2012

Novel aryne-mediated synthetic methodologies

Anton Vladimirovich Dubrovskiy
Iowa State University

Novel aryne-mediated synthetic methodologies

by

Anton Vladimirovich Dubrovskiy

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock, Co-Major Professor
Malika Jeffries-EL, Co-Major Professor
Aaron Sadow
Yan Zhao
Thomas J. Greenbowe

Iowa State University

Ames, Iowa

2012

To chemistry

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

rt	room temp
[O]	oxidant
°C	degrees Celsius
Ac	acetyl
Alk	alkyl
APCI	atmospheric-pressure chemical ionization
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
cat.	catalytic amount
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DNA	deoxyribonucleic acid

dt	doublet of triplets
EI	electron ionization
equiv	equivalents
Et	ethyl
eV	electronvolt
GC/MS	gas chromatography–mass spectrometry
h	hour
Hal	halide
HetAr	heteroaryl
Hex	hexyl
HIV	human immunodeficiency virus
HRMS	high resolution mass spectrometry
Hz	hertz
IPA	isopropyl alcohol
^{i}Pr	*iso*-propyl
J	coupling constant
L.A.	Lewis acid
LG	leaving group
m	meta
M	molar
m	multiplet
Me	methyl
MHz	megahertz

mL	milliliter
mmol	millimole
mp	melting point
Ms	mesyl
NAD	nicotinamide adenine dinucleotide
NCS	*N*-chlorosuccinimide
NIH	the National Institutes of Health
nm	nanometer
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
o	ortho
OTf	triflate
p	para
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
Py	pyridine
s	singlet
S.M.	starting material
S_NAr	nucleophilic aromatic substitution
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride

TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDMS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
TMS	trimethylsilyl
^{t}Oct	1,1-dimethylhexyl
Tol	toluene
Tr	triphenylmetyl (trityl)
Ts	tosyl
UV	ultraviolet
δ	chemical shift in ppm
Δ	elevated temperatures
μW	microwave irradiation

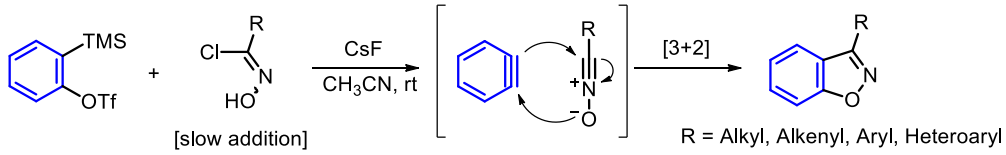
CHAPTER 1. DISSERTATION ORGANIZATION

This dissertation is divided into six chapters. Each chapter is written in American Chemical Society format as required by the *Journal of Organic Chemistry*. Chapters 3-5 are composed of an abstract, introduction, results and discussion, conclusion, experimental part, acknowledgements, and references.

Chapter 2 introduces the reader to aryne chemistry, particularly to the use of arynes in synthetic organic methodologies. About two decades after Kobayashi's discovery of a very mild way of generating this highly reactive species in 1983, the synthetic community embraced *o*-(trimethylsilyl)aryl triflates as convenient and versatile aryne precursors for the synthesis of carbocycles and heterocycles, as well as natural products and pharmaceutically promising drug candidates. The review featured in chapter 2 is focused on the construction of 5-membered ring fused heterocycles. It is intended to be combined with an overview of methodologies for the synthesis of 6-membered and larger rings heterocycles to be published later as an invited review in the journal *Organic & Biomolecular Chemistry*.

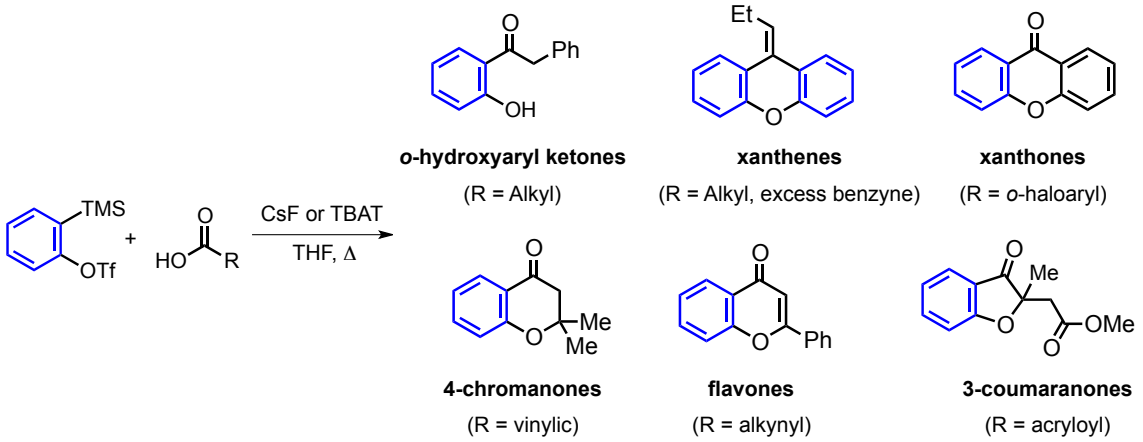
Chapter 3 is based on a communication that was published in the journal *Organic Letters* in 2010,[1] in addition to being highlighted in *Synfacts*.[2] The origins of this methodology began when a former postdoctoral fellow in the Larock group, Dr. Feng Shi, shared with me the fact that the reaction between an *in situ* generated nitrile oxide and benzyne results in a [3 + 2] cycloaddition process yielding the corresponding benzisoxazole. In my hands, the reaction was further optimized and its scope has been thoroughly studied. During this work, two communications on this same cycloaddition process by Browne[3] and Moses[4] appeared in *Tetrahedron Letters* and *Chemical Communications* respectively. This

discouraged us from publishing a full paper on this topic. However, we have initiated a collaboration with the Kansas University NIH Center of Excellence in Chemical Methodology and Library Development to mutually construct a library of potentially promising benzisoxazole-containing drug candidates. Using our reported methodology, we have successfully constructed eight benzisoxazole-containing scaffolds at Iowa State University), which the Kansas CMLD center is going to elaborate into an approximately hundred member library of potential drug candidates for testing by NIH. A paper on the combined experimental work will eventually be submitted to the journal *ACS Combinatorial Science*. The final derivatives will be run through a set of biological activity tests at the NIH center.

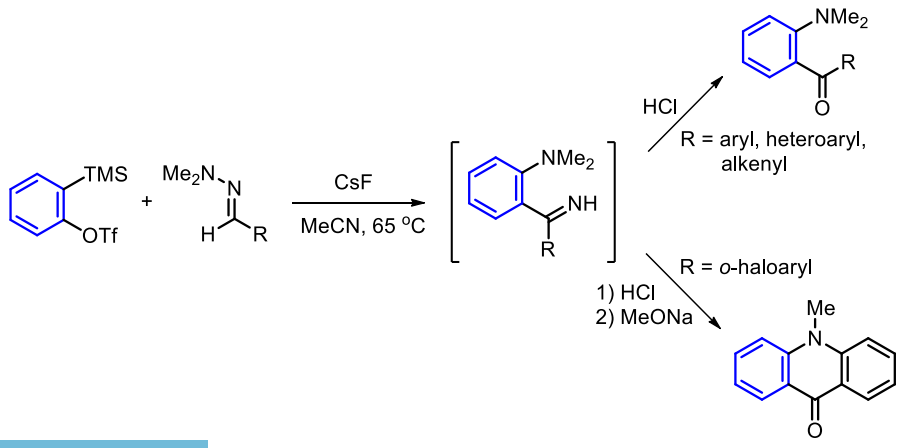


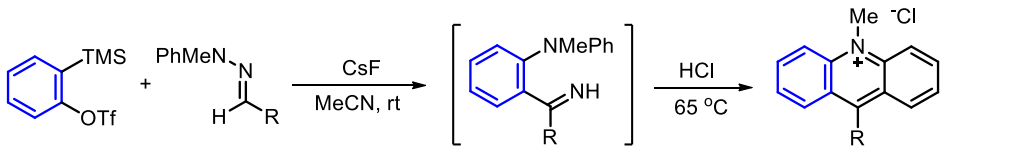
Chapter 4 is also based on a communication that we published in the journal *Organic Letters* in 2010.[5] We anticipated that initial attack of the oxygen of methacrylic acid on a benzyne, followed by an intramolecular Michael reaction, should result in formation of the corresponding coumarin product. However, an unexpected benzyne insertion into the C-O bond of the carboxylic acid occurred, followed by an intramolecular Michael addition, furnishing a 4-chromanone product. The reaction was optimized and its scope has been thoroughly studied. Methodologies leading to pharmaceutically and biologically interesting *o*-hydroxyaryl ketones, xanthenes, xanthones, 4-chromanones, flavones, and 3-coumaranones, starting from readily available carboxylic acids, have subsequently been

developed. Several naturally-occurring molecules have been synthesized using our methodology. We anticipate publishing these results in the *Journal of Organic Chemistry* eventually.



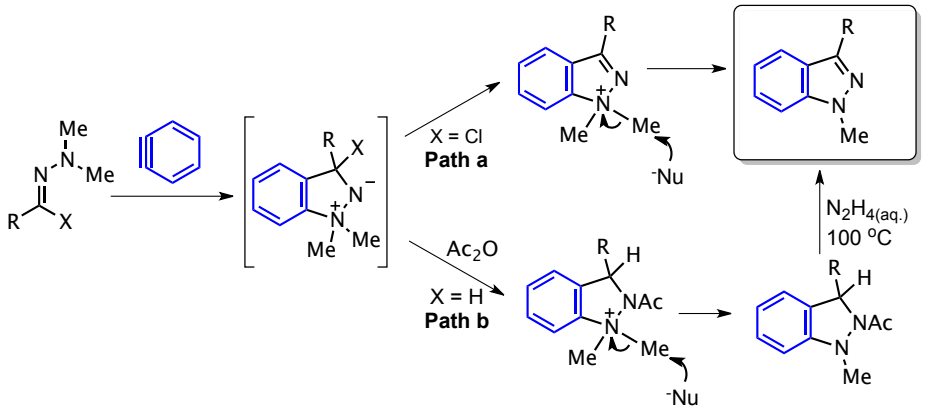
Chapter 5 is based on a communication that we published in the journal *Organic Letters* in 2011.[6] We found that readily prepared hydrazones react with arynes with the formation of *o*-(dimethylamino)aryl ketimines. The latter can be transformed in one pot into a variety of pharmaceutically and biologically useful products, including *o*-(dimethylamino)-aryl ketones, *N*-methylacridones, and acridinium salts. We anticipate publishing the combined results in the *Journal of Organic Chemistry* soon.





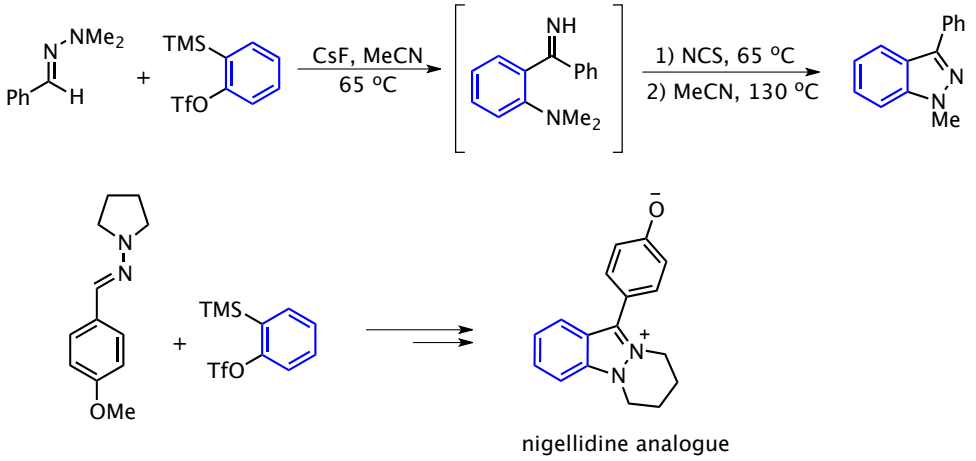
R = Alkyl, Alkenyl, Aryl, Heteroaryl

It has also been found that the cyclic structure of the intermediate leading to the *o*-(dimethylamino)aryl ketimines can be retained to produce indazoles using two complementary approaches: 1) starting from a chlorohydrazone; and 2) trapping the intermediate with Ac_2O, followed by subsequent one-pot deprotection/aromatization. In this case, 1*H*-indazoles can be obtained in good to high yields. While Nataliya A. Markina was working on the chlorohydrazone path a, I optimized the alternative approach and explored the scope of the protection/deprotection/aromatization process shown in path b. Our combined efforts resulted in a publication in the journal *Organic & Biomolecular Chemistry*.



Recently, we have discovered a third pathway leading to 1*H*-indazoles. The *o*-aminoaryl ketimine can be cyclized to a 1*H*-indazole by chlorination of the imine by NCS, followed by intramolecular displacement of the chloride. An analogue of a natural product

nigellidine has been synthesized in only two steps from a readily prepared hydrazone and the commercially available benzyne precursor.



Some general conclusions (Chapter 6) are drawn at the end of the four chapters. Finally, the ^{1}H and ^{13}C NMR spectra for all previously unknown starting materials and products are compiled in appendices A-C.

---

[1] Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180.

[2] Dubrovskiy, A.; Larock, R. *Synfacts* **2010**, *6*, 643.

[3] Crossley, J. A.; Browne, D. L. *Tetrahedron Lett.* **2010**, *51*, 2271.

[4] Spiteri, C.; Sharma, P.; Zhang, F.; Macdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, *46*, 1272.

[5] Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.

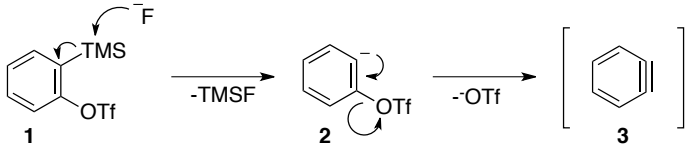
[6] Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2011**, *13*, 4136.

CHAPTER 2

USE OF ARYNES FOR THE SYNTHESIS OF 5-MEMBERED RING HETEROCYCLES

2.1. Scope of the Review

In the last decade, arynes, particularly those that can be generated from the corresponding *o*-(trimethylsilyl)aryl triflates **1**, have emerged as powerful synthons in organic synthesis. Recent reviews have covered the use of aryne-based methodologies in the areas of multicomponent reactions,[1] the formation of carbon-carbon and carbon-heteroatom bonds,[2,3] and the synthesis of natural products.[4] The very convenient, mild method for generating arynes from *o*-(trimethylsilyl)aryl triflates developed by Kobayashi in 1983 allows one to conveniently generate a highly reactive benzyne intermediate **3** at conventional temperatures, using readily accessible solvents and only moderately basic fluoride ion (Scheme 1).[5]



Scheme 1. Generation of Benzyne using the Kobayashi Method.

The Kobayashi method contrasts with other ways of aryne generation involving the use of strong bases and low temperatures, the thermolysis of potentially explosive benzenediazonium carboxylates, and the oxidation of fairly inaccessible 1-aminobenzo-triazoles using stoichiometric amounts of toxic $Pb(OAc)_4$.[6] Due to the high affinity of

fluoride for silicon (the bond dissociation energy of Si-F in TMSF is 158 kcal/mol),[7] the aryl anion **2** formed *in situ* intramolecularly extrudes a good leaving group, *e.g.* triflate, although other alternatives have been considered lately as well.[8] It is noteworthy that the same basic approach, involving the generation of an unstable intermediate due to the high stability of the Si-F bond and departure of a neighboring leaving group, has been used to generate strained cycloalkynes[9] and highly reactive *ortho*-quinone methides.[10]

The great advantage of generating a benzyne by the Kobayashi route is the ability to control the rate of benzyne generation by varying the concentration of the fluoride ion in the solution. Thus, one can instantly generate a benzyne in THF using tetrabutylammonium fluoride (TBAF), which is quite soluble in THF. It is possible to slow down the rate of benzyne generation by employing CsF in MeCN (at room and elevated temperatures) or CsF in THF (at elevated temperatures). To further slow down the formation of the benzyne, CsF in MeCN/toluene mixtures can be used. The nature and amount of the added fluoride source, the solvent, and the temperature of the reaction can have a profound effect on the overall rate and success of such aryne reactions.

As a result, there has been increasing interest in benzyne-mediated transformations and substituted aryne and heteroaryne precursors have become much more common in the literature and commercially (Figure 1). Whereas previously synthetic organic chemists tended to construct more complicated aromatic molecules by adding functionality to a simple benzene or arene, with the recent developments in aryne chemistry, chemists can now start from relatively simple functionally-substituted aliphatic molecules and add aromatic and heteroaromatic rings through straightforward one-pot aryne coupling chemistry.

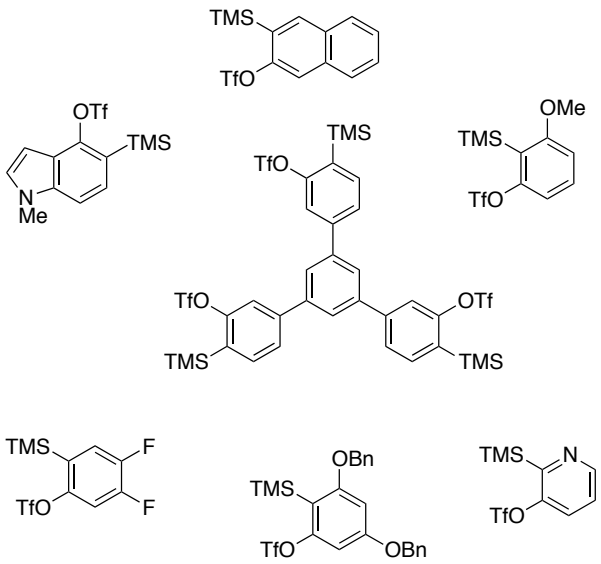


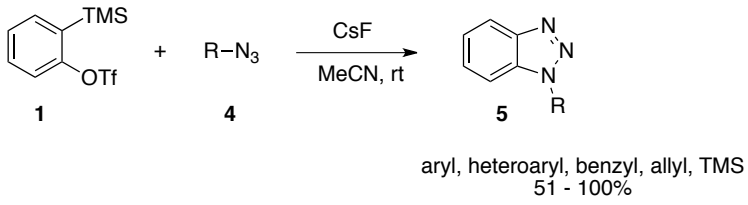
Figure 1. Examples of Silylaryl Triflates used as Aryne Precursors.

This review is focused on the construction of 5-membered ring heterocycles using Kobayashi's silylaryl triflate aryne precursors. It is organized according to the nature of the final heterocycle. The mechanism, scope and limitations of each methodology are presented.

2.2. Synthesis of 5-Membered Ring-containing Heterocycles

2.2.1. Benzotriazoles

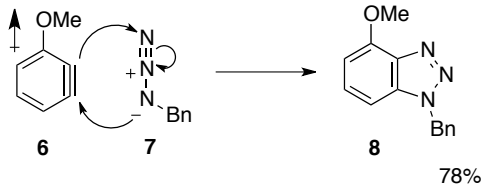
Benzynes are well known to participate in cycloaddition reactions with 1,3-dipoles. In 2008, Larock and co-workers reported the so-called "aryne click" reaction, a cycloaddition between azides **4** and benzyne generated *in situ* (Scheme 2).[11]



Scheme 2. Synthesis of Benzotriazoles Developed by Larock.

The reaction proceeds at room temperature and gives rise to the benzotriazoles **5** in 51-100% yields. Aryl azides provide excellent (83-90%) yields regardless of the substitution pattern. Benzyl and allyl azides provide the corresponding coupling products in excellent 91-100% yields. Alkyl and heteroaryl azides give slightly lower (51-93%) yields with ester, alkynyl, and hydroxyl groups being tolerated under the reaction conditions. The major limitation of the methodology is that sulfonyl azides (0% yield) and alkenyl azides (20% yield) react poorly or not at all.

Substituted benzynes provide the corresponding products in 56-78% yields. It is noteworthy that the unsymmetrical benzyne **6** provides the corresponding product **8** as a single regioisomer, a result of the anticipated[12] transition state (Scheme 3) in which the nucleophilic portion of the azide moiety adds to the more electron-deficient and more sterically accessible pseudo *meta*-position of the 3-methoxybenzyne **6**.

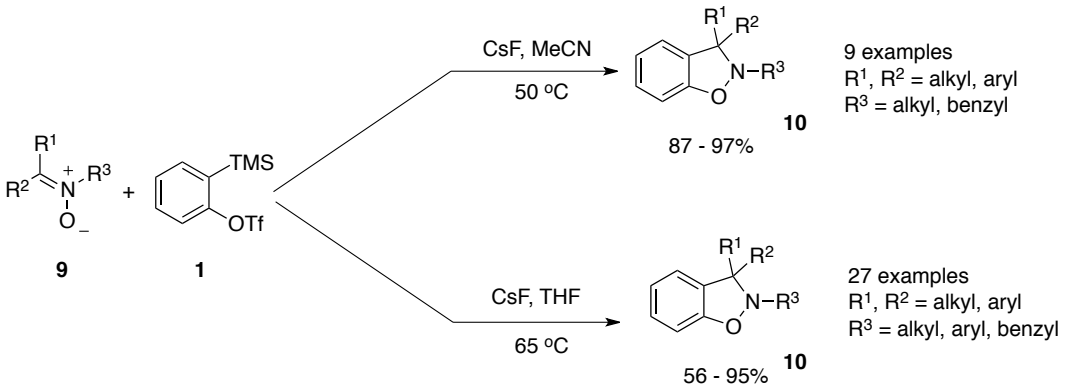


Scheme 3. The Transition State for Coupling with 3-Methoxybenzyne.

2.2.2. Benzisoxazolines

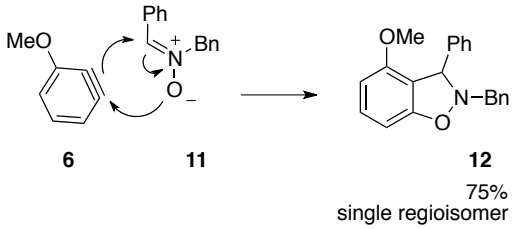
Since nitrones constitute another class of stable and isolable 1,3-dipoles, one should expect an analogous cycloaddition reaction of benzynes generated *in situ* with nitrones **9** to lead to the benzisoxazoline moiety. Indeed, under two different sets of reaction conditions (CsF/MeCN at 50 ^{o}C and CsF/THF at 65 ^{o}C), the Larock[13] and Chen[14] groups have independently reported successful one-pot syntheses of benzisoxazolines **10** in 87-97% and

56-95% yields respectively (Scheme 4). While only unsubstituted alkyl, aryl, and benzyl substituted nitrones were studied under the first set of reaction conditions (9 examples), the reaction using CsF/THF tolerates a wide range of functional groups, including a halide, thiol ether, ester, amino, alkenyl, nitrile, and nitro functional group (27 examples).



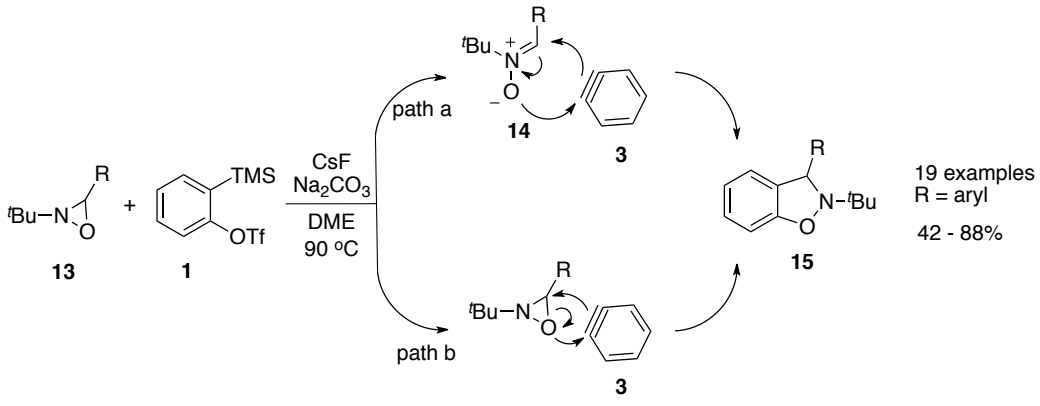
Scheme 4. Synthesis of Benzisoxazolines.

In the Larock methodology, substituted benzynes provide the corresponding products in 41-75% yields with the lowest yield observed in the case of the highly electron-deficient 4,5-difluoro-substituted benzyne. The reaction with the unsymmetrical methoxy-substituted benzyne **6** affords the single regioisomer **12**, which is consistent with the expected transition state for the cycloaddition reaction (Scheme 5).



Scheme 5. The Transition State for Coupling with 3-Methoxybenzyne.

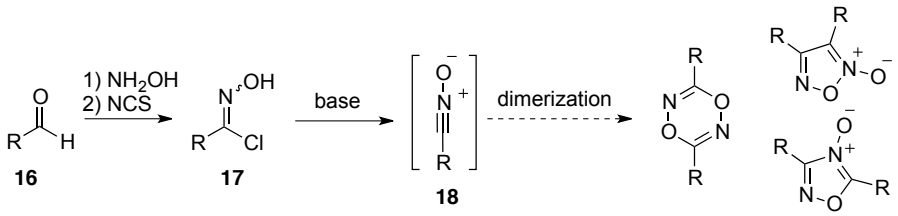
The Larock group recently reported that oxaziridines react with arynes with formation of the C-O insertion products, benzisoxazolines.[15] In this case, the bulky *tert*-butyl substituent present on the nitrogen atom seems to be required to achieve high yields. Adding stoichiometric amounts of Na_2CO_3, whose role is not obvious, and running the reaction in DME at 90 ^oC, allows one to obtain the desired benzisoxazolines **15** in 42-88% yields (Scheme 6). A variety of substituents, including halides, internal alkynes, ethers, dioxolanes, and a furyl moiety, is tolerated under the reaction conditions. The substrates that failed to provide the expected products contained a nitro group, a pyridine moiety, or an alkyl substituent on the carbon of the starting oxaziridine. The authors considered two possible mechanisms for this coupling reaction (Scheme 6): a) formation of the nitrone intermediate **14**, followed by a [3 + 2] cycloaddition with the benzyne intermediate **3**; or b) a concerted mechanism with the oxygen atom of the oxaziridine ring attacking the electrophilic benzyne **3**.[16]



Scheme 6. Synthesis of Benzisoxazolines.

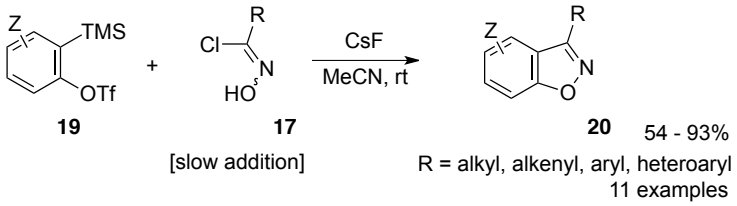
2.2.3. Benzisoxazoles

Benzisoxazoles are the expected product of a formal cycloaddition between nitrile oxides and arynes. Unfortunately, the majority of nitrile oxides are not stable and isolable and they tend to dimerize.[17] One of the convenient ways to generate nitrile oxides (**18**) is by the dehydrohalogenation of chlorooximes (**17)** (Scheme 7). The latter compounds can be easily prepared from the corresponding aldehydes by chlorination of the corresponding oximes.[18]



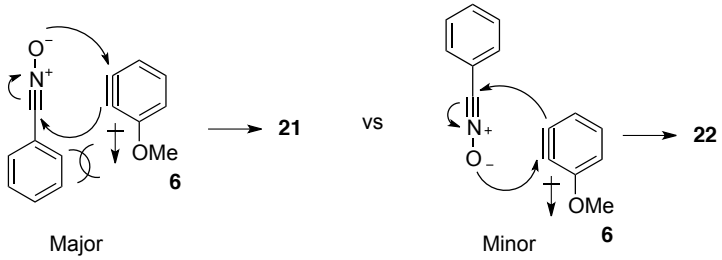
Scheme 7. Preparation of Nitrile Oxides.

The Larock group found that CsF cannot only induce the generation of benzyne from the silylaryl triflate, but can also act as a base to generate the unstable nitrile oxide from the parent chlorooxime.[19] Both intermediates are highly reactive, *e.g.* nitrile oxides are known to form different types of dimerization products.[17] Therefore, the challenge of this methodology was to find reaction conditions where the rates of benzyne and nitrile oxide generation match each other, thereby favoring the cycloaddition process over dimerization and other side reactions. Indeed, slow addition of the chlorooxime **17** to a mixture of the benzyne precursor **19** and CsF in MeCN at room temperature allows one to isolate the desired aryl, alkyl, alkenyl, and heterocycle 3-substituted benzisoxazoles **20** in 54-93% yields (Scheme 8).



Scheme 8. Synthesis of Benzisoxazoles.

Unsymmetrical 3-methoxybenzyne leads to the formation of a mixture of regioisomers with poor (1.8:1) selectivity in favor of the expected isomer **21** (Scheme 9).

