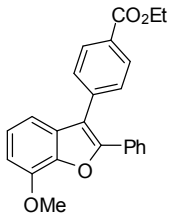
entry	iodophenol	acetylene	aryl iodide	product	yield[a] (%)
1	 **19**	**15**	**17**	 **20**	91

Table 2 continued.

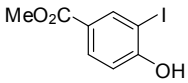
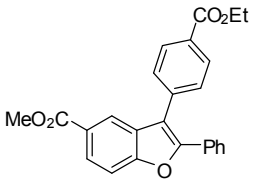
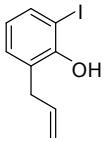
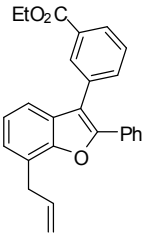
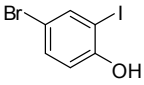
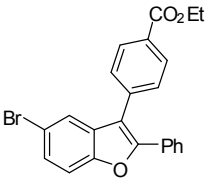
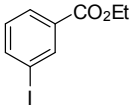
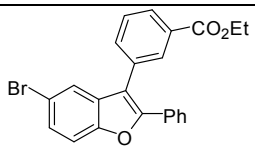
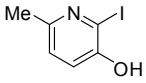
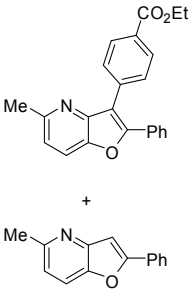
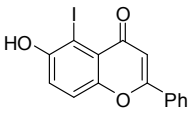
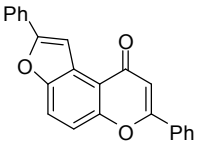
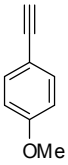
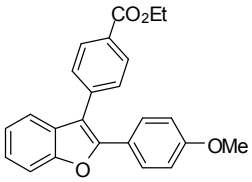
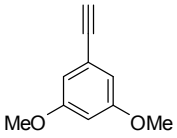
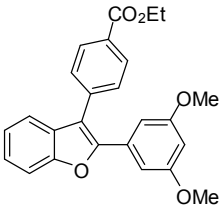
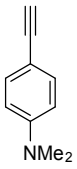
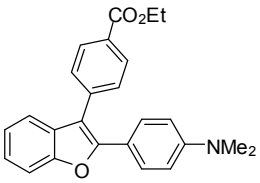
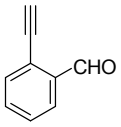
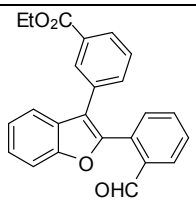
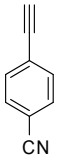
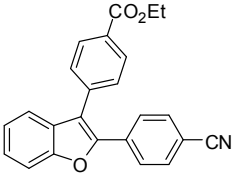
2	 **21**	**15**	**17**	 **22**	92
3	 **23**	**15**	**17**	 **24**	53
4	 **25**	**15**	**17**	 **26**	84
5	**25**	**15**	 **27**	 **28**	60[b]
6	 **29**	**15**	**17**	 **30 + 31**	12+88[c]

Table 2 continued.

7	 **32**	**15**	**17**	 **33**	58[c]
8	**14**	 **34**	**17**	 **35**	94
9	**14**	 **36**	**17**	 **37**	93
10	**14**	 **38**	**17**	 **39**	83
11	**14**	 **40**	**27**	 **41**	69[d]
12	**14**	 **42**	**17**	 **43**	trace[e]

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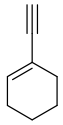
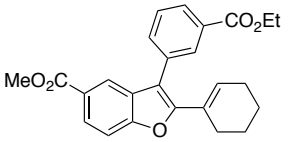
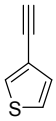
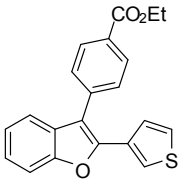
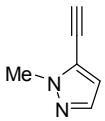
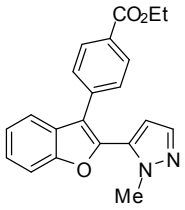
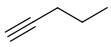
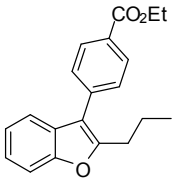
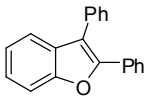
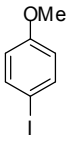
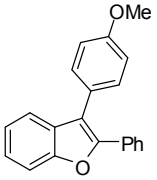
13	**21**	 **44**	**27**	 **45**	52
14	**14**	 **46**	**17**	 **47**	100
15	**14**	 **48**	**17**	 **49**	63[f]
16	**14**	 **50**	**17**	 **51**	trace[g]
17	**14**	**15**	PhI	 **52**	87
18	**14**	**15**	 **53**	 **54**	53[h]

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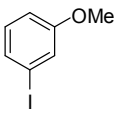
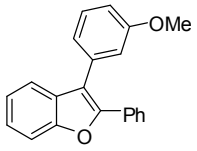
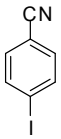
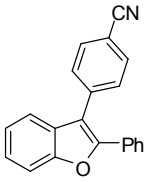
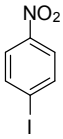
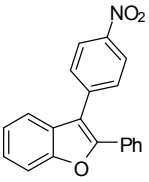
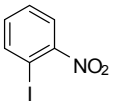
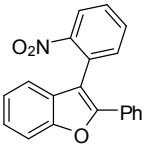
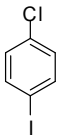
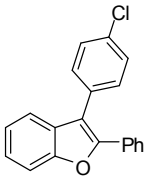
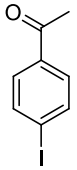
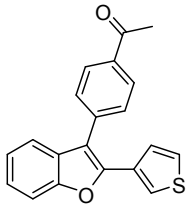
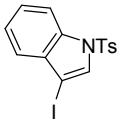
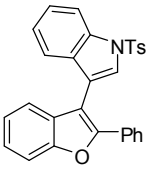
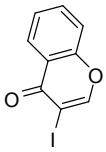
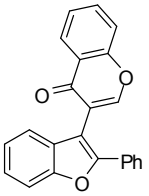
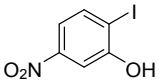
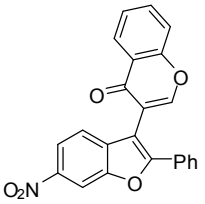
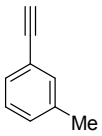
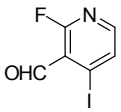
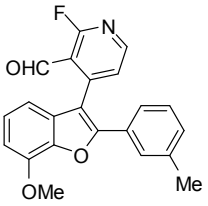
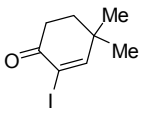
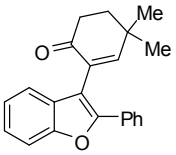
19	**14**	**15**	 **55**	 **56**	84
20	**14**	**15**	 **57**	 **58**	98
21	**14**	**15**	 **59**	 **60**	75
22	**14**	**15**	 **61**	 **62**	74
23	**14**	**15**	 **63**	 **64**	96
24	**14**	**39**	 **65**	 **66**	73

Table 2 continued.

25	**14**	**15**	 **67**	 **68**	58
26	**14**	**15**	 **69**	 **70**	43
27	 **71**	**15**	**69**	 **72**	24
28	**19**	 **73**	 **74**	 **75**	65
29	**14**	**15**	 **76**	 **77**	34

[a] Isolated yields after column chromatography. [b] This compound was prepared on a large scale and recrystallized, what might have contributed to the lower yield. [c] A substantial quantity of aryl iodide **17** remained unreactive. [d] 1.0 Equiv. of alkyne was employed. [e] The reaction afforded a complex mixture; for an alternative route to **43,** see Scheme 7. [f] 1.0 Equiv. of alkyne was employed and the first step of the process was run at 60 °C. [g] A small amount of product was observed as part of an inseparable complex mixture. [h] The second step of the process was conducted at 80 °C with the addition of $Pd(PPh_3)_4$.

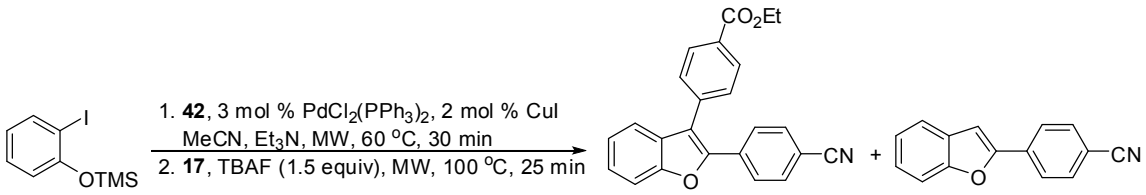
First, several different iodophenols have been investigated under our optimized reaction conditions (Table 2, entries 1-7). The electron-rich methoxy-containing phenol **19**, and the electron-poor ester-containing phenol **21** afforded the expected benzo[*b*]furans **20** and **22** in 91% and 92% yields, respectively (entries 1 and 2). When the 6-allyl-2-iodophenol **23** was employed, product **24** was formed, albeit in a lower 53% yield (entry 3). The presence of a bromine atom *para* to the hydroxy group was well tolerated and the bromo-containing benzo[*b*]furans **26** and **28** were isolated in 84% and 60% yields, respectively (entries 4 and 5). Even though the addition of THF greatly improved the solubility of many of the starting *o*-iodophenols, some substrates (*e.g.* 5-iodovanillin, 7-iodo-8-hydroxyquinoline-5-sulfonic acid, and 5-iodouracil) still exhibited insufficient solubility in the Et_3N/THF mixture to afford good results. The poor solubility prevented the first coupling step from proceeding in acceptable yield and thus sharply reducing the yield of the three-component coupling product and increasing the number of side products.

When 5-hydroxy-6-iodopicoline (**29**) was employed, the desired product **31** was isolated, but in only 12% yield (entry 6). The 3*H*-furo[2,3-*b*]pyridine **31** was isolated as a major product in 88% yield. The flavone-derived iodophenol **32** failed to produce the desired three-component coupling product and afforded compound **33** in a 58% yield, along with unreacted aryl iodide **17** (entry 7).

In order to continue our evaluation of the scope of this process, various terminal alkynes have been studied (entries 8-16). Alkynes bearing electron-donating groups, such as **34**, **36** and **38**, were well tolerated, providing benzofurans **35**, **37** and **39** in 94%, 93% and 83% yields, respectively (entries 8-10). The alkyne **40**, containing an electron-withdrawing

aldehyde group in the position *ortho* to the alkyne functionality was also tolerated, providing the product **41** in a 69% yield (entry 11). However, when a stronger electron-withdrawing cyano groups (**42**) was present in the alkyne, no cyclization product was observed (entry 12). Instead a complex reaction mixture, containing the 3*H*-benzofuran **79**, the coupling product of **42** with **17**, as well as trace amounts of other products was obtained. This result can be rationalized by examining the nucleophilicity of the alkyne moiety. When an electron-withdrawing group is present, the electron density on the carbon-carbon triple bond is decreased, thus promoting cyclization of the OH group, without interception by the desired arylpalladium iodide species. In the case of 4-cyanoethynylbenzene (**42**), by using the corresponding TMS-protected phenol **78** and adding TBAF during the second step of the sequence, we were able to obtain the desired benzo[*b*]furan product **43** in a 53% yield (Scheme 7).

Scheme 7. An alternative route employing 4-cyanoethynylbenzene



78 **43**, 53% **79**, 11%

The use of 1-ethynylcyclohexene (**44**) afforded the desired benzo[*b*]furan **45** in an 52% yield (entry 13). The heterocycle-containing terminal alkynes **46** and **48** were also well tolerated under our reaction conditions, providing thiophenyl- and methylimidazolyl-substituted benzofurans **47** and **49** in 100% and 63% yields respectively (entries 14 and 15). Unfortunately, aliphatic acetylenes [*e.g.* 1-pentyne (**50**)] led to formation of the desired

benzo[*b*]furan **51** in only trace amounts and afforded a complex reaction mixture (entry 16). The major side product in this case was the coupling product of the terminal alkyne **50** with the aryl iodide **17**, which suggests an inefficiency in the Sonogashira coupling step. Various attempts to modify the reaction conditions failed to improve the outcome of this reaction.

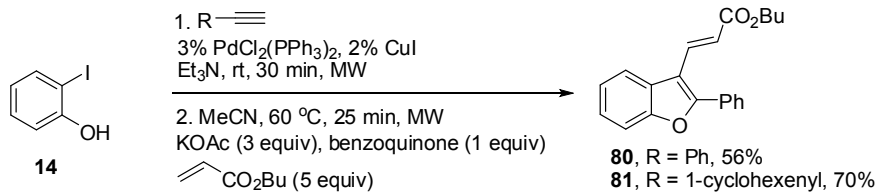
Finally, we examined the scope of the aryl iodides that can be used in this process under our optimized reaction conditions. Starting with iodobenzene, 2,3-diphenylbenzo[*b*]furan (**52**) was obtained in an 87% yield (entry 17). When 4-iodoanisole (**53**) was employed, only a 22% yield of benzofuran **54** was obtained under our optimized conditions. However, using a slightly lower temperature (80 °C) and an additional loading of the Pd catalyst in the second step improved the yield of the product **54** to 53% (entry 18). Surprisingly, the presence of an electron-donating methoxy group in the *meta*-position of the aryl iodide **55** was well tolerated and afforded the desired heterocycle **56** in an 84% yield (entry 19). Aryl iodides with electron-withdrawing groups, such as 4-iodobenzonitrile (**57**) and 4-iodonitrobenzene (**59**), also afforded the corresponding benzofurans **58** and **60** in 98% and 75% yields, respectively (entries 20 and 21). Placing the nitro group in the position *ortho* to the iodine did not affect the efficiency of the process, providing benzo[*b*]furan **62** in a 74% yield (entry 22). 4-Chloroiodobenzene (**63**) afforded the benzo[*b*]furan **64** in an excellent 96% yield (entry 23). The product **66** has been obtained in a 73% yield by employing 3-ethynylthiophene (**46**) and *p*-iodoacetophenone (**65**) (entry 24). Various heterocyclic aryl and vinylic iodides have been examined under our standard reaction conditions, providing the corresponding heterocyclic products in moderate to good yields (entries 25-28). *N*-Tosyl 3-iodoindole (**67**) afforded the desired product **68** in a 58% yield (entry 25). When employing

2-iodochromene (**69**), the bis-heterocyclic product **70** was obtained, albeit in only a 43% yield (entry 26). When 2-iodo-5-nitrophenol (**71**) was employed as a starting material with the same substrate, only a 24% yield of the benzofuran **72** could be obtained (entry 27), probably due to the electron-withdrawing effect of the nitro group, which ends up in a position *para* to the alkyne triple bond after the initial Sonogashira coupling. To our delight, the highly substituted 2-fluoro-3-formyl-4-iodopyridine (**74**) coupled with 6-methoxy-2-iodophenol (**19**) and 3-tolyl acetylene (**73**) to afford the highly substituted benzofuran **75** in a 65% yield (entry 28). Finally, the vinylic halide 2-iodo-4,4-dimethylcyclohex-2-enone (**76**) was allowed to react with *o*-iodophenol and phenyl acetylene to generate the corresponding heterocycle **77**, albeit in only a 34% yield (entry 29).

5.3.3. Study of the additional processes and further diversification

Recently, several processes describing Heck-type Pd(0) or Rh(I)-catalyzed reactions of 2-alkynylphenols with alkenes have been reported.[9] We were interested in knowing if our methodology could provide such a Heck-type transformation to afford 3-alkenylbenzofurans in a one-pot fashion from 2-iodophenol (**14**). Gratifyingly, by employing butyl acrylate and slightly modifying our reaction conditions for the second step, we were able to obtain the olefinic product **80** in a 56% yield (Scheme 8).

Scheme 8. Synthesis of benzofurans from iodophenols, alkynes and alkenes

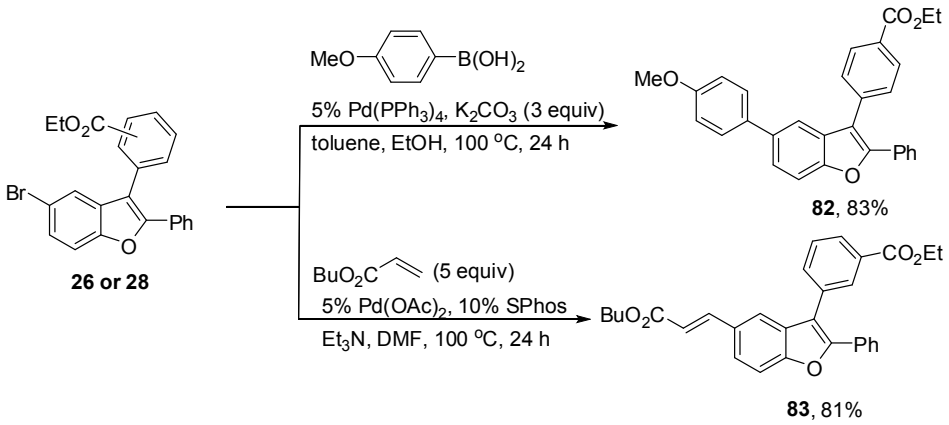


The alkyne 1-ethynylcyclohexene (**44**) also afforded the desired product **81** in a 70% yield.

We have also investigated the possibility of employing aryl boronic acids (analogous to a Suzuki-Miyaura coupling)[10] and terminal alkynes (analogous to a Sonogashira coupling)[11] in the same process. However, there was no evidence for formation of the expected 2,3-disubstituted benzo[*b*]furans in the two cases we examined using our standard reaction conditions. The major product in both cases was the corresponding 3*H*-benzofuran. This does not mean that there are no reaction conditions under which the desired Sonogashira/Suzuki-Miyaura process won't occur.

We have also attempted Pd-catalyzed couplings with the 5-bromobenzofurans **26** and **28** prepared by our benzofuran synthesis to illustrate how our benzofurans can be further diversified to provide a large variety of multisubstituted benzofurans for drug testing. Thus, Suzuki-Miyaura[10] and Mizoroki-Heck[10] couplings proceeded smoothly, affording the products **82** and **83** in 83% and 81% yields, respectively (Scheme 9).

Scheme 9. Pd-catalyzed diversification



5.3.4. Approaches towards the total syntheses of Amurensin H, Gnetuhainin B, and Gnetuhainin F

We envisioned that our three-component approach could be a useful tool for the synthesis of selected benzo[*b*]furan-containing natural products. Amurensin H, Gnetuhainin B and Gnetuhainin F were chosen as targets (Figure 1).

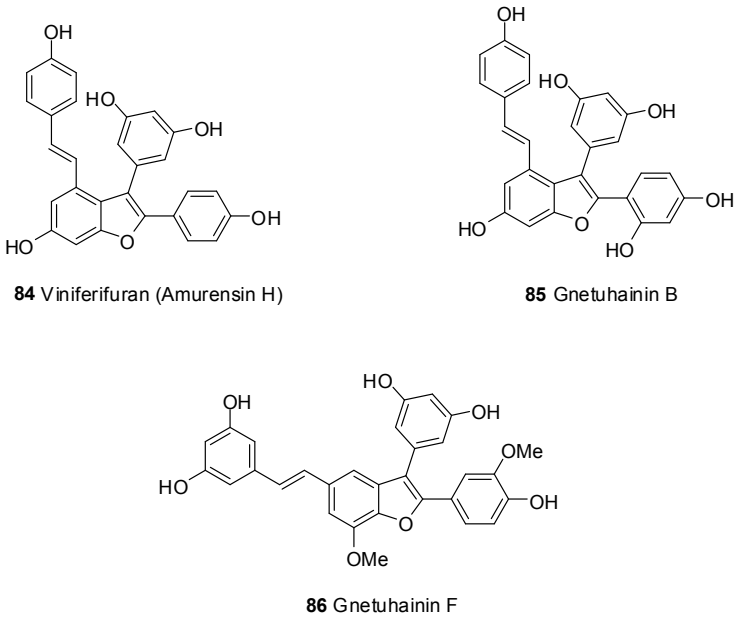
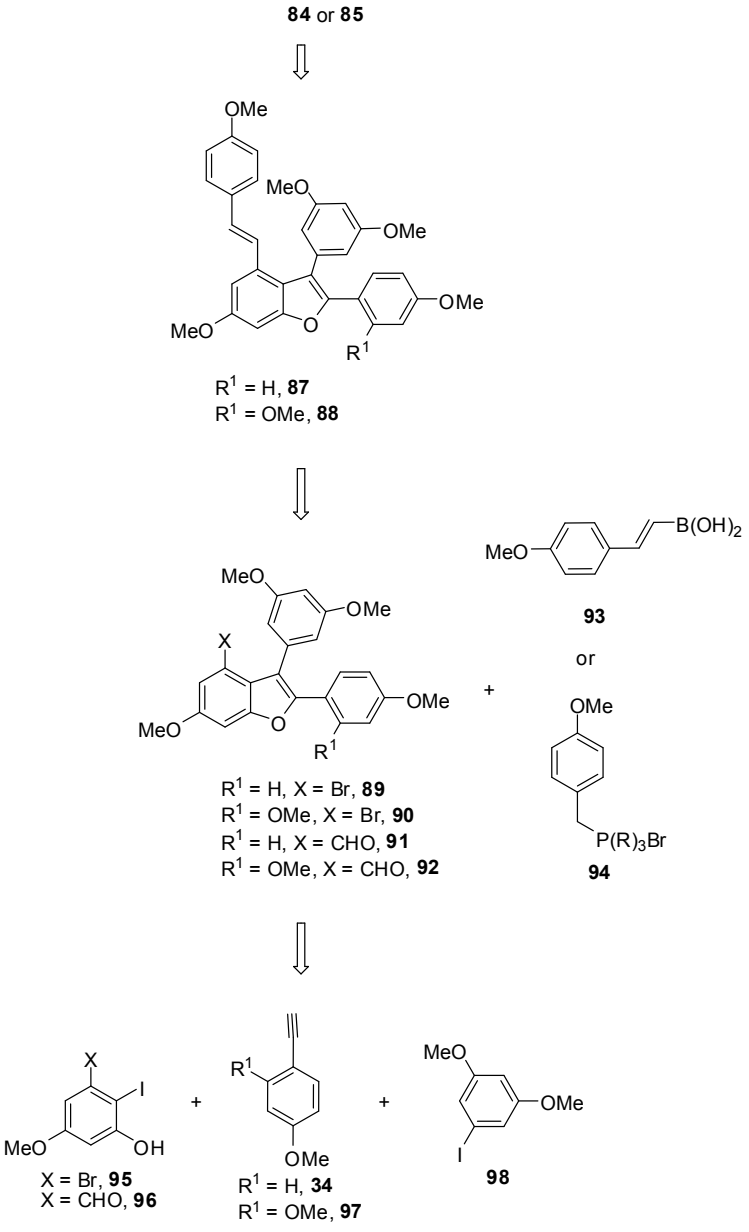


Figure 1. Structures of Amurensin H, and Gnetuhainins B and F

Compounds **84**-**86** belong to a class of oligostilbenes, known for their multiple biological activities.[12] Amurensin H (**84**) was isolated from *Vitis amurensis* and shows significant anti-inflammatory activity.[13] It was found suitable for the treatment of chronic obstructive pulmonary disease.[14] Two synthetic pathways have been reported for the total synthesis of benzofuran **84**. One involves the oxidative coupling of resveratrol,[15] and the other involved the cyclization of *ortho*-(benzyloxy)benzophenones using a phosphazene reagent.[16] Gnetuhainin B (**85**) and Gnetuhainin F (**86**) were isolated from *Gnetum hainanense*

species, a traditional Chinese medicine herb.[17,18] Compound **3** has been prepared through oxidative coupling in 9 steps starting from methyl 3,5-di(benzyloxy)benzoate in 9.8% overall yield.[19] No total synthesis of Gnetuhainin B has been reported.

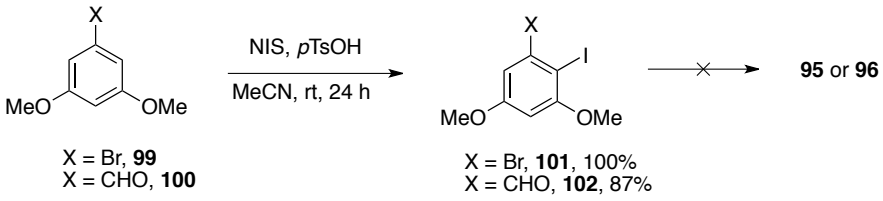
Scheme 10. Proposed retrosynthetic pathway towards benzofurans **84** and **85**



We envisioned that structurally similar benzofurans **84** and **85** could be obtained from the corresponding methoxy analogues **87** and **88** (Scheme 10). Compounds **87** and **88** could be obtained by the Pd-catalyzed couplings of boronic acid **93** with compounds **89** or **90** or by a Wittig reaction of **94** with **91** or **92**. Precursors **89-92** could be prepared using our 3-component method, starting from iodophenols **95** or **96**, commercially available alkynes **34** or **97**, and aryl iodode **98**.

First, we attempted the synthesis of iodophenol **95** (Scheme 11). Iodination of 3,5-dimethoxybromobenzene (**99**) afforded compound **101** in a quantitative yield. However, all of our attempts to selectively demethylate the methoxy group next to the iodine atom failed. Even demethylation of both methoxy groups using known reagents (*e.g.* BBr_3, HI) did not prove to be possible, resulting in complex reaction mixtures with the predominant product being 3,5-dihydroxybromobenzene.