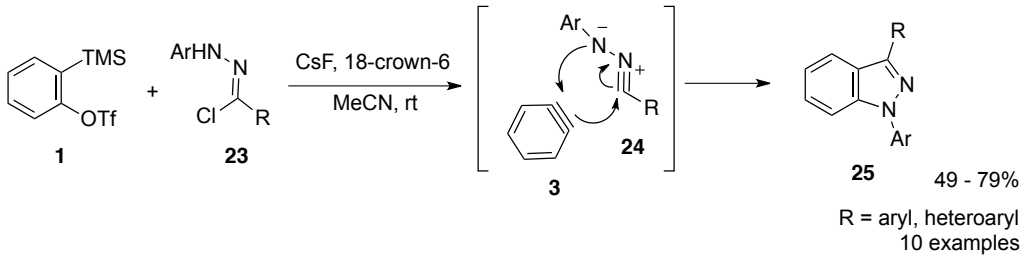


Scheme 9. Alternative Transition States with 3-Methoxybenzyne.

About the same time, two complementary methodologies appeared, developed by the research groups of Browne[20] and Moses.[21] The Browne methodology allows one to obtain aryl, alkenyl, and heteroaryl-substituted benzisoxazoles in 73-99% yields, utilizing TBAF and a 3-fold excess of the chlorooxime **17** (compared with 2 equiv in the Larock method) in THF. In this case, slow addition of the reagents to the reaction is not necessary. Moses' approach utilizes only a 1.5 fold excess of the chlorooxime **17** and TBAF in THF and affords the desired benzisoxazoles in 50-99% yields. Only aryl- and benzyl-containing chlorooximes were examined using this latter approach.

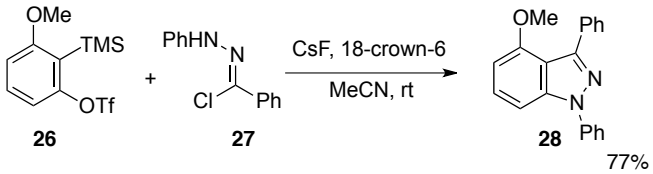
2.2.4. 1*H*-Indazoles

An aza-analogue of a nitrile oxide, namely nitrile imine **24**, can be generated *in situ* from hydrazonoyl chlorides **23** by a based-induced dehydrohalogenation. In fact, Moses and co-workers have shown that hydrazonoyl chlorides derived from chlorinated *N*-phenyl hydrazones of aryl and heteroaryl aldehydes afford the corresponding *N*-aryl substituted 1*H*-indazoles **25** after a [3 + 2] cycloaddition process with benzyne **3** (Scheme 10).[22] The yields of the products **25** range from 49% to 79%. Optimal conditions were found to use CsF in the presence of stoichiometric amounts of 18-crown-6 in MeCN at room temperature. This unusual combination of reagents suppressed formation of the undesired self-dimerization products of the highly reactive nitrile imine intermediates.



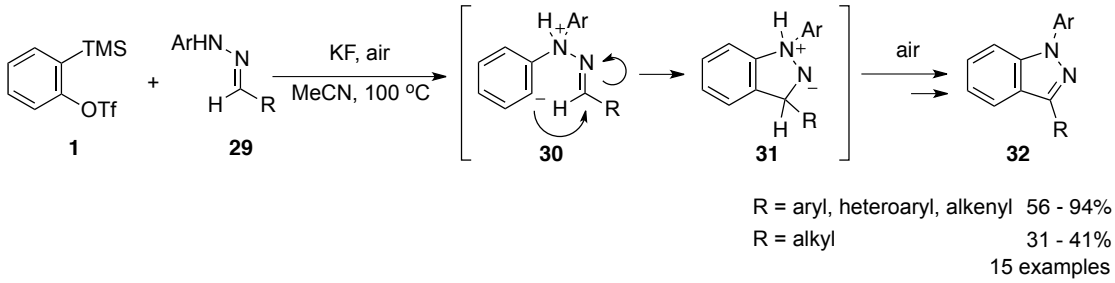
Scheme 10. Synthesis of *N*-Aryl 1*H*-Indazoles.

The reaction with 3-methylbenzyne forms a mixture of regioisomers in a ~3.7/1 ratio, while the reaction with 3-methoxybenzyne affords the anticipated product **28** as a single regioisomer (Scheme 11).

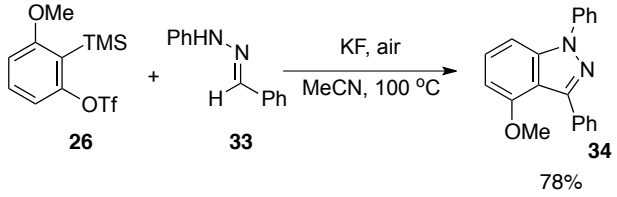


Scheme 11. Reaction with 3-Methoxybenzyne.

Shi has found that one can start from the *N*-phenyl hydrazones of aldehydes **29** and obtain the aforementioned 1*H*-indazole moiety upon reaction with a benzyne.[23] Apparently, the reaction goes through an ionic annulation pathway, followed by an aromatization step (Scheme 12). In this protocol, 3-alkyl-containing indazoles are obtained in poorer (31-41%) yields, than the products bearing aryl, heteroaryl, and alkenyl substituents (56-94%). The reaction proceeds at 100 °C in the presence of KF as the fluoride source. It also affords the indazole **34** as a single regioisomer upon reaction with benzyne (Scheme 13).



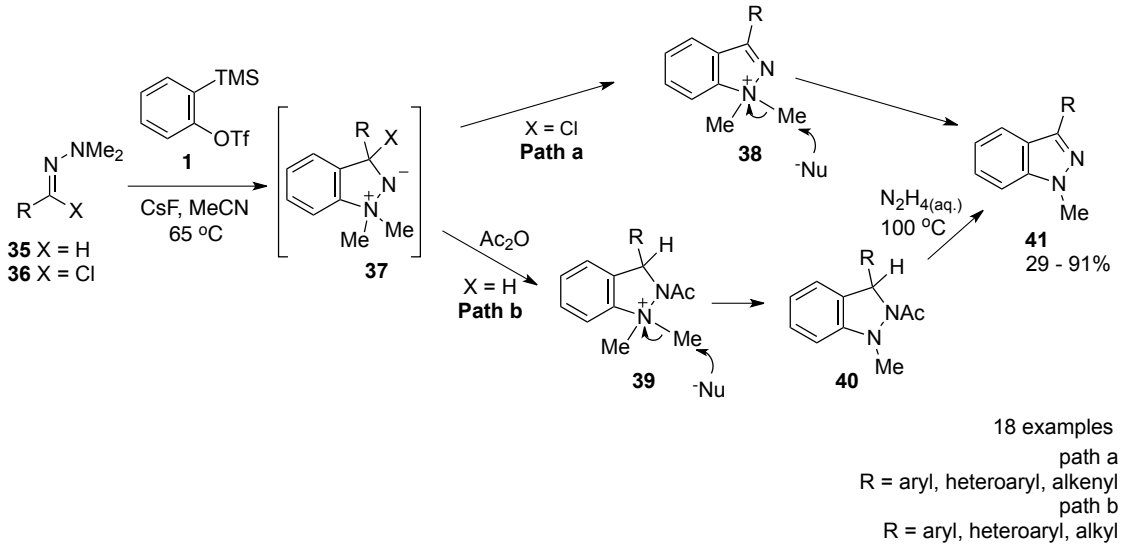
Scheme 12. Synthesis of *N*-Aryl 1*H*-Indazoles.



Scheme 13. Reaction with 3-Methoxybenzyne.

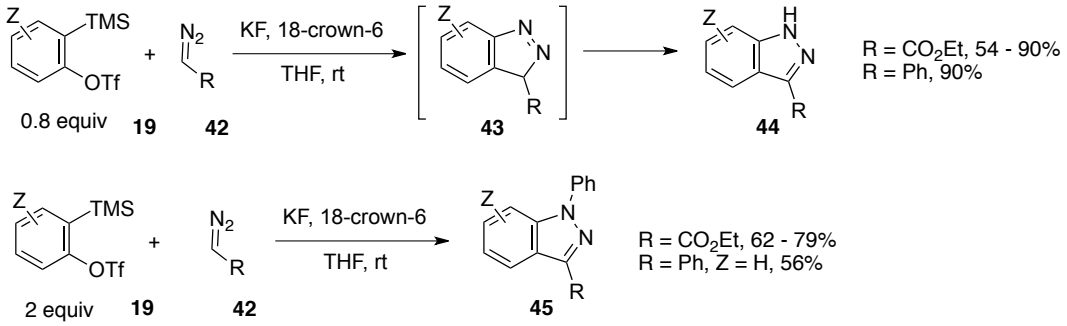
The Larock group has found[24] that the corresponding indazoline cationic intermediate of type **37** (compare with **31**), generated from the reaction of *N,N*-disubstituted hydrazones **35** and benzyne **3**, can be conveniently transformed into the desired indazole structure by one of the following modifications (Scheme 14): a) NCS-mediated chlorination of the starting hydrazone; or b) trapping the anion of type **31** by Ac_2O and subsequently cleaving the

protecting group, followed by aromatization to generate the desired indazoles **41** in 29-91% yields. The Ac_2O-mediated pathway (path b) allows one to conveniently synthesize 3-alkyl-substituted indazoles. Both methods tolerate ester, nitrile, terminal alkynyl, and halide functional groups, and some heteroaryl moieties. Using an alkenyl-containing hydrazone afforded the corresponding indazole in only a 32% yield.

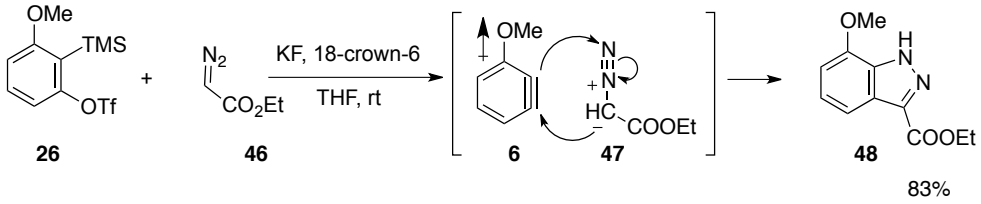


Scheme 14. Two Complimentary Pathways Leading to an Indazole.

Diazo compounds also engage in a cycloaddition reaction with a benzyne with the formation of 1*H*-indazoles. Yamamoto has shown[25] that the reaction of ethyl diazoacetate and the silylaryl triflates **19** in the presence of KF/18-crown-6 in THF at room temperature leads to formation of the corresponding unsubstituted or *N*-arylated (depending on the benzyne/substrate ratio) indazoles **44** in 54-90% yields (Scheme 15). Phenyldiazomethane successfully provided the corresponding products in 90% and 56% yields. The unsymmetrical 3-methoxybenzyne (**6**) provided the expected compound **48** as a single regioisomer in an 83% yield (Scheme 16).

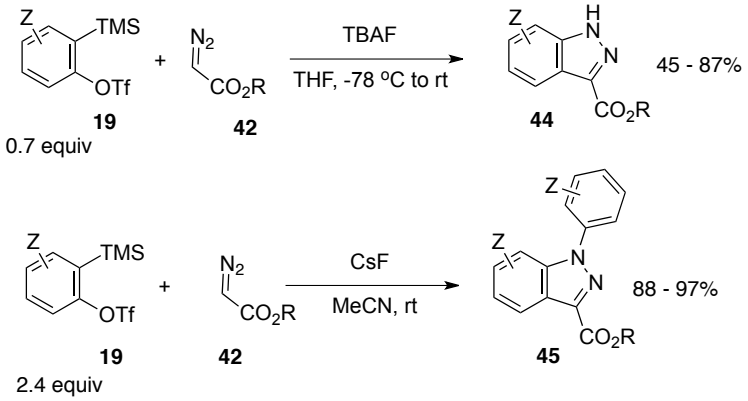


Scheme 15. Reaction of Benzyne with Diazo Compounds.

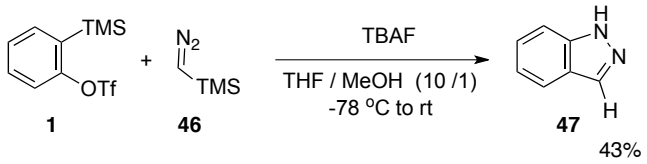


Scheme 16. Reaction with 3-Methoxybenzyne.

The Larock group found that the yield of the unsubstituted indazole **44** can be improved to 85% if the reaction is run in the presence of TBAF in THF at -78 ^{o}C (Scheme 17).[26] They also found that running the reaction with 2.4 equiv of the benzyne precursor in the presence of CsF in MeCN affords the *N*-arylated product **45** in a 97% yield. Interestingly, running the reaction of trimethylsilyl diazomethane with the benzyne precursor in a THF/MeOH mixture produces the unsubstituted indazole **47** in a 43% yield (Scheme 18).

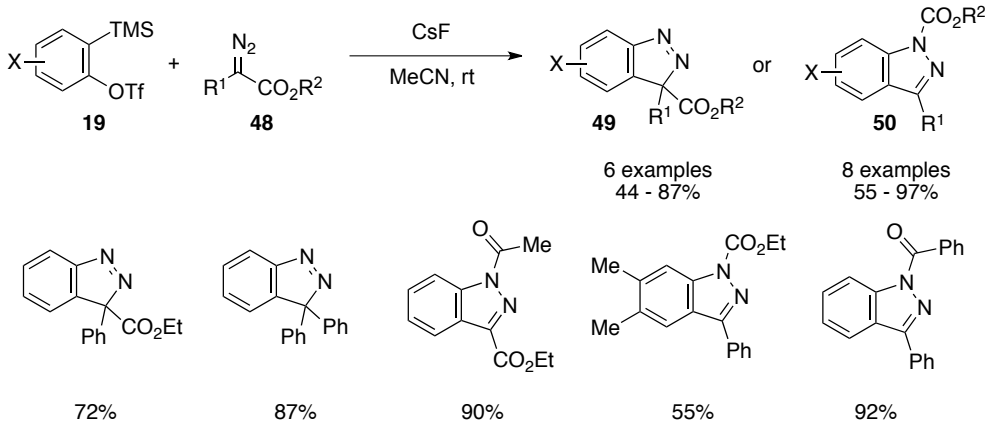


Scheme 17. Synthesis of Indazoles using Larock's Conditions.



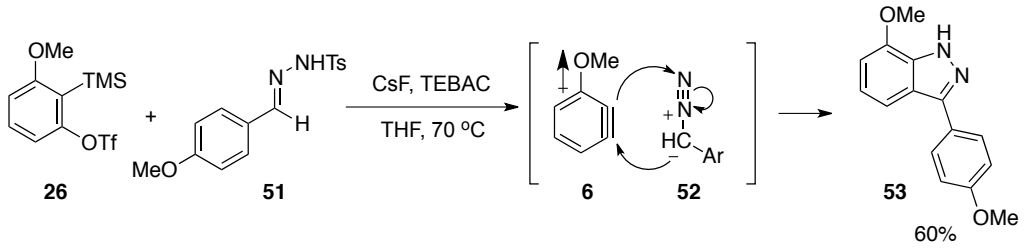
Scheme 18. Reaction with Trimethylsilyl Diazomethane.

The disubstituted stabilized diazomethane derivatives **48** in an analogous reaction provide the direct coupling products, 3,3-disubstituted 3*H*-indazoles **49**, in 44-87% yields (Scheme 19). However, in many cases the carbonyl-containing functional group further undergoes a 1,3-migration from the carbon to the nitrogen atom with formation of the *N*-substituted 1*H*-indazoles **50** in 55-97% yields. In this rearrangement, a ketone migrates in preference to an ester or amide group.



Scheme 19. Reaction with Disubstituted Diazomethane Derivatives.

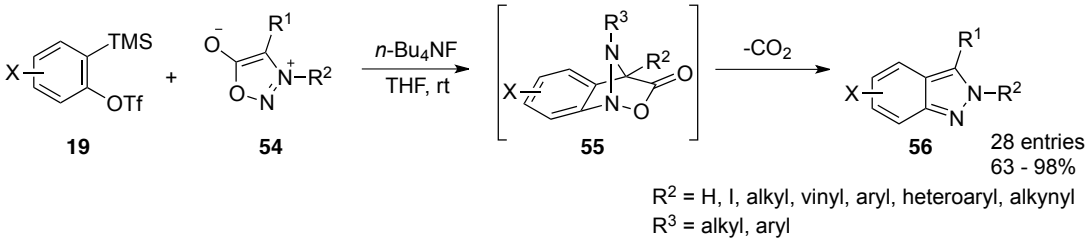
Shi has demonstrated that the diazo substrates can be generated *in situ* from the corresponding *N*-tosylhydrazones.[23,27] The optimal conditions for this transformation were found to be CsF/THF at reflux temperatures with the addition of sub-stoichiometric amounts of a common phase transfer catalyst, $[Et_3NBn]^+Cl^-$ (TEBAC). As opposed to the method with pre-prepared diazo compounds,[26] formation of the undesired *N*-arylated indazole was minimal. Hydrazones derived from aromatic and heteroaromatic aldehydes afford the unsubstituted 1*H*-indazoles in 36-85% yields. However, a substrate with a tertiary alkyl substituent (^{t}Bu) afforded the desired product in only a 33% yield. The regioselectivity of the reaction of the tosyl hydrazone **51** with the unsymmetrical benzyne **6** (Scheme 20, 60% yield) was presented as evidence for intermediate diazo formation, as well as detection of the characteristic absorption of diazo functionality in the IR spectrum of the reaction mixture of **51** with CsF.



Scheme 20. Reaction with 3-Methoxybenzyne.

2.2.5. 2*H*-Indazoles

2*H*-Indazoles have been successfully prepared by Shi and Larock using the [2 + 3] cycloaddition reaction between arynes and sydnones (**54**), which are stable mesoionic cyclic compounds, followed by CO_2 extrusion (Scheme 21). The reaction is most efficient in THF at room temperature using TBAF as the fluoride source, and affords the desired 2*H*-indazoles **56** in 63-98% yields. A wide range of functional groups is tolerated: alkyl, vinylic, benzylic, aryl, heteroaryl, alkynyl, halide, dioxolane and ketone functionalities among others. The limitations of this methodology include nitro-substituted substrates and acylated sydnones (Scheme 21, R^1 = Ac), which apparently are completely unreactive towards the benzyne.

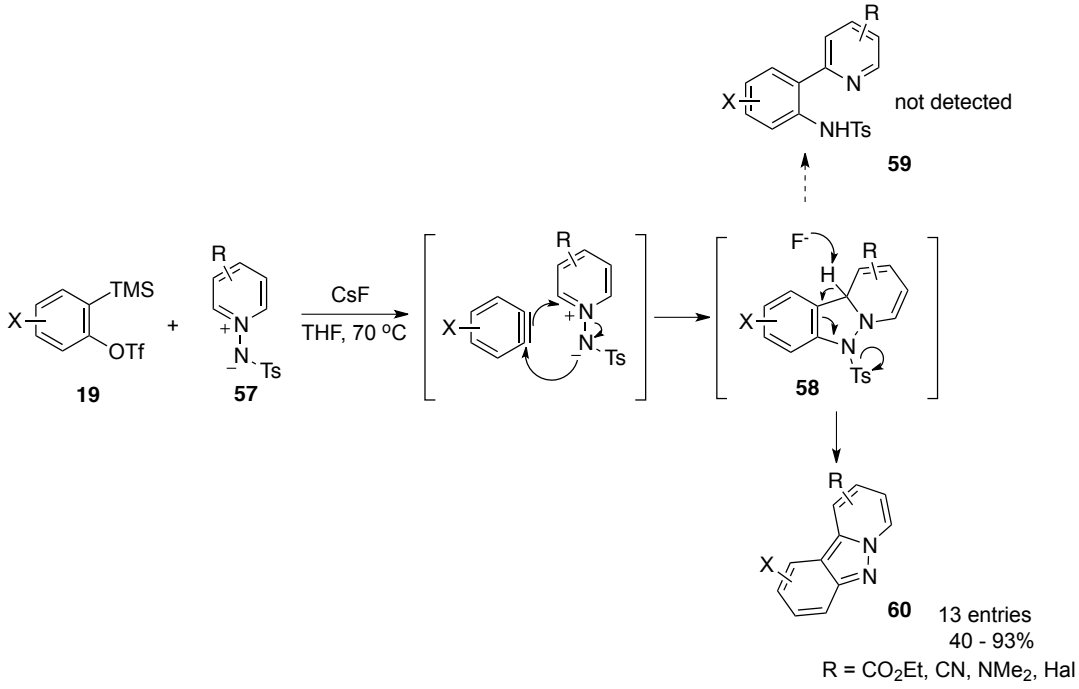


Scheme 21. Reaction of Sydnones and Arynes.

Interestingly, the unsymmetrical 3-methoxybenzyne (**6**) provided a mixture of isomeric products with a poor 1.2/1 selectivity, similar to the poor selectivity observed in the coupling process of nitrile oxides and benzyne in the synthesis of benzisoxazoles (Scheme 9).

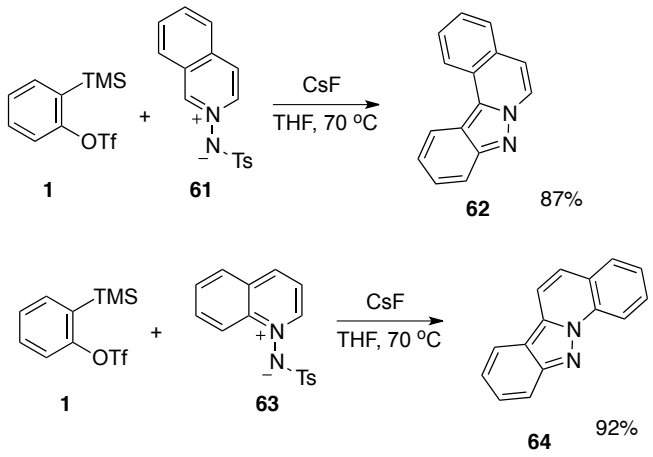
2.2.6. Pyrido[1,2-*b*]indazoles

The cycloaddition between pyridinium imide derivatives and benzyne has been reported decades ago.[28] However, the imides studied, which were stabilized by PhC(O)- and EtOC(O)- groups, afforded only 3-13% yields of the corresponding [3 + 2] cycloaddition products with the benzyne. It has recently been found that using the Ts-stabilized pyridinium imide **57** and the Kobayashi benzyne precursor **19** produces the desired coupling reaction in much higher yields.[29] The reaction presumably starts with a cycloaddition process leading to the intermediate **58** (Scheme 22). The base-promoted elimination of the tosyl anion furnishes the tricyclic moiety **60**. The excellent leaving ability of the tosyl group (and, in some cases, a nosyl group) prevents formation of the side product **59** observed in the case of the other leaving groups (*e.g.* Ac, Boc).



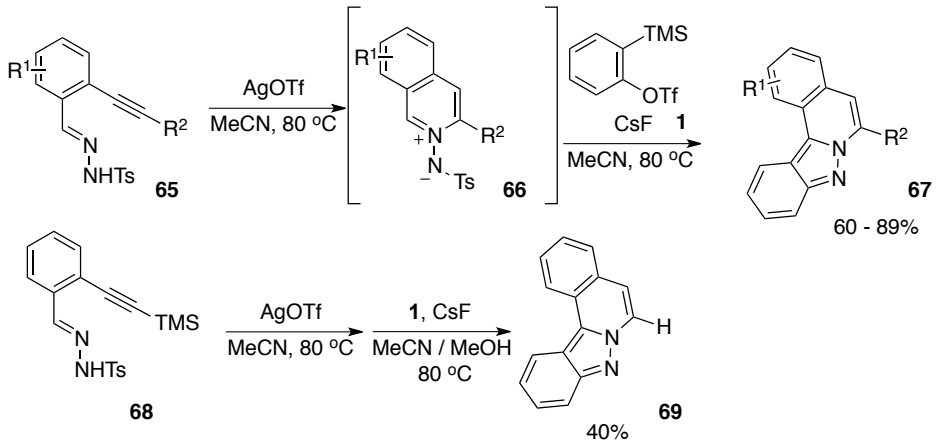
Scheme 22. Reaction of Pyridinium Imides and Arynes.

Thus, reacting the imide **57** with *o*-(trimethylsilyl)aryl triflates at 70 °C in the presence of CsF in THF affords the tricyclic pyrido[1,2-*b*]indazoles in 40-93% yields. A variety of functional groups are tolerated under the reaction conditions, such as ester, nitrile, halo, and amino functionalities. Unsymmetrical pyridinium imines result in the formation of mixtures of regioisomers with poor to modest selectivities. Employing isoquinolinium and quinolinium imides in the same transformation allows one to obtain tetracyclic heterocycles **62** and **64** in 87% and 92% yields respectively (Scheme 23).



Scheme 23. Reaction of Quinolinium and Isoquinolinium Imides and Benzyne.

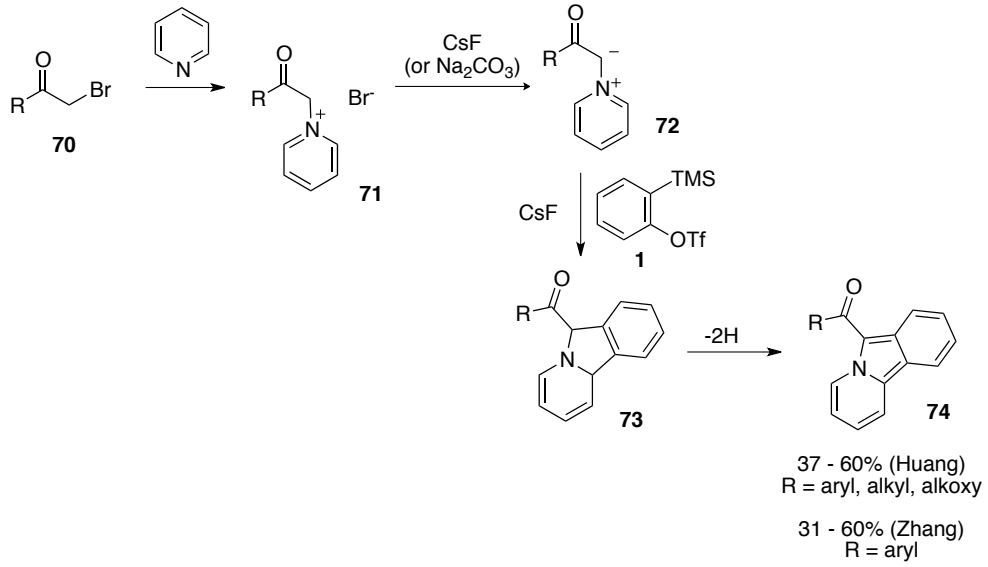
It has also been shown that the isoquinolinium imide **66** can be prepared *in situ* by the silver-catalyzed cyclization of *N'*-(2-alkynylbenzylidene)hydrazides (Scheme 24). The yields of the indazolo[3,2-*a*]isoquinolines **67** prepared utilizing this one-pot route range from 60% to 89%. The limitations of this methodology include pyridine-containing substrates,[30] and substrates containing TMS- or H-substituted alkynyl moieties, which provide the corresponding unsubstituted indazolo[3,2-*a*]isoquinoline **69** in a 40% yield (Scheme 24).



Scheme 24. *In situ* Generation of Isoquinolinium Imides.

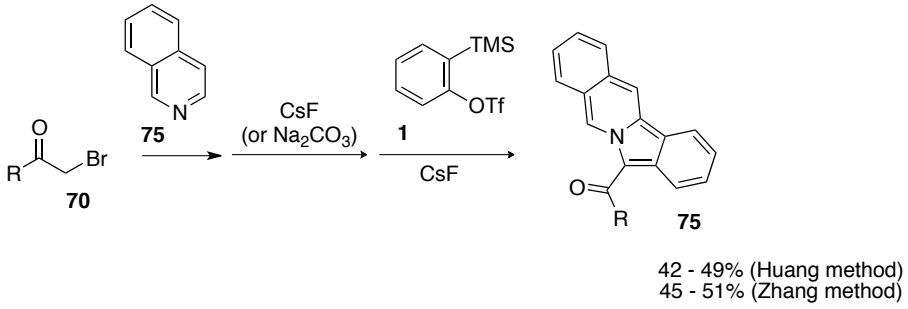
2.2.7. Pyrido[2,1-*a*]isoindoles, Indolizino[3,4,5-*ab*]isoindoles, and Related Heterocycles

Azomethine ylides are carbon analogues of the pyridinium imide **57**. The Huang[31] and Zhang[32] groups have independently reported the cycloaddition reaction of azomethine ylides **72** and arynes leading to the formation of pyrido[2,1-*a*]isoindoles **74** (Scheme 25). The reactive intermediates **72** have been generated *in situ* from pyridine and α-haloketones (**70**). Running the reaction with CsF/DME at 85 °C in the presence of stoichiometric amounts of Na_2CO_3 or using CsF/MeCN at 80 °C provided the desired products in 31-60% and 37-60% yields respectively. Alkyl- and halide-substituted aryl ketones are tolerated in both methodologies. A nitro group was also tested using the Zhang method (CsF/MeCN), which formed the anticipated products, but in lower (31-36%) yields. Alkyl ketones and esters were tested using the Huang method (CsF/Na_2CO_3/DME), forming the products in lower (37-40%) yields.



Scheme 25. Reaction of Azomethine Ylides with Arynes.

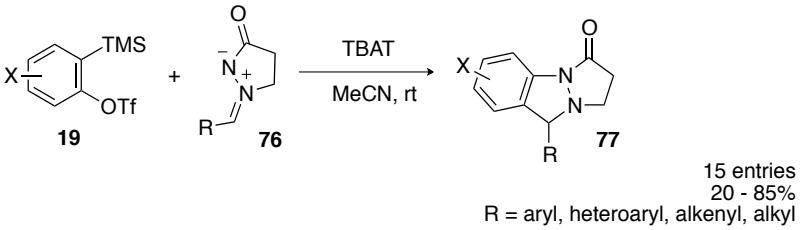
Running the above reaction with isoquinoline, instead of pyridine, lead to formation of the analogous isoindolo[2,1-*a*]isoquinolines in 42-49% (Huang) and 45-51% (Zhang) yields (Scheme 26).



Scheme 26. Reaction Arynes with Azomethine Ylides Derived from Isoquinoline.

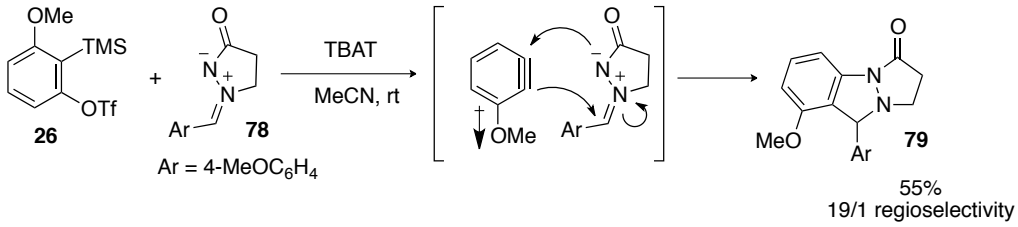
Another example of the reaction of an azomethine imine with an aryne has been demonstrated in the Larock group.[33] In this case, the stable and isolable azomethine imines **76** were prepared by the condensation of 3-pyrazolidinone with various aldehydes. Upon

cycloaddition with benzyne, tricyclic 1,2-dihydropyrazolo[1,2-*a*]indazol-3(9*H*)-ones **77** were formed in 20-85% yields (Scheme 27).



Scheme 27. Synthesis of 1,2-Dihydropyrazolo[1,2-*a*]indazol-3(9*H*)-ones.

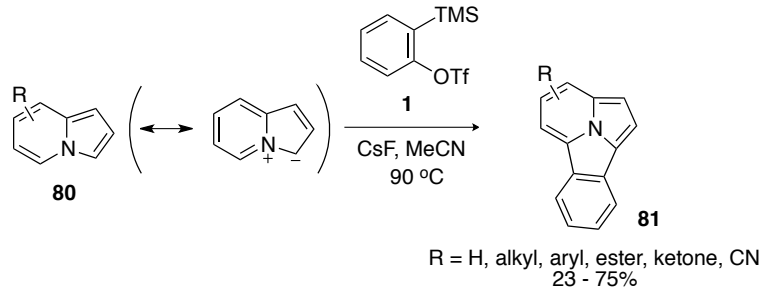
The optimal conditions for this process were found to be organic-soluble tetrabutylammonium difluorotriphenylsilicate (TBAT) in MeCN at room temperature. Along with aryl (containing halides and dioxolane functional groups), alkyl, and alkenyl substituents, a pyridinyl moiety was also tolerated under the optimized conditions. The limitations of the methodology include pyrrole- and furan-containing substrates, which lead to formation of the coupling products in only 20% and 29% yields respectively. The reaction of the azomethine imine **78** with 3-methoxybenzyne resulted in formation of the product **79** (55%) as a major regioisomer (~19:1 ratio) with the expected substitution pattern (Scheme 28).



Scheme 28. Reaction with 3-Methoxybenzyne.

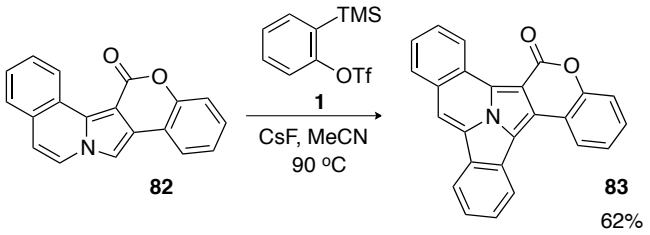
A related heterocycle, indolizino[3,4,5-*ab*]isoindole, can be prepared by the [3 + 2] cycloaddition reaction of indolizine **80** with benzyne. Running the reaction in the presence of

CsF in MeCN at 90 °C allows one to obtain the desired products **81** in 23-75% yields (Scheme 29).[34] The indolizine core can have multiple substituents, such as hydrogens, alkyl and aryl groups, and nitrile and ketone functionality.



Scheme 29. Reaction of Indolizine with Benzyne.

Running an analogous reaction with benzo-fused or heterocycle-fused indolizines provides polycyclic aromatic heterocycles in 52-93% yields (Scheme 30).

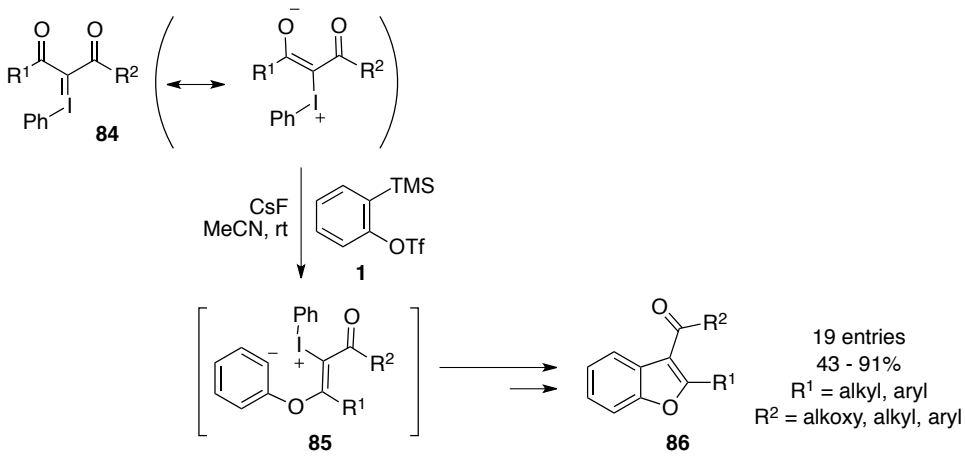


Scheme 30. An Example of the Reaction of a Fused Indolizine with an Aryne.

2.2.8. Benzofurans and Dihydrobenzofurans

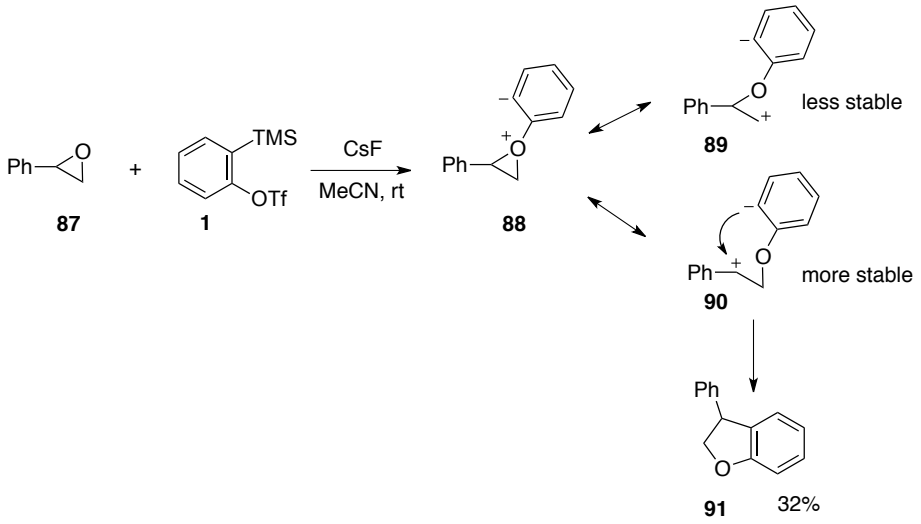
Benzofuran derivatives have been obtained in a coupling reaction between stabilized iodonium ylides **84** and arynes (Scheme 31). This reaction appears to proceed by enolate oxygen attack on the aryne ring. The resulting aryl anion **85** forms a 5- or 6-membered ring intermediate,[35] that, after extrusion of phenyl iodide, forms the observed benzofuran moiety. Running the reaction in the presence of CsF in MeCN at ambient temperatures allows one to obtain the desired products **86** in 43-91% yields. Aryl and alkyl (also haloalkyl) ketones and

esters are tolerated in this methodology. The presence of an iodo substituent on the aryl ketone moiety lowers the yield of the product **86** to 32%. Reactions with a nitrile-stabilized ylide and a 1,3-cyclohexanedione-derived ylide have resulted in formation of the anticipated benzofurans in only low (25-29%) yields.



Scheme 31. Reaction of Iodonium Ylides and Arynes.

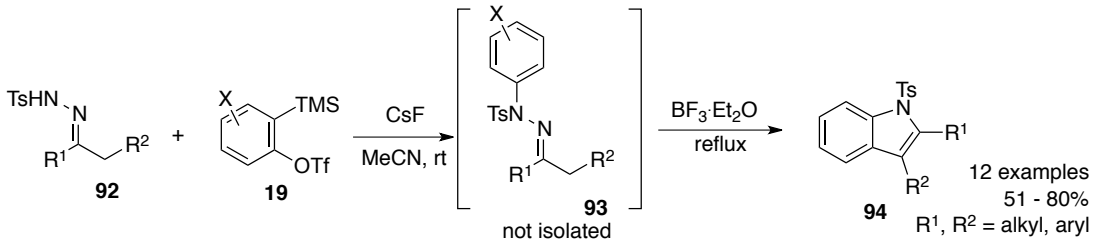
Dihydrobenzofurans can be formed by insertion of a benzyne into the C-O bond of an epoxide, albeit in low yields. Thus, the reaction of styrene oxide (**87**) with the benzyne precursor **1** in the presence of CsF in MeCN affords the heterocyclic product **91** in a 32% yield as a single regioisomer (Scheme 32). The regioselectivity of the reaction can be rationalized by the relative stability of the cationic resonance structure **90** as opposed to the structure **89**, which lacks the additional benzyl stabilization.



Scheme 32. Reaction of Styrene Oxide and Benzyne.

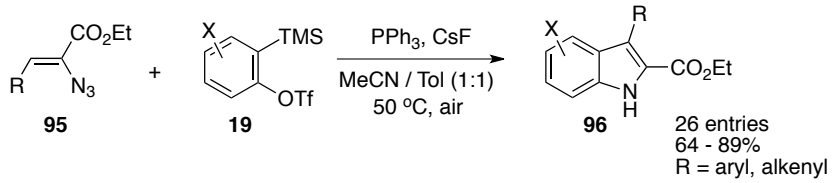
2.2.9. Indoles, Indole-indolones, Pyrroloindolones, Isatins, Indolines, and Indolin-3-ones

An interesting route to the indole scaffold has been developed by Greaney.[36] In a two step procedure, *N*-tosylhydrazones of ketones **92** are first arylated by an aryne with the formation of *N*-aryl-*N*-tosylhydrazones **93**.[37] The latter species is a convenient intermediate for an acid-catalyzed Fischer indole synthesis. Under the optimized conditions, running the *N*-arylation step using CsF/MeCN at room temperature and further subjecting the reaction mixture to stoichiometric amounts of $BF_3 \cdot Et_2O$ leads to formation of the corresponding indoles **94** in 51-80% yields. Alkyl, aryl, and ester functional groups are tolerated in this transformation (Scheme 33).

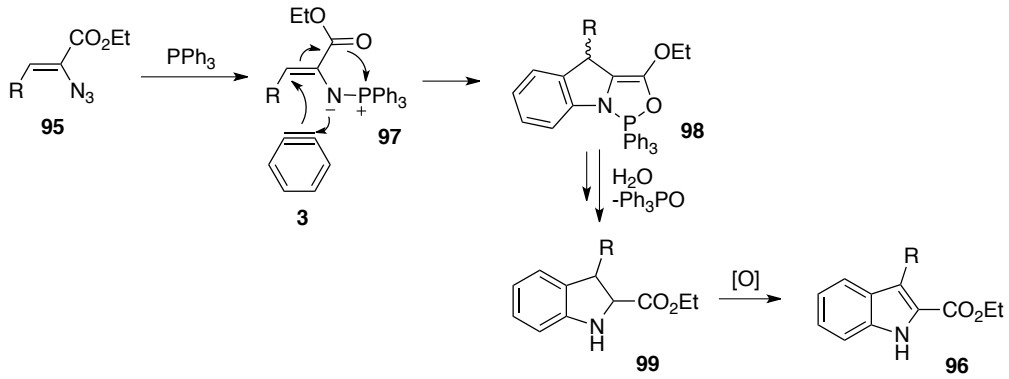


Scheme 33. Synthesis of Indoles Developed by Greaney.

An alternative route to the indole system has been developed by Wang and involves the coupling of azo-ylides with arynes (Scheme 34).[38] Azo-ylides **97** are generated *in situ* from the corresponding alkenyl azides **95** and PPh_3. Double cyclization leads to the formation of intermediate **98**, which after hydrolysis and elimination of triphenylphosphine oxide is transformed into the indoline structure **99** (Scheme 35). Aerobic oxidation of the latter furnishes the desired indoles **96** in 64-89% overall yields.

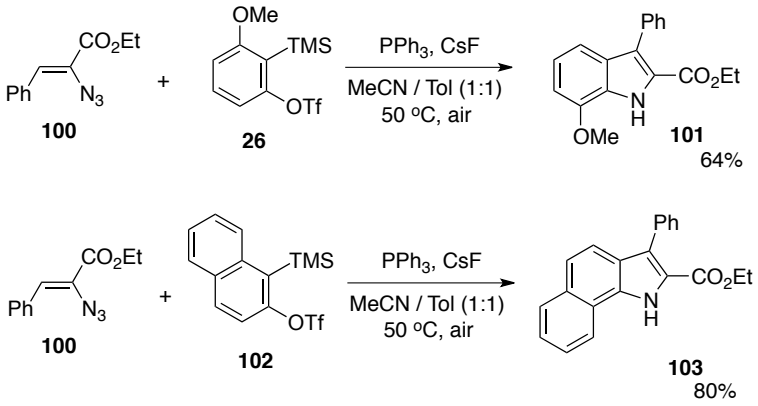


Scheme 34. Synthesis of Indoles Developed by Wang.



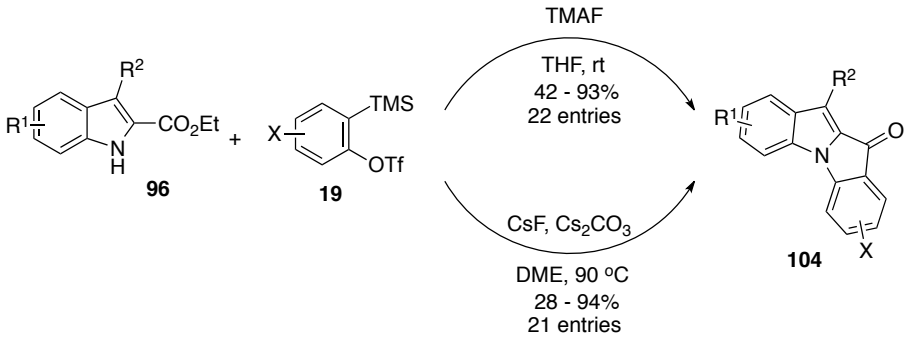
Scheme 35. Plausible Mechanism for the Coupling of Azo-ylides and Arynes.

The optimal reaction conditions involve the presence of CsF and PPh_3 in a MeCN/toluene mixture at 50 °C under aerobic conditions. The reaction tolerates aryl, alkenyl, halides, and nitro functional groups. The reaction with the unsymmetrical 3-methoxybenzyne results in formation of the expected product **101** as a single regioisomer. The reaction with the unsymmetrical naphthalyne precursor **102** results in formation of the indole **103** as a single regioisomer as well (Scheme 36).



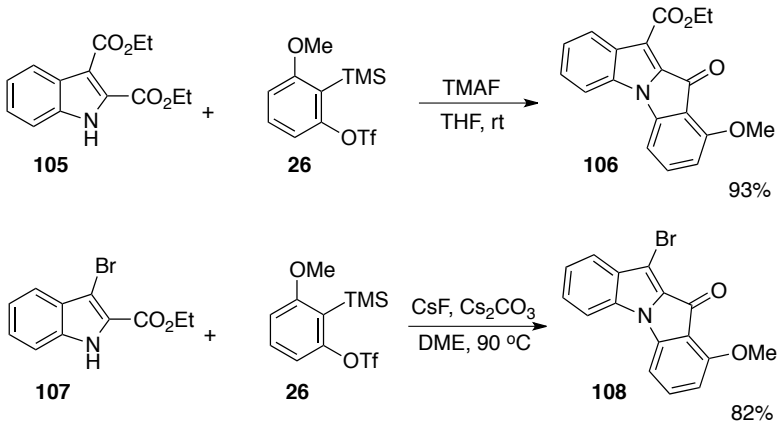
Scheme 36. Examples of Reactions with Unsymmetrical Arynes.

The indole products **96** can be used as starting materials in annulation reactions with arynes. After nucleophilic attack of the indole nitrogen on the benzyne, the resulting anion attacks the ester group with formation of the indole-indolone structure **104** (Scheme 37).



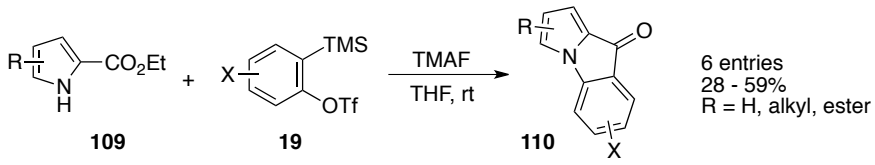
Scheme 37. Synthesis of Indole-Indolones.

The Ramtohul[39] and Larock[40] groups have independently studied this system and found that using tetramethylammonium fluoride (TMAF) in THF at room temperature (Ramtohul) or CsF in DME in the presence of Cs_2CO_3 at 90 ^oC (Larock) provides the desired tetracyclic heterocycles in 42-93% and 28-94% yields respectively. Both methodologies tolerate halo, ester, and alkoxy functionality. Under the TMAF/THF conditions, lower yields (42%) were observed with an aldehyde-containing substrate. Under the CsF/DME conditions, a nitro-containing substrate afforded the coupling product in a low 40% yield. In both cases, the reaction with 3-methoxybenzyne resulted in the formation of the anticipated products **106** and **108** as single regioisomers (Scheme 38).

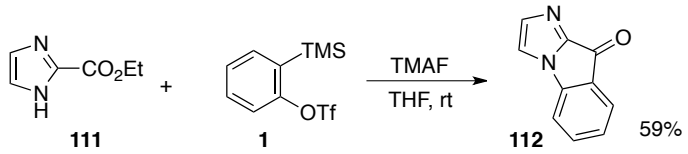


Scheme 38. Reaction with 3-Methoxybenzyne.

The analogous reaction of the pyrrole-2-carboxylate ester **109** leads to the formation of the pyrroloindolone structure **110** (Scheme 39).[39] Interestingly, the use of the aza-analogue of the starting material (**111)** allows one to obtain tricyclic imidazoloindolones in 44-59% yields (Scheme 40).

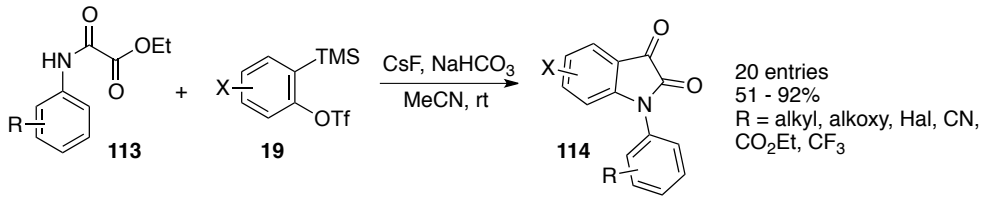


Scheme 39. Synthesis of Pyrroloindolones.



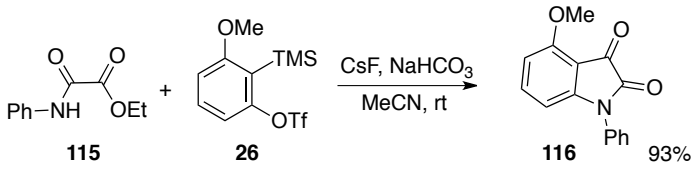
Scheme 40. Synthesis of an Aza-analogue of Pyrroloindolones.

Using a similar annulation strategy, nucleophilic attack of the nitrogen of the methyl 2-oxo-2-(arylamino)acetate system **113** on a benzyne, followed by intramolecular attack of the resulting aryl anion onto the ester group, results in ring closure and formation of an isatin (**114**) in good to high (51-92%) yields (Scheme 41).[41]



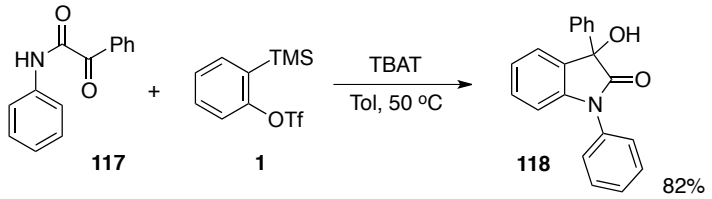
Scheme 41. Synthesis of Isatins.

The optimal conditions were found to employ CsF/MeCN in the presence of stoichiometric amounts of $NaHCO_3$ at room temperature. The reaction tolerates halide, ester, and nitrile functionalities. One observed limitation of this methodology involves nitro-substituted aryl substrates. Running the reaction with 3-methoxybenzyne results in formation of the expected product **116** in a 93% yield as a single regioisomer (Scheme 42).



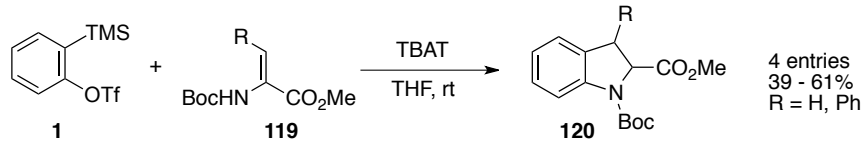
Scheme 42. Reaction with 3-Methoxybenzyne.

Interestingly, running an analogous reaction[42] of the ketone **117** with the benzyne precursor **1** resulted in the formation of the 3-hydroxyindolinone **118** in an 82% yield (Scheme 43).



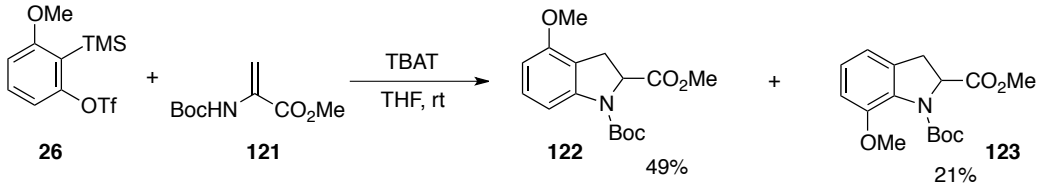
Scheme 43. Synthesis of a 3-Hydroxyindolinone.

The Stoltz group has reported an annulation approach to indolines starting from ene carbamates.[43] When reacting *N*-Boc enamines **119** with benzyne in the presence of TBAT in THF at ambient temperatures, the desired heterocycles **120** were obtained in 39-61% yields (Scheme 44). Interestingly, the Boc group is crucial to the reaction's success. Acyl-substituted enamines alter the reaction pathway and lead to the formation of isoquinolines. The reaction with *N*-Boc enamines presumably occurs through the following pathway. The stabilized ambident nucleophile attacks the electrophilic aryne intermediate through its nitrogen atom, and the resulting aryl anion undergoes an intramolecular Michael reaction to form the final indolines.



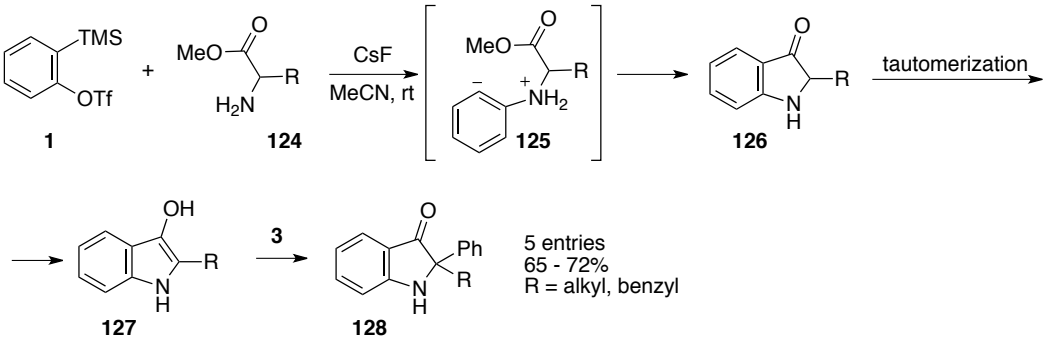
Scheme 44. Synthesis of Indolines.

The reaction with unsymmetrical 3-methoxybenzyne is consistent with initial attack of the nitrogen atom; the corresponding product **122** was isolated in a 49% yield, along with 21% of the regioisomer **123** (Scheme 45).



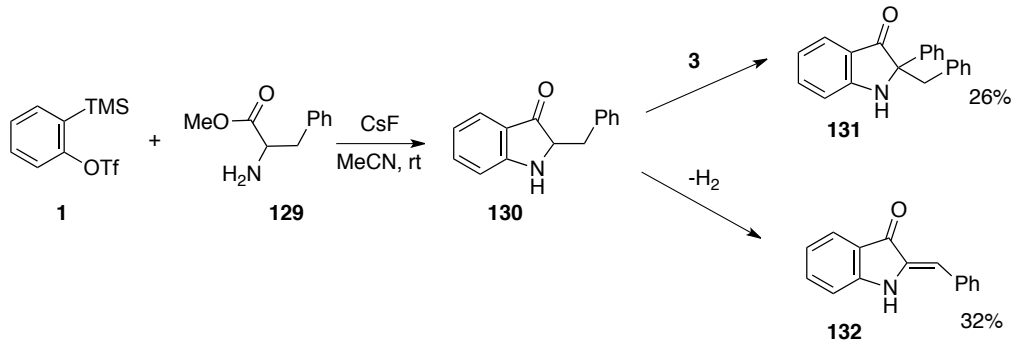
Scheme 45. Reaction with 3-Methoxybenzyne.

2-Arylindolin-3-ones can be prepared from the methyl esters of α-amino acids **124** using a similar aryne annulation strategy (Scheme 46).[44] The unprotected amino group attacks the benzyne and the resulting aryl anion **125** intramolecularly reacts with the nearby ester group. The reaction does not stop, however, since the resulting (after tautomerization) 3-hydroxyindole **127** is more reactive towards the benzyne than the starting material. The reaction stops only after *C*-arylation of the latter (presumably by an ene-reaction). The corresponding products **128** were isolated in 65-72% yields (Scheme 46).



Scheme 46. Synthesis of Indolin-3-ones.

The optimized reaction conditions employed CsF/MeCN at ambient temperatures. It is noteworthy that not all amino esters undergo the desired cyclization. For instance, the methyl esters of alanine and proline provided only the corresponding *N*-arylation products. In the case of phenylalanine (**129**), along with a 26% yield of the expected product **131**, the dehydrogenated product **132** was isolated in a 32% yield (Scheme 47).

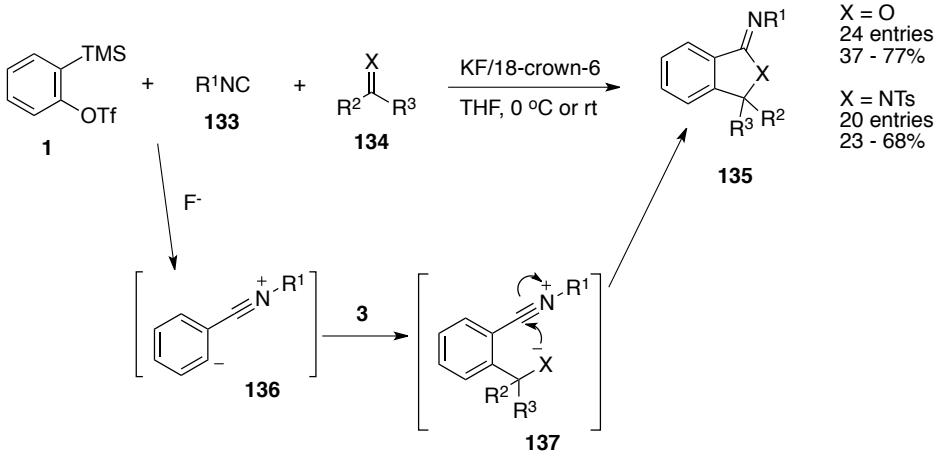


Scheme 47. Reaction of Phenylalanine and Benzyne.