Scheme 11. Unsuccessful approach toward phenols **95** and **96**



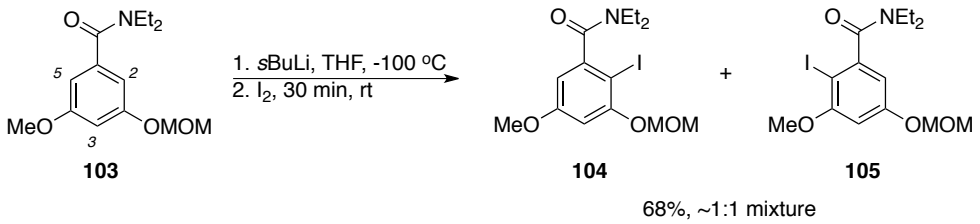
X = Br, **99**
X = CHO, **100**

X = Br, **101**, 100%
X = CHO, **102**, 87%

We then decided to proceed with the synthesis of iodophenol **96** suitable for the Wittig route. In this case, starting with compound **100**, we were able to obtain compound **102** in an 87% yield (Scheme 11). However, all attempts to demethylate compound **102** failed as well. As an alternative, we decided to investigate the possible selective lithiation of compound **103** (Scheme 12). With the good C-H activating ability of a diethylcarbamate group and a MOM directing group being ~ 1000 times more reactive than a OMe group, we expected the

exclusive lithiation of compound **103** at position 2, which followed by iodination would result in the formation of the desired compound **104**. However, even running the lithiation reaction at -100 ^{o}C, we observed no selectivity and obtained an approximately 1:1 mixture of isomers **104** and **105** (Scheme 3). This might be attributed to the extremely good activating ability of the diethylcarbamide group, so that the difference between the OMOM and OMe groups does not affect the selectivity.

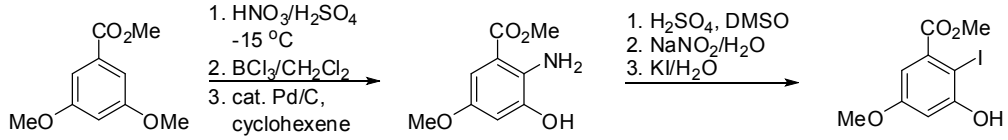
Scheme 12. Unsuccessful iodination of compound **103**



103 **104** **105**

Due to complications with the selective iodination, we decided to pursue another strategy for the synthesis of phenol **96**, where the iodine atom is introduced through deamination/iodination of an amino group. This method proved to be efficient, leading to the formation of iodophenol **108** in 57% yield from compound **107** (Scheme 13).

Scheme 13. Synthesis of iodophenol **108**



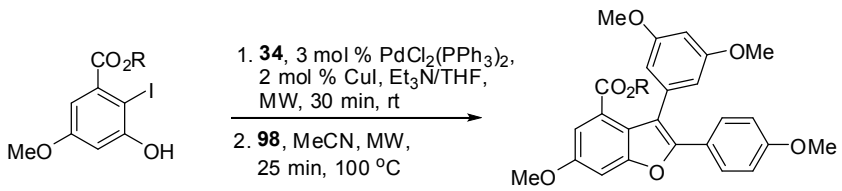
106 **107**, 66% **108**, 57%

With compound **108** in hand, we decided to postpone the transformation of the CO_2Me group to the desired aldehyde and to try our three-component coupling using the compound **108**. From our studies of the scope of our benzofuran synthesis, we knew that a

CO_2Me group is tolerated better than an aldehyde under our reaction conditions. Thus, this adjustment should be beneficial.

Unfortunately, when we tried to employ compound **108** in our three-component coupling, its solubility was insufficient. Thus, the first step was inefficient and no formation of the desired benzo[*b*]furan **110** was observed (Scheme 14). We then decided to change the CO_2Me group to a CO_2Hex group to improve the solubility and indeed the CO_2Hex analogue **109** had excellent solubility in the Et_3N/THF mixture. To our disappointment, however, the three-component coupling using compound **109** did not result in the formation of the desired benzo[*b*]furan product **111**, producing instead a complex reaction mixture, mostly composed of apparent products of decomposition of the starting materials.

Scheme 14. Unsuccessful three-component coupling employing phenols **108** and **109**



R = Me, **108**
R = Hex, **109**

R = Me, **110,** 0%
R = Hex, **111,** 0%

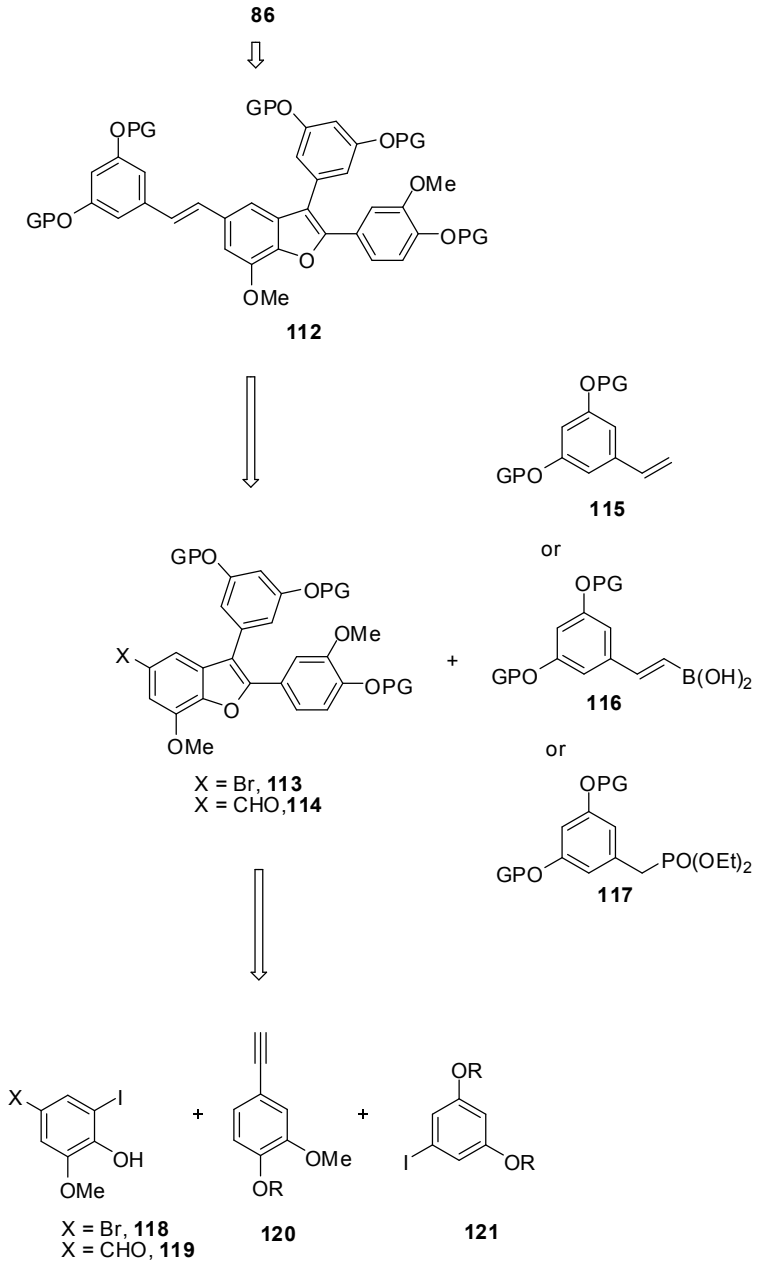
The presence of an ester group right next to the iodine might be the reason for compounds **108** and **109** being ineffective in the Sonogashira reaction.

Although our efforts did not allow us to obtain the desired compounds **84** and **85**, we are continuing to study alternative ways to complete this synthesis utilizing our three-component methodology.

For the synthesis of Gnetuhainin F (**86**), we envisioned a similar retrosynthetic strategy (Scheme 15). In this case, compound **86** might be obtained from protected compound **112**.

Benzofuran **112** could hopefully be obtained by the Pd-catalyzed reactions of **113** with **115** or **116** or, alternatively, a Wittig or Horner-Wadsworth-Emmons reaction of **114** with **117** (or a Wittig reaction with the corresponding phosphonium salt).

Scheme 15. Retrosynthetic pathway towards benzofuran **86**.



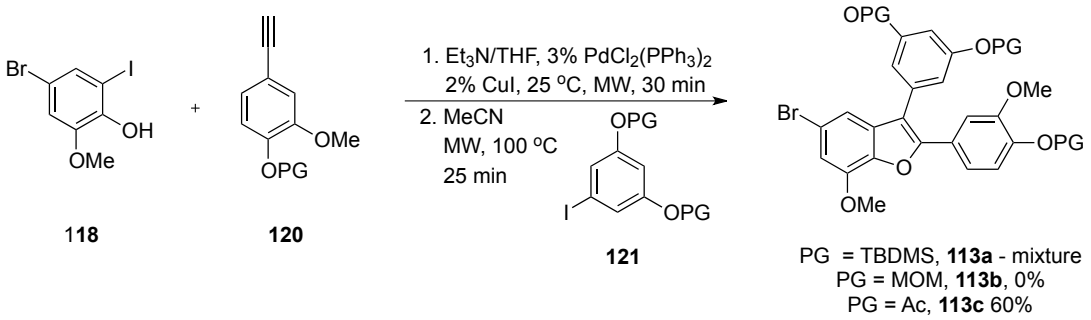
The three-component coupling could then be employed for the synthesis of **113** or **114** from phenols **118** or **119**, alkyne **120** and aryl iodide **121**.

As can be seen from Scheme 15, various protecting groups could be used for this transformation. Indeed, we found out that the choice of the protecting group plays a crucial role in the success of these reactions. Three most commonly used protecting groups have been studied: TBDMS, MOM and acetyl.

To study the possibility of the three-component coupling for the synthesis of **113** and **114**, we started with the preparation of the required precursors **118-121** in a few steps from commercially available starting materials. Iodophenols **118** and **119** and TBDMS-, MOM- and acetyl-protected **120** and **121** have all been successfully obtained in good yields.[20]

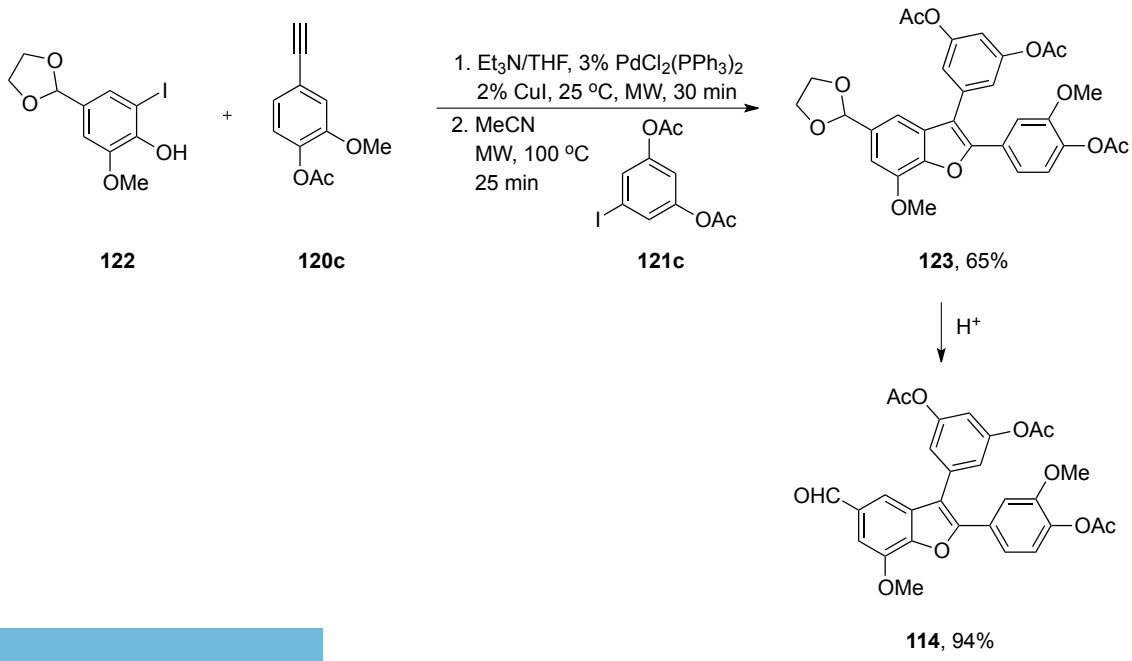
When compounds **120** and **121** with PG = TBDMS were employed with iodophenol **118**, our three-component coupling was possible, however not efficient, and afforded an inseparable mixture of the desired product **113a** and the coupling product of the aryl iodide **121a** and alkyne **120a** (Scheme 16). In the case of PG = MOM, the three-component coupling didn't prove to be efficient and none of the desired product **113b** was observed. The case of PG = acetyl was found to be the most suitable using our reaction conditions. Our three-component methodology in this case proved to be efficient and afforded the desired product **113c** in a 60% isolated yield.

Scheme 16. Three-component coupling for the synthesis of compounds **113**



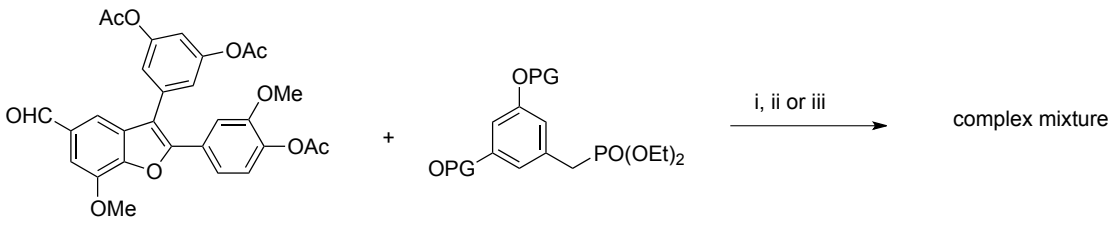
For the preparation of benzofuran **114**, we chose compounds **120** and **121** with acetyl protecting groups. Due to the poor solubility of 5-iodovanillin (**119**) in our Et_3N/THF mixture, we decided to use the protected compound **122**. When iodophenol **122** was employed in our three-component coupling with the acetyl-protected compounds **120** and **121**, the desired benzofuran product **123** was formed in a 65% yield and then transformed to the corresponding aldehyde **114** in a 94% yield (Scheme 17).

Scheme 17. Synthesis of compound **114**



After successful preparation of both compounds **113c** and **114**, we attempted their conversion to compound **112**. For compound **114**, a Horner-Wadsworth-Emmons reaction was chosen to prepare the *E*-alkene moiety of Gnetuhainin F. Both acetyl- and MOM-protected compounds **117a** and **117b** have been prepared and employed under several reaction conditions described for this type of transformation in the literature, namely employing ^{t}BuOK,[21] ^{s}BuLi or LiHMDS[22] as a base. Unfortunately, none of the desired product **112** was obtained (Scheme 18). A complex mixture mainly composed of apparent decomposition/deacetylation products of **114** was obtained in all cases.

Scheme 18. Horner-Wadsworth-Emmons reaction of benzofuran **114**



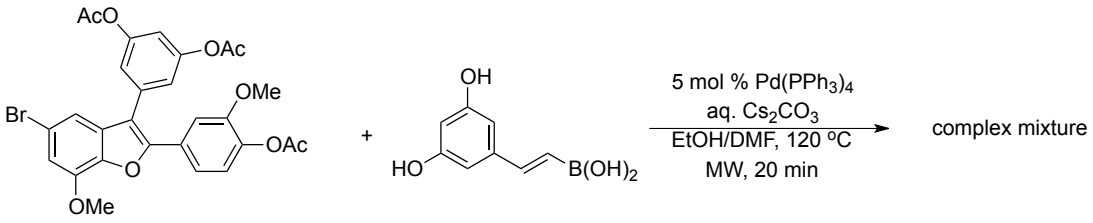
114

PG = Ac, **117a**
PG = MOM, **117b**

i) 1. **117a** or **117b**, ^{t}BuOK, THF, 0 °C, 10 min; 2. - 78 °C, then **114**, rt, 16 h. ii) 1. **117b**, ^{s}BuLi, THF, 0 °C, 10 min; 2. - 78 °C, then **114**, rt, 16 h. iii) 1. **117a**, LiHMDS, THF; 2. **114** 16 h

We then proceeded with further derivatization of compound **113c**. Suzuki coupling with unprotected boronic acid **116** (R =H) was employed. However, none of the desired product was formed (Scheme 19). In this case, the major complication of this reaction was also found to be partial deacetylation of the precursor **113**, obviously initiated by aqueous basic reaction conditions. This led to complex reaction mixtures and did not allow the desired compound **112** to be formed.

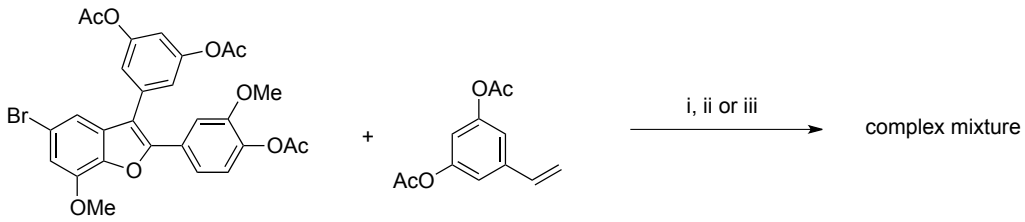
Scheme 19. Suzuki coupling of benzofuran **113c** with boronic acid **116**.



113c **116**

We then turned to an investigation of the Heck reaction of compound **113c** that would hopefully tolerate the acetyl groups. We prepared 3,5-diacetoxystyrene (**115**) and attempted a Heck reaction with compound **113c** under reaction conditions employing $NaHCO_3$,[23] K_2CO_3, or Et_3N as a base in combination with different ligands. However, only complicated reaction mixtures have been obtained (Scheme 20). This result is discouraging, since conditions i) in Scheme 20 have been suitable for the synthesis of acetyl-protected resveratrol starting from styrene **115** and 4-acetoxybromobenzene (see ref. 23).

Scheme 20. Suzuki coupling of benzofuran **113c** with styrene **115**.



113c **115**

i) cat. $Pd(OAc)_2$, cat. $P(oTol)_3$, cat. BHT, DMF, $NaHCO_3$, 150 °C, MW, 5 h
ii) 2.5% $Pd(OAc)_2$, 10% SPhos, Et_3N, DMF, 100 °C, 24 h
iii) cat. $Pd(OAc)_2$, cat. $P(oTol)_3$, K_2CO_3, DMF, 30 °C, 24 h

Even cleavage of the acetyl groups in compound **113c** was found to be challenging, leading to complex mixtures. We are now continuing our search for the optimal combination

of reaction conditions and functional groups for the successful generation of benzofuran **112** from compounds **113c** and **114**.

5.4. CONCLUSIONS

A novel convenient multicomponent process for the synthesis of 2,3-disubstituted benzo[*b*]furans under Sonogashira conditions has been developed and the scope of this process studied. Microwave irradiation has been employed, providing higher yields and shorter reaction times. This methodology has proven quite general and should prove a valuable tool in the synthesis of combinatorial libraries of benzofurans. Significant progress has been achieved in applying the developed methodology to the total synthesis of the oligostilbenes Amurensin H, Gnetuhainin B and Gnetuhainin F, but work remains to complete these syntheses.

5.5. ACKNOWLEDGEMENTS

We gratefully acknowledge the National Science Foundation and the National Institutes of Health Kansas University Center of Excellence in Chemical Methodology and Library Development (P50 GM069663) for their generous financial support of this project. We would also like to thank the research groups of Professors Nicola Pohl and George Kraus for allowing us to use their CEM microwave reactors for the room temperature experiments.

5.6. EXPERIMENTAL

5.6.1. General remarks

All microwave reactions were carried out in sealed oven-dried microwave vials. A Biotage microwave reactor was used for all experiments run at or above 60 ^{o}C. A CEM microwave reactor was used for the room temperature microwave reactions. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. The chemical shifts of the ^{1}H NMR and ^{13}C NMR spectra are reported relative to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^{1}H NMR and δ 77.23 ppm for the ^{13}C NMR), acetone-d_6 (2.05 ppm for the ^{1}H NMR and δ 29.92 ppm for the ^{13}C NMR) or DMSO-d_6 (2.50 ppm for the ^{1}H NMR and δ 39.51 ppm for the ^{13}C NMR). All coupling constants (*J*) are reported in Hertz (Hz). All commercially obtained chemicals were used as received without further purification. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points were obtained using an EZ-Melt automated melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were obtained using an Agilent QTOF 6540 mass spectrometer (ESI at a voltage of 70 eV). All mass spectra (MS) were obtained using a GCT-Agilent 6890 gas chromatograph/ mass spectrometer (EI at a voltage of 70 eV). All IR spectra were obtained using a Nicolet 380 FT-IR apparatus.

5.6.2. Preparation of the starting compounds for the three-component coupling.

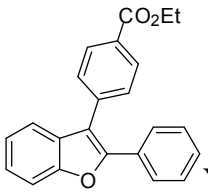
A majority of the starting materials were purchased from commercial sources and used as received. The following compounds were prepared following the procedure described in the

literature: iodophenols **19**,[24] **23**,[25] **32**,[26] and **71**;[27] 3-iodo-*N*-tosylindole (**68**),[28] 3-iodo-4*H*-chromen-4-one (**69**),[29] 2-iodo-4,4-dimethylcyclohexenone (**76**).[30]

5.6.3. General procedure for the one-pot, three-component Sonogashira/Cacchi type coupling for the synthesis of benzofurans.

The 2-iodophenol (0.5 mmol) and dichlorobis(triphenylphosphine)palladium (10.5 mg, 3 mol %) were placed in a 5 mL microwave vial and purged with argon. Dry THF (0.5 mL) was added and the reaction mixture was stirred until the iodophenol completely dissolved. Then dry triethylamine (1.0 mL) and a 3.8M solution of CuI in dry triethylamine (0.5 mL) were added and the mixture allowed to stir for 10 min. Then 1.2 equiv. of the corresponding alkyne was added; the vial was capped, purged with argon and placed in the microwave reactor for 30 min at 25 ^{o}C. The corresponding aryl iodide (0.5 mmol) and dry acetonitrile (2 mL) were added and the reaction mixture was heated in the microwave reactor at 100 ^{o}C for 25 min. After cooling, the solvents were evaporated and column chromatography using ethyl acetate/hexane as the eluent afforded the desired products.

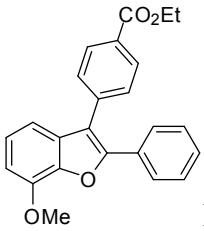
Ethyl 4-(2-phenylbenzofuran-3-yl)benzoate (18)



Yellow solid, 164.2 mg (96%): mp 100-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.21-7.26 (m, 1H), 7.26-7.36 (m, 4H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.52-7.66 (m, 5H), 8.14 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.6, 61.3, 111.4, 116.7, 119.9, 123.3, 125.1, 127.4, 128.7, 128.9, 129.8, 129.8,

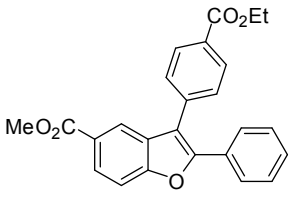
130.4, 131.6, 131.9, 137.9, 151.3, 154.2, 166.6; HRMS calc. for $C_{23}H_{18}O_3$ $[M+H]^+$ 342.1256, found 342.1260.

Ethyl 4-(7-methoxy-2-phenylbenzofuran-3-yl)benzoate (20)



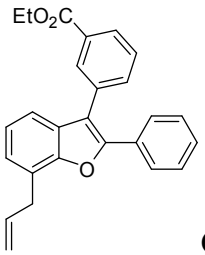
Bright yellow solid, 169.6 mg (91%): mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 3H), 4.08 (s, 3H), 4.43 (q, J = 7.1 Hz, 2H), 6.87 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 7.28-7.36 (m, 3H), 7.59 (d, J = 8.0 Hz, 2H), 7.61-7.70 (m, 2H), 8.14 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 56.4, 61.3, 107.4, 112.3, 117.0, 124.0, 127.5, 128.7, 128.9, 129.8, 129.9, 130.3, 130.3, 131.4, 137.9, 143.6, 145.6, 151.6, 166.6; HRMS calc. for $C_{24}H_{20}O_4$ $[M+H]^+$ 372.1362, found 373.1438.

Methyl 3-[4-(ethoxycarbonyl)phenyl]-2-phenylbenzofuran-5-carboxylate (22)



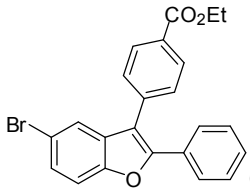
Colorless solid, 162.3 mg (92%): mp 186-187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 3H), 3.92 (s, 3H), 4.44 (q, J = 7.1 Hz, 2H), 7.29-7.47 (m, 3H), 7.46-7.73 (m, 5H), 8.09 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 8.2 Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 52.4, 61.4, 111.4, 117.1, 122.4, 125.8, 126.9, 127.4, 128.9, 129.4, 129.9, 129.9, 130.2, 130.6, 137.2, 152.7, 156.8, 166.5, 167.3; HRMS calc. for $C_{25}H_{20}O_5$ $[M+H]^+$ 401.1384, found 401.1395.

Ethyl 4-(7-allyl-2-phenylbenzofuran-3-yl)benzoate (24)



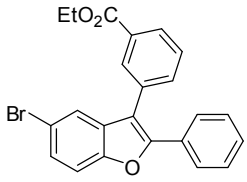
Colorless oil, 97.6 mg (53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.1 Hz, 3H), 3.79 (d, *J* = 6.7 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 5.11-5.33 (m, 2H), 5.06-5.38 (m, 2H), 6.16 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 7.11-7.40 (m, 6H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.59-7.73 (m, 3H), 8.10 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.23 (t, *J* = 1.8 Hz, 1H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 29.9, 30.2, 34.2, 61.3, 116.5, 117.0, 118.1, 123.5, 123.9, 125.1, 127.2, 128.7, 129.0, 129.3, 130.0, 130.7, 131.0, 131.6, 133.7, 134.5, 136.1, 150.9, 152.6, 166.6; HRMS calc. for $C_{26}H_{22}O_3$ $[M+H]^+$ 382.1563, found 382.1558.

Ethyl 4-(5-bromo-2-phenylbenzofuran-3-yl)benzoate (26)



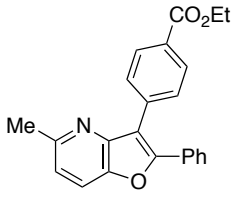
Colorless solid, 176.8 mg (84%): mp 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, *J* = 7.1 Hz, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 7.29-7.37 (m, 3H), 7.44 (d, *J* = 1.0 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.58-7.64 (m, 3H), 8.15 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 61.4, 112.9, 116.3, 116.6, 122.7, 127.5, 128.0, 128.9, 129.4, 129.8, 129.9, 130.2, 130.6, 131.9, 137.2, 152.6, 153.0, 166.5; HRMS calc. for $C_{23}H_{17}Br\ O_3$ $[M+H]^+$ 421.0361, found 421.0434.