2.2.10. Iminoisobenzofurans and Iminoisoindolines

An interesting route to iminoisobenzofurans and iminoisoindolines has been developed by Kunai and Yoshida.[45] In a multicomponent process, the isocyanide **133** reacts with the benzyne intermediate with formation of the intermediate **136**. The latter attacks an

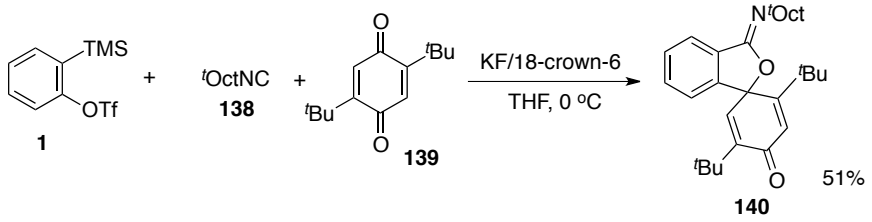
aldehyde/ketone or a *N*-tosyl imine and subsequent intramolecular cyclization leads to formation of the desired heterocycles **135** (Scheme 48). Running the reaction in the presence of KF/18-crown-6 in THF at 0 ^{o}C (X = O) or room temperature (X = NTs) allows one to isolate the desired iminoisobenzofurans **135** (X = O) and iminoisoindolines **135** (X = NTs) in 37-77% and 23-68% yields respectively.



Scheme 48. Synthesis of Iminoisobenzofurans and Iminoisoindolines.

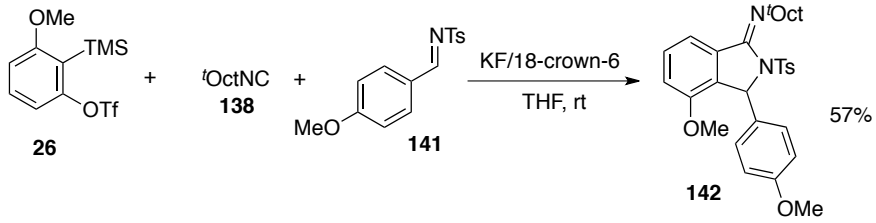
Aryl, heteroaryl, and alkyl (albeit in lower yields) aldehydes and several ketones are tolerated in the methodology leading to iminoisobenzofurans. Only tertiary alkyl isocyanides have been studied in this transformation. In the case of the iminoisoindolines, the reaction tolerates aryl and heteroaryl aldehydes, and tertiary and primary isocyanides. Interestingly, the secondary alkyl cyclohexyl isocyanide provided the lowest (23%) yield of the final product.

It is noteworthy that this methodology works well with a quinone and some of alkyl-substituted derivatives, providing the spiroheterocycles in 32-52% yields (Scheme 49).



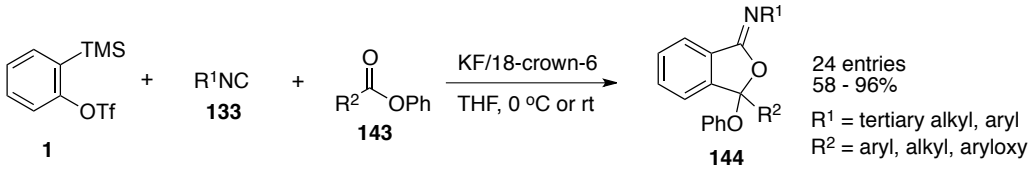
Scheme 49. Representative Synthesis of Spiroheterocycles.

The analogous reaction with unsymmetrical 3-methoxybenzyne leads to the formation of the product **142** in a 57% yield as a single regioisomer (Scheme 50). This result is consistent with initial nucleophilic attack of the isocyanide on the benzyne intermediate.



Scheme 50. Reaction with 3-Methoxybenzyne.

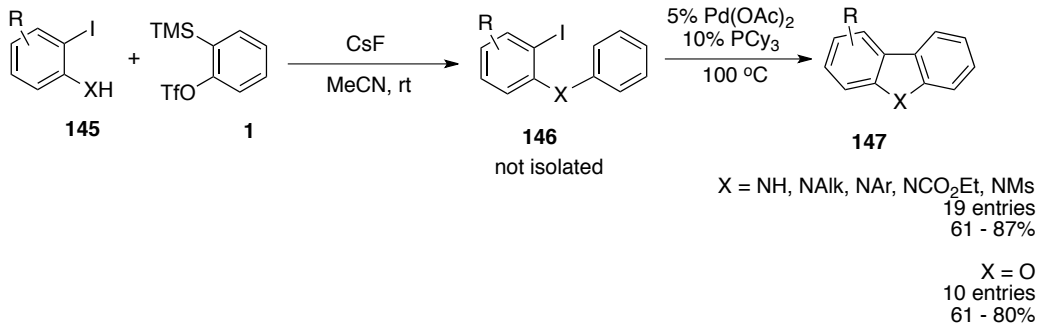
An analogous reaction with esters, instead of aldehydes/ketones/imines, has been studied by Stoltz and co-workers.[46] While alkyl esters, such as ethyl acetate, are not electrophilic enough to react with the intermediate **136**, aryl esters lead to the formation of the heterocyclic products **144** (Scheme 51). Running the reaction in the presence of TBAT in THF at 40 °C affords the final products in 58-96% yields.



Scheme 51. Reaction with Aryl Esters.

2.2.11. Carbazoles and Dibenzofurans

A two-step approach to carbazoles and dibenzofurans has been developed by Larock and co-workers.[47] In their earlier work,[48] the Larock group developed conditions for the formal insertion of arynes into the N-H bond of amines and the O-H bond of phenols. The optimal conditions were found to be CsF/MeCN at ambient temperatures. Employing *o*-iodoanilines and *o*-iodophenols in this transformation leads to the formation of the corresponding arylation products in 90-97% yields. After Pd-catalyzed intramolecular arylation (the Pd catalyst is added to the reaction mixture without isolation of the arylation products **146**), the corresponding carbazoles and dibenzofurans can be obtained in 61-87% and 61-80% yields respectively (Scheme 52).

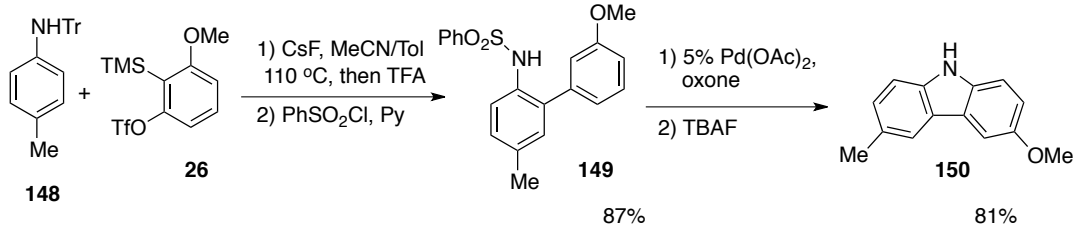


Scheme 52. Synthesis of Carbazoles and Dibenzofurans.

Both methodologies tolerate a wide range of functional groups: ketones, halides, esters, and alkoxy groups. Unsubstituted anilines, monoalkyl, monoaryl and *N*-mesyl anilines, as well as urethanes, all undergo the desired one-pot transformation with high efficiency.

Greaney reported a four-step synthesis of the antibiotic and antifungal carbazole-containing product **150** using aryne chemistry (Scheme 53). The trityl-substituted aniline **148**

was allowed to undergo an ene-reaction with 3-methoxybenzyne. The trityl group was then removed under acidic conditions and the nitrogen sulfonylated. Thus, the 2-aryl aniline **149** was isolated in an 87% yield. A Pd-catalyzed cyclization, followed by removal of the sulfonyl group resulted in the formation of the cyclic carbazole natural product **150** in an 81% yield.



Scheme 53. Synthesis of a Biologically Important Carbazole.

2.3. Conclusions

In recent years, aryne intermediates have continued their journey from objects of purely theoretical interest to indispensable tools in the synthesis of pharmaceutically and biologically interesting small molecules, as well as complex natural products. The major breakthrough in synthetic aryne chemistry has been the development of a mild, controlled method for generating the highly reactive benzyne intermediate from silylaryl triflates, which was first reported by Kobayashi in 1983. However, not until the mid-2000's did aryne methodologies start flourishing in the literature. A great variety of heterocycles can now be prepared from cheap and readily available starting materials by simple one-step or one-pot processes with high regioselectivities and in high yields. A broad variety of functional groups are tolerated under the mild reaction conditions used. However, the poor atom economy of Kobayashi's precursor and its relatively high price continue to remain a major drawback to

even wider application of this fascinating chemistry. Solutions to this problem and broader applications of the existing aryne precursors are currently being sought by many research groups. One should expect new, more efficient, more regio- and stereoselective aryne methodologies to appear in the nearest future.

2.4. References

(1) Bhojgude, S. S.; Biju, A. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 1520.

(2) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140.

(3) (a) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 3579. (b) Sanz, R. *Org. Prep. Proc. Int.* **2008**, *40*, 215. (c) Chen, Y.; Larock, R. C. In *Modern Arylation Methods*; Ackerman, J., Ed.; Wiley/VCH: New York, **2009**; pp 401-473.

(4) (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *ASAP* (DOI:10.1021/cr200478h). (b) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *ASAP* (DOI:10.1002/anie.201107485).

(5) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(6) For a general review, see: Kitamura, T. *Aust. J. Chem.* **2010**, *63*, 987.

(7) Walsh, R. Bond Dissociation Energies in Organosilicon Compounds. http://www.gelest.com /Library/10BondDiss.pdf (accessed 06/11/12).

(8) (a) Imidazolylsulfonate: Kovács, S.; Csincsi, Á. I.; Nagy, T. Z.; Boros, S.; Timári, G.; Novák, Z. *Org. Lett.* **2012**, *14*, 2022. (b) Iodide: Crossley, J. A.; Kirkham, J. D.; Browne, D. L.; Harrity, J. P. A. *Tetrahedron Lett.* **2010**, *51*, 6608. (c) Nonafluorobutanesulfonyl: Ikawa, T.; Nishiyama, T.; Nosaki, T.; Takagi, A.; Akai, S. *Org. Lett.* **2011**, *13*, 1730.

(9) Peña, D.; Iglesias, B.; Quintana, I.; Pérez, D.; Guitián, E.; Castedo, L. *Pure Appl. Chem.* **2006**, *78*, 451.

(10) (a) Barrero, A. F.; Quílez del Moral, J. F.; Mar Herrador, M.; Arteaga, P.; Cortés, M.; Benites, J.; Rosellón, A. *Tetrahedron* **2006**, *62*, 6012. (b) For aza-analogues, see: Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, 3587.

(11) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409.

(12) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793.

(13) Lu, C.; Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2279.

(14) Wu, Q.; Li, B.; Lin, W.; Shi, C.; Chen, Y.; Chen, Y. *Hecheng Huaxue* **2007**, *15*, 292.

(15) Kivrak, A.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 7381.

(16) For the similar reactivity of oxaziridines, see: Fabio, M.; Ronzini, L.; Troisi, L. *Tetrahedron* **2007**, *63*, 12896.

(17) Kelly, D. R.; Baker, S. C.; King, D. S.; de Silva, D. S.; Lord, G.; Taylor, J. P. *Org. Biomol. Chem.* **2008**, *6*, 787.

(18) Larsen, K. E.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 2985.

(19) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180.

(20) Crossley, J. A.; Browne, D. L. *Tetrahedron Lett.* **2010**, *51*, 2271.

(21) Spiteri, C.; Sharma, P.; Zhang, F.; Macdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, *46*, 1272.

(22) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368.

(23) Li, P.; Wu, C.; Zhao, J.; Rogness, D. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 3149.

(24) Markina, N. A.; Dubrovskiy, A. V.; Larock, R. C. *Org. Biomol. Chem.* **2012**, *10*, 2409.

(25) Jin, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3323.

(26) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219.

(27) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340.

(28) Yamashita, Y.; Hayashi, T.; Masumura, M. *Chem. Lett.* **1980**, 1133.

(29) Zhao, J.; Wu, C.; Li, P.; Ai, W.; Chen, H.; Wang, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 6837.

(30) (a) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem. Asian J.* **2010**, *5*, 153. (b) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2743.

(31) Huang, X.; Zhang, T. *Tetrahedron Lett.* **2009**, *50*, 208.

(32) Xie, C.; Zhang, Y.; Xu, P. *Synlett* **2008**, 3115.

(33) Shi, F.; Mancuso, R.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4067.

(34) Shen, Y.-M.; Grampp, G.; Leesakul, N.; Hu, H.-W.; Xu, J.-H. *Eur. J. Org. Chem.* **2007**, *2007*, 3718.

(35) Mechanistic studies are in progress.

(36) McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667.

(37) An expected reactivity based on: Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673.

(38) Hong, D.; Chen, Z.; Lin, X.; Wang, Y. *Org. Lett.* **2010**, *12*, 4608.

(39) Giacometti, R.; Ramtohul, Y. *Synlett* **2009**, 2010.

(40) Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003.

(41) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2011**, *76*, 4980.

(42) Conditions were adapted from: Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168.

(43) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.

(44) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822.

(45) (a) X = O: Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3935. (b) X = NTs: Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659. (c) X = O, NTs: Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793.

(46) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 4488.

(47) (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (b) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347.

(48) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.

CHAPTER 3

SYNTHESIS OF BENZISOXAZOLES BY THE [3 + 2] CYCLOADDITION OF *IN SITU* GENERATED NITRILE OXIDES AND ARYNES.[†]

Anton V. Dubrovskiy and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

3.1. Abstract

A variety of substituted benzisoxazoles has been prepared by the [3 + 2] cycloaddition of nitrile oxides and arynes. Both components, being highly reactive intermediates, have been generated *in situ* by fluoride anion from readily prepared aryne precursors and chlorooximes. The reaction scope is quite general, affording a novel, direct route to functionalized benzisoxazoles under mild reaction conditions.

3.2. Introduction

Benzisoxazoles are present in a large number of pharmaceutically important products with antipsychotic, [1] antitumor, [2] anticonvulsant, [3] antimicrobial, [4] antithrombotic [5] and cholinesterase-inhibiting[6] (Alzheimer's disease) properties (Figure 1).

[†] Adapted from *Org. Lett.* **2010**, *12*(6), 1180, with permission from the American Chemical Society © 2010.

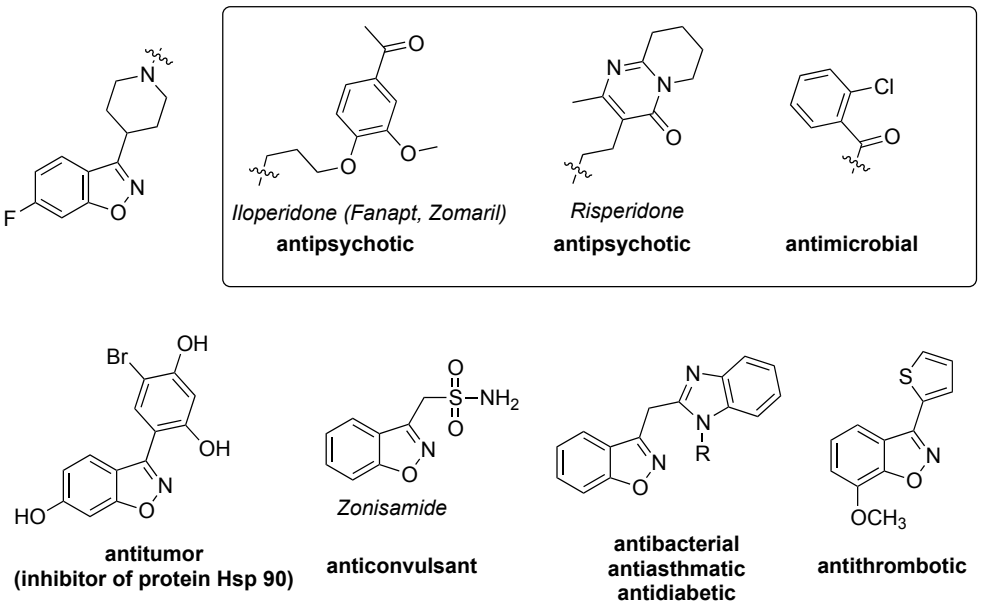
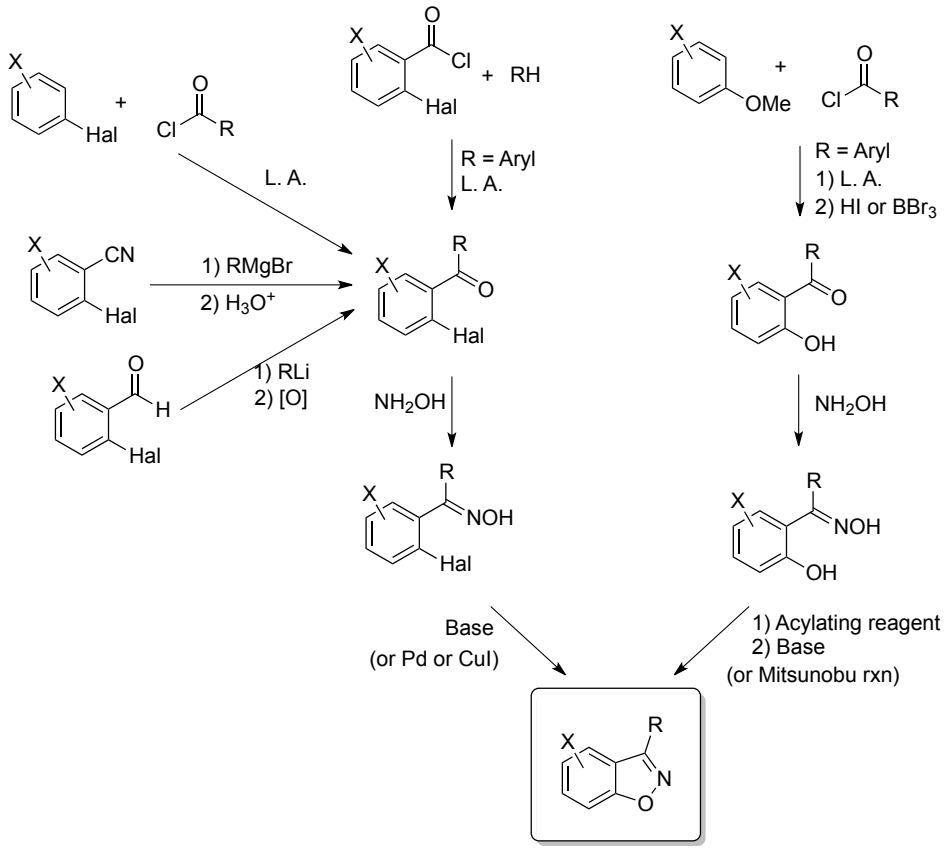


Figure 1. Examples of Medicinally Relevant Benzisoxazoles.

The traditional approaches (Scheme 1) to the synthesis of benzisoxazoles are 3-4 step syntheses, which usually involve formation of the carbon-oxygen bond (through S_NAr,[7] Pd,[8] or CuI[9] catalyzed reactions) or oxygen-nitrogen bond (through base-mediated cyclizations[10] or intramolecular Mitsunobu[11] reactions) *via* intermediate *o*-halo- or *o*-hydroxyaryl ketoximes during the final steps of the syntheses. The synthesis of the corresponding *o*-halo- or *o*-hydroxyaryl ketones often involves the strongly acidic conditions of a Friedel-Crafts reaction and the use of one of the substrates as a solvent, while in other cases it requires the use of strongly basic organometallics. Employing these methods, it is possible to synthesize particular benzisoxazoles on a large scale, but it is not as convenient to readily synthesize large numbers of diverse benzisoxazoles for biological activity screening.



Scheme 1. Traditional Approaches to Benzisoxazoles.

The idea of forming two bonds at a time, by means of a [3 + 2] cycloaddition reaction of a benzyne with a nitrile oxide, has been reported previously,[12] although the low yields (10% and 53%), limited possibilities for diversification, and the challenging experimental procedures employed were not very encouraging for the widespread utility of this approach.

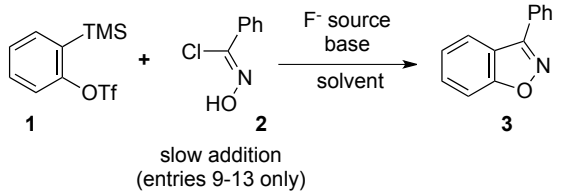
3.3. Results and Discussion

Our recent interest[13] in the chemistry of arynes generated from the corresponding *o*-(trimethylsilyl)aryl triflates under mild fluoride ion treatment has encouraged us to reexamine this approach to benzisoxazoles. Fluoride ion not only induces the formation of benzyne due to initial nucleophilic attack on the silicon of the trimethylsilyl group,[14] but,

being also a base, it could potentially[15] induce formation of the nitrile oxide from the corresponding chlorooximes. Such an approach would eliminate potential problems arising from interaction of the reagents needed for generating the two highly reactive intermediates, as well as the requirement that the two species be generated separately from each other.

Indeed, our initial attempt to react *o*-(trimethylsilyl)phenyl triflate (**1**) with *N*-hydroxybenzimidoyl chloride (**2**) in the presence of 3 equiv of CsF in acetonitrile led to formation of the desired 3-phenylbenzisoxazole (**3**) in a 46% yield (Table 1, entry 1). High resolution GC/MS of the crude mixture revealed the expected dimerization products[16] of phenyl nitrile oxide as the major by-products of the reaction.

Table 1. Optimization Studies of the Reaction of *o*-(Trimethylsilyl)phenyl Triflate (**1**) and *N*-Hydroxybenzimidoyl Chloride (**2**).[a]



entry	equiv of **1**	fluoride source (equiv)	solvent	temp (°C)	add. time of **2** (h)	% yield[b]
1	1.2	CsF (3)	MeCN	rt	-	46
2	1.2	TBAT (3)	MeCN	rt	-	<5[c]
3	1.2	CsF (3)	THF	rt	-	<5[c]
4	1.2	CsF (3)	THF	65	-	<5[c]
5	1.2	CsF (3)	MeCN	65	-	9
6	1.2	CsF (2.5)	MeCN	rt	-	23
7	2.0	CsF (6)	MeCN	rt	-	61
8	3.0	CsF (6)	MeCN	rt	-	58
9	2.0	CsF (6)	MeCN	rt	5.0	70
10	**2.0**	**CsF (6)**	**MeCN**	**rt**	**2.5**	**90**
11	2.0	CsF (6)	MeCN	rt	1.0	73
12	1.5	CsF (4.5)	MeCN	rt	2.5	69
13	1.0	CsF (3)	MeCN	rt	2.5	54

[a] All reactions were carried out on a 0.25 mmol scale in 5 mL of solvent. [b] Isolated yields, unless stated otherwise. [c] ^{1}H NMR spectroscopic yields.

Our optimization studies of this process are summarized in Table 1. The use of tetrabutylammonium triphenyldifluorosilicate (TBAT), an alternative anhydrous fluoride source, failed to provide the desired product under analogous conditions (entry 2). The use of THF, a less polar solvent, did not lead to formation of the desired benzisoxazole at either

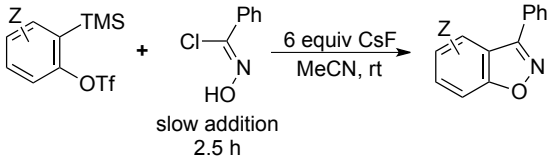
room temperature or 65 ^{o}C (entries 3 and 4). Another attempt to run the reaction at an elevated temperature in acetonitrile to increase the rate of [3 + 2] cycloaddition at the expense of nitrile oxide dimerization did not work well (entry 5). To decrease the rate of formation of the nitrile oxide and thus decrease the formation of the self-dimerization products, we attempted to use less of the base CsF, but at the same time this change resulted in a decrease in the rate of benzyne formation, which resulted in a lower (23%) yield of the benzisoxazole (entry 6). Since the rate of nitrile oxide dimerization seemed to be greater than the rate of [3 + 2] cycloaddition, we examined the use of an excess of the benzyne precursor (entries 7 and 8). Indeed, the use of 2 equiv of the benzyne precursor was found to increase the yield to 61%. To further increase the local concentration of benzyne relative to the nitrile oxide, we examined slow addition of the chlorooxime to the reaction mixture by a syringe pump (entries 9-11). The optimal time of addition, which best aligned the rates of formation of the benzyne and the nitrile oxide, was found to be 2.5 h, which allowed the benzisoxazole **3** to be isolated in a 90% yield (entry 10). Lowering the benzyne loading to 1.5 and 1.0 equiv, while still keeping the slow addition conditions resulted in lower (69% and 54% yields, respectively) of the final product **3** (entries 12 and 13).

It is noteworthy that during our work, analogous procedures have been reported by the Moses, Browne, and Chen groups. Moses and co-workers found that chlorooximes of aromatic aldehydes afford 75-99% yields of the corresponding benzisoxazoles using a 1.5-fold excess of the benzyne precursor.[17] The Browne group, using the same approach, but 3 equiv of the benzyne precursor, was able to get 73-99% yields of benzisoxazoles starting from aryl, heteroaryl, and alkenyl aldehyde-derived chlorooximes.[18] Finally, the Chen group

studied the coupling of substituted benzaldehyde-derived chlorooximes with benzynes derived from aryl disiloles under TBAF/$^{i}Pr_2NH$ reaction conditions. They were able to obtain the desired benzisoxazoles in 34-87% yields.[19]

Employing the optimal conditions shown in Table 1, entry 10, we examined the scope of this reaction using various aryne precursors (Table 2). Symmetrical naphthalyne and 4,5-dimethylbenzyne provided the corresponding benzisoxazoles **5** and **7** in 61% and 74% yields respectively (entries 2 and 3). Both electron-rich and electron-poor aryne precursors successfully participated in the [3 + 2] cycloaddition reaction, providing the desired coupling products. Thus, 3,4-dimethoxybenzyne provided the corresponding benzisoxazole **9** in a 65% yield (entry 4). The lowest yield (36%) was observed in the reaction of the highly reactive 3,4-difluorobenzyne (entry 5).[20]

Table 2. Synthesis of 3-Substituted Benzisoxazoles by the Reaction of Benzaldehyde Chlorooxime and Aryne Precursors in the Presence of CsF.[a]



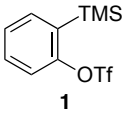
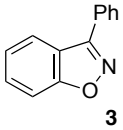
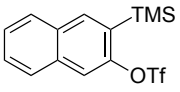
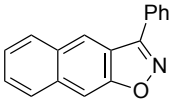
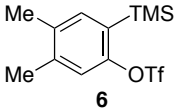
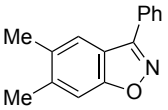
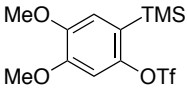
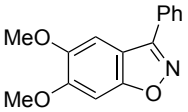
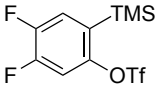
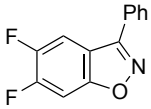
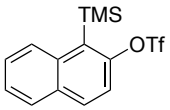
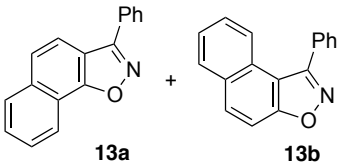
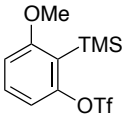
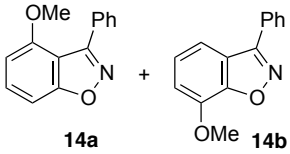
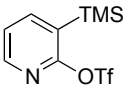
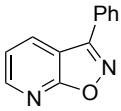
entry	aryne	product	yield[b] (%)
1	 **1**	 **3**	90

Table 2 continued.

2	 **4**	 **5**	61
3	 **6**	 **7**	74
4	 **8**	 **9**	65
5	 **10**	 **11**	36
6	 **12**	 **13a** **13b**	60 (1:1)[c]
7	 **14**	 **14a** **14b**	83 (1.8:1)[c]
8	 **15**	 **16**	13[d]

[a] Reaction conditions: a solution of benzaldehyde chlorooxime (0.25 mmol) in 3 mL of acetonitrile was added by syringe pump to a stirring mixture of silylaryl triflate (0.50 mmol) and CsF (1.50 mmol) in 3 mL of MeCN over the course of 2.5 h. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR spectroscopy (see the experimental section for details). [d] No slow addition was performed in this case.

The unsymmetrical 1,2-naphthalyne showed no regioselectivity in the [3 + 2] cycloaddition process. The two isomeric coupling products **13a** and **13b** were formed in equal amounts in a 60% combined yield (entry 6). The unsymmetrical 3-methoxybenzyne provided a mixture of regioisomers in a ~1.8:1 ratio (entry 7). Interestingly, in the latter case electronic factors dominate over steric factors with the isomer **14a** being the major product in the mixture (Figure 2).

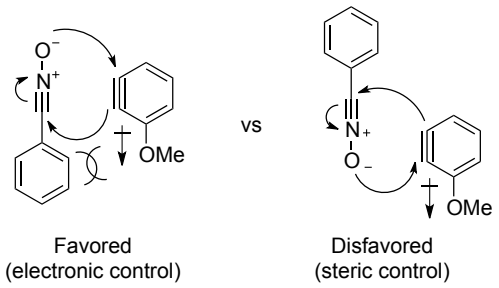
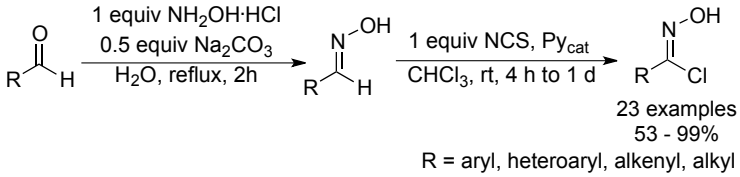


Figure 2. Electronic and Steric Factors in the Reaction of 3-Methoxybenzyne and Phenyl Nitrile Oxide.

The pyridyne precursor **15** afforded the corresponding product **16** in only a low 13% yield (entry 8). The low efficiency of the latter reaction can be explained by the high reactivity of the highly electron-deficient pyridyne system[21] and the affinity of the nitrogen of the pyridine ring for reaction with the electrophilic benzyne.[22] This perhaps explains the low yield and significant number of side-products in this reaction.

Various chlorooximes have been prepared from the corresponding readily available aldehydes in 53-99% overall yields as follows. The reaction of the aldehyde with hydroxylamine hydrochloride in the presence of Na_2CO_3 afforded the corresponding oximes,

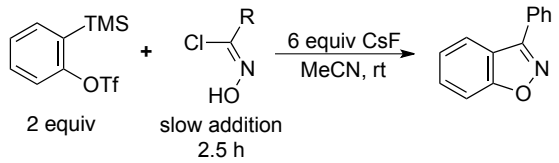
which without isolation were chlorinated using NCS and catalytic amounts of pyridine (Py) at room temperature in chloroform (Scheme 2).[23] An alternative protocol,[24] which employs chlorination by oxone and HCl, failed to provide chlorooximes bearing alkyl moieties.



Scheme 2. Preparation of the Chlorooximes.

We next investigated the scope of the reaction between *o*-(trimethylsilyl)phenyl triflate (**1**) and various chlorooximes (Table 3). Aromatic chlorooximes provided the corresponding benzisoxazoles in good to excellent yields. 3-(2-Naphthyl)benzisoxazole (**18**) was obtained in a 72% yield (entry 1). Lower yields were observed when electron-withdrawing substituents reside on the benzene ring. Thus, 3-(2-nitrophenyl)benzisoxazole (**20**) and 3-(3-nitrophenyl)benzisoxazole (**22**) were isolated in 57% and 54% yields respectively (entries 2 and 3).[25] Excellent yields were observed using chlorooximes bearing electron-donating (through resonance) methoxy substituents (entries 4-6). The corresponding products **24**, **26**, and **28** were obtained in 93%, 85%, and 81% yields respectively. Even the chlorooxime **29** bearing a bulky *o*-bromo substituent afforded the benzisoxazole **30** in a 93% isolated yield (entry 7). The perfluorophenyl-substituted benzisoxazole **32** was obtained in a 40% yield (entry 8). An alkene was also readily tolerated in the reaction. Thus, (*E*)-3-styrylbenzisoxazole (**34**) was isolated in a 70% yield (entry 9).

Table 3. Synthesis of 3-Substituted Benzisoxazoles by the Reaction of Various Chlorooximes and Benzyne in the Presence of CsF.[a]



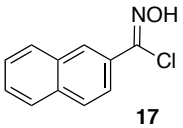
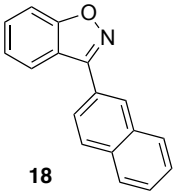
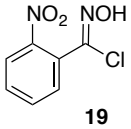
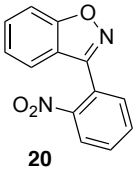
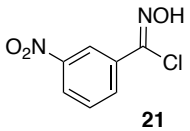
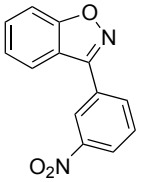
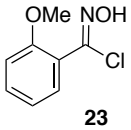
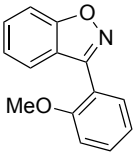
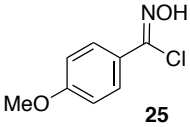
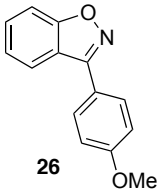
entry	chlorooxime	product	yield[b] (%)
1	 **17**	 **18**	72
2	 **19**	 **20**	57
3	 **21**	 **22**	54
4	 **23**	 **24**	93
5	 **25**	 **26**	85

Table 3 continued.

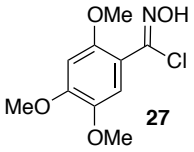
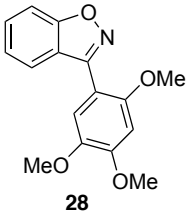
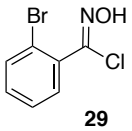
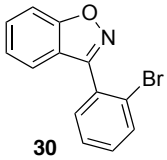
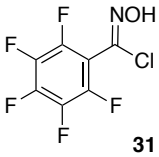
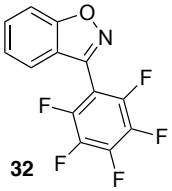
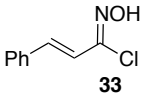
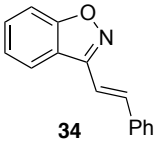
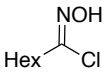
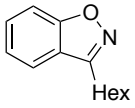
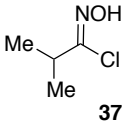
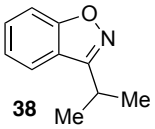
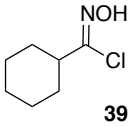
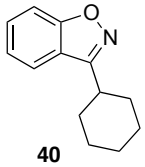
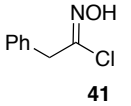
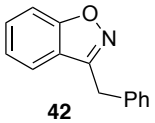
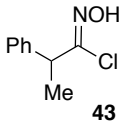
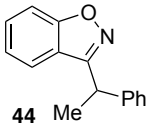
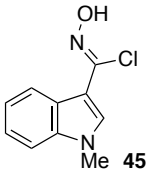
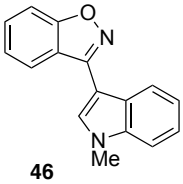
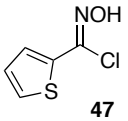
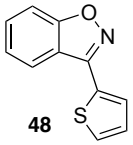
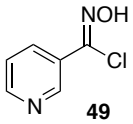
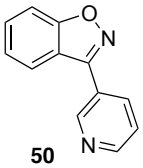
6	 **27**	 **28**	81
7	 **29**	 **30**	93
8	 **31**	 **32**	40
9	 **33**	 **34**	70
10	 **35**	 **36**	58
11	 **37**	 **38**	83
12	 **39**	 **40**	77
13	 **41**	 **42**	79
14	 **43**	 **44**	71

Table 3 continued.

15	 **45**	 **46**	61
16	 **47**	 **48**	54
17	 **49**	 **50**	0

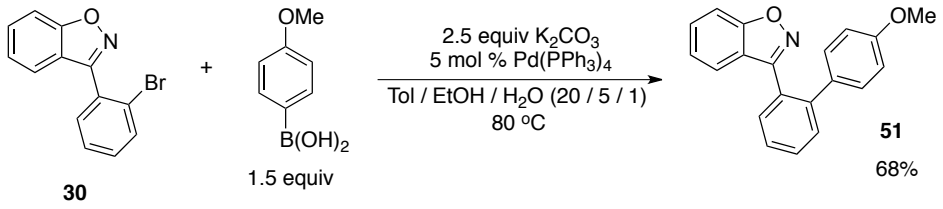
[a] Reaction conditions: a solution of the appropriate chlorooxime (0.25 mmol) in 3 mL of acetonitrile was added by syringe pump to a stirring mixture of *o*-(trimethylsilyl)phenyl triflate (0.50 mmol) and CsF (1.50 mmol) in 3 mL of MeCN over the course of 2.5 h. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR spectroscopy (see the experimental part for details).

Despite the reported instability of chlorooximes bearing alkyl moieties,[26] the primary alkyl-substituted benzisoxazole **36** was obtained in a 58% yield (entry 10). The secondary isopropyl- and cyclohexyl-substituted chlorooximes **37** and **39** afforded the corresponding benzisoxazoles in higher 83% and 77% yields (entries 11 and 12). The benzyl-substituted substrate **41** afforded the benzisoxazole **42** in a 79% yield (entry 13) and its methyl-substituted analogue **43** afforded the desired product **44** in only a slightly lower 71% yield (entry 14).

Next, we studied the cycloaddition reaction of benzyne with chlorooximes derived from heterocyclic aldehydes. The *N*-methylindole-derived chlorooxime **45** furnished the desired product **46** in a 61% yield (entry 15). Unfortunately, we could not obtain the desired

product from the 2-furancarbohydroxamoyl chloride. The reaction produced many inseparable products, presumably due to Diels-Alder reactions[14] of the furan ring with benzyne. On the other hand, the 3-thiophenecarbohydroxamoyl chloride **47** successfully provided the desired benzisoxazole **48** in a 54% yield (entry 16). Unfortunately, the cycloaddition reaction failed in the case of *N*-hydroxy-3-pyridinecarboximidoyl chloride (**49**), most likely due to its poor solubility in acetonitrile (entry 17).

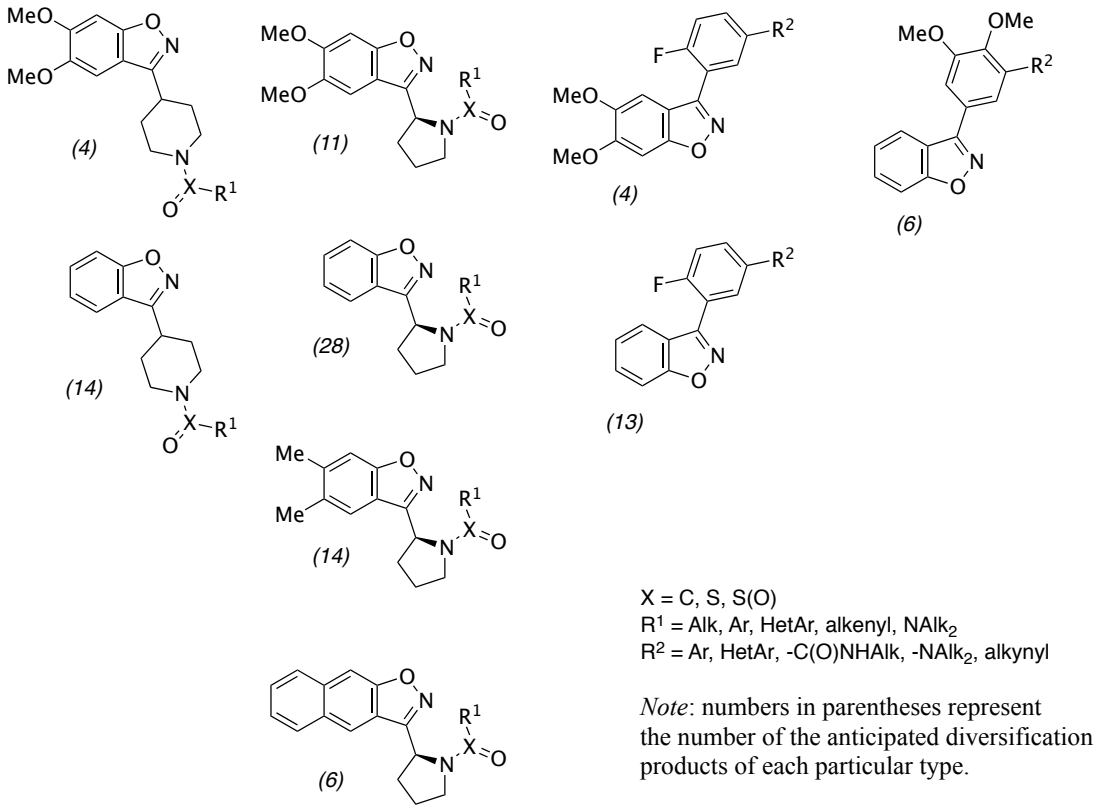
The synthesized bromo-substituted benzisoxazole **30** is a suitable substrate for further elaboration by well known Pd chemistry. We could obtain the coupling product **51** from a Suzuki-Miyaura reaction[27] in a 68% yield (Scheme 3). The successful outcome of this coupling reaction encouraged us to pursue the synthesis of a library of substituted benzisoxazoles for biological screening.



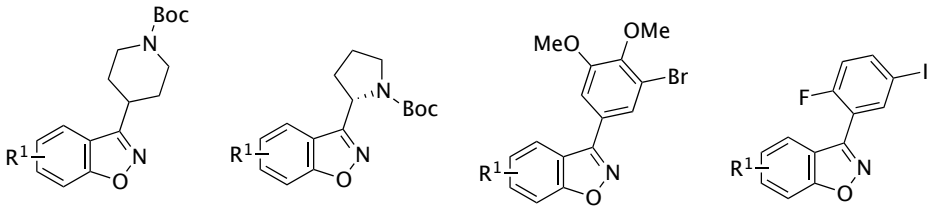
Scheme 3. The Model Suzuki-Miyaura Coupling of a Bromo-containing Benzisoxazole.

Preliminary library calculations using Lipinski's "rule of five"[28] as a criteria for the prospective target structures were carried out by the NIH Center of Excellence for Chemical Methodology and Library Development (CMLD) at Kansas University. The calculation of 808 prospective members revealed 100 members (Scheme 4) worth synthesizing and further screening suggested the synthesis of 9 key starting materials (Scheme 5).[29] These starting materials contain piperidinyl and pyrrolidinyl moieties (allowing further diversification by

acylation/sulfonylation reactions) or a halide functional group (allowing further diversification by Pd-catalyzed Suzuki-Miyaura, Sonogashira, amination and carbonylative amination processes).[30] For practical purposes, relative stable starting materials were needed. Thus, we chose to synthesize amine-containing starting benzisoxazoles as their corresponding Boc-urethanes. The amounts of the 9 required starting materials were calculated assuming a 60% yield in the final diversification step and a need for 35 mg of each final product required for the tests of biological activity.

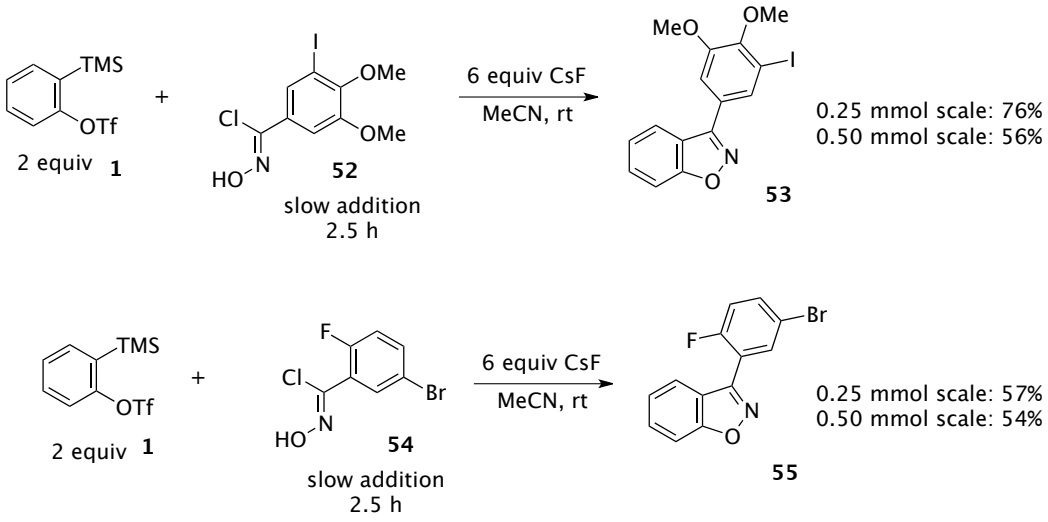


Scheme 4. Prospective Library of Benzisoxazoles.



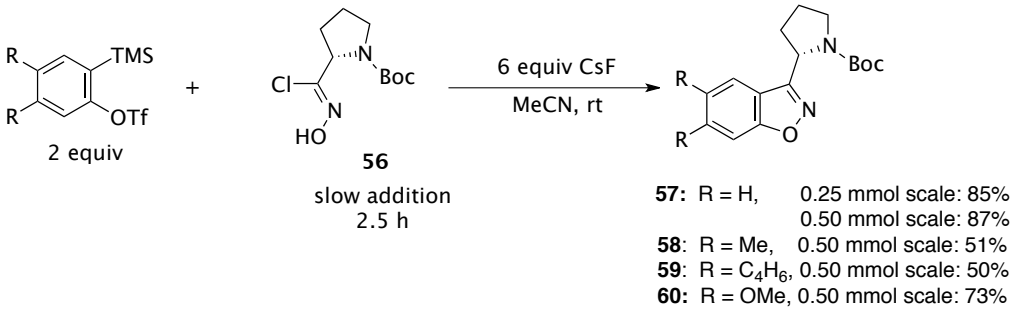
Scheme 5. Structures of the Benzisoxazole Starting Materials needed for the Diversification Reactions.

Despite the scalability issues inherent in the benzyne and chlorooxime coupling reactions, we were able to obtain all but one starting material in sufficient amounts for their further diversification. Electron-rich dimethoxy iodo-substituted chlorooxime **52** led to formation of the desired benzisoxazole **53** in a 76% yield on a standard 0.25 mmol scale (Scheme 6). The yield was significantly lower (56%) when the reaction was run on a 0.50 mmol scale. The more electron-deficient chlorooxime **54** afforded the benzisoxazole **55** in a lower 57% yield when run on a 0.25 mmol scale.



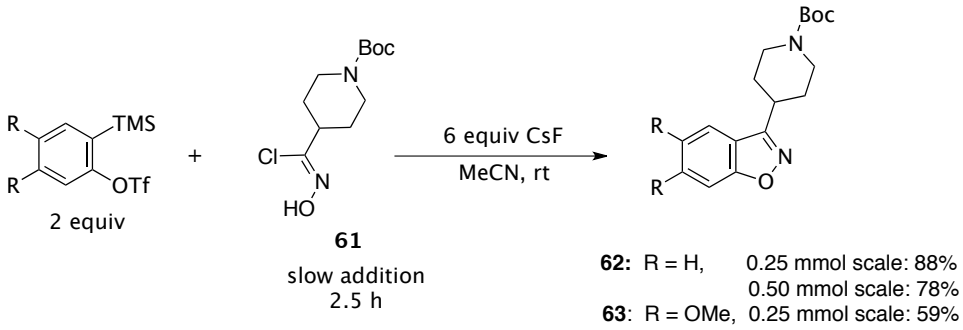
Scheme 6. Synthesis of the Aryl-substituted Starting Indazoles.

The coupling of the chiral proline-derived chlorooxime **56** with an array of symmetrical benzynes afforded the desired benzisoxazoles **57**-**60** in 50-87% yields (Scheme 7). The substituted benzynes provided slightly lower yields than the parent benzyne, with the dimethoxybenzyne being the most efficient of the three (a 73% yield of the corresponding benzisoxazole **60**). The dimethylbenzyne and the symmetrical naphthalyne provided the desired benzisoxazoles **58** and **59** in 51% and 50% yields respectively.



Scheme 7. Synthesis of the Pyrrolidine-substituted Starting Indazoles.

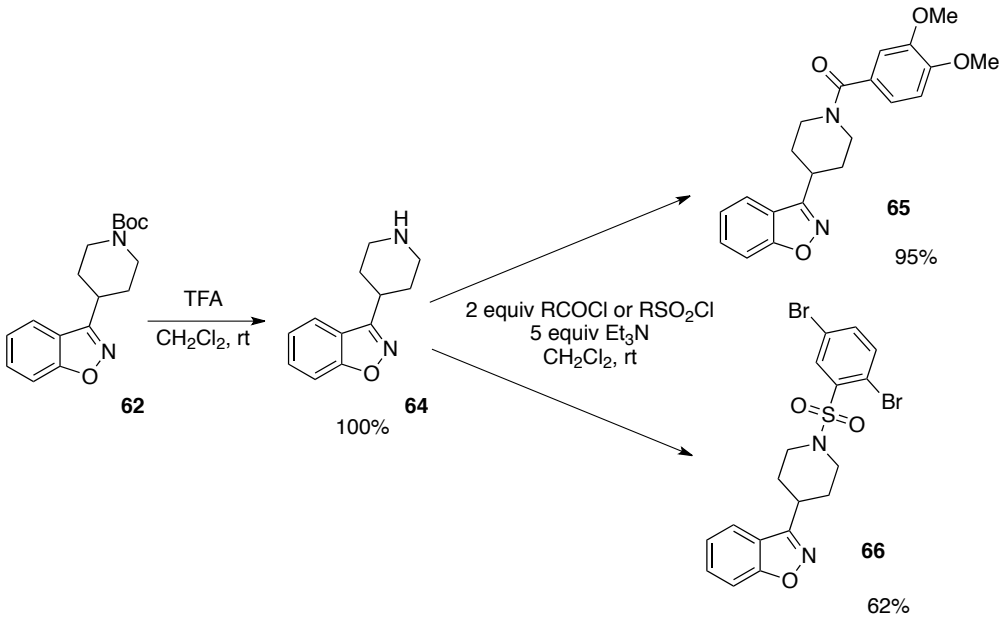
Using our methodology on an *N*-Boc piperidine-derived substrate **61** allowed us to obtain the desired benzisoxazoles **62** and **63** in 88% and 59% yields respectively (Scheme 8).



Scheme 8. Synthesis of the Piperidine-substituted Starting Indazoles.

As an example of a forthcoming diversification reaction of the targets for high throughput screening, we deprotected the *N*-Boc piperidinyl benzisoxazole **62** in a

quantitative yield under acidic hydrolysis conditions. The resulting amine **64** was then used to obtain the representative acylation product **65** and sulfonylation product **66** using standard reaction conditions in 95% and 62% yields respectively (Scheme 9).



Scheme 9. Representative Synthesis of Potential Targets for High Throughput Screening.

3.4. Conclusions

In summary, a simple, convenient and efficient protocol has been developed for the synthesis of benzisoxazoles. The reaction tolerates a variety of functional groups and provides an alternative route to potentially important benzisoxazoles bearing aryl, alkyl, alkenyl and heterocyclic substituents at the 3 position of the benzisoxazole moiety. The utility of this methodology for the construction of combinatorial libraries of compounds for biological screening has been demonstrated by the synthesis of 8 benzisoxazole-based building blocks that are now being diversified by the Kansas University NIH Center of Excellence in Chemical Methodology and Library Development.

3.5. Acknowledgement

We are grateful to the National Institutes of Health (GM079593 and GM070620) and the Kansas University NIH Center of Excellence in Chemical Methodology and Library Development (P50 GM069663) for their generous financial support. We also thank Dr. Feng Shi, while at Iowa State University, for the preparation of non-commercially available benzyne precursors.

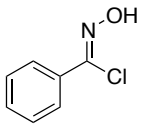
3.6. Experimental

General Information. 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 60 mesh silica gel plates, and visualization was effected by short wavelength UV light (254 nm). All melting points are uncorrected. All high resolution mass spectra were recorded using EI at 70 eV or using Agilent QTOF 6540 mass spectrometer (APCI at a voltage of 70 eV). All reagents were used directly as obtained commercially, unless otherwise noted.

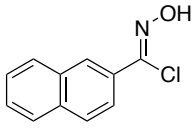
General procedure for synthesis of the starting chlorooximes.

A mixture of the aldehyde (7.0 mmol), hydroxylamine hydrochloride (9.1 mmol) and Na_2CO_3 (4.6 mmol) in 20 ml of water was refluxed for 2 h. After the reaction mixture was allowed to cool down to room temperature, it was extracted with dichloromethane (2 × 25 ml), and the organic fractions were combined and concentrated under reduced pressure. The residue was dissolved in 25 ml of chloroform (in some cases where there was poor solubility, an additional 3 ml of methanol were necessary) and a drop of pyridine was added. After 5 min, *N*-chlorosuccinimide (7.0 mmol) was added portionwise to the reaction mixture while

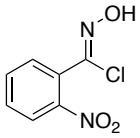
stirring. After the reaction was complete (4 h to 1 d, monitored by TLC), the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired chlorooximes.



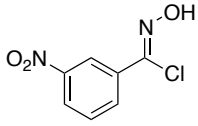
***N*-Hydroxybenzimidoyl chloride (2).** This compound was obtained as a brown solid from commercially available *syn*-benzaldoxime in a 96% yield: mp 48-49 °C (lit.[31] mp 50 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.46 (m, 3H), 7.85 (d, J = 8.0 Hz, 2H), 8.28 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[31]



***N*-hydroxy-2-naphthimidoyl chloride (17).** This compound was obtained as pale brown crystals in a 61% yield: mp 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.83-7.97 (m, 4H), 8.02 (s, 1H), 8.35 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[32]

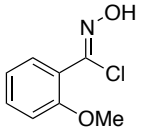


***N*-Hydroxy-2-nitrobenzimidoyl chloride (19).** This compound was obtained as a white solid in a 99% yield: mp 96-98 °C (lit.[31] mp 95-98 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H).

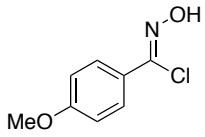


***N*-Hydroxy-3-nitrobenzimidoyl chloride (21).** This compound was obtained as a pale white solid in a 97% yield: mp 100-102 °C (lit.[31] mp 99-100 °C); ^{1}H NMR

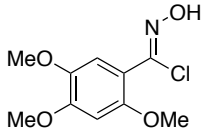
(400 MHz, $CDCl_3$) δ 7.61 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.39 (s, 1H), 8.70 (s, 1H).



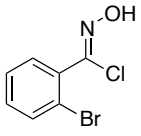
***N*-Hydroxy-2-methoxybenzimidoyl chloride (23).** This compound was obtained as a pale yellow solid in a 92% yield: mp 105-108 °C (lit.[33] mp 110.5-112 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.97-7.05 (m, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 9.46 (s, 1H); HRMS (EI) calcd for $C_8H_8ClNO_2$ 185.02435, found 185.02476. The ^{1}H NMR spectral data are in good agreement with the literature data.[34]



***N*-Hydroxy-4-methoxybenzimidoyl chloride (25).** This compound was obtained as a pale white solid in a 99% yield: mp 82-83 °C (lit.[33] mp 84.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.92 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.87 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[35]

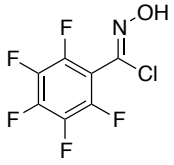


***N*-Hydroxy-2,4,5-trimethoxybenzimidoyl chloride (27).** This compound was obtained as a fine pale brown solid in a 79% yield: mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.56 (s, 1H), 7.28 (s, 1H), 9.48 (s, 1H).

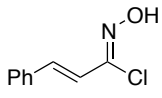


***N*-Hydroxy-2-bromobenzimidoyl chloride (29).** This compound was obtained as a pale yellow solid in an 81% yield: mp 59-60 °C (lit.[36] mp 68-69 °C); ^{1}H NMR (300

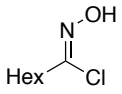
MHz, $CDCl_3$) δ 7.29 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 8.59 (s, 1H).



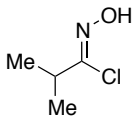
***N*-Hydroxy-perfluorobenzimidoyl chloride (31).** This compound was obtained as a colorless liquid in a 53% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H); HRMS (EI) calcd for C_7HClF_5NO 244.96668, found 244.96712.



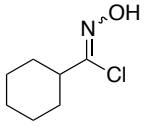
(2*Z*)-*N*-Hydroxy-3-phenylacrylimidoyl chloride (33). This compound was obtained as a bright yellow amorphous solid in an 80% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J = 15.6 Hz, 1H), 7.29-7.50 (m, 6H), 8.39 (s, 1H).



***N*-Hydroxyheptanimidoyl chloride (35).** This compound was obtained as a colorless liquid in a 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 10.0 Hz, 3H), 1.30 (m, 7H), 1.53 (m, 1H), 1.63 (m, 1H), 2.50 (m, 1H), 8.34 (s, 1H).

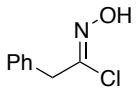


***N*-Hydroxyisobutyrimidoyl chloride (37).** This compound was obtained as a colorless liquid in an 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.8 Hz, 6H), 2.81 (m, 1H), 8.82 (s, 1H).

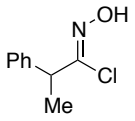


***N*-Hydroxycyclohexanecarbimidoyl chloride (39).** This compound was obtained as a colorless liquid in a 90% yield as a 1:0.9 mixture of isomers: ^{1}H NMR (400

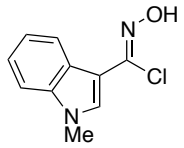
MHz, $CDCl_3$) δ 1.23-1.98 (m, 1.0 × 10H + 0.9 × 10H), 2.20 (m, 1H, relative intensity 0.9), 2.52 (t, J = 11.6 Hz, 1H, relative intensity 1.0), 8.99 (s, 1H).