Ethyl 3-(5-bromo-2-phenylbenzofuran-3-yl)benzoate (28)



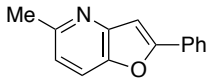
Colorless solid: mp 103-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.28-7.35 (m, 3H), 7.44 (d, J = 1.2 Hz, 2H), 7.50-7.71 (m, 5H), 8.12 (dt, J = 7.6, 1.4 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 61.4, 112.9, 116.2, 116.5, 122.7, 126.4, 127.2, 127.9, 128.8, 128.9, 129.2, 129.4, 129.5, 130.0, 130.9, 131.8, 132.3, 132.8, 134.4, 152.4, 152.9, 166.5; HRMS calc. for $C_{23}H_{18}BrO_3$ $[M+H]^+$ 421.0434, found 421.0440.

Ethyl 4-(5-methyl-2-phenylfuro[3,2-*b*]pyridin-3-yl)benzoate (30)



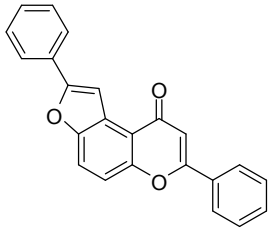
Brown oil, 20.1 mg (12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.1 Hz, 3H), 2.66 (s, 3H), 4.37 (s, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.33-7.40 (m, 3H), 7.63-7.72 (m, 3H), 7.77 (d, J = 7.9 Hz, 2H), 8.13 (d, J = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 24.7, 61.2, 116.9, 118.4, 119.6, 126.4, 127.8, 128.9, 128.9, 129.6, 129.8, 130.2, 130.2, 136.2, 146.2, 147.3, 155.3, 166.8; HRMS calc. for $C_{23}H_{20}NO_3$ $[M+H]^+$ 358.1438, found 358.1445.

5-Methyl-2-phenylfuro[3,2-*b*]pyridine (31)



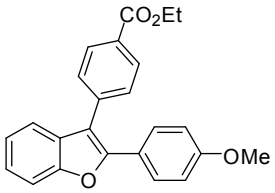
Brown solid, 91.7 mg (88%): mp 114-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 7.06 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 0.9 Hz, 1H), 7.35-7.42 (m, 1H), 7.43-7.53 (m, 2H), 7.65 (d, J = 8.8 Hz, 1H), 7.82-7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 102.3, 118.3, 118.9, 125.4, 129.1, 129.6, 130.1, 146.8, 148.5, 154.8, 159.7; HRMS calc. for $C_{14}H_{12}NO$ $[M+H]^+$ 210.0913, found 210.0914.

2,7-Diphenyl-9*H*-furo[3,2-*f*]chromen-9-one (33)



Beige solid, 98.4 mg (58%): mp 200-203 °C (decomposed); ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88-6.96 (m, 1H), 7.34-7.42 (m, 1H), 7.42-7.58 (m, 6H), 7.79-7.83 (m, 1H), 7.92-7.96 (m, 4H), 8.09-8.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 103.6, 108.0, 113.9, 116.9, 116.9, 125.3, 126.2, 126.3, 128.9, 129.1, 129.2, 130.0, 131.5, 131.9, 151.4, 153.8, 159.0, 162.8, 179.1; HRMS calc. for $C_{23}H_{15}O_3$ $[M+H]^+$ 339.1016, found 339.1020.

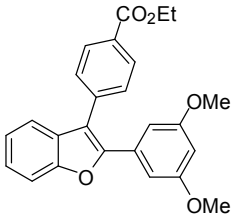
Ethyl 4-[2-(4-methoxyphenyl)benzofuran-3-yl]benzoate (35)



Yellow solid, 175.0 mg (94%): mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3H), 3.78 (s, 3H), 4.41 (q, J = 7.1 Hz, 2H), 6.83 (d, J = 8.8 Hz,

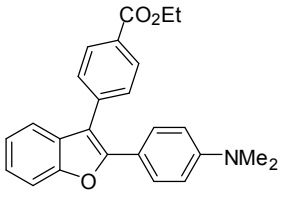
2H), 7.22 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.52-7.61 (m, 5H), 8.13 (d, J = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.6, 55.4, 61.2, 111.2, 114.2, 115.2, 119.6, 122.9, 123.2, 124.6, 128.9, 129.5, 129.8, 130.3, 134.1, 138.2, 151.5, 154.1, 160.1, 166.6; HRMS calc. for $C_{24}H_{20}O_4$ $[M+H]^+$ 372.1362, found 372.1372.

Ethyl 4-[2-(3,5-dimethoxyphenyl)benzofuran-3-yl]benzoate (37)



Cream colored solid, 186.3 mg (93%): mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J = 7.1 Hz, 3H), 3.70 (s, 6H), 4.44 (q, J = 7.1 Hz, 2H), 6.45 (s, 1H), 6.81 (s, 2H), 7.27 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 8.18 (dd, J = 8.2, 1.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 55.5, 61.3, 101.6, 101.6, 105.2, 111.4, 117.1, 119.9, 123.3, 125.2, 129.8, 129.9, 130.3, 131.9, 137.9, 150.9, 154.0, 160.8, 166.5; HRMS calc. for $C_{25}H_{22}O_5$ $[M+H]^+$ 403.1540, found 403.1549.

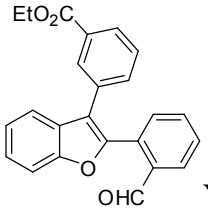
Ethyl 4-[2-(4-(dimethylamino)phenyl)benzofuran-3-yl]benzoate (39)



Yellow-green oil, 160.1 mg (83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, J = 7.2 Hz, 3H), 2.99 (s, 6H), 4.47 (q, J = 7.1 Hz, 2H), 7.29 (dt, J = 17.4, 7.0 Hz, 2H), 6.66 (d, J = 8.5 Hz, 2H), 7.29 (dt, J = 17.4, 7.0 Hz, 2H), 7.48-7.61 (m, 4H), 7.67 (d, J = 8.0 Hz, 2H), 8.19 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 40.3, 61.1, 111.1,

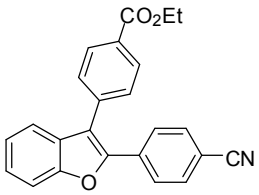
111.9, 113.7, 117.9, 119.2, 123.0, 124.1, 128.5, 129.2, 129.8, 130.1, 130.2, 138.8, 150.6, 152.7, 153.9, 166.7; HRMS calc. for $C_{25}H_{23}NO_3$ $[M+H]^+$ 386.1751, found 386.1759.

Ethyl 4-[2-(2-formylphenyl)benzofuran-3-yl]benzoate (41)



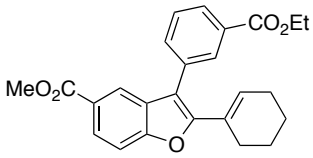
Yellow oil, 128.6 mg (69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.47-7.64 (m, 5H), 7.73 (d, *J* = 7.8 Hz, 1H), 8.01 (t, *J* = 7.6 Hz, 2H), 8.14 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.5, 61.3, 111.8, 117.6, 120.5, 120.7, 123.8, 125.8, 128.3, 128.3, 129.0, 129.3, 129.8, 130.5, 131.3, 131.6, 131.9, 132.9, 133.8, 134.3, 148.6, 155.1, 166.2, 191.0; HRMS calc. for $C_{24}H_{18}O_4$ $[M+H]^+$ 371.1278, found 371.1276.

Ethyl 4-[2-(4-cyanophenyl)benzofuran-3-yl]benzoate (43)



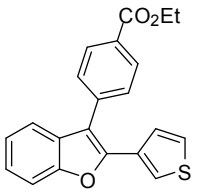
Colorless solid, 97.5 mg (53%): mp 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.1 Hz, 3H), 4.45 (q, *J* = 7.1 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 8.1 Hz, 5H), 7.73 (d, *J* = 8.1 Hz, 2H), 8.19 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 56.9, 61.4, 111.6, 111.9, 118.8, 119.7, 120.5, 123.8, 126.3, 127.3, 129.6, 129.8, 130.5, 130.7, 132.5, 134.7, 136.9, 148.7, 154.4, 166.4; HRMS calc. for $C_{24}H_{17}NO_3$ $[M+H]^+$ 367.1208, found 367.1212.

Ethyl 4-[2-(cyclohex-1-en-1-yl)benzofuran-3-yl]benzoate (45)



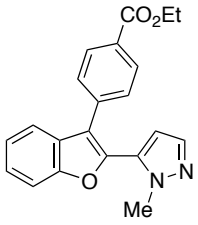
Yellow oil, 104.1 mg (52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.1 Hz, 3H), 1.62 (t, *J* = 3.2 Hz, 4H), 2.12 (br s, 2H), 2.18 (br s, 2H), 3.88 (s, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 6.41-6.48 (m, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.61-7.66 (m, 1H), 8.01 (dd, *J* = 10.8, 1.5 Hz, 2H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 21.9, 22.6, 25.9, 26.6, 52.2, 61.3, 110.8, 115.5, 121.9, 125.2, 126.4, 127.9, 128.9, 128.9, 130.6, 131.0, 131.1, 131.2, 133.2, 134.5, 154.5, 156.0, 166.6, 167.4; HRMS calc. for $C_{25}H_{25}O_5$ $[M+H]^+$ 405.1697, found 405.1706.

Ethyl 4-[2-(thiophen-3-yl)benzofuran-3-yl]benzoate (47)



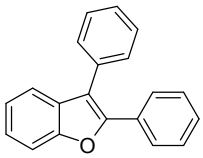
Yellow oil, 174.2 mg (100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.44 (q, *J* = 7.1 Hz, 2H), 7.21 (t, *J* = 5.2 Hz, 1H), 7.24-7.30 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.58-7.70 (m, 3H), 8.18 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 61.3, 111.3, 115.9, 119.8, 123.4, 123.8, 125.0, 126.1, 126.2, 129.7, 130.0, 130.3, 131.6, 137.7, 148.3, 154.0, 166.6; HRMS calc. for $C_{21}H_{16}O_3S$ $[M+H]^+$ 349.0893, found 349.0900.

Ethyl 4-[2-(1-methyl-1*H*-pyrazol-5-yl)benzofuran-3-yl]benzoate (49)



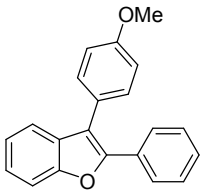
Green amorphous solid, 109.4 mg (63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.1 Hz, 3H), 3.63 (s, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.42-7.49 (m, 1H), 7.55 (t, *J* = 6.8 Hz, 3H), 7.60-7.72 (m, 2H), 8.11 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 61.3, 111.6, 120.2, 123.7, 125.5, 128.1, 128.6, 128.7, 129.1, 129.9, 130.4, 132.1, 132.2, 132.3, 136.8, 154.8, 166.4 (N-CH_3 does not show up); HRMS calc. for $C_{21}H_{18}N_2O_3$ $[M+H]^+$ 347.1390, found 347.1398.

2,3-Diphenylbenzofuran (52)[31]



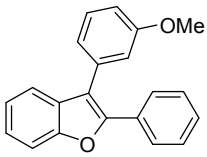
Yellow-green solid, 117.6 mg (87%): mp 116-119 °C [lit. mp 123 °C][32]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.36 (m, 5H), 7.46 (m, 6H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.3, 117.7, 120.3, 123.1, 124.9, 127.2, 127.8, 128.6, 128.6, 129.2, 129.9, 130.5, 130.9, 133.1, 150.7, 154.2.

3-(4-Methoxyphenyl)-2-phenylbenzofuran (54)[33]



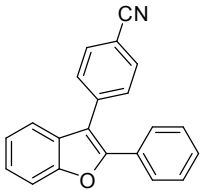
Yellow amorphous solid, 79.7 mg (53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.98-7.05 (m, 2H), 7.23-7.27 (m, 1H), 7.28-7.36 (m, 4H), 7.41-7.45 (m, 2H), 7.50 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.69 (dd, J = 8.2, 1.6 Hz, 2H).

3-(3-Methoxyphenyl)-2-phenylbenzofuran (56)[34]



Yellow oil, 125.7 mg (84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.98-7.03 (m, 1H), 7.13 (dd, J = 11.5, 4.9 Hz, 2H), 7.24-7.45 (m, 6H), 7.56-7.63 (m, 2H), 7.75 (dd, J = 8.1, 1.5 Hz, 2H).

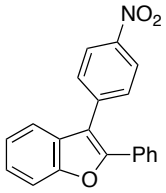
3-(4-Cyanophenyl)-2-phenylbenzofuran (58)



Yellow solid, 140.1 mg (98%): mp 113-115 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 7.5 Hz, 1H), 7.32-7.39 (m, 4H), 7.48 (d, J = 7.7 Hz, 1H), 7.59 (dt, J = 11.4, 4.6 Hz, 5H), 7.69-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.4, 111.6, 115.9, 118.9, 119.6,

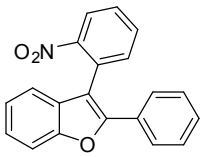
123.6, 125.4, 127.5, 128.9, 129.2, 129.3, 130.0, 130.5, 132.9, 138.3, 151.8, 154.3; HRMS calc. for $C_{21}H_{13}NO$ $[M+H]^+$ 296.107, found 296.1073.

3-(4-Nitrophenyl)-2-phenylbenzofuran (60)[34]



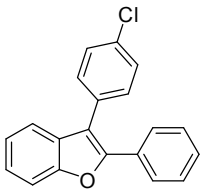
Yellow solid, 114.5 mg (73%): mp 135-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.28 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.36-7.39 (m, 4H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 3H), 7.70 (d, *J* = 8.2 Hz, 2H), 8.33 (dd, *J* = 8.7, 1.7 Hz, 2H).

3-(2-Nitrophenyl)-2-phenylbenzofuran (62)



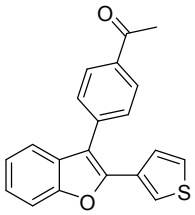
Yellow crystals, 116.6 mg (74%): mp 119-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.25 (m, 2H), 7.28-7.39 (m, 4H), 7.51 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.52-7.60 (m, 3H), 7.62 (td, *J* = 7.7, 1.6 Hz, 1H), 7.68 (td, *J* = 7.5, 1.5 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 111.6, 113.4, 119.5, 123.5, 125.2, 125.2, 126.9, 128.2, 128.9, 128.9, 129.4, 129.8, 130.1, 133.6, 133.6, 149.9, 151.4, 154.0; HRMS calc. for $C_{20}H_{13}NO_3$ $[M+H]^+$ 316.0968, found 316.0977.

3-(4-Chlorophenyl)-2-phenylbenzofuran (64)



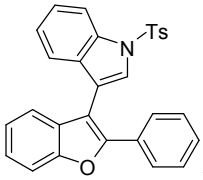
Yellow solid, 145.6 mg (96%): mp 100-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.28 (m, 1H), 7.35 (dd, *J* = 10.2, 5.7 Hz, 4H), 7.45 (s, 4H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.4, 116.5, 119.9, 123.3, 125.1, 127.3, 128.7, 128.8, 129.5, 130.0, 130.5, 131.3, 131.5, 133.7, 143.7, 150.9; HRMS calc. for $C_{20}H_{13}ClO$ $[M+H]^+$ 305.0728, found 305.0731.

1-[4-(2-(Thiophen-3-yl)benzofuran-3-yl)phenyl]ethanone (66)



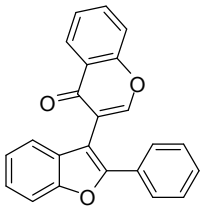
Cream colored solid, 116.1 mg (73%): mp 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 7.20 (d, *J* = 5.1 Hz, 1H), 7.27 (dd, *J* = 7.3, 5.5 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.65 (dd, *J* = 8.6, 5.6 Hz, 3H), 8.09 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 111.4, 115.8, 119.8, 123.4, 123.9, 125.1, 126.1, 126.3, 129.1, 129.6, 130.2, 131.6, 136.5, 138.1, 148.3, 154.0, 197.9; HRMS calc. for $C_{20}H_{14}O_2S$ $[M+H]^+$ 318.0715, found 318.0731.

3-(2-Phenylbenzofuran-3-yl)-1-tosyl-1*H*-indole (68)



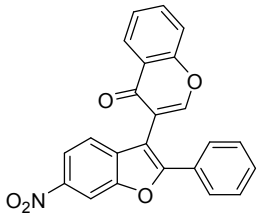
Yellow amorphous solid, 134.1 mg (58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.25 (ddd, *J* = 21.5, 15.1, 8.0 Hz, 7H), 7.37 (dd, *J* = 15.9, 8.5 Hz, 3H), 7.57-7.64 (m, 3H), 7.76 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 8.13 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 108.1, 111.5, 114.1, 114.9, 120.3, 121.4, 123.2, 123.7, 125.1, 125.3, 125.4, 126.9, 127.1, 128.6, 128.7, 130.0, 130.2, 130.5, 130.6, 135.4, 135.7, 145.3, 152.1, 154.3; HRMS calc. for $C_{29}H_{21}NO_3S$ $[M+H]^+$ 463.1242, found 463.1315.

3-(2-Phenylbenzofuran-3-yl)-4*H*-chromen-4-one (70)



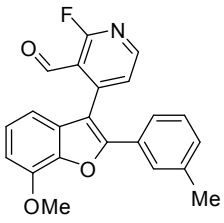
Cream colored solid, 73.4 mg (43%): mp 183-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.28 (m, 1H), 7.29-7.40 (m, 4H), 7.40-7.45 (m, 1H), 7.50 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.53-7.59 (m, 2H), 7.73-7.78 (m, 3H), 8.01 (s, 1H), 8.36 (dd, *J* = 8.0, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.8, 111.5, 118.3, 118.5, 120.5, 123.3, 124.5, 125.0, 125.8, 126.7, 127.3, 128.9, 128.9, 130.4, 130.5, 134.1, 153.1, 154.3, 155.4, 156.7, 176.2; HRMS calc. for $C_{23}H_{14}O_3$ $[M+H]^+$ 339.1016, found 339.1015.

3-(6-Nitro-2-phenylbenzofuran-3-yl)-4*H*-chromen-4-one (72)



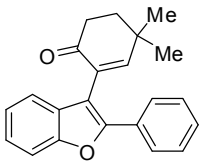
Yellow solid, 44.0 mg (24%): mp 200-203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 3.1 Hz, 3H), 7.50-7.60 (m, 3H), 7.74-7.81 (m, 3H), 8.03 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.9, 115.5, 117.1, 118.6, 119.1, 120.6, 124.3, 126.1, 126.7, 127.6, 129.1, 129.2, 130.2, 134.5, 136.2, 145.3, 152.9, 155.7, 156.6, 158.3, 176.1; HRMS calc. for $C_{23}H_{13}NO_5$ $[M+H]^+$ 384.0866, found 384.0863.

2-Fluoro-4-[7-methoxy-2-(*m*-tolyl)benzofuran-3-yl]nicotinaldehyde (75)



Yellow solid, 116.0 mg (65%): mp 177-180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.09 (s, 3H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 3.2 Hz, 4H), 7.36 (d, *J* = 5.1 Hz, 1H), 7.47 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 56.5, 108.0, 111.5, 124.6, 124.9, 125.2, 125.2, 127.9, 128.9, 129.0, 130.7, 131.0, 139.1, 140.5, 143.6, 145.8, 149.3, 152.3, 152.6, 153.6, 161.4, 164.7, 187.1, 187.1 (extra peaks due to ^{13}C-^{19}F coupling); HRMS calc. for $C_{22}H_{16}FNO_3$ $[M+H]^+$ 361.1114, found 362.1187.

4,4-Dimethyl-2-(2-phenylbenzofuran-3-yl)cyclohex-2-enone (77)

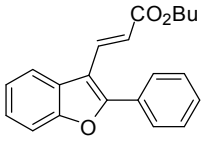


Yellow solid, 54.3 mg (34%): mp 100-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 6H), 2.08 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 6.82 (s, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 3H), 7.33-7.48 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 33.9, 35.3, 36.3, 111.3, 112.5, 115.5, 120.1, 122.9, 124.7, 127.0, 128.6, 130.2, 130.3, 130.9, 151.9, 154.0, 160.7, 197.2; HRMS calc. for $C_{22}H_{20}O_2$ $[M+H]^+$ 339.1356, found 339.1348.

5.6.4. General procedure for the synthesis of benzofurans 80 and 81 by three-component Sonogashira/Heck type coupling.

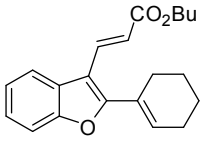
The 2-iodophenol (0.5 mmol) and dichlorobis(triphenylphosphine)palladium (10.5 mg, 3 mol %) were placed in a 5 mL microwave vial and purged with argon. Dry THF (0.5 mL) was added and the reaction mixture was stirred until the iodophenol completely dissolved. Then dry triethylamine (1.0 mL) and a 3.8M solution of CuI in dry triethylamine (0.5 mL) were added and the mixture allowed to stir for 10 min. Then 1.2 equiv of the corresponding alkyne was added; the vial was capped, purged with argon and placed in the microwave reactor for 30 min at 25 ^{o}C. The corresponding alkene (2.5 mmol), dry acetonitrile (2 mL), benzoquinone (0.5 mmol), and anhydrous KOAc (1.5 mmol) were added and the reaction mixture was heated in a microwave reactor at 60 ^{o}C for 25 min. After cooling and standard aqueous work up, the reaction mixture was subject to column chromatography using ethyl acetate/hexane as the eluent to afford the desired products.

Butyl (*E*)-3-(2-phenylbenzofuran-3-yl)acrylate (80)



Orange amorphous solid, 88.9 mg (56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.48 (h, *J* = 7.3 Hz, 2H), 1.67-1.76 (m, 2H), 4.26 (t, *J* = 6.6 Hz, 2H), 4.14-4.41 (m, 2H), 6.71 (s, 1H), 7.31-7.41 (m, 2H), 7.52 (dt, *J* = 13.4, 6.9 Hz, 4H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.5, 31.0, 64.6, 111.8, 112.8, 115.5, 119.4, 121.2, 123.9, 125.5, 126.9, 128.7, 129.1, 129.9, 136.0, 154.7, 157.7, 167.6; HRMS calc. for $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485, found 321.1491.

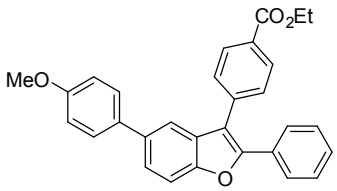
Butyl (*E*)-3-[2-(cyclohex-1-en-1-yl)benzofuran-3-yl]acrylate (81)



Yellow amorphous solid, 113.6 mg (70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.4 Hz, 3H), 1.45 (dd, *J* = 14.8, 7.4 Hz, 2H), 1.68-1.82 (m, 6H), 2.32 (s, 2H), 2.52 (s, 2H), 4.24 (t, *J* = 6.6 Hz, 2H), 6.33 (s, 1H), 6.56 (d, *J* = 16.1 Hz, 1H), 7.26-7.31 (m, 2H), 7.45 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.4, 21.9, 22.5, 26.2, 26.6, 31.0, 64.4, 111.4, 111.8, 117.6, 120.9, 123.6, 124.9, 126.8, 128.4, 134.9, 136.7, 153.9, 160.6, 167.9; HRMS calc. for $C_{21}H_{24}O_3$ $[M+H]^+$ 324.1725, found 325.1799.

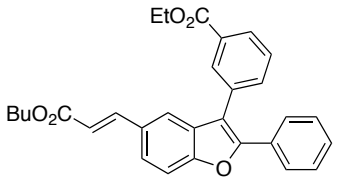
5.6.5. Elaboration of the bromo-containing benzofurans by Pd-catalyzed couplings

Ethyl 4-[5-(4-methoxyphenyl)-2-phenylbenzofuran-3-yl]benzoate (82)



In a 2 mL microwave vial, compound **26** (42.2 mg, 0.1 mmol), 4-methoxyphenylboronic acid (18.2 mg, 0.12 mmol), and tetrakis(triphenylphosphine)palladium (5.8 mg) were dissolved in a 1:1 mixture of EtOH/DMF (1.6 mL), then 1M aq. Cs_2CO_3 (0.25 mL) was added and the mixture was heated in a microwave reactor at 120 ^oC for 20 min. The mixture was diluted with satd. aq. Na_2SO_4 and extracted with ethyl acetate (3 x 15 mL), dried ($MgSO_4$) and evaporated. Column chromatography using ethyl acetate/ hexanes (1:10) as the eluent afforded 35.6 mg (80%) of product **82** as a colorless solid: mp 127-129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (dd, J = 7.4, 6.8 Hz, 3H), 3.85 (d, J = 0.5 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 6.97 (d, J = 8.2 Hz, 2H), 7.30-7.38 (m, 3H), 7.53 (t, J = 8.1 Hz, 3H), 7.63 (dt, J = 17.1, 5.9 Hz, 6H), 8.17 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 55.6, 61.3, 111.5, 114.4, 116.9, 117.9, 124.5, 127.4, 128.6, 128.8, 128.9, 129.8, 129.9, 130.3, 130.4, 130.5, 134.2, 136.8, 137.9, 151.9, 153.6, 159.1, 166.6; HRMS calc. for $C_{30}H_{24}O_4$ $[M+H]^+$ 449.1747, found 449.1675.

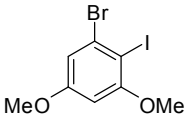
Ethyl 3-[5-((*E*)-3-butoxy-3-oxoprop-1-en-1-yl)-2-phenylbenzofuran-3-yl]benzoate (83)



In a 2 mL vial, compound **28** (41.5 mg, 0.1 mmol), butyl acrylate (17.9 µL, 0.12 mmol), palladium acetate (0.6 mg) and SPhos (4.1 mg) were dissolved in DMF (0.5 mL). Then triethylamine (0.12 mL) was added and the mixture was heated at 100 ^{o}C for 24 h. The mixture was diluted with brine and extracted with ethyl ether (3 x 15 mL), dried ($MgSO_4$) and evaporated. Column chromatography using ethyl acetate/ hexanes (1:10) as the eluent afforded 37.1 mg (81%) of product **83** as a cream colored solid: mp 77-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.42 (m, 5H), 1.69 (m, 2H), 4.20 (t, *J* = 6.7 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.41 (d, *J* = 15.9 Hz, 1H), 7.29-7.36 (m, 3H), 7.50-7.68 (m, 7H), 7.76 (d, *J* = 16.0 Hz, 1H), 8.14 (d, *J* = 7.7 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.5, 19.4, 31.0, 61.4, 64.6, 111.9, 116.7, 117.4, 120.1, 125.2, 127.2, 128.8, 129.1, 129.3, 129.5, 130.0, 130.2, 130.9, 131.8, 132.9, 134.4, 144.9, 152.2, 155.2, 166.4, 167.4; HRMS calc. for $C_{30}H_{28}O_5$ $[M+H]^+$ 468.1937, found 469.2010.

5.6.6. Experimental details related to the synthesis of Amurensin H, Gnetuhainin B and Gnetuhainin F

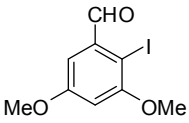
1-Bromo-2-iodo-3,5-dimethoxybenzene (101)



Compound **101** was prepared from a commercially available compound **99** employing an iodination procedure described for analogous compounds. [35] 3,5-Dimethoxybromobenzene (2 g, 9.2 mmol) and 1.75 g (9.2 mmol) of *p*TsOH were dissolved

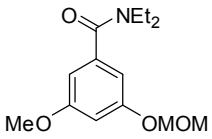
in MeCN (80 mL) and 2.1 g (9.2 mmol) of NIS were added. The reaction mixture was allowed to stir at rt for 24 h, followed by aqueous work up and recrystallization from methanol. Product **101** was obtained as a colorless solid, 3.15 g (100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.84 (s, 3H), 6.34 (d, J = 2.6 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H).

2-Iodo-3,5-dimethoxybenzaldehyde (102)



Compound **102** was prepared from commercially available 3,5-dimethoxybenzaldehyde following the procedure described for the preparation of compound **101**. Compound **102** was obtained as a yellow solid in an 87% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.87 (s, 3H), 6.62 (d, J = 2.9 Hz, 1H), 7.01 (d, J = 2.9 Hz, 1H), 10.12 (s, 1H).

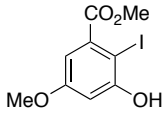
***N*,*N*-Diethyl-3-methoxy-5-(methoxymethyl)benzamide (103)**



Compound **103** was prepared in 4 steps from commercially available 3,5-dihydroxybenzoic acid. Preparation of methyl 3-hydroxy-5-methoxybenzoate has been carried out according to a procedure described in the literature.[36] Then methyl 5-hydroxy-3-methylbenzoate (1.5 g, 8.2 mmol) was dissolved in dry DMF (10 mL), 0.53 g of NaH (1.5 equiv., 12.3 mmol) was added and the solution was stirred for 10 min. After that, 1 mL of MOMCl (12.3 mmol) was added and the reaction mixture stirred for 2 h at rt. The reaction mixture was diluted with a H_2O/Et_2O mixture, extracted with Et_2O and dried, affording 1.86 g (100%) of the methyl 3-methoxy-5-(methoxymethyl)benzoate as a colorless oil. The 3-

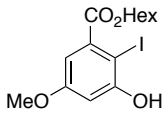
methoxy-5-(methoxymethyl)benzoate was then converted into compound **103** using a procedure analogous to one described in the literature.[37] Compound **103** was obtained as a colorless oil in a 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (br s, 3H), 1.23 (br s, 3H), 3.25 (br d, *J* = 7.8 Hz, 2H), 3.46 (s, 3H), 3.52 (br d, *J* = 7.7 Hz, 2H), 3.79 (s, 3H), 5.15 (s, 2H), 6.55 (br s, 1H), 6.60 (br s, 1H), 6.63 (br s, 1H).

Methyl 3-hydroxy-2-iodo-5-methoxybenzoate (108)



Compound **108** was prepared from compound **107**, synthesized following a previously described procedure.[38] Compound **107** (1.49 g, 7.58 mmol) was dissolved in DMSO (20 mL) and 30% aq. H_2SO_4 (8 mL) was added and the reaction mixture was stirred for 5 min at rt. Then the reaction mixture was cooled to 0 ^{o}C and 0.79 g (11.4 mmol) of $NaNO_2$ dissolved in 4 mL of H_2O was added and the reaction mixture stirred at the same temperature for 30 min. Then 2.5 g (15 mmol) of KI were added. The reaction mixture was allowed to slowly reach rt and kept at that temperature for 4 h. Work-up was carried out according to a procedure described for an analogous process.[39] After column chromatography, compound **108** was obtained as a dark brown oil in a 57% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.93 (s, 3H), 6.23 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 56.3, 79.4, 106.0, 116.3, 126.4, 162.9, 166.9, 179.1.

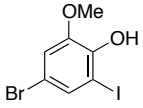
Hexyl 3-hydroxy-2-iodo-5-methoxybenzoate (109)



For the preparation of compound **109**, 0.5 g (2.54 mmol) of compound **108** was treated with 1-hexanol (10 mL) and 1 g of K_2CO_3 and heated to 100 ^{o}C for 16 h. After

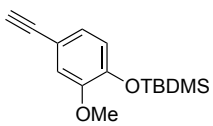
evaporation of the solvents, following a procedure described for the preparation of compound **108**, the desired compound **109** was obtained as a dark red amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75-1.00 (m, 3H), 1.21-1.44 (m, 6H), 1.59-1.78 (m, 2H), 3.77 (s, 3H), 4.29 (t, J = 6.6 Hz, 2H), 6.17 (d, J = 2.3 Hz, 1H), 6.73 (d, J = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 25.8, 28.6, 31.5, 56.2, 66.8, 105.9, 116.1, 126.8, 162.5, 166.8, 179.2.

4-Bromo-2-iodo-6-methoxyphenol (118)



Compound **118** was prepared by a modification of a procedure described for the bromination of guaiacol.[40] 2-Iodo-6-methoxyphenol (**19**, 0.975 g, 3.9 mmol) was dissolved in dry DMF (0.8 mL), the reaction mixture was cooled to 0 ^{o}C and then NBS (0.69 g, 3.9 mmol) in DMF (0.8 mL) was added dropwise. The reaction mixture was stirred for 30 min at 0 ^{o}C and then slowly quenched with an ice cold water/ethyl ether mixture at the same temperature. (The yield of the product dropped significantly when the reaction temperature was not kept at or below 0 ^{o}C). The organic fraction was separated, washed and dried over $MgSO_4$. The reaction mixture was purified using column chromatography and the desired compound **118** was obtained as a brown solid (0.96 g, 75%): m.p. = 77-79 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 4H), 6.04 (s, 1H), 6.94 (d, J = 2.1 Hz, 1H), 7.43 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.7, 81.6, 112.5, 114.3, 132.4, 145.3, 146.4.

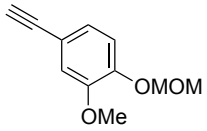
***tert*-Butyl(4-ethynyl-2-methoxyphenoxy)dimethylsilane (120a)**



This compound has been synthesized from 4-ethynyl-2-methoxyphenol, which was obtained following a literature procedure.[41] The TBDMS protection of 4-ethynyl-

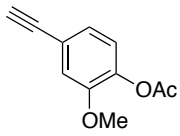
2-methoxyphenol was carried out according to the procedure described in the literature for an analogous substrate[42] and yielded compound **120a** as a yellow oil in a 64% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.99 (s, 9H), 3.00 (s, 1H), 3.80 (s, 3H), 6.78 (dd, *J* = 7.9, 0.4 Hz, 1H), 6.96-7.04 (m, 2H).

5-Ethynyl-2-(methoxymethyl)anisole (120b)



This compound has been prepared by a procedure analogous to that of compound **120a**. The MOM protection procedure was analogous to the one employed in the synthesis of compound **103**. This yielded compound **120b** as a colorless solid in a 67% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 1H), 3.50 (s, 3H), 3.88 (s, 3H), 5.24 (s, 2H), 7.01 (d, *J* = 1.5 Hz, 1H), 7.05-7.09 (m, 2H).

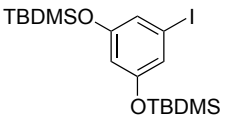
4-Ethynyl-2-methoxyphenyl acetate (120c)



Commercially available 4-bromo-2-methoxyphenol (1.02 g, 5.0 mmol) and acetic anhydride (0.71 mL, 7.5 mmol) were dissolved in dichloromethane (10 mL). Then conc. H_2SO_4 (25 mg) was added and the mixture was stirred for 30 min at rt. The reaction was then subjected to an aqueous work-up analogous to the one described in the literature,[43] resulting in 4-bromo-2-methoxyphenyl acetate**,** obtained as a colorless solid, 1.21 g (99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.82 (s, 3H), 6.90 (d, *J* = 8.6 Hz, 1H), 7.03-7.12 (m, 2H). 4-Bromo-2-methoxyphenyl acetate (1.21 g, 4.9 mmol), palladium acetate (53.8 mg, 0.24 mmol), CuI (23 mg, 0.12 mmol), and tris(*tert*-butyl)phosphinetetrafluoroborate (69.6

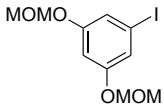
mg, 0.24 mmol) were dissolved in diisopropylamine (10 mL) and purged with argon. Trimethylsilyl acetylene (1.38 mL, 9.8 mmol) was added and the reaction mixture was stirred at 40 °C for 2 h. The work-up was conducted analogous to a procedure described in the literature.[44] The desired alkyne was obtained as a colorless solid (1.28 g, 100%). The resulting product was dissolved in THF (29 mL) and water (3.5 mL) and a 1M solution of TBAF in THF (5.7 mL) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The volatile solvents were evaporated and the aqueous layer was extracted with ethyl acetate. The organic fractions were dried, evaporated, affording 0.74 g (80%) of the desired compound **120c** as a colorless solid: m.p. = 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.07 (s, 1H), 3.82 (s, 3H), 6.99 (d, J = 8.0 Hz, 1H), 7.06-7.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 56.0, 77.3, 83.2, 116.0, 120.8, 123.0, 125.1, 140.5, 150.9, 168.8.

1-Iodo-3,5-bis(*tert*-butyldimethylsiloxy)benzene (121a)



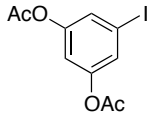
This compound has been prepared from 3,5-dihydroxyiodobenzene following a TBDMS-protection procedure analogous to the one employed in the synthesis of compound **120a**, yielding compound **121a** as a colorless oil in a 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 12H), 0.98 (s, 18H), 6.29 (d, J = 2.1 Hz, 1H), 6.84 (d, J = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.2, 18.4, 25.9, 93.7, 112.2, 123.1, 157.1.

1-Iodo-3,5-bis(methoxymethoxy)benzene (121b)



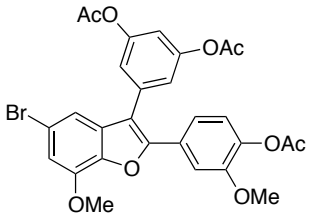
This compound has been prepared from 3,5-dihydroxyiodobenzene following a MOM-protection procedure analogous to the one employed in the synthesis of compound **103**, yielding compound **121b** as a colorless oil in a 41% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 6H), 5.12 (s, 4H), 6.68 (td, J = 2.2, 0.5 Hz, 1H), 7.06 (dd, J = 2.2, 0.5 Hz, 2H).

3,5-Diacetoxyiodobenzene (121c)



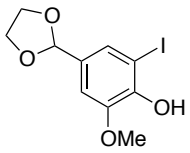
3,5-Dihydroxyiodobenzene (0.27 g, 1.16 mmol) was dissolved in dichloromethane (3 mL); Ac_2O (0.33 mL, 3.49 mmol) and H_2SO_4 (1.2 mg) were added and the mixture was stirred at rt for 1 h. Then conc. aq. $NaHCO_3$ solution was added at 0 ^{o}C and the mixture was allowed to warm up to room temperature. The organic phase was collected, dried ($MgSO_4$) and evaporated. Compound **121c** was obtained as a colorless solid (0.34 g, 91%) and used without further purification: m.p. = 77-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 6.92 (t, J = 2.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 69.5, 92.7, 115.6, 128.4, 151.3, 168.8; HRMS calc. for $C_{10}H_9IO_4$ $[M+Na]^+$ 342.9438, found 342.9441.

2-(4-Acetoxy-3-methoxyphenyl)-5-bromo-3-(3,5-diacetoxyphenyl)-7-methoxybenzofuran (113c)



Compound **113c** was synthesized following the general procedure for a three-component Sonogashira/Cacchi type cyclization and was obtained as a brown amorphous solid (340.6 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 2.31 (s, 3H), 3.67 (s, 3H), 4.03 (s, 3H), 6.95 (s, 1H), 7.00 (s, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 1.2 Hz, 2H), 7.15 (s, 1H), 7.21 (s, 1H), 7.35 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.3, 55.9, 56.6, 110.9, 111.0, 111.1, 114.9, 115.6, 115.7, 116.6, 119.8, 120.6, 123.3, 128.2, 132.6, 134.2, 140.4, 142.2, 145.7, 151.2, 151.5, 151.8, 168.9; HRMS calc. for $C_{28}H_{24}BrO_9$ $[M+H]^+$ 583.0525, found 583.0598.

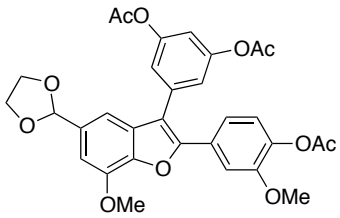
4-(1,3-Dioxolan-2-yl)-2-iodo-6-methoxyphenol (122)



Compound **122** was prepared following a procedure described for an analogous reaction.[45] 5-Iodovanillin (1.0 mmol) and ethylene glycol (5.0 mmol) were dissolved in toluene. Then acidic aluminum oxide was added and the resulted mixture was refluxed for 24 h. After cooling, the mixture was filtered, washed with dichloromethane/water and the organic phase was dried ($MgSO_4$) and evaporated. Column chromatography using ethyl acetate/hexanes (1:3) as the eluent afforded 196 mg (62%) of product **122** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.97-4.06 (m, 2H),

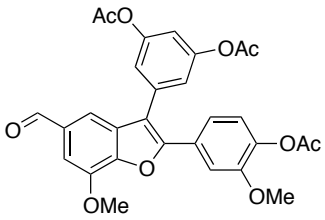
4.08-4.16 (m, 2H), 5.69 (s, 1H), 6.16 (s, 1H), 6.96 (s, 1H), 7.42 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 56.5, 65.5, 80.9, 95.7, 103.0, 108.9, 129.1, 131.6, 146.2, 146.6.

2-(4-Acetoxy-3-methoxyphenyl)-3-(3,5-diacetoxyphenyl)-5-(1,3-dioxolan-2-yl)-7-methoxybenzofuran (123)



Compound **123** was synthesized following the general procedure for the three-component Sonogashira/Cacchi type cyclization and was obtained as a bright yellow oil (340.6 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 2.30 (s, 3H), 3.67 (s, 3H), 4.00-4.05 (m, 2H), 4.07 (s, 3H), 4.14-4.23 (m, 2H), 5.84 (s, 1H), 6.97-7.05 (m, 3H), 7.12 (d, J = 2.2 Hz, 2H), 7.19 (d, J = 13.7 Hz, 2H), 7.37 (dd, J = 8.3, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.3, 55.9, 56.4, 65.5, 104.2, 105.5, 110.9, 111.1, 115.4, 116.5, 117.6, 119.7, 120.7, 123.2, 128.6, 131.2, 134.1, 134.8, 140.2, 143.8, 145.4, 151.1, 151.7, 168.9, 168.9; HRMS calc. for $C_{31}H_{29}O_{11}$ $[M+H]^+$ 577.1704, found 577.1711.

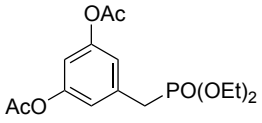
2-(4-Acetoxy-3-methoxyphenyl)-3-(3,5-diacetoxyphenyl)-5-formyl-7-methoxybenzofuran (114)



Compound **114** (85.4 mg, 0.155 mmol) was dissolved in THF (0.3 mL), 10% aq. HCl (62 μL) was added at 0 °C, and the reaction mixture was stirred for 20 min. An aqueous work-up was conducted according to a procedure described in the

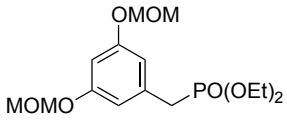
literature.[46] Compound **114** was obtained as a yellow oil (75.8 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 2.30 (s, 3H), 3.67 (s, 3H), 4.08 (s, 3H), 6.99-7.06 (m, 2H), 7.14 (d, *J* = 2.1 Hz, 2H), 7.18 (s, 1H), 7.37 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.40 (s, 1H), 7.61 (s, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.3, 55.9, 56.4, 105.1, 111.1, 115.7, 116.7, 118.5, 119.8, 120.6, 123.4, 127.9, 131.5, 133.9, 133.9, 140.6, 146.2, 146.8, 151.3, 151.9, 152.2, 168.9, 191.8, 191.9; HRMS calc. for $C_{29}H_{25}O_{10}$ $[M+H]^+$ 533.1442, found 533.1443.

3,5-Diacetoxybenzyl diethyl phosphonate (117a)



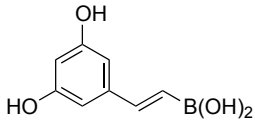
This compound has been prepared in 4 steps starting from commercially available 3,5-dihydroxybenzyl alcohol. Acetylation of the 3,5-dihydroxybenzyl alcohol has been carried out according to a procedure described for an analogous transformation,[47] which yielded 3,5-diacetoxybenzyl alcohol as a colorless oil in a 65% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 6H), 4.56 (s, 2H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 2H). This compound has been treated with PBr_3, according to a procedure described in the literature,[48] which yielded 3,5-diacetoxybenzyl bromide as a colorless oil in a 53% yield. 3,5-Diacetoxybenzyl bromide was then reacted with $P(OEt)_3$, following a procedure described in the literature for an analogous transformation,[49] which yielded compound **117a** as a colorless oil in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 6H), 2.27 (s, 6H), 3.13 (d, *J* = 21.7 Hz, 2H), 3.92-4.05 (m, 4H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.88-7.04 (m, 2H).

3,5-Di(methoxymethoxy)benzyl diethyl phosphonate (117b)



This compound has been prepared from methyl 3,5-dihydroxybenzoate following a MOM-protection procedure analogous to the one employed in the synthesis of compound **103**, affording methyl 3,5-di(methoxymethoxy)benzoate as a colorless oil in a 60% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 6H), 3.90 (s, 3H), 5.19 (s, 4H), 6.91 (t, J = 2.3 Hz, 1H), 7.37 (dd, J = 2.4, 1.3 Hz, 2H). Then 1.25 g (4.88 mmol) of this compound was dissolved in dry DME (9 mL), 0.92 g of $LiAlH_4$ was added, and the reaction mixture was stirred until complete conversion of the starting material was observed (by TLC analysis). After quenching with methanol (4.5 mL) and carrying out an aqueous work-up, 1.05 g (95%) of 3,5-di(methoxymethoxy)benzyl alcohol was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (s, 6H), 4.63 (s, 2H), 5.16 (s, 4H), 6.65 (t, J = 2.3 Hz, 1H), 6.71 (dd, J = 2.1, 0.6 Hz, 2H). 3,5-Di(methoxymethoxy)benzyl alcohol was then converted into compound **117b** following a literature procedure described for analogous substrates,[50] which yielded compound **117b** as a colorless oil in a 75% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H), 3.08 (d, J = 21.7 Hz, 2H), 3.45 (s, 6H), 4.03 (dd, J = 7.9, 7.0 Hz, 4H), 5.13 (s, 4H), 6.63 (m, 3H).

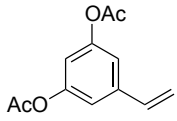
(*E*)-(3,5-dihydroxystyryl)boronic acid (116)



This compound has been prepared from commercially available (*E*)-2-(3,5-dimethoxystyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 0.5 g (1.72 mmol) of which

was dissolved in CH_2Cl_2 (5 mL), the reaction mixture cooled to -78 ^oC, and then treated with neat BBr_3 (4 equiv, 0.66 mL). The reaction mixture was stirred at -78 ^oC for 1 h, then allowed to warm to room temperature and stirred for an additional 1 h. After quenching the reaction mixture with H_2O, extraction with ethyl acetate, and flash column purification, using ethyl acetate as the eluent resulted in compound **116** being obtained as a brown oil in a 40% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 4H), 6.22 – 6.33 (m, 2H), 6.49 (d, J = 2.2 Hz, 2H), 7.19 (d, J = 18.1 Hz, 1H).

3,5-Diacetoxystyrene (115)[51]



This compound has been prepared following the method described in the literature.[51] ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 5.31 (d, J = 10.8 Hz, 1H), 5.73 (d, J = 17.5 Hz, 1H), 6.64 (dd, J = 17.5, 10.9 Hz, 1H), 6.82 (s, 1H), 7.02 (s, 2H).

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CHAPTER 6

One-pot Synthesis of 1-Alkyl-1*H*-indazoles from 1,1-Dialkylhydrazones *via* Aryne Annulation

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6.1. ABSTRACT

The reaction of readily accessible 1,1-dialkylhydrazones with commercially available *o*-(trimethylsilyl)aryl triflates provides a direct one-step route to pharmaceutically important 1-alkylindazoles. The products are obtained in high yields by one-pot NCS-chlorination/aryne annulation or Ac_2O-acylation/deprotection/aromatization protocols.

6.2. INTRODUCTION

1*H*-Indazoles represent an important class of heterocyclic compounds that exhibit a wide range of biological and pharmaceutical activities,[1] including anti-inflammatory,[2] antitumor,[3] and anti-HIV[4] activity among others. Selected examples of 1-alkyl-1*H*-indazoles with notable pharmacological activities include granisetron, a serotonin 5-HT_3 receptor antagonist used to treat nausea and vomiting after chemotherapy;[5] lonidamine, used for the

treatment of brain tumors;[6] and CL-958, an antitumor agent, which is currently in clinical evaluation (Figure 1).[7]

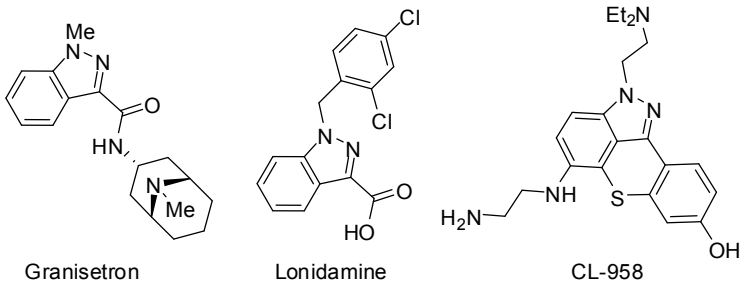
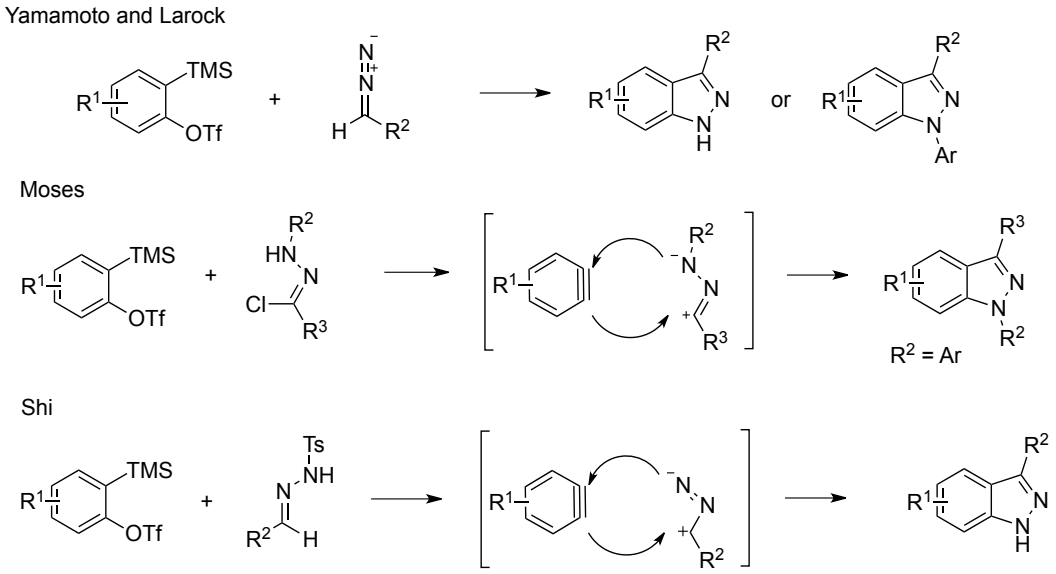


Figure 1. Biologically active 1-alkyl-1*H*-indazoles.

Various methods for the synthesis of the 1*H*-indazole core have been developed.[8] However, most of them employ harsh reaction conditions, thus have limited the scope and applicability. Recently, several methodologies have been reported that involve aryne intermediates in [3 + 2] cycloaddition reactions with diazo compounds, [9] *N*-tosylhydrazones,[10,11] and *in situ* generated nitrile imines (Scheme 1).[12]

Scheme 1. Known aryne-madiated processed for the syntehsis of 1H-indazoles



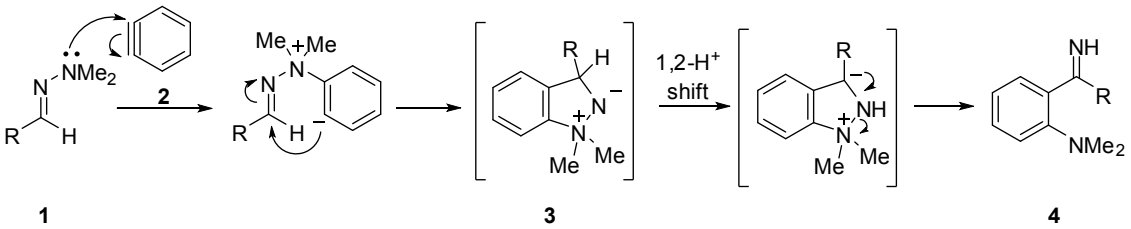
These methods afford 1*H*-indazoles, 1-acyl-1*H*-indazoles or 1-aryl-1*H*-indazoles under mild reaction conditions. However, no aryne-annulation approach to 1-alkyl-1*H*-indazoles has yet been reported.