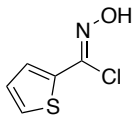
***N*-Hydroxy-2-phenylacetimidoyl chloride (41).** This compound was obtained as a pale yellow solid in a 98% yield: mp 79-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 7.27-7.36 (m, 5H), 8.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.0, 127.7, 128.9, 129.3, 134.5, 141.5. The ^{1}H NMR spectral data are in good agreement with the literature data.[37]



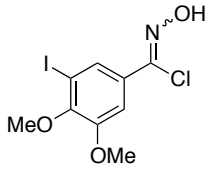
***N*-Hydroxy-2-phenylpropanimidoyl chloride (43).** This compound was obtained as pale yellow liquid in a 94% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (d, J = 7.2 Hz, 3H), 3.96 (m, 1H), 7.19-7.37 (m, 5H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 47.1, 127.6, 127.8, 128.9, 140.4, 145.3.



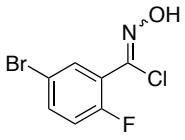
***N*-Hydroxy-1-methyl-*1H*-indole-3-carbimidoyl chloride (45).** This compound was obtained as a dark red amorphous solid in a 55% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 7.15 (m, 1H), 7.27 (m, 2H), 7.46 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.87 (s, 1H).



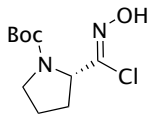
***N*-Hydroxythiophene-2-carbimidoyl chloride (48).** This compound was obtained as a brown amorphous solid in a 56% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, J = 5.1, 3.9 Hz, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.52 (d, J = 3.9 Hz, 1H), 9.95 (s, 1H).



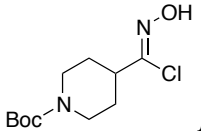
***N*-Hydroxy-3-iodo-4,5-dimethoxybenzimidoyl chloride (52).** This compound was obtained as a pale pink solid in a 77% yield: mp 114-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ 3.83-3.92 (m, 6H), 6.98-7.36 (m, 1H), 7.52-7.84 (m, 1H), 7.92 (s, 1H, OH).



***N*-Hydroxy-5-bromo-2-fluorobenzimidoyl chloride (54).** This compound was obtained as white crystals in a 72% yield: mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ 6.97-7.08 (m, 1H), 7.52-7.65 (m, 1H), 7.72-7.83 (m, 1H), 8.31 (s, 1H, OH).



(*S*)-*N'*-Boc-*N*-Hydroxypyrrolidine-2-carbimidoyl chloride (56). This compound was obtained as a white solid in a 55% yield using the reported procedure:[38] mp 110-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of isomers) δ 1.40-1.45 (m, 9H), 1.71-2.25 (m, 4H), 3.31-3.60 (m, 2H), 4.39-4.77 (m, 1H), 8.90 (s, 1H, OH). The ^{1}H NMR spectral data are in good agreement with the literature data.[38]

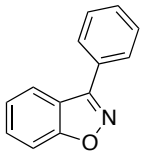


***N'*-Boc-*N*-hydroxypiperidine-4-carbimidoyl chloride (61).** This compound was obtained as a white solid in a 65% yield using the reported procedure:[38] mp 145-147 °C;

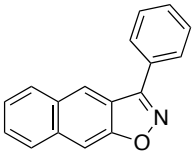
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.62-1.70 (m, 2H), 1.91 (d, J = 13.8 Hz, 2H), 2.52-2.64 (m, 1H), 2.78 (t, J = 12.3 Hz, 2H), 4.13 (br s, 2H), 8.09 (s, 1H).

General procedure for synthesis of the benzisoxazoles.

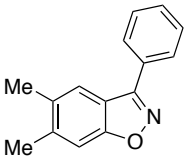
A solution of the appropriate chlorooxime (0.25 mmol) in 3 mL of acetonitrile was added by syringe pump to a stirring mixture of the silylaryl triflate (0.50 mmol) and CsF (1.50 mmol) in 3 mL of acetonitrile over the course of 2.5 h. After the addition was complete, the reaction mixture was allowed to stir for an additional 6 h at room temperature. Then the solvent was evaporated, 15 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 15 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired benzisoxazoles.



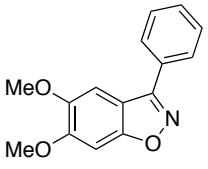
3-Phenylbenzisoxazole (3). This compound was obtained as a pale brown solid in a 90% yield: mp 81-82 ^{o}C (lit.[39] mp 80-82 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 7.4 Hz, 1H), 7.56-7.67 (m, 5H), 7.93-7.99 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 120.7, 122.4, 124.1, 128.3, 129.2, 129.3, 130.0, 130.4, 157.5, 164.1; HRMS (EI) calcd for $C_{13}H_9NO$ 195.0684, found 195.0687. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[40]



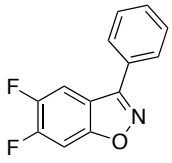
3-Phenylnaphth[2,3]isoxazole (5). This compound was obtained as orange crystals in a 61% yield: mp 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 4.0 Hz, 1H), 7.61 (m, 4H), 8.01 (m, 3H), 8.08 (d, J = 7.8 Hz, 2H) 8.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.3, 122.0, 125.0, 127.8, 128.2, 128.4, 129.0, 129.4, 130.7, 130.7, 134.3, 157.6, 160.2; HRMS (EI) calcd for $C_{17}H_{11}NO$ 245.0841, found 245.0846.



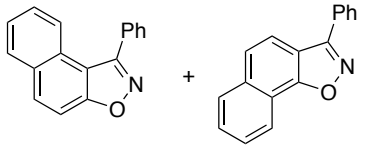
5,6-Dimethyl-3-phenylbenzisoxazole (7). This compound was obtained as a pale yellow oil in a 74% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.42 (s, 3H), 7.41 (s, 1H), 7.54 (m, 3H), 7.64 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.1, 110.4, 118.7, 121.7, 128.2, 129.2, 130.2, 133.2, 140.2, 156.9, 163.4; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1003.



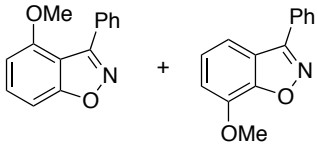
5,6-Dimethoxy-3-phenylbenzisoxazole (9). This compound was obtained as a pale white solid in a 65% yield: mp 100-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.99 (s, 3H), 7.10 (s, 1H), 7.17 (s, 1H), 7.54 (m, 3H), 7.90 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.6, 56.7, 92.8, 101.3, 112.2, 128.1, 129.3, 129.4, 130.2, 147.9, 152.9, 157.3, 160.4; HRMS (EI) calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0901.



5,6-Difluoro-3-phenylbenzisoxazole (11). This compound was obtained as a pale yellow solid in a 36% yield: mp 82-85 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 6.5, 8.2 Hz, 1H), 7.58 (m, 3H), 7.69 (t, J = 8.2 Hz, 1H), 7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.3 (d, J = 22.3 Hz), 108.8 (d, J = 20.8 Hz), 115.9 (d, J = 7.7 Hz), 128.1, 128.2, 129.5, 130.9, 148.9 (dd, J = 244.8, 15.0 Hz), 152.8 (dd, J = 254.0, 16.2 Hz), 157.7, 159.7 (d, J = 10.8 Hz); HRMS (EI) calcd for $C_{13}H_7F_2NO$ 231.0496, found 231.0501.

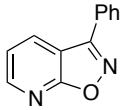


Mixture of 1-phenylnaphth[1,2]isoxazole and 3-phenylnaphth[2,1]isoxazole (~1:1 ratio) (13a and 13b). This mixture (~1:1 ratio) was obtained as a brown amorphous solid in a 60% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-8.02 (m, 10H + 11H), 8.49 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.7, 114.7, 116.0, 118.5, 119.6, 122.0, 122.8, 125.4, 125.6, 127.4, 127.5, 127.6, 128.0, 128.4, 129.0, 129.3, 130.1, 131.0, 132.5, 133.0, 133.9, 158.1, 159.5, 162.5, 163.9; HRMS (EI) calcd for $C_{17}H_{11}NO$ 245.0841, found 245.0846.

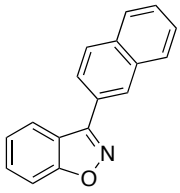


Mixture of 4-methoxy-3-phenylbenzisoxazole and 7-methoxy-3-phenylbenzisoxazole (~1.8:1 ratio) (14a and 14b). This mixture was obtained as a pale brown oil in a 74% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 1.8 × 3H), 4.06 (s, 1.0 × 3H), 6.67 (d, J = 7.9 Hz, 1.8 × 1H), 7.00 (d, J = 7.8 Hz, 1 × 1H), 7.20 (d, J = 8.3 Hz, 1.8 ×

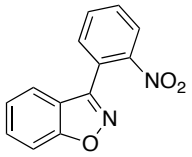
1H), 7.27 (t, J = 7.9 Hz, 1 × 1H), 7.44-7.58 (m, 2.8 × 4H), 7.93 (m, 2.8 × 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 56.6, 102.9, 103.7, 110.1, 113.8, 115.5, 122.5, 125.2, 128.3, 128.7, 129.1, 129.3, 129.9, 130.3, 130.4, 131.6, 133.8, 144.9, 154.6, 155.0, 157.7, 158.1, 166.0; HRMS (EI) calcd for $C_{14}H_{11}NO_2$ 225.0790, found 225.0794.



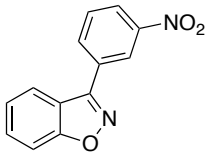
3-Phenylisoxazolo[5,4]pyridine (16). This compound was obtained as a yellow amorphous solid in a 13% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 7.8, 4.8 Hz, 1H), 7.55-7.60 (m, 3H), 7.94-7.99 (m, 2H), 8.35 (d, J = 7.8 Hz, 1H), 8.68 (d, J = 4.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.1, 120.0, 127.7, 128.6, 129.4, 130.8, 132.4, 150.6, 157.4, 170.3; HRMS (EI) calcd for $C_{12}H_8N_2O$ 196.0637, found 196.0642. Note: the coupling constants of the pyridine protons (4.6 and 7.8 Hz) are almost identical with the analogue of the expected isomer[41] (4.5 and 7.8 Hz) as compared to the analogue of the reverse isomer[42] (4.3 and 8.4 Hz). Also, the chemical shifts of the carbons at the juncture of the two rings are consistent with the reported values for the analogue isomer.[41]



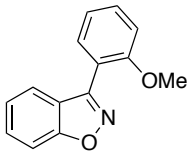
3-(2-Naphthyl)benzisoxazole (18). This compound was obtained as a pale brown oil in a 72% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, J = 7.5 Hz, 1H), 7.55-7.65 (m, 3H), 7.69 (m, 1H), 7.93 (m, 1H), 7.97-8.11 (m, 3H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 120.8, 122.5, 124.2, 125.2, 126.6, 127.0, 127.4, 128.1, 128.8, 130.0, 133.5, 134.2, 157.4, 164.1; HRMS (EI) calcd for $C_{17}H_{11}NO$ 245.0841, found 245.0846.



3-(2-Nitrophenyl)benzisoxazole (20). This compound was obtained as a pale yellow solid in a 57% yield: mp 100-102 °C (lit.[43] mp 105-108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.1 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.70 – 7.84 (m, 3H), 8.21 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 121.0, 121.0, 123.8, 124.2, 125.1, 130.2, 131.1, 132.4, 133.6, 148.8, 155.8, 163.2; HRMS (EI) calcd for $C_{13}H_8N_2O_3$ 240.0535, found 240.0539.

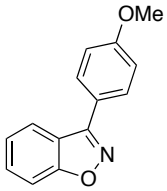


3-(3-Nitrophenyl)benzisoxazole (22). This compound was obtained as colorless pale white needles in a 54% yield: mp 167-169 °C (lit.[12b] mp 176 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 7.4 Hz, 1H), 7.68 (m, 2H), 7.77 (t, J = 8.0 Hz, 1H) 7.96 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 7.7 Hz, 1H), 8.40 (d, J = 8.2 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.7, 119.9, 121.8, 123.1, 124.8, 125.1, 130.5, 131.0, 134.0, 148.9, 155.5, 164.4; HRMS (EI) calcd for $C_{13}H_8N_2O_3$ 240.0535, found 240.0539.

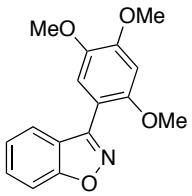


3-(2-Methoxyphenyl)benzisoxazole (24). This compound was obtained as a colorless oil in a 93% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.11 (m, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.53 (m, 2H), 7.66 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 110.0,

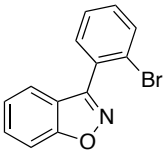
111.6, 117.9, 121.2, 122.1, 123.4, 123.7, 129.7, 131.5, 131.8, 156.7, 157.7, 163.4; HRMS (EI) calcd for $C_{14}H_{11}NO_2$ 225.0790, found 225.0794.



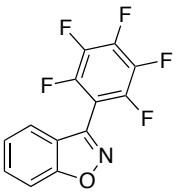
3-(4-Methoxyphenyl)benzisoxazole (26). This compound was obtained as a creamy white solid in an 85% yield: mp 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.08 (d, J = 8.5 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 110.3, 114.7, 120.7, 121.5, 122.4, 123.9, 129.6, 129.8, 157.0, 161.3, 163.9; HRMS (EI) calcd for $C_{14}H_{11}NO_2$ 225.0790, found 225.0794. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[43]



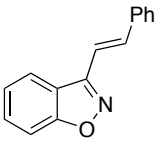
3-(2,4,5-Trimethoxyphenyl)benzisoxazole (28). This compound was obtained as a dark oil in an 81% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 6.69 (s, 1H), 7.22 (s, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 56.7, 56.7, 98.0, 109.0, 109.9, 114.3, 122.0, 123.3, 123.9, 129.6, 143.6, 151.8, 152.5, 156.5, 163.5; HRMS (EI) calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1004.



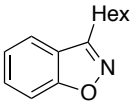
3-(2-Bromophenyl)benzisoxazole (30). This compound was obtained as a pale yellow oil in a 93% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.53-7.69 (m, 4H), 7.78 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.3, 121.4, 123.1, 123.8, 127.8, 130.1, 130.2, 131.6, 132.2, 133.8, 158.2, 163.4; HRMS (EI) calcd for $C_{13}H_8BrNO$ 272.9789, found 272.9797.



3-(Perfluorophenyl)benzisoxazole (32). This compound was obtained as a white solid in a 40% yield: mp >300 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, J = 9.8 Hz, 1H), 7.60-7.78 (m, 3H); HRMS (EI) calcd for $C_{13}H_4F_5NO$ 285.0213, found 285.0220.

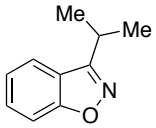


(*E*)-3-Styrylbenzisoxazole (34). This compound was obtained as dark brown crystals in a 70% yield: mp 75-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.46 (m, 5H), 7.55-7.70 (m, 5H), 8.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 115.9, 117.6, 120.5, 122.1, 127.3, 129.1, 129.4, 130.0, 136.1, 137.0, 155.6, 163.8; HRMS (EI) calcd for $C_{15}H_{11}NO$ 221.0841, found 221.0846.

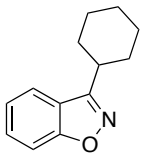


3-*n*-Hexylbenzisoxazole (36). This compound was obtained as a brown oil in a 58% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H), 1.12-1.48 (d, J = 7.7 Hz,

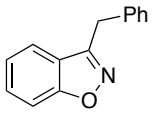
6H), 1.85 (quintet, J = 7.6 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H), 7.29 (m, 1H), 7.54 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.7, 25.6, 27.9, 29.3, 31.7, 110.1, 121.5, 122.0, 123.2, 129.8, 158.9, 163.1; HRMS (EI) calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1316.



3-Isopropylbenzisoxazole (38). This compound was obtained as a dark brown oil in an 82% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, J = 7.0 Hz, 6H), 3.41 (m, 1H), 7.29 (m, 1H), 7.54 (m, 2H), 7.72 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 27.1, 110.2, 121.0, 121.8, 123.1, 129.7, 163.3, 163.3; HRMS (EI) calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0845.

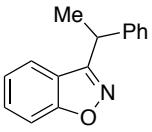


3-Cyclohexylbenzisoxazole (40). This compound was obtained as a dark brown oil in a 77% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.52 (m, 3H), 1.72-1.79 (m, 3H), 1.91 (m, 2H), 2.12 (m, 2H), 3.10 (m, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.53 (m, 2H), 7.72 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.5, 31.6, 36.6, 110.2, 121.2, 121.9, 123.1, 129.7, 162.5, 163.2; HRMS (EI) calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1157.

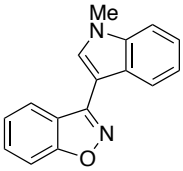


3-Benzylbenzisoxazole (42). This compound was obtained as brown crystals in a 79% yield: mp 77-79 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (s, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 6.5 Hz, 1H), 7.30-7.34 (m, 4H), 7.40 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.7 Hz,

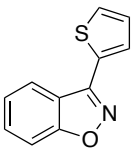
1H), 7.55 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 110.1, 121.6, 121.9, 123.4, 127.2, 129.0, 129.1, 136.4, 157.5, 163.5; HRMS (EI) calcd for $C_{14}H_{11}NO$ 209.0841, found 209.0846.



3-(1-Phenylethyl)benzisoxazole (44). This compound was obtained as a dark brown oil in a 71% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (d, J = 7.2 Hz, 3H), 4.54 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.22-7.29 (m, 2H), 7.30-7.37 (m, 4H), 7.45 (t, J = 7.7 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 38.3, 110.0, 121.2, 122.1, 123.3, 127.2, 127.7, 129.0, 129.7, 142.5, 161.2, 163.4; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1000.

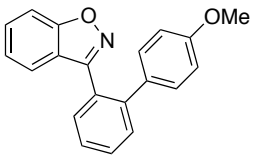


3-(1-Methyl-1*H*-indol-3-yl)benzisoxazole (46). This compound was obtained as yellow crystals in a 61% yield: mp 156-157 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.28-7.41 (m, 4H), 7.57 (t, J = 7.7 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 104.4, 109.7, 110.2, 115.5, 121.3, 122.3, 122.5, 123.2, 123.4, 126.2, 129.3, 129.7, 137.3, 153.2, 163.0; HRMS (EI) calcd for $C_{16}H_{12}N_2O$ 248.0950, found 248.0955.



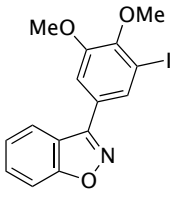
3-(2-Thiophenyl)benzisoxazole (48). This compound was obtained as a dark brown oil in a 54% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 1H), 7.41 (t, J = 7.3 Hz,

1H), 7.55 (d, J = 5.1 Hz, 1H), 7.62 (m, 2H), 7.82 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.4, 115.5, 120.2, 122.2, 128.1, 128.2, 128.4, 130.2, 152.5, 163.9; HRMS (EI) calcd for $C_{11}H_7NOS$ 201.0248, found 201.0252.



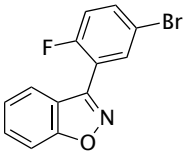
Representative Suzuki-Miyaura procedure[27] *for the preparation of* **3-(4'-methoxy-[1,1'-biphenyl]-2-yl)benzisoxazole (51).** To a 4 dram vial was added the bromine-containing benzisoxazole **30** (0.15 mmol), *p*-methoxyphenylboronic acid (1.5 equiv), K_2CO_3 (2.5 equiv) and 5 mol% of $Pd(PPh_3)_4$ in 20:5:1 toluene:ethanol:water. The solution was vigorously stirred for 5 min at room temperature, flushed with argon, and then heated to 80 ^{o}C for 16 h. Upon cooling to room temperature, the resulting reaction mixture was extracted with CH_2Cl_2. The combined organic layers were concentrated and purified by column chromatography (Hexanes/EtOAc mixture) to yield the desired coupling product in a 68% yield as a colorless glassy semisolid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 6.70 (d, J = 8.8 Hz, 2H), 6.93-7.05 (m, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.35-7.63 (m, 5H), 7.68 (d, J = 7.1 Hz, 1H).

Starting materials for combinatorial library construction.[44]

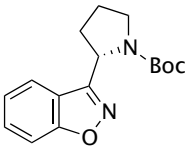


3-(3-Iodo-4,5-dimethoxyphenyl)benzisoxazole (53). This compound was obtained in a 76% yield on a 0.25 mmol scale and in a 56% yield on a 0.50 mmol scale: ^{1}H

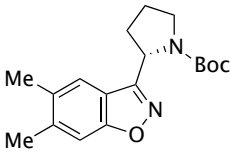
NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.96 (s, 3H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.51 (s, 1H), 7.56-7.69 (m, 2H), 7.87-7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4, 60.9, 93.0, 110.5, 112.5, 120.3, 122.2, 124.3, 126.9, 129.8, 130.2, 150.9, 153.3, 155.9, 164.1; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{13}INO_3$ 381.9935, found 381.9945.



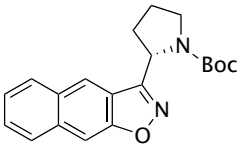
3-(5-Bromo-2-fluorophenyl)benzisoxazole (55). This compound was obtained in a 57% yield on a 0.25 mmol scale and in a 54% yield on a 0.50 mmol scale: ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 9.2 Hz, 1H), 7.38 (t, *J* = 6.8 Hz, 1H), 7.57-7.69 (m, 3H), 7.79 (dd, *J* = 8.1, 3.2 Hz, 1H), 7.98 (dd, *J* = 6.1, 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.3, 117.5, 118.3, 118.6, 120.8, 122.8, 122.9, 124.3, 130.4, 133.9, 135.1, 135.2, 153.2, 157.8, 161.1, 164.0 (extra peaks due to C-F coupling); HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_8BrFNO$ 291.9768, found 291.9768.



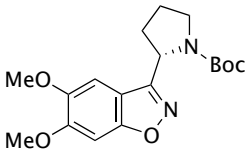
(*S*)-3-(*N*-Boc-pyrrolidin-2-yl)benzisoxazole (57). This compound was obtained in an 85% yield on a 0.25 mmol scale and in an 87% yield on a 0.50 mmol scale: ^1H NMR (600 MHz, rotamers present, $CDCl_3$) δ 1.28-2.56 (m, 9H), 3.47-3.83 (m, 2H), 5.08-5.51 (m, 1H), 7.27-7.31 (m, 1H), 7.46-7.78 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.1, 24.4, 28.0, 28.5, 31.8, 33.7, 46.9, 47.0, 53.6, 54.2, 80.0, 109.9, 119.7, 121.4, 121.5, 123.3, 123.4, 129.7 (×2), 154.1, 154.5, 160.0, 160.9, 163.1, 163.3 (extra peaks due to rotamers); HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{21}N_2O_3$ 289.1547, found 289.1543.



(*S*)-5,6-Dimethyl-3-(*N*-Boc-pyrrolidin-2-yl)benzisoxazole (58). This compound was obtained in a 51% yield (0.50 mmol scale): ^{1}H NMR (400 MHz, rotamers present, $CDCl_3$) δ 1.03-1.38 (m, 9H), 1.83-2.44 (m, 10H), 3.40-3.72 (m, 2H), 5.01-5.35 (m, 1H), 7.13-7.37 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.65, 5.11, 20.0, 20.9, 24.1, 24.3, 28.0, 28.5, 31.8, 33.6, 46.8, 46.9, 53.6, 54.2, 79.8, 79.9, 110.0, 117.8, 118.5, 120.6, 120.8, 132.3, 132.5, 139.8, 139.9, 154.2, 154.5, 159.5, 160.3, 162.5, 162.7 (extra peaks due to rotamers); HRMS (APCI) calcd for $[M+Na]^+$ $C_{18}H_{24}N_2NaO_3$ 339.1679, found 339.1673.

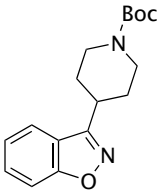


(*S*)-3-(*N*-Boc-pyrrolidin-2-yl)naphtho[2,3]isoxazole (59). This compound was obtained in a 50% yield (0.50 mmol scale): ^{1}H NMR (600 MHz, rotamers present, $CDCl_3$) δ 1.09-1.53 (m, 9H), 2.01-2.60 (m, 4H), 3.59-3.92 (m, 2H), 5.24-5.64 (m, 1H), 3.59-3.92 (m, 2H), 7.86-8.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.65, 5.11, 24.2, 24.4, 28.0, 28.5, 31.6, 33.6, 46.9, 47.1, 53.8, 54.4, 80.0, 80.1, 104.7, 104.9, 120.8, 121.1, 121.2, 121.8, 124.5, 124.7, 127.4, 127.6, 128.0, 129.2, 130.1, 134.2, 154.2, 154.6, 159.4, 159.6, 160.1, 160.9 (extra peaks due to rotamers); HRMS (APCI) calcd for $[M+Na]^+$ $C_{20}H_{22}N_2NaO_3$ 361.1523, found 361.1517.

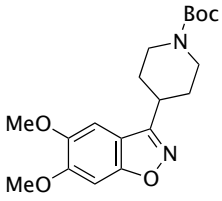


(*S*)-5,6-Dimethoxy-3-(*N*-Boc-pyrrolidin-2-yl)benzisoxazole (60). This compound was obtained in a 73% yield (0.50 mmol scale): ^{1}H NMR (600 MHz, rotamers

present, $CDCl_3$) δ 1.14-1.48 (m, 9H), 1.97-2.49 (m, 4H), 3.52-3.75 (m, 2H), 3.83-4.03 (m, 6H), 5.13-5.42 (m, 1H), 6.83-7.21 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 3.65, 5.11, 24.0, 24.4, 28.1, 28.5, 31.1, 33.9, 46.8, 46.9, 53.4, 54.1, 56.1, 56.3, 56.5, 56.7, 79.8, 79.9, 92.3, 92.4, 100.4, 101.1, 101.7, 104.6, 111.2, 111.3, 111.7, 112.1, 113.3, 147.2, 148.9, 152.6, 154.2, 154.6, 159.4, 160.7 (extra peaks due to rotamers); HRMS (APCI) calcd for $[M+Na]^+$ $C_{18}H_{24}N_2NaO_5$ 371.1577, found 371.1572.

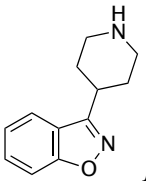


3-(*N*-Boc-piperidin-4-yl)benzisoxazole (62). This compound was obtained in an 88% yield on a 0.25 mmol scale and in a 78% yield on a 0.50 mmol scale; 0.5 mL of CH_2Cl_2 were used to dissolve the starting chlorooxime due to poor solubility in MeCN: ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.87-2.11 (m, 4H), 2.96 (t, J = 12.5 Hz, 2H), 3.19-3.31 (m, 1H), 4.22 (br s, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.49-7.58 (m, 2H), 7.69 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 30.4, 34.8, 79.9, 110.4, 120.8, 121.6, 123.4, 130.0, 155.0, 160.9, 163.4; HRMS (APCI) calcd for $[M+Na]^+$ $C_{17}H_{22}N_2NaO_3$ 325.1523, found 325.1517.



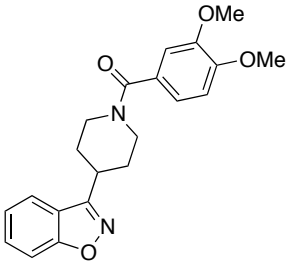
5,6-Dimethoxy-3-(*N*-Boc-piperidin-4-yl)benzisoxazole (63). This compound was obtained in a 59% yield (0.25 mmol scale); 0.5 mL of CH_2Cl_2 were used to dissolve the starting chlorooxime due to poor solubility in MeCN: ^1H NMR (600 MHz,

$CDCl_3$) δ 1.46 (s, 9H), 1.83-2.09 (m, 4H), 2.94 (s, 2H), 3.10-3.20 (m, 1H), 3.91 (s, 3H), 3.93 (s, 3H), 4.20 (s, 2H), 6.92 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.4, 30.2, 34.4, 56.3, 56.5, 79.6, 92.6, 100.4, 112.0, 147.1, 152.7, 154.8, 159.5, 160.5; HRMS (APCI) calcd for $[M+Na]^+$ $C_{19}H_{26}N_2NaO_5$ 385.1734, found 385.1730.

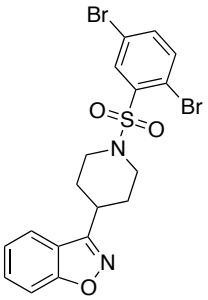


Representative procedure for deprotection of N-Boc-containing benzisoxazoles: **3-(piperidin-4-yl)benzisoxazole (64).** 0.16 Mmol of *N*-Boc-protected benzisoxazole **62** in 3 mL of CH_2Cl_2/trifluoroacetic acid (1/1 mixture) was stirred at room temperature for 2 h. The reaction mixture was extracted from a saturated aqueous solution of Na_2CO_3 (20 mL) with CH_2Cl_2 (2 × 20 mL). The organic layers were combined and concentrated under reduced pressure to provide the desired amine **64** as a pale yellow amorphous solid in a quantitative yield: ^1H NMR (400 MHz, $CDCl_3$) δ 1.90-2.12 (m, 4H), 2.83 (td, J = 12.1, 2.9 Hz, 3H), 3.19-3.27 (m, 3H), 7.22-7.31 (m, 1H), 7.48-7.56 (m, 2H), 7.74 (d, J = 7.9 Hz, 1H).