6.3. RESULTS AND DISCUSSION

6.3.1. Background

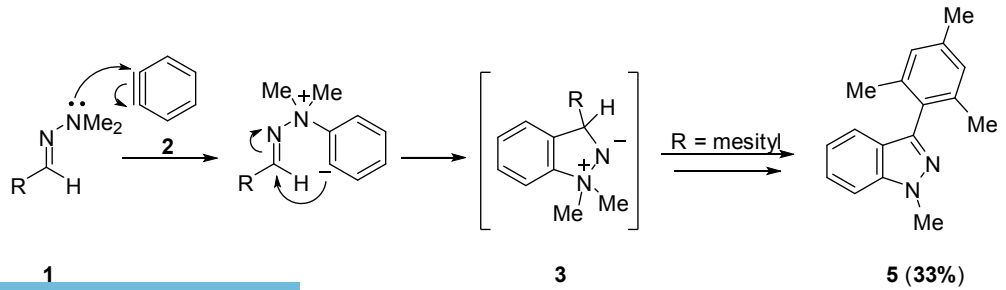
Larock group has previously shown that the reaction of a variety of *N*,*N*-dialkylhydrazones with arynes seemingly proceeds through a cyclic intermediate **3** that subsequently undergoes ring opening to form the corresponding *o*-(dialkylamino)aryl imines **4** (Scheme 2).[13]

Scheme 2. Unusual entry of the mesityl-derived hydrazone



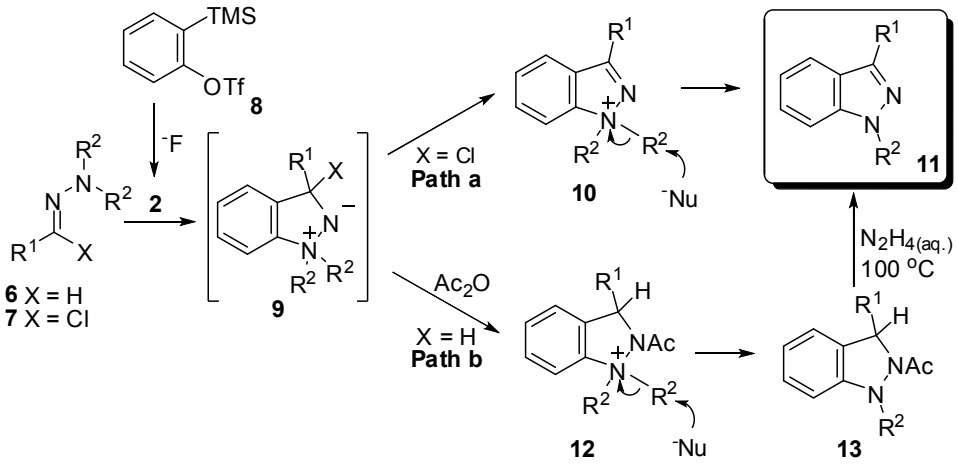
An unexpected result was obtained in the case of the mesityl-substituted substrate, where the corresponding indazole **5** was formed, albeit in only a 33% yield (Scheme 3).

Scheme 3. Unusual entry of the mesityl-derived hydrazone



In order to improve the scope and efficiency of this process, we envisioned that one can retain the cyclic nature of the intermediate **9** in two complementary ways (Scheme 4), namely by having a nearby leaving group (path a) or trapping the amide **9** with a trapping agent (path b).[14]

Scheme 4. Two pathways towards indazoles



6.3.2. One-pot protocol employing NCS

To our delight, we found that the reaction of *N,N*-dimethylhydrazone chloride **7** (R^1 = Ph, R^2 = Me) with benzyne **2**, generated *in situ* from *o*-(trimethylsilyl)aryl triflate[15] **8** in presence of fluoride source, proceeds smoothly to afford indazole **11** in an 81% yield (Scheme 4, path a).

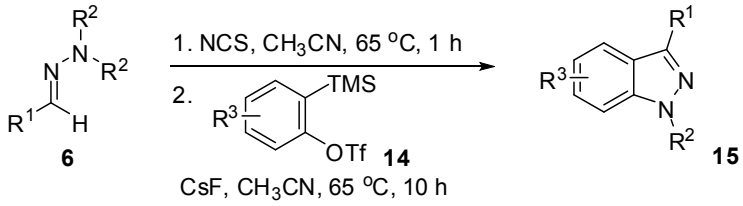
However, it did not prove to be efficient to purify and isolate the labile starting materials **7**. We promptly investigated the possibility of a one-pot procedure wherein the chlorine-containing hydrazones are not isolated, but generated *in situ* from 1,1-dialkylhydrazones **6** and NCS and further reacted with the *o*-(trimethylsilyl)aryl triflate **8** in

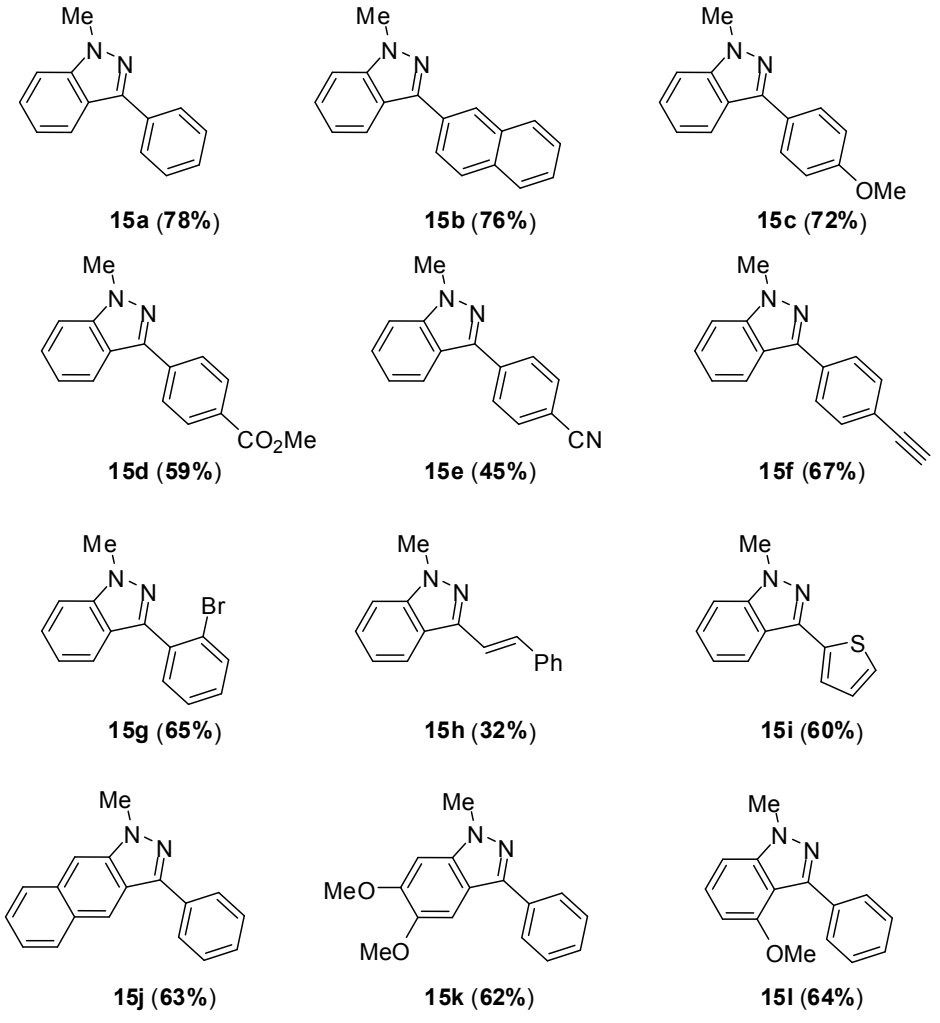
the presence of a fluoride source.[16] To our delight, the desired indazole **11** was obtained in a 78% yield. The optimal reaction conditions were found to be 1.1 equiv. of NCS per 1 equiv. of the hydrazone **6**, and a slight excess of the substrate **6** (1.2 equiv) per 1 equiv. of the aryne precursor **8**. Both steps conveniently proceed in acetonitrile at 65 °C.

With the optimal conditions in hand, we next examined the scope and limitations of this method (Table 1). A range of hydrazones was studied first. Aryl, alkenyl and heteroaryl hydrazones afforded the corresponding indazoles **15a-i** in 32-78% yields. Electron-poor aryl hydrazones afforded the corresponding indazoles **15d** and **15e** in lower yields (59 and 45% respectively). The presence of a cyano group, terminal alkyne moiety, and an *ortho*-bromo substituent was tolerated under these reaction conditions. Unfortunately, hydrazones with R^1 = 4-nitrophenyl, 2-furyl, 2,3,5-trimethoxyphenyl and alkyl groups did not afford the desired indazoles, seemingly due to complications during the NCS chlorination step.

Other aryne precursors were also tested. Symmetrical naphthalyne and dimethoxybenzyne precursors afforded the desired indazoles **15j** and **15k** in good 63 and 62% yields respectively. The unsymmetrical 3-methoxybenzyne precursor provided exclusively the 4-OMe regioisomer **15l** in a 64% yield. The structure of the product **15l** is consistent with the proposed mechanism (Scheme 4, path a).[17]

Table 1. Reaction Scope

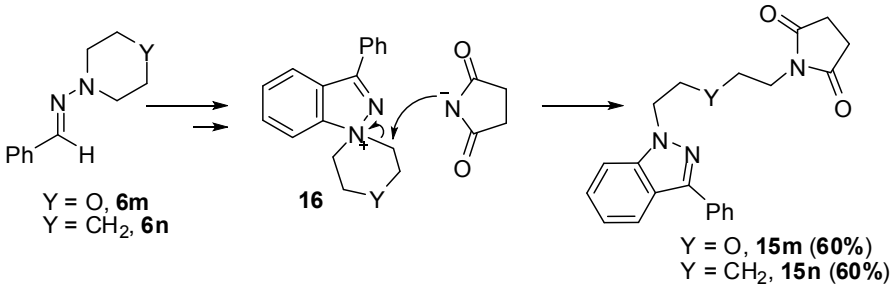




When cyclic hydrazones derived from *N*-aminopiperidine and *N*-aminomorpholine were employed in this one-pot process, the interesting products **15m** and **15n** were obtained, both in a 60% yield (Scheme 5). In these cases, the initially formed indazoliumsalt **16** undergoes

ring-opening by the succinimide moiety present in the reaction media from the chlorination step.[18]

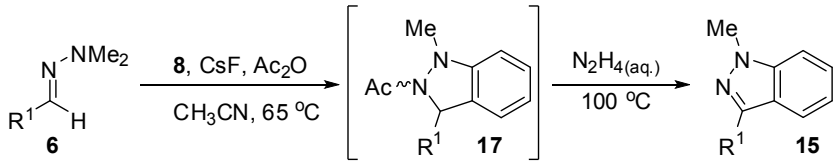
Scheme 5. Reaction of cyclic hydrazones

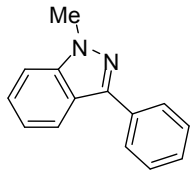


6.3.3. One-pot protocol employing Ac_2O/N_2H_4

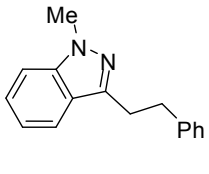
In order to overcome some limitations of the methodology using NCS, we also studied the reaction between the hydrazone **6a** (R^1 = Ph) and the benzyne precursor **8** in the presence of acetic anhydride (Scheme 2, path b). We were pleased to observe formation of the corresponding trapped product **17a** (R^1 = Ph) in an 83% yield, which could also be subsequently deacetylated and aromatized *in situ* to produce the indazole **15a** (overall yield for the 2 steps of 63%). After some optimization studies, we were able to obtain the latter in an 83% overall yield without isolating the intermediate product **17a**. The scope of this process is summarized in Table 2.

Table 2. Reaction Scope for Ac_2O/N_2H_4 protocol

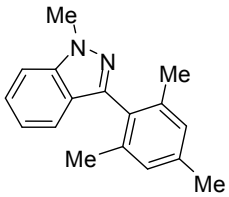




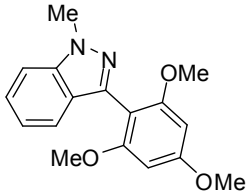
15a (**83%**)



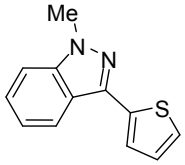
15o (**80%**)



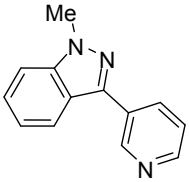
15p (**91%**)



15q (**76%**)



15i (**39%**)
(56% using Boc_2O)



15r (**29%**)

Gratifyingly, a variety of substituents in the R^1 position of the hydrazone are well tolerated. For example, the product **15o** is obtained in an 80% yield. The electron-rich hydrazones, that failed to react efficiently under our NCS-mediated protocol, have afforded the corresponding indazoles **15p** and **15q** in excellent yields (91 and 76%), despite their steric encumbrance. On the other hand, electron-deficient hydrazones, such as 2-thiophenyl and 3-pyridyl hydrazones, provide the corresponding products **15i** and 15r in only 39 and 29% yields respectively.

6.4. CONCLUSIONS

In summary, 1-alkyl-1*H*-indazoles can be prepared from arynes and hydrazones in high yields by one-pot NCS-chlorination/aryne annulation protocol. This chemistry provides a convenient route to 1-alkyl-1*H*-indazoles from readily available *N*,*N*-dimethylhydrazones and presents a valuable extention of the known synthetic routes to indazoles.

6.5. ACKNOWLEDGEMENT

We thank the National Science Foundation and the National Institutes of Health Kansas University Center of Excellence in Chemical Methodology and Library Development (P50 GM069663) for their generous financial support.

6.6. EXPERIMENTAL

6.6.1. General remarks

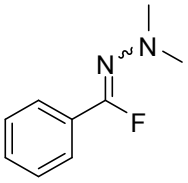
The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Chemical shifts are reported in δ units (ppm) by assigning the TMS resonance in the ^{1}H NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C NMR spectrum as 77.23 ppm. All coupling constants (*J*) are reported in Hertz (Hz). All commercial reagents were used directly as obtained. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points were obtained using an EZ-Melt automated melting point apparatus and are uncorrected. High resolution mass

spectra (HRMS) were obtained using an Agilent QTOF 6540 mass spectrometer (ESI at a voltage of 70 eV). All mass spectra (MS) were obtained using a GCT-Agilent 6890 gas chromatograph/ mass spectrometer (EI at a voltage of 70 eV). All IR spectra were obtained using a Nicolet 380 FT-IR apparatus.

6.6.2. Preparation of hydrazones 6

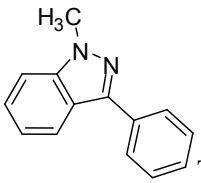
The starting hydrazones were prepared according to the procedure described in our recent communication.[13] The characterization of hydrazones **6a-6c**, **6g**, **6h**, **6j-6m**, **6p** and **6r** can be found therein.

6.6.3. Data for the crude *N′,N′*-dimethylbenzohydrazonoyl fluoride (7a')



^{1}H NMR (400 MHz, CD_3CN) δ 2.83 (s, 6H), 7.44 (m, 3H), 7.73 (d, J = 7.9 Hz, 2H) (succinimide peak: δ 2.60); ^{19}F NMR (400 MHz, CD_3CN) δ -66.6; MS (EI) *m/z* (%) 166 (M^+, 100%), 103 (20%), 77 (19%), 42 (21%); HRMS (ESI) calcd for $[M+H]^+$ $C_9H_{12}FN_2$ 167.0907, found 167.0975.

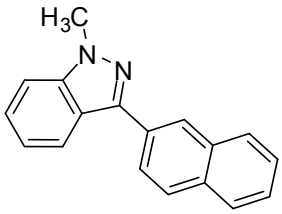
6.6.4. General procedure for the preparation of indazoles 15 by a one-pot NCS procedure. [1-Methyl-3-phenyl-1*H*-indazole[19] (15a) as an example]



To a solution of benzaldehyde dimethylhydrazone **6a** (46 mg, 0.31 mmol, 1.25 equiv.) in 1 mL of acetonitrile under an inert atmosphere *N*-chlorosuccinimide (46 mg,

0.34 mmol, 1.38 equiv) was added and the reaction mixture was stirred for 1 h at 65 °C. Then an additional 4 mL of acetonitrile, together with CsF (114 mg, 0.75 mmol, 3 equiv.) and *o*-(trimethylsilyl)phenyl triflate (61 μL, 0.25 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at 65 °C for an additional 10 h (monitored by TLC). After cooling to room temperature, the reaction mixture was filtered through a short column of celite and concentrated under vacuum. The crude reaction mixture was subjected to column chromatography using ethyl acetate : hexanes (1:10) as eluent and afforded 40.6 mg (78 %) of product **15a**, gray solid: mp 81-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.21 (s, 1H), 7.42 (t, *J* = 4.3 Hz, 3H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.72, 109.38, 121.09, 121.53, 121.81, 126.45, 127.57, 127.99, 128.98, 133.89, 141.63, 143.91; MS (EI) *m/z* (%) 208 (M^+, 100%), 77 (10%); HRMS (EI) calcd for $[M+H]^+$ $C_{14}H_{13}N_2$ 209.1073, found 209.1075; IR (CH_2Cl_2, cm^{-1}) 2939 (m), 1617 (s), 1495 (s), 1351 (s).

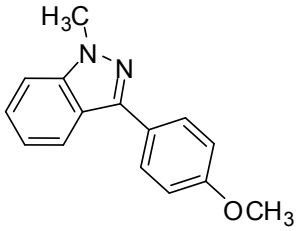
1-Methyl-3-(naphthalen-2-yl)-1*H*-indazole (15b)



Product **15b** was isolated as a yellow oil in a 76% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 3H), 7.27 (ddd, *J* = 7.7, 5.2, 2.0 Hz, 1H), 7.46 (d, *J* = 5.2 Hz, 2H), 7.53 (td, *J* = 5.2, 4.6, 2.1 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.98 (t, *J* = 7.9 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.81, 109.47, 121.25, 121.61, 121.95, 125.67, 126.19, 126.45, 126.52, 127.94, 128.42, 128.65, 131.37, 133.14,

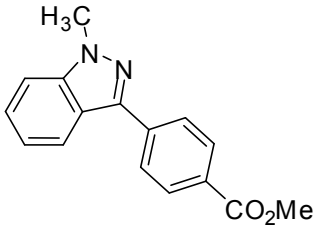
133.82, 141.69, 143.73; MS (EI) *m/z* (%) 258 (M^+, 100%); HRMS (EI) calcd for $[M+H]^+$ $C_{15}H_{15}N_2O$ 259.123, found 259.1234; IR (CH_2Cl_2, cm^{-1}) 2937 (m), 1615 (s), 1494 (m).

3-(4-Methoxyphenyl)-1-methyl-1*H*-indazole (15c)



Product **15c** was isolated as a yellow oil in a 72% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.11 (s, 3H), 7.05 (dd, *J* = 9.0, 2.2 Hz, 2H), 7.20 (ddd, *J* = 7.9, 5.5, 2.3 Hz, 1H), 7.41 (d, *J* = 5.4 Hz, 2H), 7.90 (dd, *J* = 9.0, 2.2 Hz, 2H), 7.99 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.66, 55.53, 109.29, 114.42, 120.83, 121.52, 121.64, 126.38, 126.50, 128.74, 141.53, 143.73, 159.55; MS (EI) *m/z* (%) 238 (M^+, 100%), 223 (61%), 195 (22%); HRMS (EI) calcd for $[M+H]^+$ $C_{15}H_{15}N_2O$ 239.1179, found 239.1179; IR (CH_2Cl_2, cm^{-1}) 3007 (w), 2938 (m), 2838 (m), 1614 (s), 1530 (s), 1035 (s).

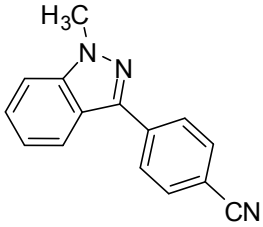
Methyl 4-(1-methyl-1*H*-indazol-3-yl)benzoate (15d)



Product **15d** was isolated as a yellow solid in a 59% yield: mp 117-121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.14 (s, 3H), 7.25 (dt, *J* = 8.1, 4.2 Hz, 1H), 7.44 (d, *J* = 3.5 Hz, 2H), 8.04 (dd, *J* = 11.3, 8.5 Hz, 3H), 8.16 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.91, 52.34, 109.61, 121.29, 121.65, 121.82, 126.63, 127.12, 129.24, 130.30, 138.38, 141.68, 142.57, 167.17; MS (EI) *m/z* (%) 266 (M^+, 100%), 235

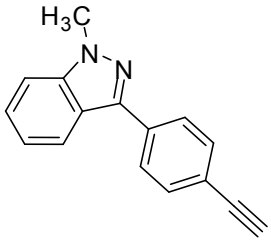
(61%), 208 (12%), 192 (13%); HRMS (EI) calcd for $[M+H]^+$ $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1133; IR (CH_2Cl_2, cm^{-1}) 2951 (m), 1720 (s), 1611 (s), 1114 (s).

4-(1-Methyl-1*H*-indazol-3-yl)benzonitrile (15e)



Product **15e** was isolated as a light yellow solid in a 45% yield: mp 144-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 3H), 7.25-7.30 (m, 1H), 7.46 (d, J = 3.6 Hz, 2H), 7.74-7.79 (m, 2H), 7.99 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.02, 109.82, 111.08, 119.26, 120.96, 121.68, 122.02, 126.81, 127.63, 132.79, 132.96, 138.50, 141.61, 141.76 (the latter peak possibly appears due to the conformational restriction at the C-3 carbon of the indazole); MS (EI) *m/z* (%) 233 (M^+, 100%); HRMS (EI) calcd for $[M+H]^+$ $C_{15}H_{12}N_3$ 234.1026, found 234.1025; IR (CH_2Cl_2, cm^{-1}) 2941 (w), 2228 (s), 1610 (s).

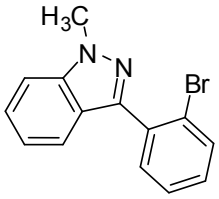
3-(4-Ethynylphenyl)-1-methyl-1*H*-indazole (15f)



Product **15f** was isolated as a yellow solid in a 67% yield: mp 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 1H), 4.13 (s, 3H), 7.18-7.28 (m, 1H), 7.43 (s, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H), 8.00 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.84, 78.04, 83.91, 109.53, 115.50, 121.33, 121.42, 121.70,

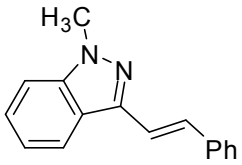
126.57, 127.20, 132.76, 134.36, 141.63, 142.87; MS (EI) *m/z* (%) 232 (M^+, 100%); HRMS (EI) calcd for $[M+H]^+$ $C_{16}H_{13}N_2$ 233.1073, found 233.1078; IR (CH_2Cl_2, cm^{-1}) 3296 (s), 2940 (w), 2107 (w), 1615 (m), 1493 (m).

3-(2-Bromophenyl)-1-methyl-1*H*-indazole (15g)



Product **15g** was isolated as a yellow oil in a 65% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 3H), 7.18 (ddd, *J* = 7.8, 5.6, 2.1 Hz, 1H), 7.30 (td, *J* = 7.7, 1.7 Hz, 1H), 7.38-7.48 (m, 3H), 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.72-7.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.86, 109.31, 120.76, 122.13, 122.66, 123.54, 126.49, 127.47, 129.91, 132.61, 133.46, 134.54, 140.78, 143.93; MS (EI) *m/z* (%) 288 ($[M+2]^+$, 90%), 286 (M^+, 100%), 206 (15%); HRMS (EI) calcd for $[M+H]^+$ $C_{14}H_{12}BrN_2$ 287.0178, found 287.0183; IR (CH_2Cl_2, cm^{-1}) 2939 (m), 1617 (m), 1495 (m), 1027 (m).

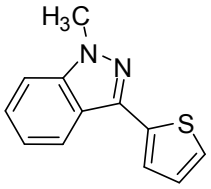
(*E*)-1-Methyl-3-styryl-1*H*-indazole (15h)



Product **15h** was isolated as a light brown solid in a 32% yield: mp 72-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 3H), 7.24 (s, 2H), 7.40 (dd, *J* = 9.5, 6.6 Hz, 3H), 7.43-7.54 (m, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.76, 109.43, 120.19, 121.13, 121.20, 122.21, 126.64, 126.68, 127.91, 128.93, 130.45, 137.61, 141.46, 142.29; MS (EI) *m/z* (%) 234 (M^+, 90%), 233 ($[M-H]^+$,

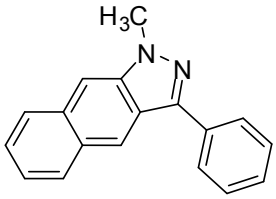
100%), 218 (48%); HRMS (EI) calcd for $[M+H]^+$ $C_{16}H_{15}N_2$ 235.1230, found 235.123; IR (CH_2Cl_2, cm^{-1}) 3082 (w), 2937 (m), 1614 (m), 1493 (m), 962 (s).

1-Methyl-3-(thiophen-2-yl)-1*H*-indazole (15i)



Product **15i** was isolated as a yellow-green oil in a 60% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 3H), 7.17 (dd, J = 4.9, 3.7 Hz, 2H), 7.20-7.26 (m, 2H), 7.33-7.37 (m, 2H), 7.38-7.46 (m, 3H), 7.63 (d, J = 3.6 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.75, 109.44, 121.29, 121.32, 124.46, 124.94, 126.77, 127.82, 136.23, 138.98, 141.48; MS (EI) *m/z* (%) 214 (M^+, 100%), 199 (25%); HRMS (EI) calcd for $[M+H]^+$ $C_{12}H_{11}N_2S$ 215.0637, found 215.0640; IR (CH_2Cl_2, cm^{-1}) 3397 (m), 2948 (m), 2842 (m), 2798 (m), 1595 (m), 1494 (m).

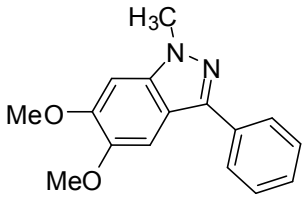
1-Methyl-3-phenyl-1*H*-benzo[*f*]indazole (15j)



Product **15j** was isolated as a yellow solid in a 63% yield: mp 137-139 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (s, 3H), 7.33-7.39 (m, 1H), 7.46 (q, J = 6.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.78 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 7.3 Hz, 2H), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.87, 104.18, 120.32, 123.15, 123.52, 126.22, 127.60, 127.77, 128.19, 129.09, 129.45, 132.57, 133.71,

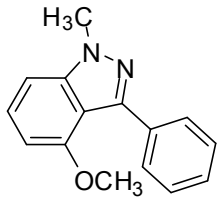
140.52, 143.73; MS (EI) *m/z* (%) 258 (M^+, 100%); HRMS (EI) calcd for $[M+H]^+$ $C_{18}H_{14}N_2$ 259.1230, found 259.1224.

5,6-Dimethoxy-1-methyl-3-phenyl-1*H*-indazole (15k)



Product **15k** was isolated as a yellow solid in a 62% yield: mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.99 (s, 3H), 4.06 (s, 3H), 6.74 (s, 1H), 7.28 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.89 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.84, 56.25, 56.46, 90.65, 100.77, 114.67, 127.29, 127.73, 128.97, 134.08, 137.28, 143.19, 146.53, 150.82; MS (EI) *m/z* (%) 268 (M^+, 100%), 253 (62%), 210 (17%); HRMS (EI) calcd for $[M+H]^+$ $C_{16}H_{17}N_2O_2$ 269. 1285, found 269.1290; IR (CH_2Cl_2, cm^{-1}) 3008 (w), 2937 (m), 2832 (m), 1713 (s), 1630 (s), 1206 (s).

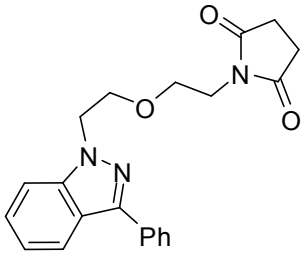
4-Methoxy-1-methyl-3-phenyl-1*H*-indazole (15l)



Product **15l** was isolated as a yellow solid in a 64% yield: mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.09 (s, 3H), 6.52 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.31-7.42 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.86, 55.39, 99.92, 101.98, 112.91, 127.71, 127.78, 127.96, 129.70, 134.15, 143.57, 144.55, 154.72; MS (EI) *m/z* (%) 238 (M^+, 100%), 223 (18%), 208

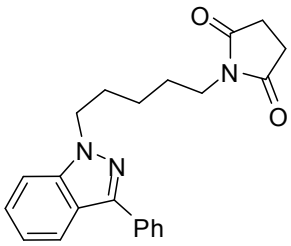
(20%);HRMS (EI) calcd for $[M+H]^+$ $C_{15}H_{15}N_2O$ 239.1179, found 239.1179; IR (CH_2Cl_2, cm^{-1}) 2937 (m), 2840 (w), 1614 (s), 1584 (s), 1507 (s), 1358 (s), 1182 (m).

1-[2-(2-(3-Phenyl-1*H*-indazol-1-yl)ethoxy)ethyl]pyrrolidine-2,5-dione (15m)



Product **15m** was isolated as a colorless oil in a 60% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 4H), 3.53-3.60 (m, 2H), 3.60-3.66 (m, 2H), 3.95 (t, J = 5.2 Hz, 2H), 4.56 (t, J = 5.3 Hz, 2H), 7.16-7.25 (m, 1H), 7.38-7.46 (m, 2H), 7.46-7.56 (m, 3H), 7.95 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.09, 38.19, 49.22, 67.23, 69.82, 110.21, 121.20, 121.26, 121.71, 126.51, 127.70, 128.10, 129.02, 133.83, 142.00, 144.36, 177.20; MS (EI) *m/z* (%) 363 (M^+, 30%), 220 (28%), 207 (100%), 194 (32%), 77 (16%); HRMS (EI) calcd for $[M+H]^+$ $C_{21}H_{22}N_3O_3$ 364.1656, found 364.1664; IR (CH_2Cl_2, cm^{-1}) 2944 (m), 2873 (m), 2798 (m), 1776 (m), 1704 (s), 1399 (m), 1123 (s).

1-[5-(3-Phenyl-1*H*-indazol-1-yl)pentyl]pyrrolidine-2,5-dione (15n)



Product **15n** was isolated as an orange oil in a 60% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (m, 2H), 1.62 (m, 2H), 1.99 (m, 2H), 2.62 (s, 4H), 3.48 (t, J = 7.3 Hz, 2H), 4.42 (t, J = 7.1 Hz, 2H), 7.20 (t, J = 7.0 Hz, 1H), 7.39 (dd, J = 14.4, 6.7 Hz, 3H), 7.50 (t, J = 7.6 Hz, 2H), 7.96 (d, J = 7.6 Hz, 2H), 8.01 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 24.27, 27.41, 28.28, 29.55, 38.66, 48.75, 109.40, 121.05, 121.54, 121.77, 126.34, 127.61, 127.93, 128.94, 133.90, 141.06, 143.86, 177.35; MS (EI) *m/z* (%) 361 (M^+, 100%), 249 (53%), 194 (48%), 77 (29%); HRMS (EI) calcd for $[M+H]^+$ $C_{22}H_{24}N_3O_2$ 362.1863, found 362.1870; IR (CH_2Cl_2, cm^{-1}) 2937 (m), 2862 (m), 1773 (m), 1693 (s), 1491 (s), 1351 (s).

6.7. REFERENCES AND NOTES

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16. During our optimization studies, we have investigated the first NCS-chlorination step by conducting the reaction in CD_3CN and monitoring the completeness of the reaction by ^1H NMR spectroscopy. We have found that the hydrazone **6a** was fully converted to the chlorohydrazone **7a** in about 30 minutes. We have also found that upon addition of CsF to the resulting reaction mixture, the chlorohydrazone **7a** is instantly converted to its fluoro analogue **7a'** (supported by HRMS).
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18. Supporting the mechanism outlined in Scheme 2, GC/MS analysis of the crude reaction mixture for the preparation of **15a** showed a peak (m/z = 113.1) corresponding to *N*-methylsuccinimide. Additionally, the absence of a peak (m/z = 264.32) corresponding to the dimerization product of compound **6a** suggests that this reaction does not proceed through a [3+2] cycloaddition of an azomethyneimine and an aryne.
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CHAPTER 7

Synthesis of Pyrido[1,2-*a*]indole Malonates and Amines through Aryne Annulation

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7.1. ABSTRACT

Pyrido[1,2-*a*]indoles are known as medicinally and pharmaceutically important compounds, but there is a lack of efficient methods for their synthesis. We report a convenient and efficient route to these privileged structures starting from easily accessible 2-substituted pyridines and aryne precursors. A small library of compounds has been synthesized utilizing the developed method, affording variously substituted pyrido[1,2-*a*]indoles in moderate to good yields.

7.2. INTRODUCTION

Selected examples of pyridoindoles have been shown to possess important biological activities (Figure 1). (-)-Goniomitine isolated from the root bark of *Gonioma Malagasy* has

shown significant antitumor activity against several types of cancer cells.[1] A series of indolo[2,1-*a*]isoquinoline compounds have been shown to possess a wide range of biological activities, including cytostatic,[2,3] antiviral,[4] immunosuppressive[5] and tubulin polymerization inhibiting activities.[6] Another series of compounds known as metosenes have shown significant antitumor activity.[7] However, the fully aromatic pyridoindole core has been mentioned in the literature only briefly, mainly due to the challenges in the preparation of this system.[8] Recent efforts, as shown herein, have focused on utilizing the nucleophilic nature of carefully designed pyridines for the synthesis of pyrido[1,2-*a*]indoles.

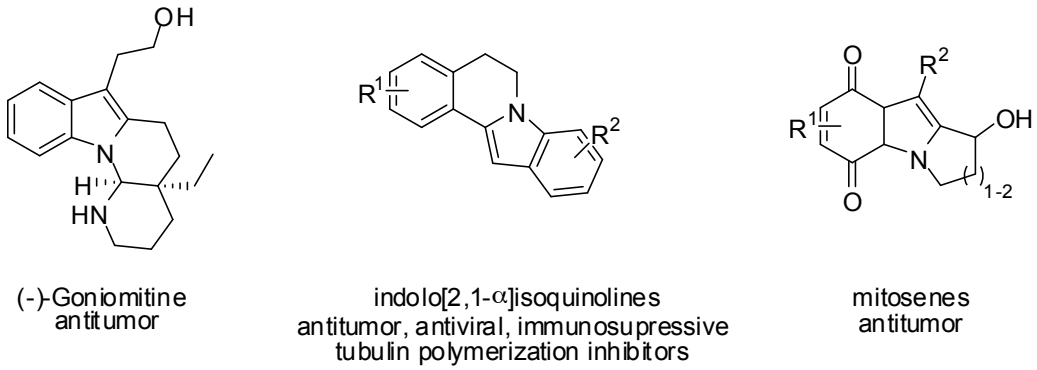


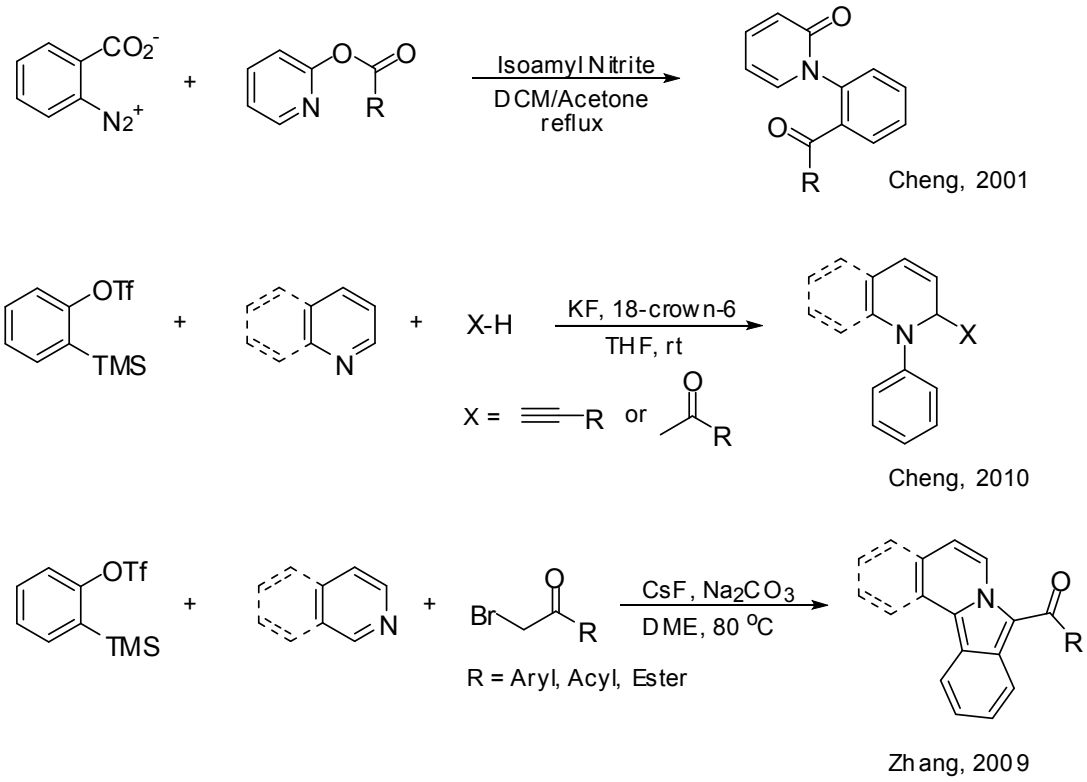
Figure 1. Biologically active compounds containing a pyridoindole core.

The highly electrophilic nature of arynes, as well as recent advances in the development of mild methods for their generation and increasing numbers of commercially available aryne precursors provide a great environment for the development of useful synthetic reactions between arynes and a wide variety of nucleophiles.[9] Developmnent of aryne chemistry allowed to access to a number of interesting heterocycles and carbocycles in few steps, including indoles,[10] xanthones,[11] acridines,[12] indazoles,[13] and benzotriazoles,[14] among others, using mild and functional group tolerant reaction conditions. Our group has a long-term

interest in exploring the full potential of aryne-based methodologies.[15]

A few reports have demonstrated pyridine-aryne couplings. In 2001, Cheng and co-workers reported the reaction of 2-pyridyl carboxylates and benzynes (Scheme 1).[16] In 2010, the same group reported that the multicomponent reaction of pyridines, arynes, and terminal acetylenes or methyl ketones leads to a series of 1,2-disubstituted pyridines.[17] Before that, similar work was reported using acetonitrile as the proton source and secondary nucleophile in place of the terminal acetylene.[18] Additionally, Zhang has reported the reaction of arynes with pyridyl analogues generated *in situ* from pyridines or quinolines and alpha-bromo carbonyl compounds (Scheme 1).[19]

Scheme 1. Aryne-mediated processes involving pyridines



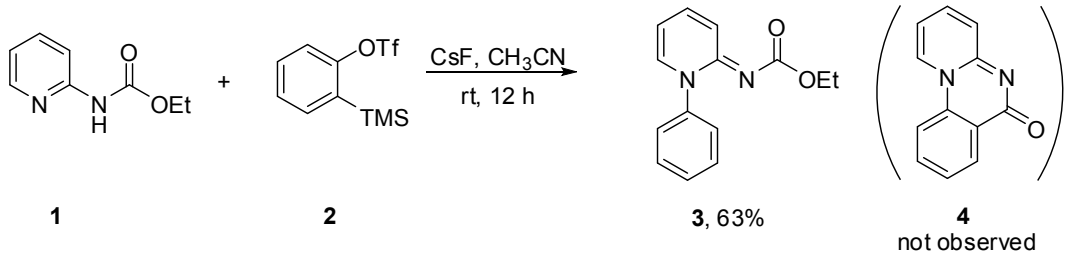
One of the challenges of pyridine-based aryne coupling reactions is neutralization of the newly formed quaternary nitrogen cation. Wanting to incorporate the pyridine ring system into a larger ring system, a series of electrophilic groups in the position 2 of the pyridine ring were envisioned to be compatible mechanistically with arynes, namely Michael acceptors and imines, leading to the stabilized pyrido[1,2-*a*]indole aromatic ring system.

7.3. RESULTS AND DISCUSSION

7.3.1. Aryne annulation of pyridin-2-ylmethyleneamines

Initially, we attempted a reaction between ethyl pyridin-2-ylcarbamate (**1**) with the Kobayashi benzyne precursor **2**,[20] hoping to obtain pyrido[1,2-*a*]quinazolinone **4** (Scheme 2). Instead, the product **3** was isolated in a 63% yield. This might be due to the presence of the fairly acidic amide hydrogen in the starting compound **1**.

Scheme 2. Reaction of ethyl pyridin-2-ylcarbamate (**1**) with benzyne

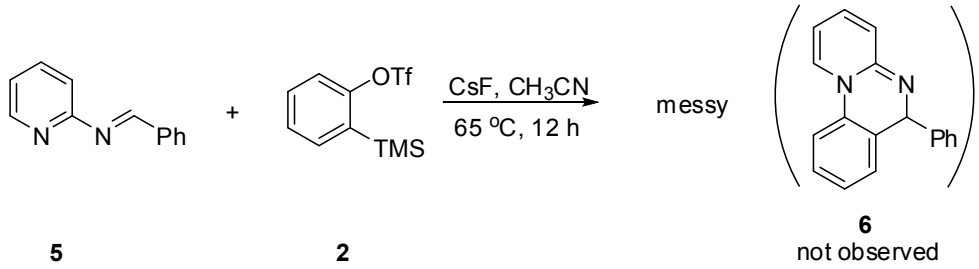


1 **2** **3**, 63% **4** not observed

We then decided to eliminate the acidic hydrogen by switching to a different starting material, namely imine **5** (Scheme 3). In this case, messy reaction mixture was obtained, without any evidence supporting the formation of **6**. We attempted to run this reaction using different solvent (THF or toluene) or replacing CsF with other fluoride sources (e.g. TBAF or

TBAT), but it did not improve the reaction outcome, providing messy reaction mixtures. When the reaction was run in THF at 65 °C, small amount of an unidentified product was isolated with its molecular weight corresponding to the addition of 3 benzyne molecules to the starting imine **5**. Indeed one can imagine that the imine nitrogen atom in the resulted compound **6** is nucleophilic enough to further attack the aryne intermediate, thus providing a complex mixture of overreacted products.

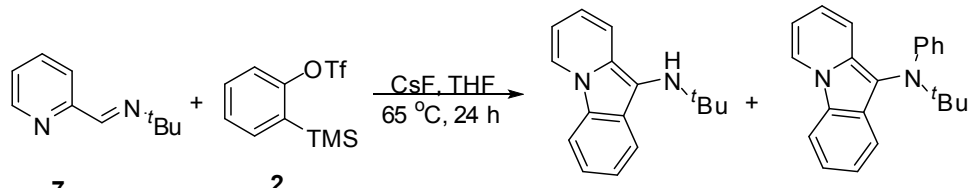
Scheme 3. Reaction of benzylidenepyridinamine (**5**) with benzyne



5 **2** **6** not observed

We then decided to slightly modify the structure of imine **5** and explore analogous imines derived from 2-pyridinecarboxaldehyde, which should lead to the formation of the five-membered heterocycles, namely pyridoindoles. Thus, imine **7** was allowed to react with benzyne to form a mixture of pyridoindoles **8** and **9** in a combined yield of 56% (Scheme 4).

Scheme 4. Reaction of 2-imino-pyridine **7** with benzyne



7 **2** **8**, 25% **9**, 31%

In this case the reactive nitrogen atom in initially formed compound **8** was partially

trapped with one molecule of aryne intermediate to form **9**.

7.3.2. Optimization of the reaction conditions

Attempts were made to inhibit the subsequent arylation process (Table 1). However, in all cases, roughly equimolar mixtures of **8** and **9** were obtained in modest yields (entries 1-4). After evaluating the reaction conditions that should favor formation of the free amino product, we were able to suppress the formation of product **9** and obtain product **8** exclusively, albeit in only 18% yield (entry 5). Alternatively, the subsequent arylation product **9** could be promoted by using an excess of the benzyne precursor (3 equiv) and an elevated reaction temperature (entry 6).

Table 1. Optimization of Aryne Annulations with Pyridin-2-ylmethanimines

entry	**2** (equiv)	fluoride source (equiv)	temp (°C)	% yield[a]
1	1.0	TBAT	rt	62 (34:28)[b]
2	1.2	CsF (3)	65	56 (25:31)[b]
3	2.0	CsF (3)	65	67 (36:31)[b]
4	3.0	CsF (6)	65	70 (55:15)[b]
5	1.2	TBAF (1.4)	-78 to 100	18[c]
6	3.0	CsF (6)	100	72[d]

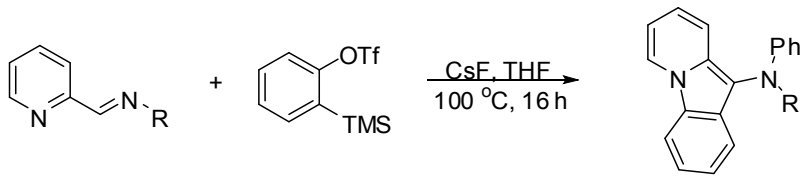
[a] Isolated yields. [b] Combined yield (**8**:**9**). [c] Yield of **8**. [d] Yield of **9**.

7.3.3. Study of the scope of the reaction

With optimal conditions in hand for the synthesis of *N*-aryl-2-pyrido[1,2-*a*]indoles, a series of diverse imines were allowed to react with benzyne precursor **2** (Table 2). To our delight, our optimized conditions provided the corresponding pyridoindoles in good yields starting from a variety of alkyl imines, even with allyl imine **16** and the sterically bulky

adamantyl imine **14** (entries 1-5). Unfortunately, propargyl imine **18** did not provide any of the desired product (entry 6). Additionally, heterocycle-containing primary amines were condensed with 2-pyridinecarboxaldehyde to form a series of imines capable of reacting with benzyne, including substrates containing the medicinally-relevant benzodioxole (**19**), thiophene (**21**), and amide (**23**) functionality (entries 7-9). A major drawback was the fact that all substrates that contained a CH_2 unit directly attached to the imine nitrogen afforded pyridoindoles that were not stable on silica gel and polymerized rapidly. This caused some problems with purification of these compounds, but we found that the addition of 5% triethylamine to both the silica gel and the eluent helped stabilize the compounds and afforded clean products in slightly higher yields. However, despite the instability of the product, even the diimine **25**, derived from 1,2-diaminoethane afforded the corresponding double-annulation product **26** in a 51% yield (entry 10). The halogenated substrates **27** and **29** reacted poorly compared to the corresponding parent substrate **7**, affording the corresponding pyridoindoles **28** and **30** in 34 and 22% yields (entries 11 and 12). Furthermore, the 6-substituted pyridinylmethanimines **31** and **32** did not react with benzyne according to TLC analysis (entries 13 and 14). The quinoline-based imine **33** reacted smoothly to form the desired product **34** in a 75% yield (entry 15). When thiazole derivative **35** was allowed to react using our optimized reaction conditions the desired product **36** was formed, albeit in only 27% yield (entry 16). Unfortunately, the 4-methoxyaniline-derived imine **37** under our optimized reaction conditions afforded a complicated mixture with only trace amounts of the desired pyridoindole based on ^{1}H NMR data (entry 17).

Table 2. Synthesis of Pyridoindoles from *N*-Pyridin-2-yl-methanimines and Arynes[a]



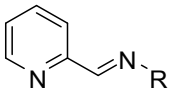
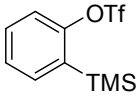
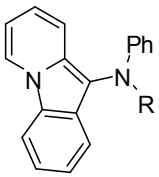
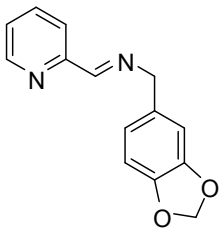
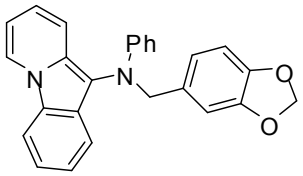
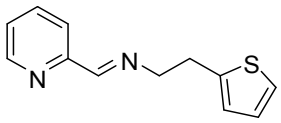
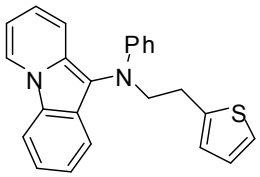
entry	starting material	aryne	product	yield (%)[b]
		 **2**		
1	R = ^{t}Bu, **7**		R = ^{t}Bu, **9**	72
2	R = ^{i}Pr, **10**		R = ^{i}Pr, **11**	66
3	R = Cy, **12**		R = Cy, **13**	75
4	R = Ada, **14**		R = Ada, **15**	62
5	R = Allyl, **16**		R = Allyl, **17**	54
6	R = Propargyl, **18**		R = Propargyl, **-**	0[c]
		**2**		
7	**19**		**20**	78
		**2**		
8	**21**		**22**	70

Table 2 continued.

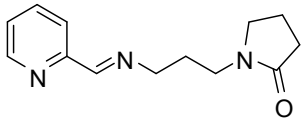
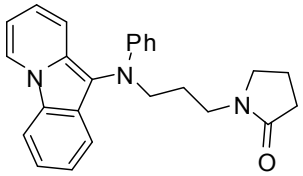
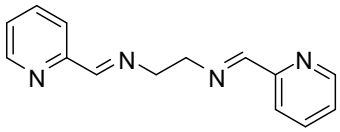
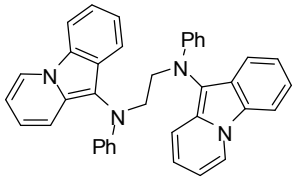
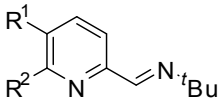
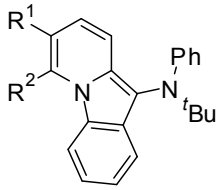
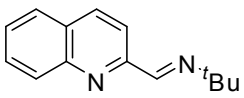
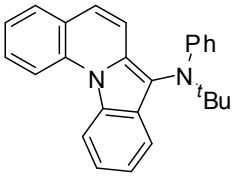
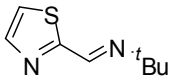
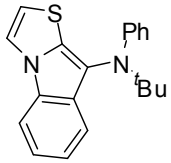
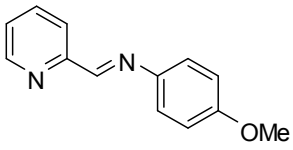
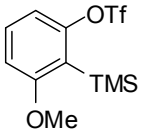
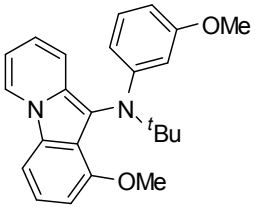
9	 **23**	**2**	 **24**	60
10	 **25**	**2**	 **26**	51
11	 R^1 = Br, R^2 = H, **27**	**2**	 R^1 = Br, R^2 = H, **28**	34[d]
12	R^1 = F, R^2 = H, **29**		R^1 = F, R^2 = H, **30**	22[d]
13	R^1 = H, R^2 = Br, **31**		-	0[e]
14	R^1 = H, R^2 = 4-OMeC_6H_4, **32**		-	0[e]
15	 **33**	**2**	 **34**	75
16	 **35**	**2**	 **36**	27

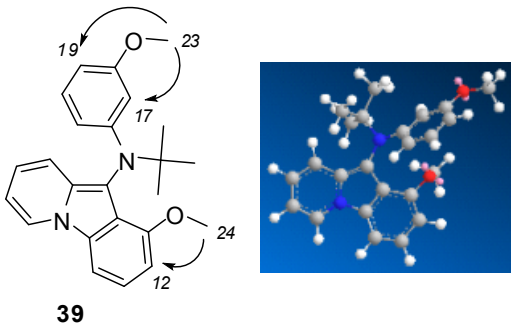
Table 2 continued.