General procedure for acylation/sulfonylation of the amine ***64****.* To 0.10 mmol of benzisoxazole **64** in 2 mL of CH_2Cl_2, 5 equiv of Et_3N and 2 equiv of the appropriate acylating/sulfonylating agent were added. After stirring 10 h, the reaction mixture was evaporated and the product was isolated using column chromatography (Hex/EtOAc mixture).



[4-(Benzisoxazol-3-yl)piperidin-1-yl)](3,4-dimethoxyphenyl)-methanone (65) (example of the acylation reaction). This compound was obtained as a colorless amorphous solid in a 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94-2.20 (m, 4H), 3.11-3.47 (m, 3H), 3.89 (s, 6H), 6.86 (d, J = 8.6 Hz, 1H), 6.99-7.03 (m, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.51-7.60 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H).



3-[1-(2,5-Dibromophenylsulfonyl)piperidin-4-yl)]benzisoxazole (66) (example of the sulfonylation reaction). This compound was obtained as a pale yellow solid in a 62% yield: mp 157-158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10-2.20 (m, 4H), 3.11 (dt, J = 13.6, 6.7 Hz, 2H), 3.24-3.31 (m, 1H), 3.96 (dt, J = 12.9, 3.8 Hz, 2H), 7.31 (t, J = 7.0 Hz, 1H), 7.54 (dd, J = 13.9, 6.6 Hz, 3H), 7.62 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 8.27 (s, 1H).

3.7. References

(1) (a) Davis, L.; Effland, R. C.; Klein, J. T.; Dunn, R. W.; Geyer, H. M. III; Petko, W. M. *Drug Design and Discovery* **1992**, *8*, 225. (b) Strupczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Stache, U.; Glamkowski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, *28*, 761. (c) Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. H. L.; Megens, A. A. H. P.; Meert, T. F. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 685. (d) Strupczewski, J. T.; Bordeau, K. J.; Chiang, Y.; Glamkowski, E. J.; Conway, P. G.; Corbett, R.; Hartman, H. B.; Szewczak, M. R.; Wilmot, C. A.; Helsley, G. C. *J. Med. Chem.* **1995**, *38*, 1119.

(2) (a) Gopalsamy, A.; Shi, M.; Golas, J.; Vogan, E.; Jacob, J.; Johnson, M.; Lee, F.; Nilakantan, R.; Petersen, R.; Svenson, K.; Chopra, R.; Tam, M. S.; Wen, Y.; Ellingboe, J.; Arndt, K.; Boschelli, F. *J. Med. Chem.* **2008**, *51*, 373. (b) Jain, M.; Kwon, C.-H. *J. Med. Chem.* **2003**, *46*, 5428.

(3) (a) Stiff, D. D.; Zemaitis, M. A. *Drug Metab. Dispos.* **1990**, *18*, 888. (b) Uno, H.; Kurokawa, M.; Masuda, Y.; Nishimura, H. *J. Med. Chem.* **1979**, *22*, 180.

(4) Priya, B. S.; Basappa; Swamy, S. N.; Rangappa, K. S. *Bioorg. Med. Chem.* **2005**, *13*, 2623.

(5) Nuhrich, A.; Varache-Lembege, M.; Renard, P.; Devaux, G. *Eur. J. Med. Chem.* **1994**, *29*, 75.

(6) (a) Villalobos, A.; Blake, J. F.; Biggers, C. K.; Butler, T. W.; Chapin, D. S.; Chen, Y. L.; Ives, J. L.; Jones, S. B.; Liston, D. R.; Nagel, A. A.; Nason, D. M.; Nielsen, J. A.;

Shalaby, I. A.; White, W. F. *J. Med. Chem.* **1994**, *37*, 2721. (b) Rangappa, K. S.; Basappa *J. Phys. Chem.* **2005**, *18*, 773.

(7) (a) Bunnet, J. F.; Yih, S. Y. *J. Am. Chem. Soc.* **1961**, *83*, 3805. (b) Plattner, J. J.; Fung, A. K. L.; Parks, J. A.; Pariza, R. J.; Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Dodge, P. W. *J. Med. Chem.* **1984**, *27*, 1016.

(8) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695.

(9) De, P.; Nonappa; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, *9*, 2767.

(10) (a) Roman, G.; Comanita, E.; Comanita, B. *Tetrahedron* **2002**, *58*, 1617. (b) Shelke, K. F.; Sapkal, S. B.; Shitole, N .V.; Shingate, B. B.; Shingare, M. S. *Org. Commun.* **2009**, *2*, 72. (c) Dale, T. J.; Sather, A. C.; Rebek, J. *Tetrahedron Lett.* **2009**, *50*, 6173.

(11) Poissonnet, G. *Synth. Commun.* **1997**, *27*, 3839.

(12) (a) Minisci, F.; Quilico, A. *Gazz. Chim. Ital.* **1964**, *46*, 428. (b) Sasaki, T.; Yoshioka, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 826.

(13) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409.

(14) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(15) In the literature, Na_2CO_3 or aliphatic amines are most commonly used, see: Lam, P. Y. S.; Adams, J. J.; Clark, C. G.; Calhoun, W. J.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1795.

(16) Kelly, D. R.; Baker, S. C.; King, D. S.; de Silva, D. S.; Lord, G.; Taylor, J. P. *Org. Biomol. Chem.* **2008**, *6*, 787.

(17) Spiteri, C.; Sharma, P.; Zhang, F.; Macdonald, S. J. F.; Keeling, S.; Moses, J. E. *Chem. Commun.* **2010**, *46*, 1272. There is also one example of a benzylic aldehyde-derived chlorooxime providing the product in a 50% yield.

(18) Crossley, J. A.; Browne, D. L. *Tetrahedron Lett.* **2010**, *51*, 2271.

(19) Ma, X.; Chen, Y.; Zhang, Y.; Xu, D.; Cao, W.; Chen, J. *Eur. J. Org. Chem.* **2012**, *2012*, 1388.

(20) For a similar observation, see: Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003.

(21) Fang, Y.; Larock, R. C. *Tetrahedron Lett.* **2012**, *68*, 2819.

(22) (a) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem. Asian J.* **2010**, *5*, 153.

(23) Larsen, K. E.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 2985.

(24) Vela, M. A.; Kohn, H. *J. Org. Chem.* **1992**, *57*, 6650.

(25) Electron-withdrawing groups are known to stabilize nitrile oxides thus making them more reluctant to cyclize, see: Wakefield, B. J.; Wright, D. J. *J. Chem. Soc. C* **1970**, 1165.

(26) Kumar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2006**, *47*, 1457.

(27) Cho, C.-H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 900.

(28) The synthetic targets were generally chosen with cLogP ≤5, a molecular weight ≤500 g/mol, the number of hydrogen bond acceptors ≤10, the number of hydrogen bond donors

≤5, and the number of rotatable bonds in the molecule ≤12. One Lipinski violation was allowed.

(29) The synthesis of these starting blocks was performed at Iowa State University. The further diversification of these blocks is being performed by the Kansas University NIH Center of Excellence in Chemical Methodology and Library Development.

(30) See examples of the use of these procedures for the synthesis of combinatorial libraries in: Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Comb. Chem. High Throughput Screening* **2012**, *15*, 451.

(31) Ismail, T.; Shafi, S.; Singh, P. P.; Qazi, N. A.; Sawant, S. D.; Ali, I.; Khan, I. A.; Kumar, H. M. S.; Qazi, G. N.; Alam, M. S. *Ind. J. Chem., Sec. B* **2008**, *47B*, 740.

(32) Tóth, M.; Kun, S.; Bokor, E.; Benltifa, M.; Tallec, G.; Vidal, S.; Docsa, T.; Gergely, P.; Somsák, L.; Praly, J.-P. *Bioorg. Med. Chem.* **2009**, *17*, 4773.

(33) McGillivray, G.; Ten Krooden, E. *S. Afr. J. Chem.* **1986**, *39*, 54.

(34) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.

(35) Di Nunno, L.; Vitale, P.; Scilimati, A.; Simone, L.; Capitelli, F. *Tetrahedron* **2007**, *63*, 12388.

(36) Hussein, A. Q.; El-Abadelah, M. M.; Sabri, W. S. *J. Heterocycl. Chem.* **1983**, *20*, 301.

(37) Cherest, M.; Lusinchi, X. *Tetrahedron* **1986**, *42*, 3825.

(38) Wallberg, A.; Nilsson, K.; Holm, B.; Nagard, M.; Granberg, K.; Slassi, A.; Edwards, L.; Isaac, M.; Xin, T.; Stefanac, T. US 0259862, 2007; *Chem. Abstr.* **2007**, *147*, 522250.

(39) Shutske, G. M. *J. Org. Chem.* **1984**, *49*, 180.

(40) De Prithwiraj, N.; Pandurangan, K.; Maitra, U.; Wailes, S. *Org. Lett.* **2007**, *9*, 2767.

(41) Sieburth, S. M.; Chen, J.; Ravindran, K.; Chen, J.-L. *J. Am. Chem. Soc.* **1996**, *118*, 10803.

(42) Camparini, A.; Ponticelli, F.; Tedeschi, P. *J. Chem. Soc., Perkin Trans.* 1 **1982**, 2391.

(43) Spiteri, C.; Mason, C.; Zhang, F.; Ritson, D. J.; Sharma, P.; Keeling, S.; Moses, J. E. *Org. Biomol. Chem.* **2010**, *8*, 2537.

(44) The remaining characterization of these compounds will be performed at the Kansas University NIH Center of Excellence for Chemical Methodology and Library Development. For some of the products ^{1}H and ^{13}C NMR are not informative due to the large number of signals resulting from the presence of rotamers caused by the Boc group.

CHAPTER 4

INTERMOLECULAR C-O ADDITION OF CARBOXYLIC ACIDS TO ARYNES: SYNTHESIS OF *o*-HYDROXYARYL KETONES, XANTHONES, 4-CHROMANONES, AND FLAVONES.[†]

Anton V. Dubrovskiy and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

4.1. Abstract

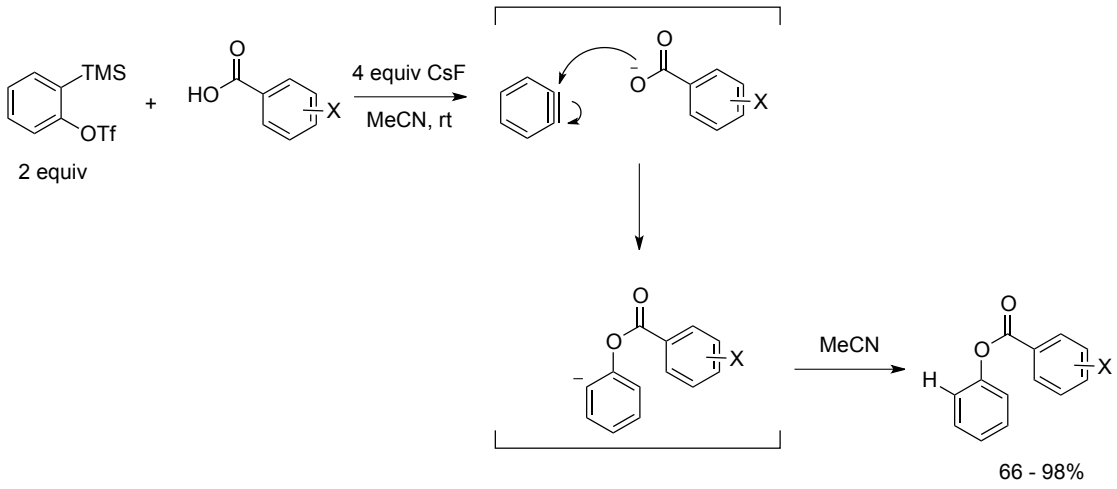
A novel, efficient and expedient route to biologically and pharmaceutically important *o*-hydroxyaryl ketones, xanthones, 4-chromanones, and flavones has been developed starting from readily available carboxylic acids and commercially available *o*-(trimethylsilyl)aryl triflates.

4.2. Introduction

The insertion of arynes into C-N,[1] C-C,[2] C-Si,[3] C-Sn,[4] and C-Hal[5] bonds and the C=O of aldehydes[6] is now a well known reaction. The insertion of a benzene ring into the C-O bond of a carboxylic acid would afford a powerful synthetic approach to a range of complex and biologically important molecules. However, we have previously reported that the reaction of arenecarboxylic acids and arynes in MeCN affords excellent yields of the corresponding aryl esters, *i.e.* the reaction occurs by insertion into the O-H bond of the carboxylic acid (Scheme 1).[7] In a closer examination of this chemistry, we have now found

[†] Adapted from *Org. Lett.* **2010**, *12*(14), 3117, with permission from the American Chemical Society © 2010.

reaction conditions, which afford good to excellent yields of the corresponding C-O insertion products. Subsequent chemistry of the resulting *o*-hydroxyaryl ketones affords a novel approach to xanthones, 4-chromanones and flavones.



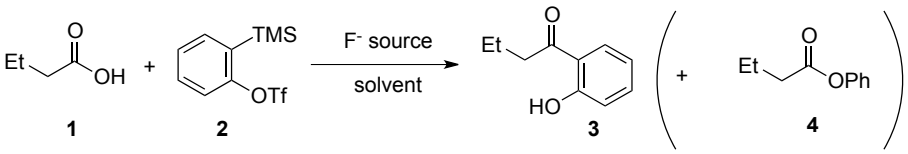
Scheme 1. Known Reaction of Arenecarboxylic Acids and Arynes in MeCN.

4.3. Results and Discussion

4.3.1. Synthesis of *o*-Hydroxyaryl Ketones

We allowed butyric acid (**1**) to react with the Kobayashi benzyne precursor *o*-(trimethylsilyl)phenyl triflate[8] (**2**) in the presence of fluoride ion in acetonitrile (Table 2). At both room temperature and at 65 °C, as expected,[7] the *O*-arylation product, ester **4**, was predominately formed (entries 1 and 2). To avoid the formation of the monoarylation product **4**, rather than using relatively acidic acetonitrile as the solvent, we turned to far less acidic THF. To our delight, together with the ester **4**, the C-O insertion product **3** was formed in a 26% yield (entry 3).

Table 1. Optimization of Benzyne Insertion into the C-O bond of an Aliphatic Carboxylic Acid.[a]

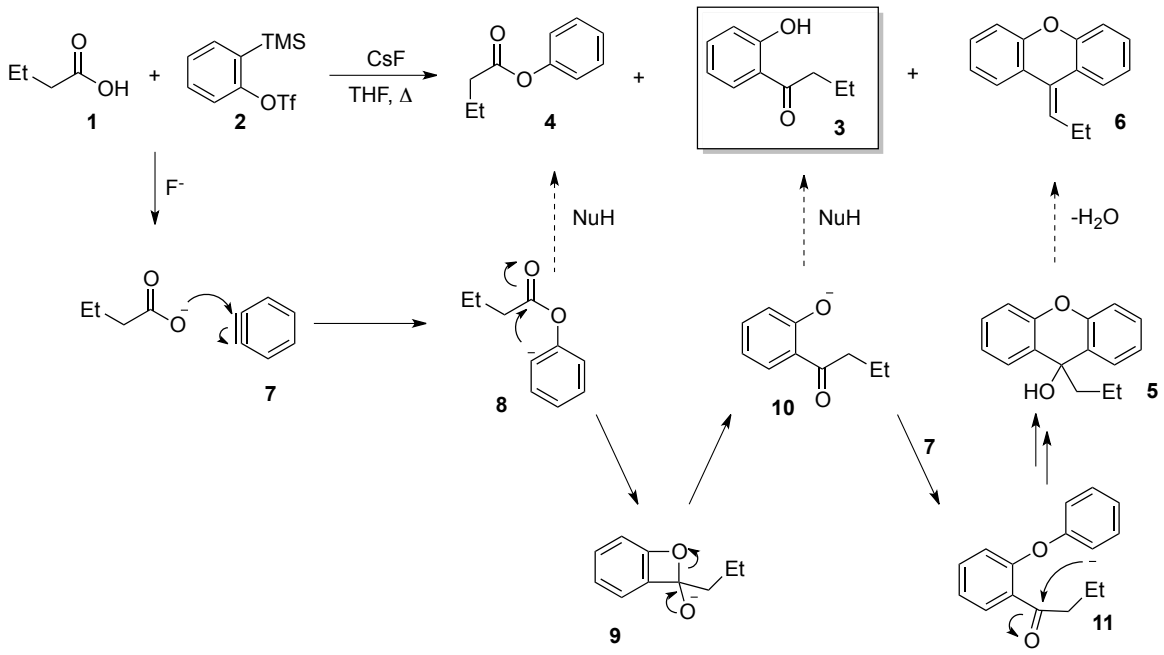


entry	equiv of **2**	fluoride source (equiv)	solvent, mL	temp. (°C)	% yield[b]
1	1.0	CsF (3)	MeCN, 5	rt	0[c]
2	1.0	CsF (3)	MeCN, 5	65	0[c]
3	1.0	CsF (3)	THF, 5	65	26
4	1.0	CsF (3)	THF, 5	125	43
5	1.0	CsF (3)	DME, 5	65	20[c]
6	1.0	CsF (3)	DME, 5	125	27[c]
7[d]	1.0	CsF (3)	THF, 5	125	14[c]
8[e]	1.0	CsF (3)	THF, 5	125	4[c]
9	1.2	CsF (3)	THF, 15	125	50
10	**1.5**	**CsF (4)**	**THF, 15**	**125**	**77**
11	1.75	CsF (4.7)	THF, 15	125	70
12	2	CsF (6)	THF, 15	125	34
13	1.5	TBAT (2)	Tol, 5	50	34[c]

[a] All reactions were carried out on a 0.25 mmol scale in 5 mL of solvent during a 24 h period. [b] Isolated yields, unless stated otherwise. [c] ^{1}H NMR spectroscopic yields. [d] 1 Equiv of K_2CO_3 was added to the reaction mixture. [e] 1 Equiv of Cs_2CO_3 was added to the reaction mixture.

A closer examination of the reaction mixture revealed that additional products inseparable by chromatography, namely tertiary alcohol **5** and xanthene **6**, both bis-aryne insertion products, are produced. Based on our findings, we propose the following mechanism for the formation of products **3**-**6** (Scheme 2). The aryl anion intermediate **8**, formed after nucleophilic attack of the carboxylate group of the carboxylic acid on the highly

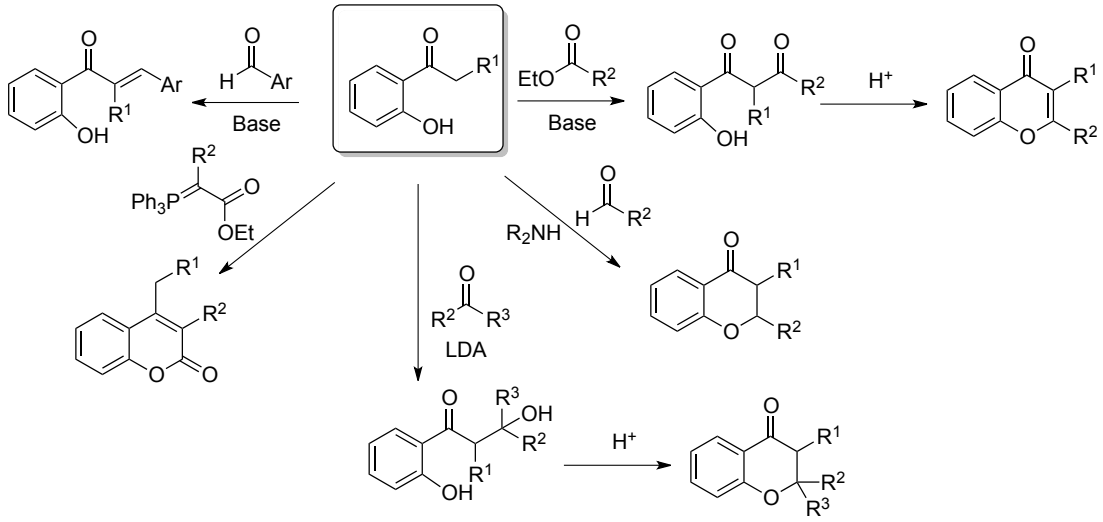
electrophilic benzyne (**7**) generated *in situ*, apparently undergoes a formal anionic Fries rearrangement to the phenoxide **10** by a four-membered ring intermediate **9**.[9] This results in formation of the desired *o*-hydroxyaryl ketone **3** after proton abstraction from the reaction media. The monoarylation product **4** can arise from protonation of the aryl anion **8**. The by-product **5** is presumably formed from reaction of the phenoxide **10** with a second equivalent of benzyne **7**,[10] which, after dehydration, forms the xanthene **6**. The proposed 4-membered ring intermediate **9** is consistent with similar intermediates reported recently by Greaney's group in a related study of primary aromatic amides.[1b]



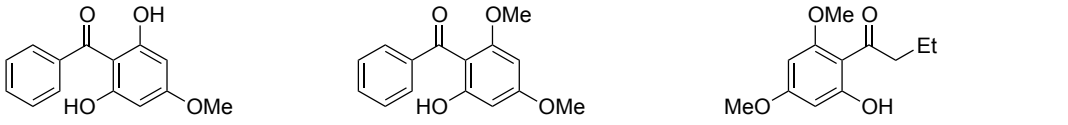
Scheme 2. Proposed Mechanism for the Reaction of Butyric Acid and Benzyne.

The formation of the product **3** encouraged us to pursue this project, since it provides an expeditious route to *o*-hydroxyaryl ketones, important precursors for the synthesis of biologically useful flavones and chalcones,[11] from readily available carboxylic acids

(Scheme 3). Most traditional synthetic approaches to *o*-hydroxyaryl ketones ultimately proceed by the Friedel-Crafts acylation of phenols with acyl chlorides in the presence of Lewis acids,[12] or the Fries rearrangement of suitable phenyl esters.[13] Both of these procedures suffer from regioselectivity issues and proceed in the presence of strong Lewis acids, which limits the potential of this transformation. It is noteworthy that *o*-hydroxyaryl ketones are an important class of biologically interesting structures,[14] and some of them, such as cotoin and hydrocotoin, have been found in nature (Scheme 4).[15]



Scheme 3. Synthetic Utility of *o*-Hydroxyaryl Ketones.



cotoin
isolated from *Aniba Coto, Aniba Duckei, Garcinia Virgata*

hydrocotoin
isolated from *Aniba Pseudo-Coto*

isolated from *Dysophylla Tomentosa*

Scheme 4. Examples of Naturally-occurring *o*-Hydroxyaryl Ketones.

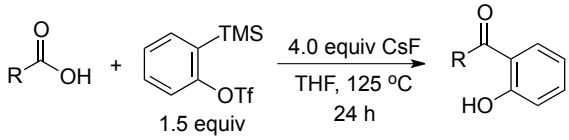
Unexpectedly, running the reaction at higher temperatures allowed us to achieve higher yields of the desired hydroxyaryl ketone, at the same time lowering the relative ratios

of the major side-products **5** and **6**. Running the reaction at 125 ^{o}C (sealed vial) allowed us to isolate the desired hydroxyaryl ketone **3** in a 43% yield (Table 1, entry 4). Changing the solvent to DME resulted in lower yields of the desired product **3** and higher ratios of the arylation product **4** at both 65 ^{o}C and 125 ^{o}C (entries 5 and 6). To check out the possibility that the undesired protonation of the intermediate **8** is caused by the proton of the starting acid, we attempted to run the reaction in the presence of a stoichoimetric amount of different bases. Unfortunately, the use of K_2CO_3 as an additive resulted in a lower (14%) yield, which might be caused by the poor solubility of the butyrate formed (entry 7). Running the reaction in the presence of Cs_2CO_3 resulted in a still lower (4%) yield of the desired product with significant amounts of the ester **4** and the alkene **6** being detected (entry 8). Other bases (*e.g.*, NaH, Na_2CO_3, KOPiv, *sym*-collidine) failed to improve the yield of the desired hydroxyaryl ketone as well. Using the sodium salt of the butyric acid or its TMS-ether resulted in lower yields of the desired product **3** and higher relative ratios of the alkene **6**.

Increasing the amount of the benzyne precursor **1** from 1.0 to 1.2 equiv and diluting the reaction mixture resulted in an increased (50%) yield of the desired product (entry 9). A further increase in the amount of the benzyne precursor (up to 2 equiv) revealed that the highest yield (entry 10, 77%) can be achieved with a 1.5-fold excess of the benzyne precursor to the starting butyric acid (entries 9-12). A further increase in the amount of benzyne results in higher ratios of the bis-arylated products **5** and **6**, thus lowering the yield of the desired product **3**. Extending the time of the reaction and using extra amounts of CsF does not have any significant effects on the yield of the desired ketone **3**. We also attempted to run the reaction under Greaney's conditions (TBAT in toluene at 50 ^{o}C), which were

optimized for amides.[1b] However, only a 34% yield of the product **3** was observed in this case, while the undesired ester **4** was detected in a 54% yield (entry 13). We subsequently applied our optimized conditions (Table 1, entry 10) to other carboxylic acids (Table 2).

Table 2. Reaction of Carboxylic Acids with Arynes.[a]



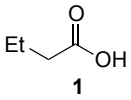
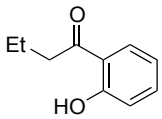
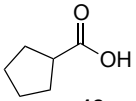
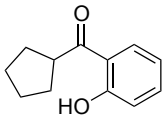
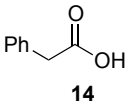
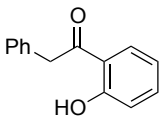
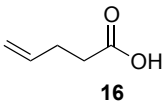
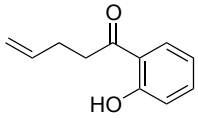
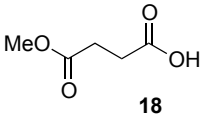
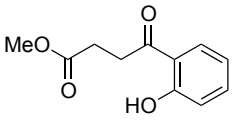
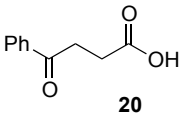
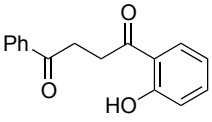
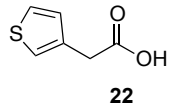
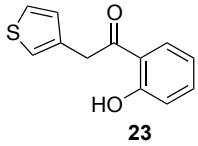
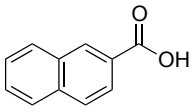
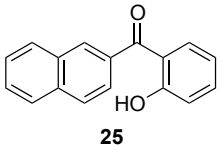
entry	acid	product	yield[b] (%)
1	 **1**	 **3**	77
2	 **12**	 **13**	68
3	 **14**	 **15**	62
4	 **16**	 **17**	72
5	 **18**	 **19**	58
6	 **20**	 **21**	39

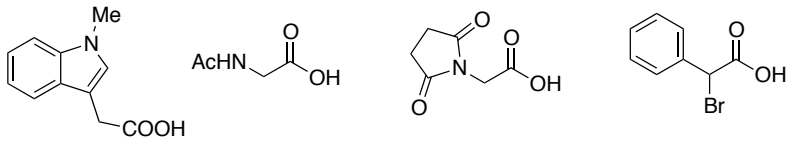
Table 2 continued.

7	 **22**	 **23**	30
8	 **24**	 **25**	44

[a] Reaction conditions: 0.25 mmol of acid, 1.5 equiv of benzyne precursor and 4.0 equiv of CsF in 15 mL of THF were heated in a closed vial at 125 °C for 24 h. [b] Isolated yield.

This method well tolerates cycloalkyl and benzyl groups. The corresponding products **13** and **15** were obtained in 68% and 62% yields respectively (entries 2 and 3). The alkene-containing product **17** was successfully isolated in a 72% yield (entry 4). The ester- and ketone-containing acids **18** and **20** provided the desired products in lower 58% and 39% yields respectively (entries 5 and 6).

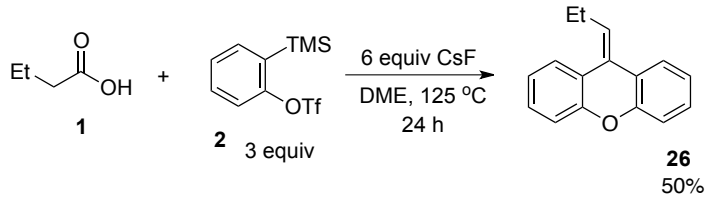
A number of α-substituted carboxylic acids was tried under our optimized reaction conditions (Scheme 5). Unfortunately, presumably due to an increased acidity of the α-protons next to the reacting acid functionality, as well as the low solubility of some of these substrates in THF, most of these attempts resulted in the formation of inseparable mixtures of by-products with the undesired arylation products often being formed in considerable amounts. One of the most successful examples of this type of acid is 3-thiopheneacetic acid (**22**), which resulted in the formation of the hydroxyaryl ketone **23** in a 35% yield (entry 7).



Scheme 5. Representative Examples of Failed Substrates.