17	 **37**	**2**	-	trace[f]
18	**7**	 **38**	 **39**	80

[a] For the details of experimental procedure, see the experimental section. [b]Isolated yield after column. chromatography. [c]The product was not observed or isolated. [d]The yield was determined by ^{1}H NMR spectral analysis. [e]Recovered unreacted starting material. [f]The reaction afforded a complicated mixture that contained trace amounts of the desired product based on ^{1}H NMR spectral analysis.

7.3.4. Additional studies

Additionally, an unsymmetrical aryne precursor **38** has been employed in the reaction with imine **7**, which provided compound **39** in an 80% yield. The exact structure of the compound **39** has been determined by COSY and NOE experiments (Figure 2).



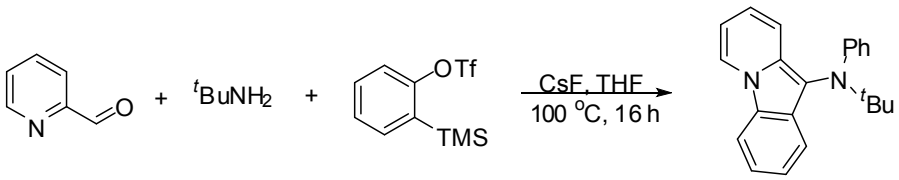
39

Figure 2. Characteristic NOEs observed in the ^{1}H - ^{1}H NOESY analysis (NOESY, 400 MHz, $CDCl_3$) and 3D structure (generated in Chem3D, C: gray; H: white; N: blue; O: red) for compound **39**.

An NOE experiment showed the methoxy protons (C24) coupling to the doublet (C12) and the methoxy protons (C23) coupling to a singlet (C17) and a doublet (C19). If a different isomer had been formed, then the methoxy group (C23) should have ended up ortho to the nitrogen, thus only one coupling of hydrogens at C23 should have been observed.

In addition, we studied the possibility of converting the reaction presented in Scheme 4 into a one-pot protocol without isolation of the imine **7**. We were pleased to find that reaction between the aldehyde **40**, amine **41** (1 equiv) and aryne precursor **2**, under the optimized reaction conditions afforded the desired pyridoindole product **9** in a 60% yield (Scheme 5).

Scheme 5. A one-pot approach for the synthesis of pyridoindoles

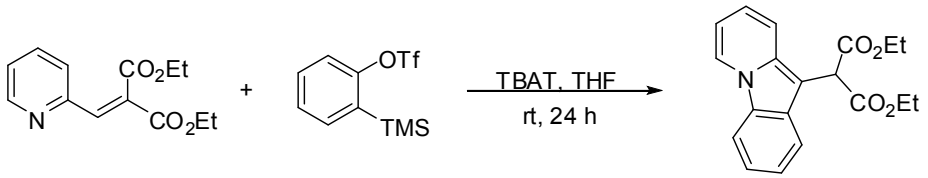


40 **41** **2** **9**, 60%

7.3.5. Aryne Annulation of pyridin-2-malonates[21]

We also shown that in addition to imines, 2-(pyridin-2-ylmethylene)malonates can also participate in the discovered aryne annulation, providing access to the 2-(pyrido[1,2-*a*]indol-10-yl)malonates. Thus, when compound **42** was reacted with benzyne precursor **2** under slightly different reaction conditions the desired pyridoindole **43** was isolated in a 68% yield (Scheme 6).

Scheme 6. Reaction of diethyl 2-(pyridin-2-ylmethylene)malonate **42** with benzyne

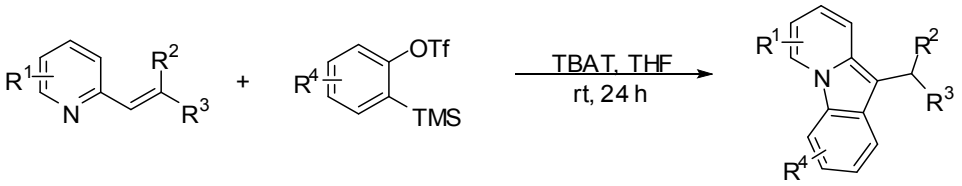


42 **2** **43**, 68%

Selected examples of the scope of this process are shown in Table 3. The methodology tolerates a variety of different esters, providing dimethyl ester, a diethyl ester, a and a dibenzyl ester products **43**, **45** and **49** in good yields (entries 1,2 and 4), whereas sterically hindered di-*t*-butyl ester **46** afforded lower 40% yield of product **47** (entry 3). Similarly to the results obtained with imines (Table 2, entries 11-15), lower yields of final products were obtained when various substituents were placed on the pyridine ring. For example, when a halogen-containing pyridines **50**, **52** and **54** were subjected to the optimized conditions corresponding pyridoindoles **51**, **53** and **55** were isolated in 39, 45 and 51% yields, respectively (entries 5-7). One interesting trend noted is the fact that the yields seemed to increase as the halogen decreased in electronegativity. With quinoline substrate **56** only 32% yield of product **57** was obtained (entry 8), comparing to 75% yield of the product **34** (Table 2, entry 15). However, when a substituent was placed at the 6-position of the pyridine ring (entry 9) the formation of the desired pyridoindole was not observed, analogously to the experiments with imines (table 2, entry 14). β-Keto esters have also been condensed with 2-pyridinecarboxaldehyde in order to obtain the corresponding pyridine-containing Michael acceptors. The methyl ketone **59** (a mixture of *E* and *Z* isomers), afforded product **60** in a 61% yield (entry 10). Unfortunately, thiazole derivative **61** did not afford desired

pyridoindole (entry 11), compared to the lower yield of product **36** (Table 2, entry 16).

Table 3. Synthesis of Pyridoindoles from 2-(Pyridin-2-yl-methylene)malonates and Arynes[a]



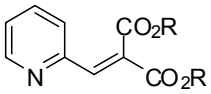
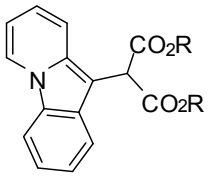
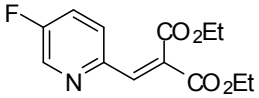
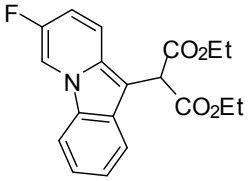
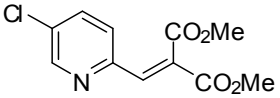
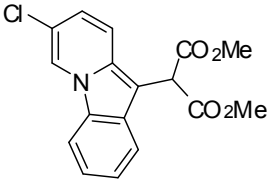
entry	starting material	aryne	product	yield (%)[b]
				
1	R = Et, **42**	**2**	R = Et, **43**	68
2	R = Me, **44**		R = Me, **45**	74
3	R = t-Bu, **46**		R = t-Bu, **47**	40
4	R = Bn, **48**		R = Bn, **49**	72
		**2**		
5	**50**		**51**	39
		**2**		
6	**52**		**53**	45

Table 3 continued.

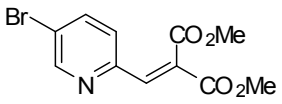
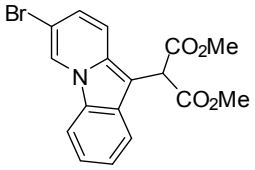
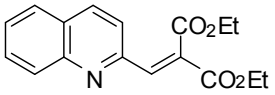
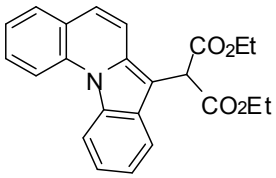
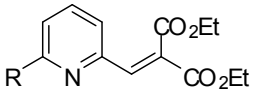
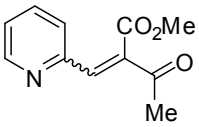
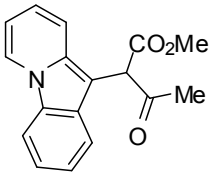
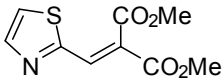
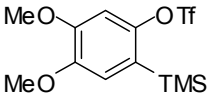
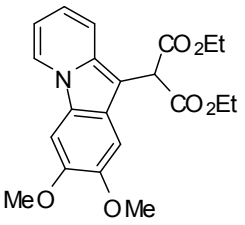
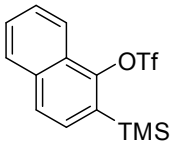
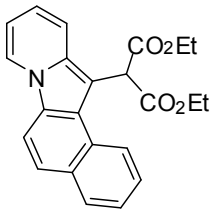
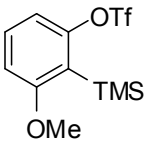
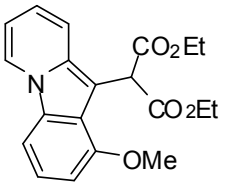
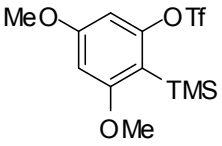
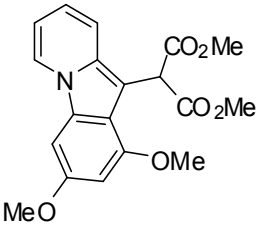
7	 **54**	**2**	 **55**	51
8	 **56**	**2**	 **57**	32
9	 R = 4-$MeOC_6H_4$, **58**	**2**	-	-[c]
10	 **59**	**2**	 **60**	61
11	 **61**	**2**	-	-[b,d]
12	**42**	 **62**	 **63**	64

Table 3 continued.

13	**42**	 **64**	 **65**	66
14	**42**	 **39**	 **66**	75
15	**44**	 **67**	 **68**	73

[a] For the details of experimental procedure, see the experimental section. [b] Isolated yield after column chromatography. [c] The product was not observed or isolated. [d] No reaction. [e] A complicated mixture was observed on TLC analysis.

It was pleasing to see that our conditions tolerated a variety of different benzyne precursors (entries 12-15). Symmetrical benzyne precursor **62** yielded pyrido[1,2-*a*]indole **63** in a 64% yield (entry 12). A series of unsymmetrical benzyne precursors **64**, **39**, and **67** have been examined and all produced single regioisomers in good yields (entries 13-15). These results are in good agreement with previously reported studies on the regioselectivity of reactions involving unsymmetrical aryne precursors[22] and provide additional evidence that

the aryne is initially attacked by the nitrogen of the pyridine ring.

A series of 1D-NOESY and/or 1D-COSY experiments confirmed the structures shown (Figure 3). For example, an NOE interaction was observed between the malonate hydrogen at C14 of **65** and two doublet protons (C5 and C20). Furthermore, using a 1D-COSY experiment, these two doublets were observed to couple to two triplet protons. If the other regioisomer had been formed, the two doublets found to interact with the malonate hydrogen at through 1D-NOESY experiment would have coupled to both a triplet proton and a doublet proton in a 1D-COSY experiment. For compounds **66** and **68**, NOE interactions between the malonate hydrogen (C14) and the methoxy protons (C19) were observed along with coupling to the doublet hydrogen at C5.

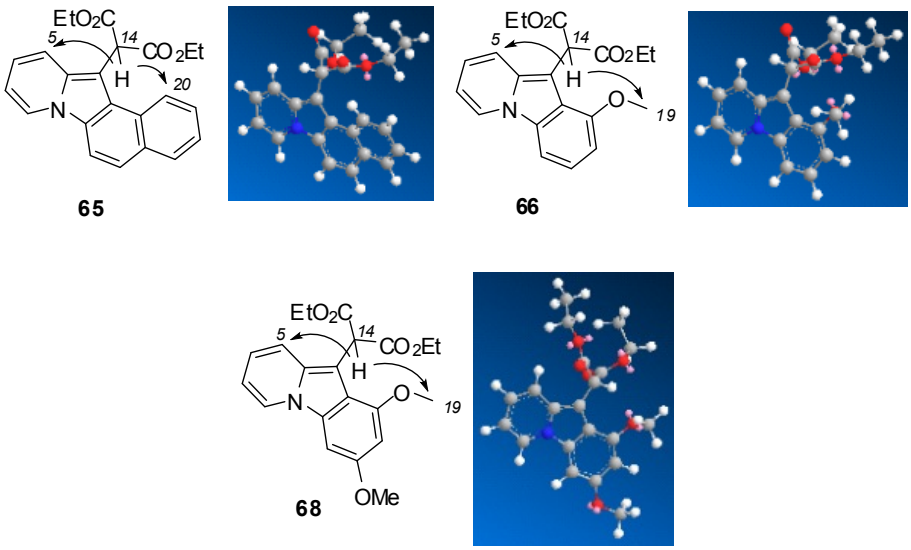
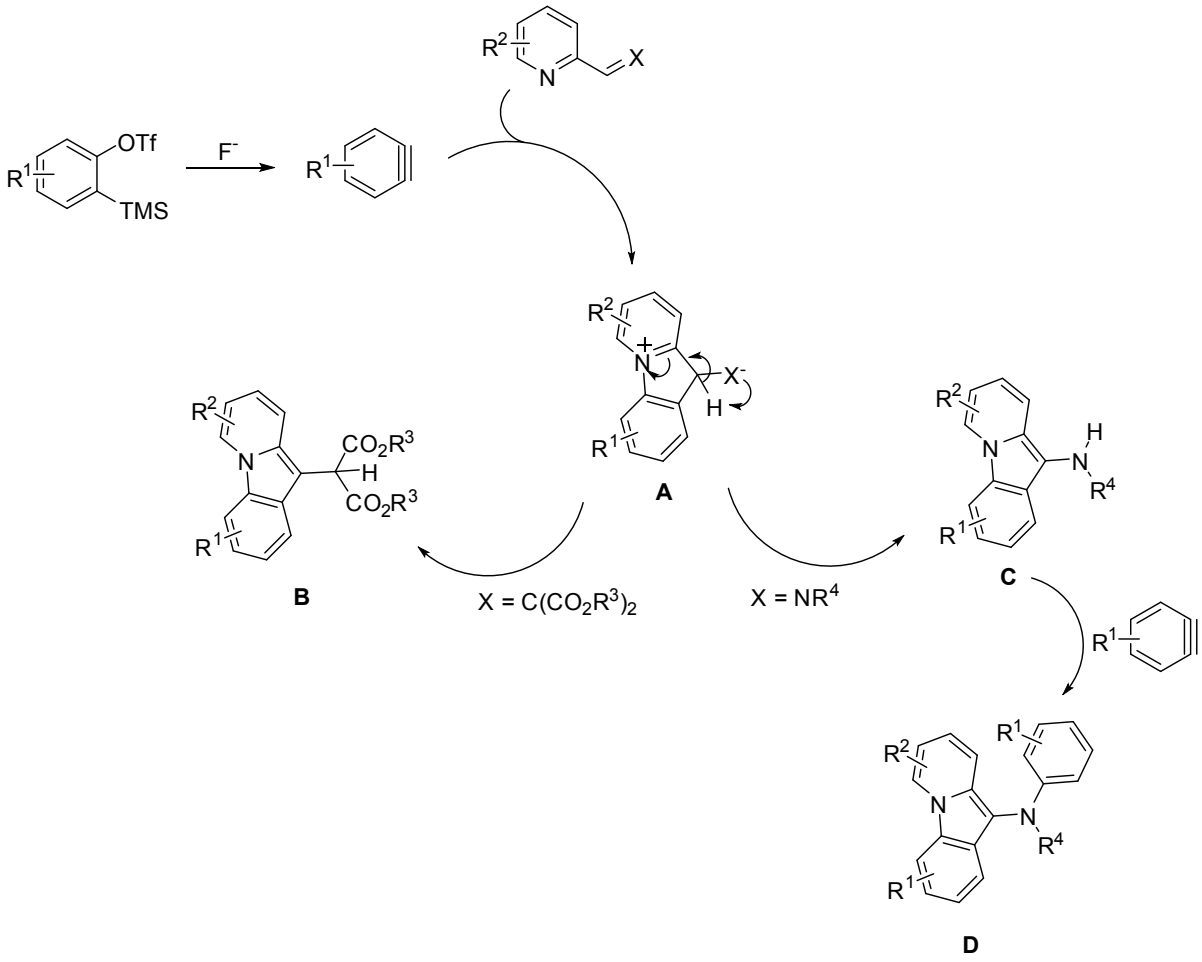


Figure 3. Characteristic NOEs observed in the ^{1}H - ^{1}H NOESY analysis (NOESY, 400 MHz, $CDCl_3$) and 3D structures (generated in Chem3D, C: gray; H: white; N: blue; O: red) for compounds **65**, **66** and **68**.

7.3.6. Reaction mechanism

A proposed reaction mechanism is shown in Scheme 7. Initially, the pyridyl nitrogen attacks the aryne as a nucleophile, pushing electrons onto an adjacent aromatic carbon. Then the newly formed aryl carbanion attacks the neighboring electrophile to form intermediate **A**, which subsequently abstracts a hydrogen to afford the neutralized aromatic structures **B** or **C**. In the case of *N*-pyridin-2-yl-methanimines (X = NR) **C**, a subsequent aryne reaction takes place to form the arylated amine **D**.

Scheme 7. Proposed mechanism for formation of the pyrido[1,2-*a*]indoles



7.4. CONCLUSIONS

In conclusion, certain readily obtainable 2-substituted pyridines when allowed to react with arynes, give a variety of biologically relevant pyrido[1,2-*a*]indoles in good overall yields under mild reaction conditions. Thus a new route to an understudied heterocyclic ring system has been developed. The optimized methodology tolerates a variety of functional groups, with substituents on the pyridine ring being less efficient. A number of various 2-substituted pyridines reacted with benzyne precursors, both symmetrical and unsymmetrical, to yield the desired pyrido[1,2-*a*]indoles in good yields.

7.5. ACKNOWLEDGEMENTS

We gratefully acknowledge the National Science Foundation and the National Institutes of Health Kansas University Center of Excellence in Chemical Methodology and Library Development (P50 GM069663) for their generous financial support. We would also like to thank Dr. Feng Shi and Anton Dubrovskiy for their help in preparing benzyne precursors.

7.6. EXPERIMENTAL

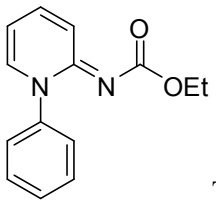
7.6.1. General remarks

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained

commercially. Compounds **1**[23] and **5**[24] were prepared according to the literature procedures.

7.6.2. Preparation of (*E*)-ethyl 1-phenylpyridin-2(1*H*)-ylidenecarbamate (3)

Compound **1** (41.6 mg, 0.25 mmol) was placed in a vial with a screw cap. CsF (113.9 mg, 0.75 mmol) was added, the mixture flushed with argon and diluted with dry acetonitrile (5 mL), then 2 (73 L, 0.3 mmol) was added, the vial was sealed and the reaction mixture stirred at room temperature for 16 h. After reaction completion and standard aqueous work up the crude reaction mixture was purified by column chromatography (ethyl acetate: hexanes (2:1)).



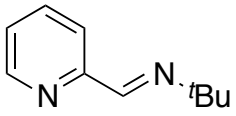
This compound was obtained in a 63% yield (38.2 mg) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 8.00 (dd, J = 9.4, 1.1 Hz, 1H), 7.45 – 7.53 (m, 3H), 7.38 – 7.44 (m, 2H), 7.34 (dd, J = 7.2, 1.8 Hz, 2H), 6.45 (td, J = 6.7, 1.4 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.34., 160.53,, 142.41,, 139.22, 138.78, 129.63,, 129.01, 126.81, 120.68, 109.33, 61.18, 14.84; HRMS (EI) calcd for $C_{14}H_{15}N_2O_2$ 243.1128, found 243.1135.

7.6.3. General procedure for preparation of the pyridin-2-ylmethanimines

The commercially available aldehyde (2.34 mmol) was added to a 5-10 mL round-bottom flask equipped with a magnetic stir bar. The flask was sealed, purged with argon, and water (0.6 mL) was added. To the resulting suspension or solution was added the corresponding amine (1-3 equiv) and the mixture was stirred at room temperature overnight.

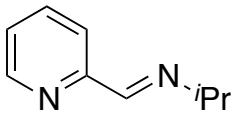
Then the reaction mixture was subjected to an aqueous work up using ethyl acetate or diethyl ether as the organic phase. The organic layer was separated, dried over anhydrous $MgSO_4$, and the solvent was removed to afford the pure imine.

***tert*-Butyl(pyridin-2-yl-methylene)amine (7)**[25]



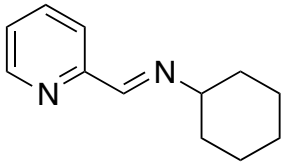
This compound was obtained as a yellow liquid (322.2 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.0 Hz, 1 H), 8.36 (s, 1 H), 8.02 (d, J = 7.9 Hz, 1 H), 7.73 (t, J = 7.7 Hz, 1 H), 7.29 (ddd, J = 7.5, 4.9, 1.2 Hz, 1 H), 1.31 (s, 9 H).

Isopropyl(pyridin-2-yl-methylene)amine (10)[26]



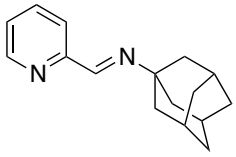
This compound was obtained as a brown liquid (250.2 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.5 Hz, 1 H), 8.38 (s, 1 H), 7.98 (d, J = 7.9 Hz, 1 H), 7.72 (t, J = 7.7 Hz, 1 H), 7.34-7.25 (m, 1 H), 3.70-3.57 (m, 1 H), 1.27 (d, J = 6.3 Hz, 6 H).

Cyclohexyl(pyridin-2-yl-methylene)amine (12)[27]



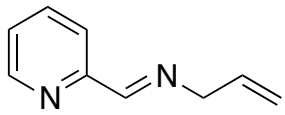
This compound was obtained as a brown liquid (440.1 mg, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 4.9 Hz, 1 H), 8.39 (s, 1 H), 7.98 (d, J = 7.9 Hz, 1 H), 7.72 (t, J = 6.8 Hz, 1 H), 7.29 (ddd, J = 7.4, 4.9, 1.2 Hz, 1 H), 3.29 (tt, J = 10.3, 4.0 Hz, 1 H), 1.91-1.49 (m, 7 H), 1.46-1.14 (m, 3 H).

Adamantyl(pyridin-2-yl-methylene)amine (14)



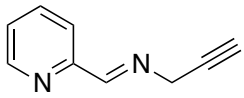
This compound was obtained as a yellow solid (516.1 mg, 92%): mp = 40-42 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 3.1 Hz, 1 H), 8.34 (s, 1 H), 8.01 (d, *J* = 6.9 Hz, 1 H), 7.71 (t, *J* = 7.1 Hz, 1 H), 7.32-7.23 (m, 1 H), 2.16 (s, 3 H), 1.82 (s, 6 H), 1.71 (q, *J* = 12.5 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 155.8, 149.4, 136.7, 124.5, 121.1, 58.3, 43.2, 36.7, 29.7; HRMS (EI) calcd for $C_{16}H_{20}N_2$ 241.1699, found 241.1700.

Allyl(pyridin-2-yl-methylene)amine (16)[28]



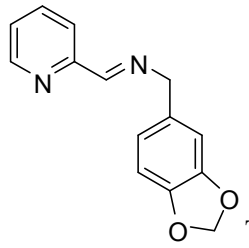
This compound was obtained as a dark brown oil (270.4 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.8 Hz, 1 H), 8.40 (s, 1 H), 8.18-7.88 (m, 1H), 7.75 (t, *J* = 7.7 Hz, 1 H), 7.45-7.28 (m, 1 H), 6.24-5.95 (m, 1H), 5.37-5.04 (m, 2 H), 4.32 (dd, *J* = 5.8, 1.4 Hz, 2 H).

Propargyl(pyridin-2-yl-methylene)amine (18)



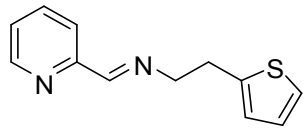
This compound was obtained as a brown liquid (262.3 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 1.7 Hz, 1 H), 8.66 (d, *J* = 3.8 Hz, 1 H), 7.98 (d, *J* = 7.9 Hz, 1 H), 7.75 (t, *J* = 6.9 Hz, 1 H), 7.37-7.29 (m, 1 H), 4.64-4.51 (m, 2 H), 2.55 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.4, 149.7, 136.8, 125.2, 121.7, 78.5, 76.4, 47.3; HRMS (EI) calcd for $C_9H_8N_2$ 145.0760, found 145.0761.

1-(Benzo[1,3]dioxol-5-yl)-*N*-(pyridin-2-yl-methylene)methanamine (19)



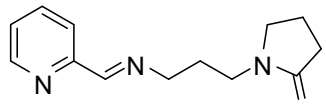
This compound was obtained as a pale yellow solid (505.8 mg, 90%): mp 75-77 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.8 Hz, 1 H), 8.43 (s, 1 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 7.72 (t, *J* = 7.7 Hz, 1 H), 7.35-7.26 (m, 1 H), 6.83 (s, 1 H), 6.78 (s, 2 H), 5.92 (s, 2 H), 4.76 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 154.6, 149.5, 147.9, 146.8, 136.7, 132.6, 124.9, 121.5, 121.5, 108.9, 108.9, 108.4, 101.1, 101.1, 101.0, 64.8; HRMS (EI) calcd for $C_{14}H_{12}N_2O_2$ 241.0972, found 241.0978.

***N*-(Pyridin-2-ylmethylene)-2-(thiophen-2-yl)ethanamine (21)**



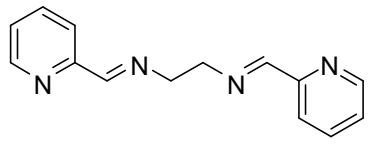
This compound was obtained as a yellow oil (409.3 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1 H), 8.33 (s, 1 H), 8.00 (d, *J* = 7.9 Hz, 1 H), 7.75 (td, *J* = 7.8, 1.7 Hz, 1 H), 7.32 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1 H), 7.13 (dd, *J* = 5.1, 1.2 Hz, 1 H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1 H), 6.85 (dd, *J* = 3.4, 0.9 Hz, 1 H), 3.95 (td, *J* = 7.1, 1.3 Hz, 2 H), 3.27 (t, *J* = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 154.6, 149.6, 142.3, 136.8, 131.7, 126.9, 125.4, 125.0, 123.9, 121.6, 62.8, 31.5; HRMS (EI) calcd for $C_{12}H_{12}N_2S$ 217.0794, found 217.0797.

(*E*)-1-[3-(Pyridin-2-ylmethyleneamino)propyl]pyrrolidin-2-one (23)



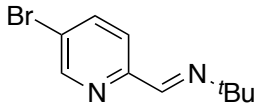
This compound was obtained as a yellow oil (226.5 mg, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 3.8 Hz, 1 H), 8.34 (s, 1 H), 7.90 (d, J = 7.9 Hz, 1 H), 7.70 (ddt, J = 9.4, 7.7, 1.8 Hz, 1 H), 7.32-7.22 (m, 1H), 3.64 (t, J = 6.9 Hz, 2 H), 3.36 (q, J = 6.8 Hz, 4 H), 2.31 (t, J = 8.1 Hz, 2 H), 2.02-1.86 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 162.5, 154.4, 149.6, 136.7, 124.9, 121.6, 59.0, 47.3, 40.8, 31.2, 28.5, 18.0; HRMS (EI) calcd for $C_{13}H_{18}N_3O$ 232.1444, found 232.1447.

(N^1E,N^2E)-N^1,N^2-Bis(pyridin-2-ylmethylene)ethane-1,2-diamine (25)



This compound was obtained as a yellow solid (298.9 mg, 54%): mp = 61-63 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.1 Hz, 2 H), 8.40 (s, 2 H), 7.96 (d, J = 7.9 Hz, 2 H), 7.71 (td, J = 7.7, 1.8 Hz, 2 H), 7.28 (ddd, J = 7.5, 4.9, 1.3 Hz, 2 H), 4.05 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 154.5, 149.6, 136.7, 124.9, 121.5, 61.5; HRMS (EI) calcd for $C_{14}H_{15}N_4$ 239.1291, found 239.1297.

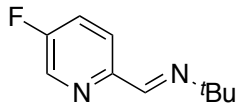
***tert*-Butyl-(5-bromopyridin-2-ylmethylene)amine (27)**



This compound was obtained as a brown solid (545.2 mg, 97%): mp 35-37 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.6 Hz, 1 H), 8.29 (s, 1 H), 7.93 (d, J = 8.4 Hz, 1 H), 7.84 (dd, J = 8.5, 1.8 Hz, 1 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

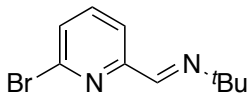
155.5, 154.2, 150.5, 139.4, 122.3, 121.9, 58.3, 29.7; HRMS (EI) calcd for $C_{10}H_{13}BrN_2$ 241.0335, found 241.0336.

***tert*-Butyl-(5-fluoropyridin-2-ylmethylene)amine (29)**



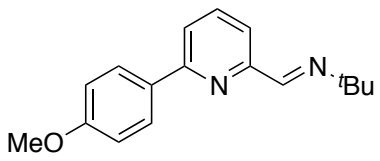
This compound was obtained as a yellow oil (193.8 mg, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.8 Hz, 1 H), 8.32 (s, 1 H), 8.05 (dd, *J* = 8.8, 4.8 Hz, 1 H), 7.43 (td, *J* = 8.2, 2.6 Hz, 1 H), 1.29 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 ($^1J_{CF}$ 257 Hz), 155.2, 152.1 ($^3J_{CF}$ 4 Hz), 137.5 ($^2J_{CF}$ 24 Hz), 123.6 ($^2J_{CF}$ 19 Hz), 122.3 ($^3J_{CF}$ 4 Hz), 58.0, 29.8; HRMS (EI) calcd for $C_{10}H_{13}FN_2$ 181.1136, found 181.1137.

***tert*-Butyl-(6-bromopyridin-2-ylmethylene)amine (31)**



This compound was obtained as colorless crystals (515.2 mg, 91%): mp 50-52 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 8.00 (dd, *J* = 7.6, 0.9 Hz, 1 H), 7.57 (t, *J* = 7.5 Hz, 1 H), 7.46 (dd, *J* = 7.8, 0.9 Hz, 1 H), 1.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 155.4, 141.4, 139.0, 128.9, 119.5, 58.4, 29.7; HRMS (EI) calcd for $C_{10}H_{13}BrN_2$ 241.0355, found 241.0339.

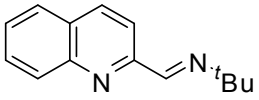
***tert*-Butyl[6-(4-methoxyphenyl)pyridin-2-ylmethylene]amine (32)**



This compound was obtained as a cream colored solid (305.2 mg, 97%): mp 81-83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.06-7.92 (m, 3 H), 7.73 (t, *J* = 7.7 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.00 (d, *J* = 8.6 Hz, 2 H), 3.85 (s, 3 H),

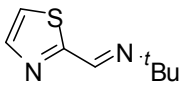
1.35 (d, J = 2.5 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 157.4, 156.7, 155.5, 137.2, 131.9, 128.3, 120.6, 118.3, 114.3, 57.9, 55.5, 29.8; HRMS (EI) calcd for $C_{17}H_{21}N_2O$ 269.1648, found 269.1653.

***tert*-Butyl(quinolin-2-ylmethylene)amine (33)**



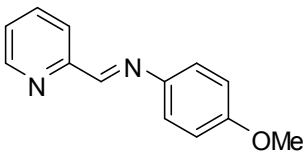
This compound was obtained as a yellow solid (417.8 mg, 84%): mp 54-56 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1 H), 8.20 (q, J = 8.7 Hz, 2 H), 8.12 (d, J = 8.4 Hz, 1 H), 7.84 (d, J = 8.1 Hz, 1 H), 7.73 (t, J = 7.7 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 1.36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 155.8, 147.8, 136.5, 129.8, 129.5, 128.8, 127.8, 127.2, 118.4, 58.2, 29.8; HRMS (EI) calcd for $C_{14}H_{16}N_2$ 213.1386, found 213.1391.

***tert*-Butyl(thiazol-2-ylmethylene)amine (35)**



This compound was obtained as a pale yellow liquid (198.3 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 7.87 (d, J = 2.8 Hz, 1 H), 7.35 (d, J = 3.1 Hz, 1 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 143.9, 123.8, 121.2, 58.5, 29.6; HRMS (EI) calcd for $C_8H_{12}N_2S$ 169.0794, found 169.0795.

(*E*)-4-methoxy-*N*-(pyridin-2-ylmethylene)aniline (37)[29]



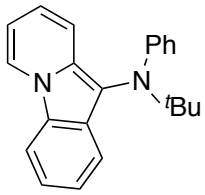
This compound was obtained as a yellow oil (441.2 mg, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 5.0 Hz, 1 H), 8.63 (s, 1 H), 8.19 (d, J = 7.8 Hz, 1 H), 7.80 (td, J = 7.8, 1.8 Hz, 1 H), 7.34 (d, J = 8.7 Hz, 3 H), 6.95 (d, J = 8.8 Hz, 2 H), 3.84 (s,

3 H).

7.6.4. General procedure for preparation of the *N*-methyl-*N*-phenylpyrido[1,2-*a*]indol-10-amines

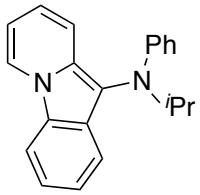
To a dry 4 dram vial equipped with a magnetic stir bar and screw cap, CsF (228 mg., 1.5 mmol, 6 equiv) was added under an inert atmosphere of nitrogen. Then, the corresponding imine (0.25 mmol), THF (5 mL), and the aryne precursor (0.75 mmol, 3 equiv) were added and the vial was tightly sealed. The reaction mixture was vigorously stirred at 100 ºC for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate, filtered and concentrated under reduced pressure. The crude reaction mixture was then purified by column chromatography using hexanes or ethyl acetate/hexane mixtures with the addition of 1% triethylamine as the eluent to afford pure product.

***N*-(*tert*-Butyl)-*N*-phenylpyrido[1,2-*a*]indol-10-amine (9)**



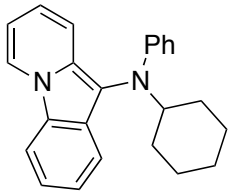
This compound was obtained a yellow oil (56.1 mg, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.1 Hz, 1 H), 7.83 (dd, *J* = 10.4, 8.2 Hz, 2 H), 7.48 (dt, *J* = 9.4, 1.2 Hz, 1 H), 7.40-7.34 (m, 1 H), 7.26 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2 H), 6.80 (ddd, *J* = 9.4, 6.3, 1.0 Hz, 1 H), 6.38 (ddd, *J* = 7.4, 6.4, 1.2 Hz, 1 H), 1.26 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 134.5, 128.7, 128.3, 127.9, 124.3, 123.1, 122.4, 119.9, 119.4, 119.0, 117.6, 117.8, 112.6, 110.4, 107.9, 57.6, 30.4; HRMS (EI) calcd for $C_{22}H_{22}N_2$ 314.1625, found 314.1633.

***N*-(Isopropyl)-*N*-phenylpyrido[1,2-*a*]indol-10-amine (11)**



This compound was obtained as a yellow solid (49.9 mg, 66%): mp 129-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.0 Hz, 1 H), 7.94 (d, *J* = 7.3 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.35-7.29 (m, 1 H), 7.11 (t, *J* = 7.8 Hz, 1 H), 6.88-6.82 (m, 1 H), 6.64 (dd, *J* = 18.4, 7.8 Hz, 1 H), 6.50 (t, *J* = 6.6 Hz, 1 H), 4.63-4.46 (m, 1 H), 1.25 (d, *J* = 6.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 134.8, 129.2, 128.4, 128.3, 124.4, 123.0, 122.4, 120.0, 119.5, 117.8, 116.4, 113.2, 110.4, 108.1, 107.0, 49.7, 21.5; HRMS (EI) calcd for $C_{21}H_{20}N_2$ 301.1699, found 301.1699.

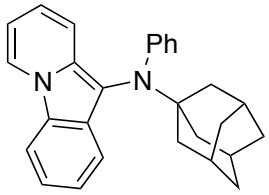
***N*-Cyclohexyl-*N*-phenylpyrido[1,2-*a*]indol-10-amine (13)**



This compound was obtained as a yellow oil (61.1 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.0 Hz, 1 H), 7.94 (d, *J* = 7.1 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 3 H), 7.11 (t, *J* = 7.9 Hz, 2 H), 6.88-6.81 (m, 1 H), 6.65 (t, *J* = 7.1 Hz, 1 H), 6.60 (d, *J* = 8.2 Hz, 2 H), 6.50 (t, *J* = 6.6 Hz, 1 H), 4.08 (t, *J* = 11.4 Hz, 1 H), 2.21 (d, *J* = 12.1 Hz, 2 H), 1.76 (d, *J* = 13.3 Hz, 2 H), 1.58 (d, *J* = 16.9 Hz, 1 H), 1.44 (q, *J* = 13.2 Hz, 2 H), 1.34-1.07 (m, 3 H), 0.98-0.87 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 134.6, 129.2, 128.3, 128.2, 124.3, 123.0, 122.4, 120.0, 119.6, 117.9, 116.3, 113.1, 110.4, 108.1, 107.7, 58.5, 32.0, 26.3, 25.8; HRMS (EI) calcd for $C_{24}H_{24}N_2$ 341.2012, found

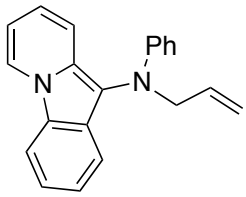
341.2013.

***N*-Adamantyl-*N*-phenylpyrido[1,2-*a*]indol-10-amine (15)**



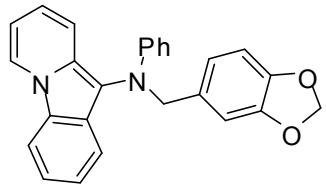
This compound was obtained as a yellow solid (61.2 mg, 62%): mp 128-130 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.0 Hz, 1 H), 7.86 (dd, *J* = 13.5, 8.2 Hz, 2 H), 7.49 (d, *J* = 9.4 Hz, 1 H), 7.38 (t, *J* = 7.1 Hz, 1 H), 7.32-7.23 (m, 2 H), 7.16-7.00 (m, 4 H), 6.85 (dd, *J* = 8.4, 6.3 Hz, 1 H), 6.74 (t, *J* = 6.9 Hz, 1 H), 6.44 (t, *J* = 6.2 Hz, 1 H), 2.19 (s, 6 H), 2.09 (s, 3 H), 1.65 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 135.1, 129.5, 128.2, 127.9, 124.2, 123.0, 122.3, 119.7, 119.2, 118.1, 112.2, 110.3, 107.9, 58.1, 42.5, 36.7, 30.5. HRMS (EI) calcd for $C_{28}H_{28}N_2$ 393.2325, found 393.2324.

***N*-Allyl-*N*-phenylpyrido[1,2-*a*]indol-10-amine (17)**



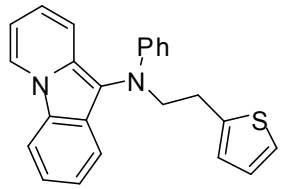
This compound was obtained as an orange oil (40.2 mg, 54%) and was highly unstable in various solvents and neat. Due to the low stability a clean ^{13}C NMR spectrum of this compound could not be obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.1 Hz, 1 H), 7.92 (d, *J* = 7.1 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.32 (d, *J* = 4.9 Hz, 2 H), 7.13 (t, *J* = 8.0 Hz, 2 H), 6.88-6.79 (m, 1 H), 6.70 (s, 3 H), 6.50 (s, 1 H), 6.12-5.97 (m, 1H), 5.31 (dd, *J* = 17.2, 1.7 Hz, 1 H), 5.14 (dd, *J* = 10.3, 1.6 Hz, 1 H), 4.40 (dt, *J* = 5.5, 1.6 Hz, 2 H); HRMS (EI) calcd for $C_{21}H_{18}N_2$ 298.1470, found 298.1466.

***N*-(Benzo[1,3]dioxol-5-ylmethyl)-*N*-phenylpyrido[1,2-*a*]indol-10-amine (20)**



This compound was obtained as an orange oil (76.6 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.1 Hz, 1 H), 7.92 (d, *J* = 8.3 Hz, 1 H), 7.60 (d, *J* = 7.3 Hz, 1 H), 7.36-7.28 (m, 2 H), 7.23 (d, *J* = 9.3 Hz, 1 H), 7.11 (t, *J* = 8.0 Hz, 2 H), 6.94 (s, 1 H), 6.89 (d, *J* = 8.6 Hz, 1 H), 6.83 (dd, *J* = 8.7, 6.8 Hz, 1 H), 6.72 (d, *J* = 7.9 Hz, 1 H), 6.68 (d, *J* = 7.9 Hz, 3 H), 6.47 (t, *J* = 6.7 Hz, 1 H), 5.90 (s, 2 H), 4.96 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 147.9, 146.5, 133.9, 132.1, 129.1, 128.1, 125.7, 124.5, 123.1, 122.4, 120.2, 120.1, 118.7, 117.2, 113.5, 112.1, 110.6, 108.4, 108.0, 107.8, 101.1, 101.0, 101.0, 56.8; HRMS (EI) calcd for $C_{26}H_{19}N_2O_2$ 392.1519, found 392.1527.

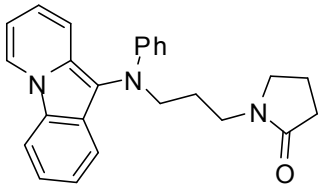
***N*-Phenyl-*N*-[2-(thiophen-2-yl)ethyl]pyrido[1,2-*a*]indol-10-amine (22)**



This compound was obtained as an orange oil (65.2 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.1 Hz, 1 H), 7.97 (d, *J* = 7.0 Hz, 1 H), 7.61-7.54 (m, 1 H), 7.39-7.32 (m, 2 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 5.1 Hz, 1 H), 6.95-6.90 (m, 1 H), 6.90-6.84 (m, 1 H), 6.81 (s, 1 H), 6.72 (t, *J* = 8.1 Hz, 3 H), 6.52 (t, *J* = 6.7 Hz, 1 H), 4.12-4.03 (m, 2 H), 3.31-3.20 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 141.8, 132.7, 130.5, 129.4, 128.2, 127.1, 126.2, 125.0, 124.5, 123.6, 123.2, 122.6, 120.2, 118.6, 117.0, 112.9, 110.6, 108.2, 54.1, 28.8; HRMS (EI) calcd for $C_{24}H_{20}N_2S$

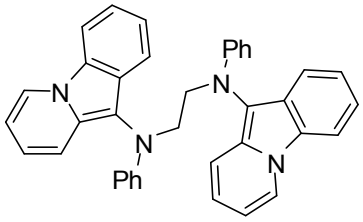
369.1420, found 369.1414.

1-[3-(Phenyl(pyrido[1,2-*α*]indol-10-yl)amino)propyl]pyrrolidin-2-one (24)



This compound was obtained as an orange oil (57.8 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.1 Hz, 1 H), 7.94 (d, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 6.9 Hz, 1 H), 7.32 (t, *J* = 6.0 Hz, 2 H), 7.25 (d, *J* = 9.7 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 2 H), 6.87 (dd, *J* = 9.3, 6.4 Hz, 1 H), 6.67 (dd, *J* = 21.0, 7.7 Hz, 3 H), 6.50 (t, *J* = 6.8 Hz, 1 H), 3.31 (t, *J* = 7.4 Hz, 2 H), 3.81 (t, *J* = 7.7 Hz, 2 H), 3.22 (t, *J* = 7.0 Hz, 2 H), 2.33 (t, *J* = 8.2 Hz, 2 H), 1.92 (t, *J* = 7.6 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 149.3, 132.6, 129.3, 128.1, 126.2, 124.5, 123.2, 122.6, 120.2, 118.6, 117.0, 116.9, 112.9, 110.7, 110.6, 108.2, 49.7, 47.2, 40.7, 31.2, 26.4, 18.0; HRMS (EI) calcd for $C_{25}H_{26}N_3O$ 384.2070, found 384.2063.

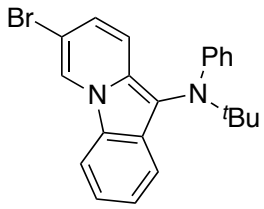
***N*^{1},*N*^{2}-Diphenyl-*N*^{1},*N*^{2}-di(pyrido[1,2-α]indol-10-yl)ethane-1,2-diamine (26)**



This compound was obtained as a yellow solid (69.2 mg, 51%): mp 268-271 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.1 Hz, 2 H), 7.98- 7.85 (m, 2 H), 7.60-7.45 (m, 2 H), 7.40-7.28 (m, 4 H), 7.17 (d, *J* = 9.2 Hz, 2 H), 6.96 (dd, *J* = 8.6, 7.1 Hz, 4 H), 6.80 (dd, *J* = 9.0, 6.6 Hz, 2 H), 6.59 (t, *J* = 7.3 Hz, 2 H), 6.48 (dd, *J* = 11.2, 7.4 Hz, 6 H),

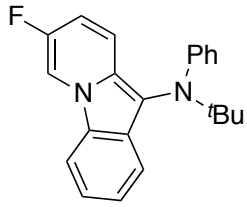
4.15 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 132.6, 129.2, 128.2, 126.1, 124.5, 123.2, 122.6, 120.1, 118.4, 116.9, 112.8, 110.7, 110.6, 108.1, 50.3; HRMS (EI) calcd for $C_{38}H_{30}N_4$ 542.2465, found 542.2472.

7-Bromo-*N*-(*tert*-butyl)-*N*-phenylpyrido[1,2-*a*]indol-10-amine (28)



This compound was obtained as an orange oil in a 34% yield (NMR yield based on the addition of 1,4-dimethoxybenzene as an internal standard): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.85 (d, *J* = 8.1 Hz, 1 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 7.33 (dt, *J* = 18.6, 8.6 Hz, 3 H), 7.05 (t, *J* = 8.0 Hz, 2 H), 6.87 (t, *J* = 8.2 Hz, 3 H), 6.69 (t, *J* = 7.2 Hz, 1 H), 1.52 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 132.5, 128.7, 128.4, 127.8, 125.5, 124.4, 123.5, 120.9, 119.8, 119.3, 118.7, 118.0, 114.1, 110.4, 102.5, 57.6, 30.4; HRMS (EI) calcd for $C_{22}H_{21}BrN_2$ 392.0883, found 392.0892.

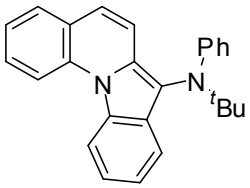
7-Fluoro-*N*-(*tert*-butyl)-*N*-phenylpyrido[1,2-*a*]indol-10-amine (30)



This compound was obtained as an orange solid in a 22% yield (NMR yield based on the addition of 1,4-dimethoxybenzene as an internal standard): mp 104-105 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 3.3 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 7.34 (ddd, *J* = 24.9, 12.8, 6.3 Hz, 3 H), 7.05 (t, *J* = 8.0 Hz, 2 H), 6.88 (d,

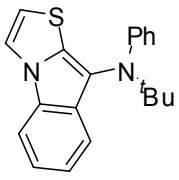
J = 8.1 Hz, 2 H), 6.81 (t, *J* = 7.9 Hz, 1 H), 6.68 (t, *J* = 7.3 Hz, 1 H), 1.53 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 150.3, 149.4, 132.4, 128.9, 128.4, 123.0, 120.5, 120.0, 119.4, 118.9, 118.8, 118.0, 115.7, 115.4, 113.7, 110.4, 110.3, 109.9, 57.6, 30.4 (extra peaks due to 13C-19F coupling); HRMS (EI) calcd for $C_{22}H_{21}FN_2$ 333.1762, found 333.1754.

***N*-(*tert*-Butyl)-*N*-phenylindolo[1,2-*a*]quinolin-7-amine (34)**



This compound was obtained as a yellow oil (68.3 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.3 Hz, 1 H), 8.50 (d, *J* = 8.5 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.63 (t, *J* = 8.5 Hz, 2 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.40-7.30 (m, 3 H), 7.08 (dd, *J* = 14.5, 8.9 Hz, 3 H), 6.90 (d, *J* = 8.1 Hz, 2 H), 6.69 (t, *J* = 7.2 Hz, 1 H), 1.59 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 137.0, 134.7, 131.7 129.8, 129.1 129.0, 128.5, 124.8 124.2, 123.0, 122.2, 119.9, 118.42, 117.8, 117.5, 116.8, 115.7, 114.5, 57.5, 30.4; HRMS (EI) calcd for $C_{26}H_{24}N_2$ 365.2012, found 365.2003.

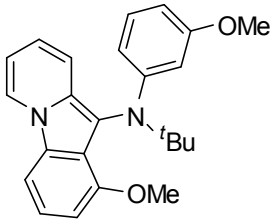
***N*-(*tert*-Butyl)-*N*-phenylthiazolo[3,2-α]indol-9-amine (36)**



This compound was obtained as a colorless solid (21.7 mg, 27%): mp 102-103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 4.2 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 2 H), 7.21 (t, *J* = 7.4 Hz, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.08 (dt, *J* = 16.6, 8.2 Hz, 4 H), 6.77 (t, *J* = 6.9 Hz, 1 H), 6.53 (d, *J* = 4.2 Hz, 1 H), 1.51 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 136.3,

132.2, 128.4, 128.2, 121.8, 121.5, 119.6, 119.1, 118.7, 114.9, 110.3, 108.8, 108.7, 58.4, 30.5; HRMS (EI) calcd for $C_{20}H_{20}N_2S$ 321.1420, found 321.1421**.**

***N*-(*tert*-Butyl)-1-methoxy-*N*-(3-methoxyphenyl)pyrido[1,2-α]indol-10-amine (39)**



This compound was obtained as a yellow oil (75.0 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.2 Hz, 1 H), 7.48 (d, *J* = 8.3 Hz, 1 H), 7.27 (d, *J* = 10.3 Hz, 1 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 6.92 (t, *J* = 8.2 Hz, 1 H), 6.80-6.69 (m, 2 H), 6.47-6.33 (m, 3H), 6.18 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.84 (s, 3 H), 3.66 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 154.2, 151.4, 133.0, 129.2, 128.4, 124.0, 121.7, 120.6, 30.0, 119.9, 118.1, 111.4, 111.3, 108.4, 104.7, 103.3, 102.5, 100.4, 57.8, 55.4, 55.1; HRMS (EI) calcd for $C_{24}H_{27}N_2O_2$ 375.2067, found 375.2060**.**

7.7. REFERENCES AND NOTES

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CHAPTER 8

General Conclusions

Over the course of the work described in this dissertation, several novel methodologies have been successfully developed and applied to the synthesis of medicinally-relevant heterocycles, including indoles, benzo[*b*]furans, 1,2-dihydroisoquinolines, 1*H*-indazoles, and pyrido[1,2-*a*]indoles. In these methods, well-studied transition metal-catalyzed processes and newly discovered aryne-mediated processes have been found applicable and efficient when applied to the synthesis of a variety of heterocycles. Most of these processes have also been transformed into multicomponent processes. As a result of this work, a novel three-component reaction of indoles, 2-alkynylbenzaldehydes and amines has been discovered and a library of over a hundred 1,2-dihydroisoquinolines has been prepared and sent out for biological testing. A novel method for the synthesis of 2,3-disubstituted indoles and *N*-methylindoles under Sonogashira conditions has been developed and applied to the synthesis of 24 indole scaffolds. A related method for the synthesis of 2,3-disubstituted benzofurans under Sonogashira conditions has also been optimized and successfully applied to the synthesis of a variety of medicinally-relevant benzofurans. A total synthesis of naturally-occurring oligostilbenes has been initiated based on the methodology developed and significant progress has been made in that direction. A one-pot method for the synthesis of 1-alkyl-1*H*-indazoles has been developed utilizing the reaction between 1,1-dialkylhydrazones, NCS and arynes. This process proved to be efficient and resulted in the

synthesis of 13 indazoles, as well as several interesting extensions. Finally, the synthesis of a small library of medicinally-relevant pyrido[1,2-*a*]indoles has been accomplished by the reaction of arynes with 2-substituted pyridines. A three-component version of this methodology has also proved successful.

The variety and notable efficiency of the methods developed illustrates the incredible potential that lies in the thoughtful combination of already known and well-studied approaches for the generation of complex molecules in a one-pot fashion from readily available starting materials.

The number of publications on multicomponent and combinatorial chemistry has grown immensely in the last few decades. The number of the new methods that have been developed during these years is even greater. One can expect an explosion in the growth in the field of multicomponent reactions in the near future, resulting in the gradual transformation of known methods of organic syntheses into greener, highly efficient and waste-free strategies.

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