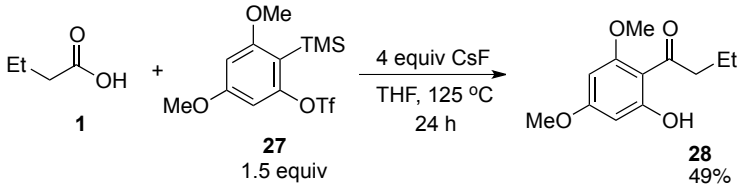
In the case of arenecarboxylic acids, perhaps due to the increased acidity of the resulting hydroxyaryl ketones, over-arylation products were a major concern not only because of decreased yields of the desired insertion products, but also because of complications during their isolation. Thus, in the case of *p*-nitrobenzoic acid, the corresponding tertiary alcohol analogous to intermediate **5** could be isolated in a 54% yield and none of the desired hydroxyaryl ketone was detected. Changing the electronic properties of the substituents on the phenyl ring had little effect on the outcome of the reaction. The desired products of *p*-methoxy- and *p*-methylbenzoic acids were formed in less than 30% yields (as measured by NMR spectroscopic analysis). Unfortunately, none of these products could be isolated due to a number of side-products with similar polarities. One of the most successful reactions was with *β*-naphthoic acid (**24**), which afforded the corresponding *o*-hydroxyaryl ketone **25** in a 44% yield (entry 8).

Allowing butyric acid to react with an excess (3 equiv) of the benzyne precursor in DME, it is possible to obtain the dehydrated bis-aryne insertion xanthene product **26** in a 50% yield (Scheme 6).[16] Xanthenes are a pharmauceutically important scaffold with many members shown to possess antimalarial,[17] antitrypanosomal,[18] antileishmanial,[18] and antitumor[19] activities.



Scheme 6. Synthesis of a Xanthene.

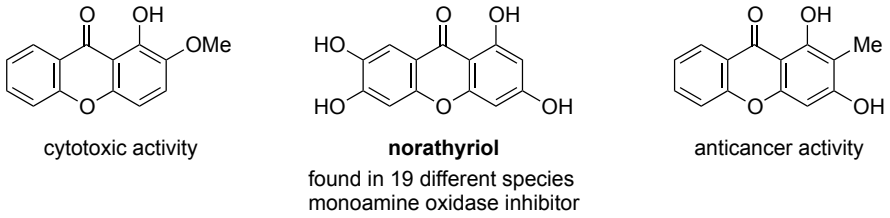
We also examined the reaction of butyric acid with the unsymmetrical dimethoxy-substituted benzyne precursor **27**.[20] We were delighted to observe the regioselective formation of the desired isomer **28** in a 49% yield (Scheme 7). The regioselectivity is consistent with that reported by the Stoltz group.[20] The product **28** is a natural product that has been found in an Indian shrub *Dysophylla stellata* Benth.[21]



Scheme 7. Synthesis of a Naturally-occurring Hydroxyaryl Ketone.

4.3.2. Synthesis of Xanthones

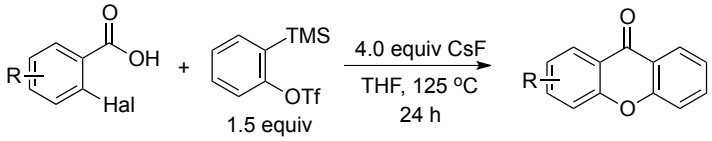
Since the low efficiency of the reaction of arenecarboxylic acids with arynes is likely due to the high reactivity of the phenolic OH group of the resulting *o*-hydroxyaryl ketones towards arynes, trapping the phenol by an intramolecular S_NAr reaction could provide an interesting route to xanthones and analogues, which are very important ring systems in biology and pharmacy (Scheme 8).[22]



Scheme 8. Examples of Biologically Important Xanthones.

Indeed, a close examination of the reaction between *o*-methoxybenzoic acid and benzyne revealed that about 58% of the starting material has been converted to the xanthone **30** and only 12% could be assigned as the expected *o*-hydroxyaryl ketone. When *o*-halobenzoic acids are allowed to react with the benzyne precursor and CsF under our optimized conditions, we were delighted to see formation of the xanthone **30** (Table 3). While *o*-chloro and *o*-iodobenzoic acids provided poor yields (30% and 38% respectively), the *o*-fluoro-substituted substrate **29** afforded the desired xanthone in an 80% yield (entry 1).

Table 3. Reaction of *o*-Haloarenecarboxylic Acids with Arynes.[a]



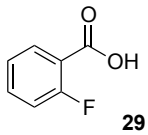
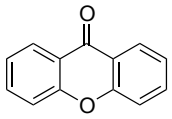
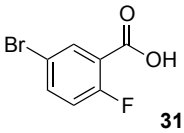
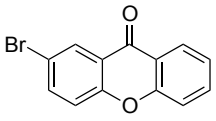
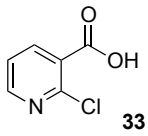
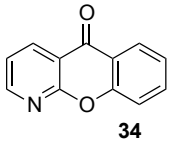
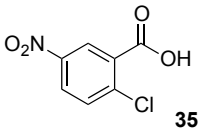
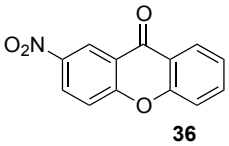
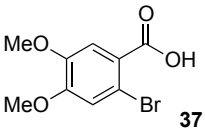
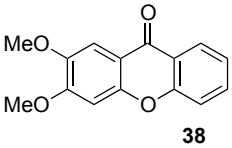
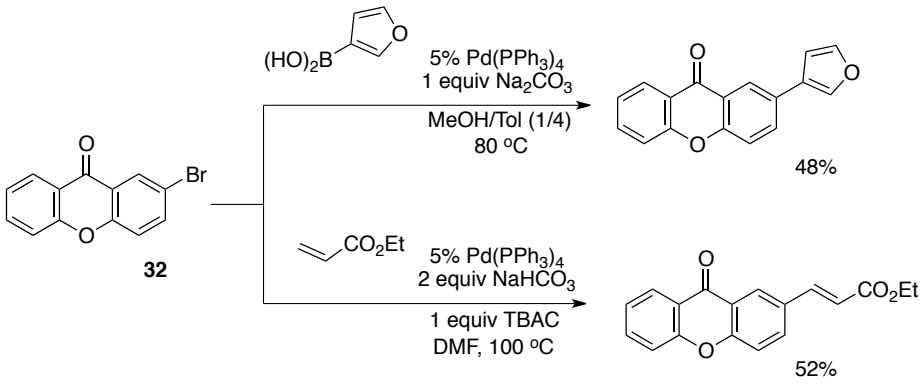
entry	acid	product	yield[b] (%)
1	 **29**	 **30**	80
2	 **31**	 **32**	79

Table 3 continued.

3	 **33**	 **34**	22
4	 **35**	 **36**	87[c]
5	 **37**	 **38**	59[c,d]

[a] Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the benzyne precursor and 4.0 equiv of CsF in 15 mL of THF were heated in a closed vial at 125 °C for 24 h. [b] Isolated yield. [c] Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the aryne precursor, and 2.0 equiv of TBAT in 5 mL of toluene were heated at 60 °C for 24 h. [d] The isolated *o*-hydroxyaryl ketone was heated in MeCN in the presence of 2 equiv of K_2CO_3 at 100 °C for 24 h to provide the desired xanthone.

Our xanthone process tolerates other halides present in the benzoic acid moiety. Thus, the bromo-substituted xanthone **32** was isolated in a 79% yield (entry 2). The presence of the bromide functionality provides a useful handle for further diversification of the system if a combinatorial library of these compounds is desired. Examples of Heck and Suzuki coupling processes for 2-bromoxanthone (**32**) have been demonstrated by the Larock group in the past (Scheme 9).[23]



Scheme 9. Diversification of Halogen-Substituted Xanthones.

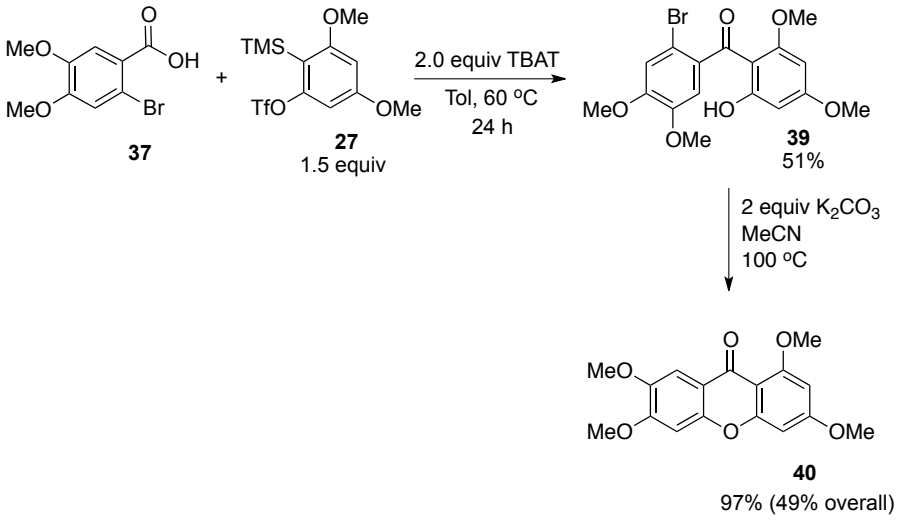
We were delighted to obtain 4-aza-xanthone (**34**), albeit in only a 22% yield (entry 3), starting from 2-chloronicotinic acid (**33**), since a number of the reported reactions involving benzynes, even under milder reaction conditions, do not tolerate the nucleophilic nitrogen of a pyridine ring.[24]

The reaction of the electron-poor nitro-substituted carboxylic acid **35** under our optimized reaction conditions provided the desired xanthone **36** in only a 48% yield, with complications during isolation of the desired product. However, running this reaction under reaction conditions reported by the Greaney group for a related insertion into the C-N bond of aromatic amides[1b] afforded the xanthone **36** in a high 87% yield (entry 4).

The reaction of the electron-rich dimethoxy-substituted benzoic acid **37** with benzyne afforded only trace amounts of the desired product **38** in both THF and DME. Employing the reaction conditions reported by the Greaney group, in this case provided the uncyclized *o*-hydroxyaryl ketone that upon cyclization in acetonitrile at elevated temperatures in the presence of K_2CO_3 afforded the desired xanthone **38** in a 59% overall yield (entry 5). Interestingly, the bis-demethylated version of xanthone **38** has been shown to significantly

inhibit the growth of melanoma cancer cells and the mitogenic response of human lymphocytes to a common mitogen PHA.[25]

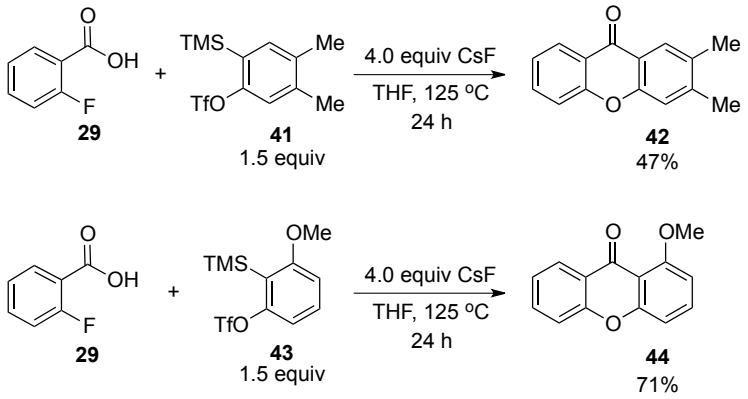
Our standard xanthone protocol has also been used for the reaction of carboxylic acid **37** with the unsymmetrical dimethoxybenzyne precursor **27** (Scheme 10). After the benzyne insertion and subsequent induced S_NAr reaction, the final tetraoxygenated xanthone **40** was isolated in a 49% overall yield. It is noteworthy that the compound **40** is found in nature, as well as partially demethylated analogues.[26] The tetrademethylated version, norathyriol, has been found in at least 19 different natural sources and has been shown to possess hypotensive activity.[27] It is also an effective inhibitor of cutaneous plasma extravasation[28] and a monoamine oxidase inhibitor.[29]



Scheme 10. Synthesis of a Biologically Interesting Xanthone.

Reacting *o*-fluorobenzoic acid with the benzyne precursors **41** and **43** under our CsF/THF optimized conditions afforded the corresponding xanthones **42** and **44** in 47% and 71% yields respectively (Scheme 11). The low yield in the case of substrate **41** may be

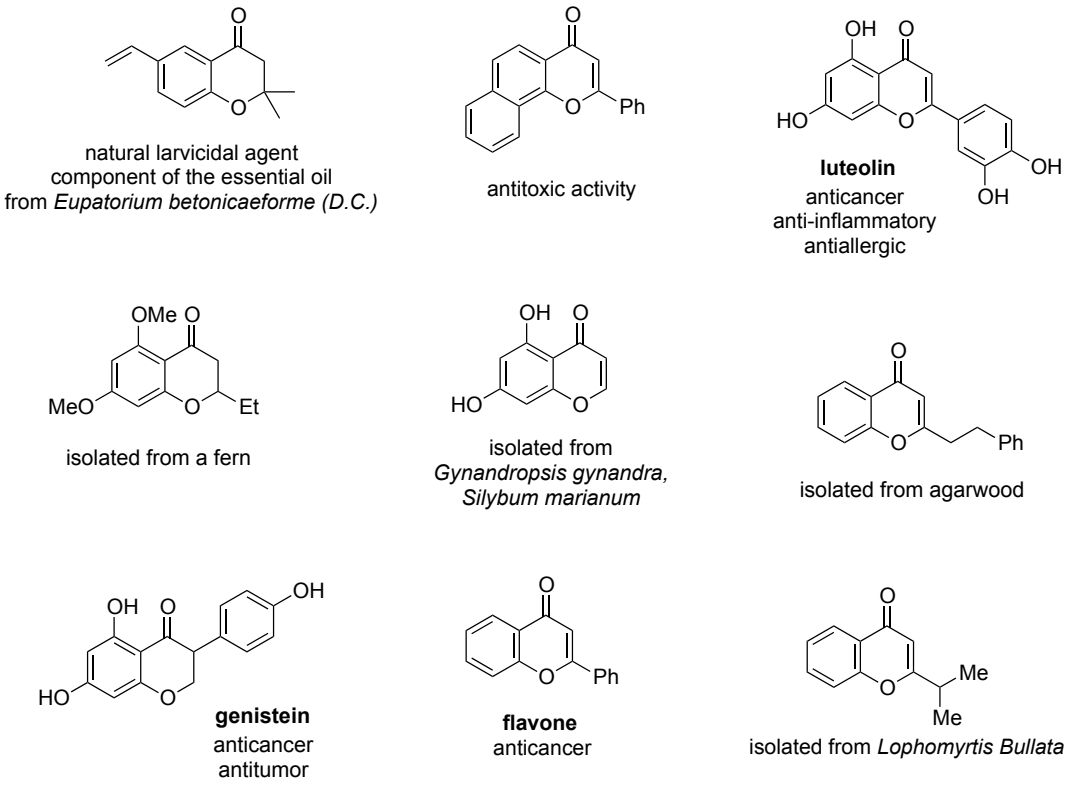
attributed to the poor solubility of the cyclized product **42**. The unsymmetrical benzyne precursor **43** provided the product **44** as a single regioisomer.[30]



Scheme 11. Reaction of *o*-Fluorobenzoic Acid with Substituted Benzynes.

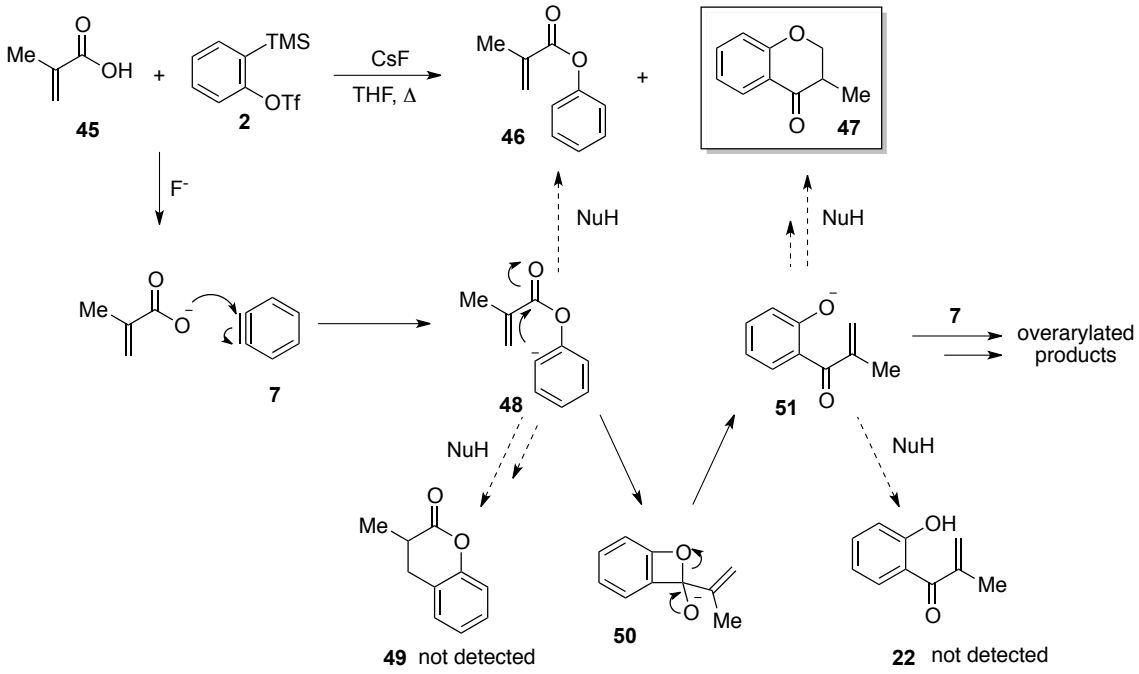
4.3.3. Synthesis of 4-Chromanones and Flavones

The phenolate anion (see intermediate **10** in Scheme 2) formed *in situ* could also potentially undergo a Michael addition reaction. This could provide a novel route to biologically important 4-chromanones, flavones, and chromones from readily available acrylic and propiolic acids (Scheme 12).[31]



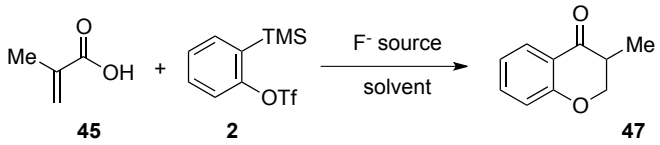
Scheme 12. Examples of Biologically Important 4-Chromanones, Flavones, and Chromones.

Indeed, when methacrylic acid (**45**) was allowed to react under the optimized reactions conditions used in the synthesis of *o*-hydroxyaryl ketones, the 4-chromanone **47** was formed, but only in a 58% yield (Table 4, entry 1). Surprisingly, none of the product **49** that could result from the ring-closure of intermediate **48** was detected, which suggests that the formation of the 4-membered ring intermediate **50** is a more favorable pathway (Scheme 13). None of the uncyclized product **22** was detected either, suggesting a very fast rate of cyclization for the final Michael addition reaction.



Scheme 13. The Proposed Mechanism for the Reaction of Methacrylic Acid and Benzyne.

Table 4. Optimization of Benzyne Insertion into the C-O bond of Methacrylic Acid.[a]



entry	equiv of **2**	fluoride source (equiv)	solvent, mL	temp. (°C)	% yield[b]
1	1.50	CsF (4)	THF, 10	120	58
2	1.50	CsF (4)	THF, 10	120	57[c]
3	1.50	CsF (4)	THF, 10	120	57[d]
4	1.75	CsF (5.8)	THF, 10	120	67
5	2.00	CsF (6.7)	THF, 10	120	69
6	2.25	CsF (7.5)	THF, 10	120	65
7	2.00	CsF (6.7)	THF, 10	90	50

Table 4 continued.

8	2.00	CsF (6.7)	DME, 10	120	43
9	2.00	CsF (6.7)	DME, 10	90	31
10	1.20	CsF (4)	THF, 15	120	48
11	1.50	CsF (5)	THF, 15	120	70
12	1.75	CsF (5.8)	THF, 15	120	80
13	2.00	CsF (6.7)	THF, 15	120	77
14	1.0 + 0.6	CsF (3 + 3)	THF, 15	120	74
15	1.0 + 1.0	CsF (3 + 3)	THF, 15	120	80
16	**1.5 + 0.5**	**CsF (4 + 1)**	**THF, 15**	**120**	**84**

[a] All reactions were carried out on a 0.25 mmol scale in 5 mL of solvent during a 24 h period. [b] Isolated yields, unless stated otherwise. [c] The TES ether of methacrylic acid was used. [d] The TBDMS ether of methacrylic acid was used.

Running the methacrylic acid reaction in the presence of various bases (*e.g.* Cs_2CO_3, Et_3N, $^{i}Pr_2NEt$, *sym*-collidine) failed to improve the yield of the reaction. Running the analogous reaction with either the TES- or TBDMS-ethers of methacrylic acid both afforded the desired product **47** in a 57% yield (entries 2 and 3).

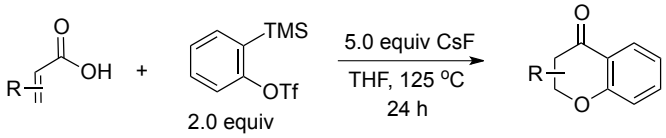
Using higher loadings of the benzyne precursor **2** (entries 4 and 5) provided the desired 4-chromanone in a 69% yield when 2 equiv of benzyne precursor were employed (entry 5). Employing even more of the benzyne precursor failed to improve the yield (entry 6). To see if this transformation is sensitive to temperature, we allowed the reaction to proceed at 90 ^{o}C. However, only a 50% yield of the product was observed in this case (entry 7). Switching the solvent to DME resulted in a lower yield of the desired product at both 120 ^{o}C and 90 ^{o}C (entries 8 and 9). Running the reaction under microwave conditions at 120 ^{o}C

had little effect on the reaction, while lowering the temperature to 65 ^{o}C under microwave conditions resulted in only trace amounts of the product **47**.

After additional optimization, we have found that diluting the reaction mixture helps to improve the yield of the 4-chromanone **47** by ~10% (entries 10-13). Apparently, one of the side reactions is caused by an intermolecular process. One of the significant challenges observed in this transformation is the poor reactivity of the starting carboxylic acid. As a result, running the reaction with <1.5 equiv of the benzyne precursor does not lead to complete conversion of the starting carboxylic acid.[32] Running the reaction with >2.0 equiv of the precursor **2** allows the acid to react completely. However, it also results in increased amounts of overarylation products (*e.g.* an alcohol analogous to intermediate **5** in Scheme 2). Running the reaction under dilute conditions with 1.75 equiv of the benzyne precursor provided an 80% yield of the desired product **47** (entry 12).

Finally, adding the benzyne precursor and CsF in two separate portions (entries 14-16) allowed us to improve the yield up to 84% (entry 16).[33] The latter reaction conditions were applied to a number of other 2-alkenoic acids (Table 5).

Table 5. Reaction of Acrylic Acids with Arynes.[a]



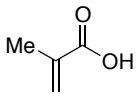
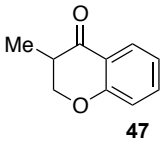
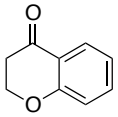
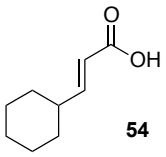
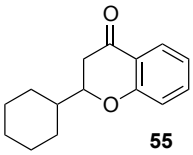
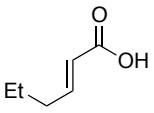
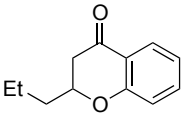
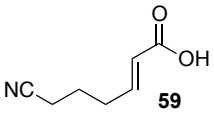
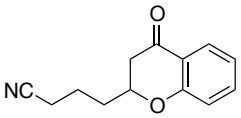
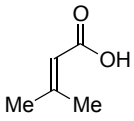
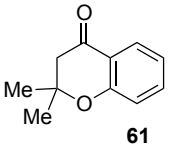
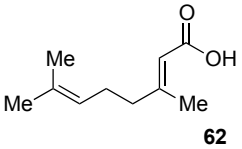
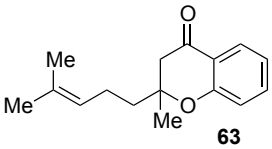
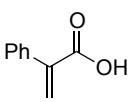
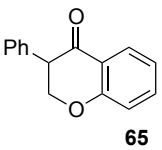
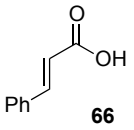
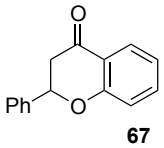
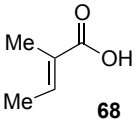
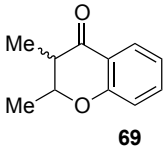
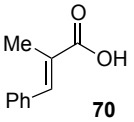
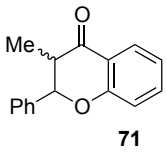
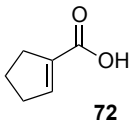
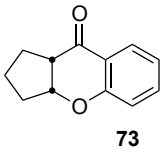
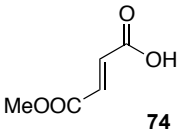
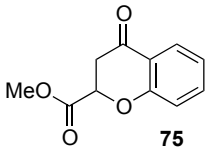
entry	acid	product	yield[b] (%)
1	 **45**	 **47**	84
2	 **52**	 **53**	13
3	 **54**	 **55**	85
4	 **56**	 **57**	82
5	 **59**	 **59**	71
6	 **60**	 **61**	77
7	 **62**	 **63**	64
8	 **64**	 **65**	56

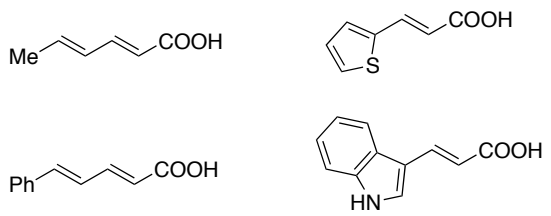
Table 5 continued.

9	 **66**	 **67**	74[c]
10	 **68**	 **69**	76[d]
11	 **70**	 **71**	67[e]
12	 **72**	 **73**	78
13	 **74**	 **75**	0

[a] Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of aryne precursor and 4.0 equiv of CsF in 15 mL of THF were heated in a closed vial at 125 °C for 18 h. Then an additional 0.5 equiv of the aryne precursor and 1.0 equiv of CsF were added and the heating continued at 125 °C for 6 h. [b] Isolated yield. [c] The yield also includes the product obtained after base-induced cyclization of the *o*-hydroxyaryl ketone (see the Supporting Information). [d] The *E/Z* ratio is ~1.8/1. [e] The *E/Z* ratio is ~5.1/1.

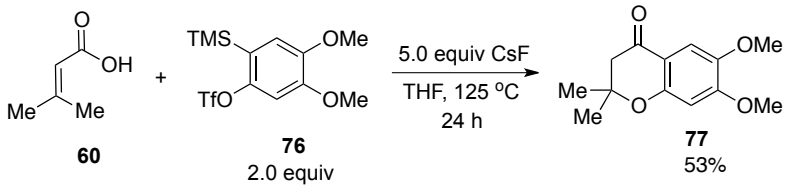
Interestingly, acrylic acid, perhaps due to its instability at high temperatures, provided the corresponding product **53** in only a 13% yield (entry 2). In contrast, 3-alkyl-substituted acrylic acids provided the corresponding cyclohexyl-substituted and propyl-substituted 4-chromanones **55** and **57** in 85% and 82% yields respectively (entries 3 and 4). The carboxylic acid **58** with a nitrile substituent at the end of an alkyl chain provided the 4-chromanone **59** in a 71% yield (entry 5). 3,3-Dialkyl-substituted acrylic acids [3-methyl-

2-butenoic acid (**60**) and geranic acid (**62**)] provided the corresponding chromanones **61** and **63** in good yields (77% and 64% respectively) (entries 6 and 7). α-Phenylacrylic acid (**64**) provided the cyclized product **65** in a 56% yield (entry 8). Interestingly, in the case of cinnamic acid (**66**), 60% of the desired product **67** was obtained along with the uncyclized *o*-hydroxyaryl chalcone. Treating the reaction mixture with a base (piperidine/THF/H_2O)[34] cyclized the hydroxyaryl ketone to the desired flavanone **67** in a 74% overall yield (entry 9). 2,3-Disubstituted acrylic acids provided diastereomeric mixtures of chromanones **69** and **71** in 76% and 67% yields respectively (entries 10 and 11). Cyclopentene-1-carboxylic acid (**72**) afforded the tricyclic product **73** in a 78% yield with exclusively a *cis* configuration at the 5,6-ring junction (entry 12). Unfortunately, monomethyl fumarate (as well as monomethyl maleate), bearing an group on the carbon-carbon double bond, did not provide any of the expected chromanone product (entry 13). One possible explanation might be the decreased nucleophilicity of the carboxylic group toward the benzyne caused by the presence of the two electron-withdrawing groups. Other carboxylic acids that provided low yields (less than 30%) of the expected products include 2,4-dialkenoic acids and 3-heteroaryl-substituted acrylic acids (Scheme 14). These substrates could potentially engage in Diels-Alder reactions with the dienophylic benzyne at such high temperatures.



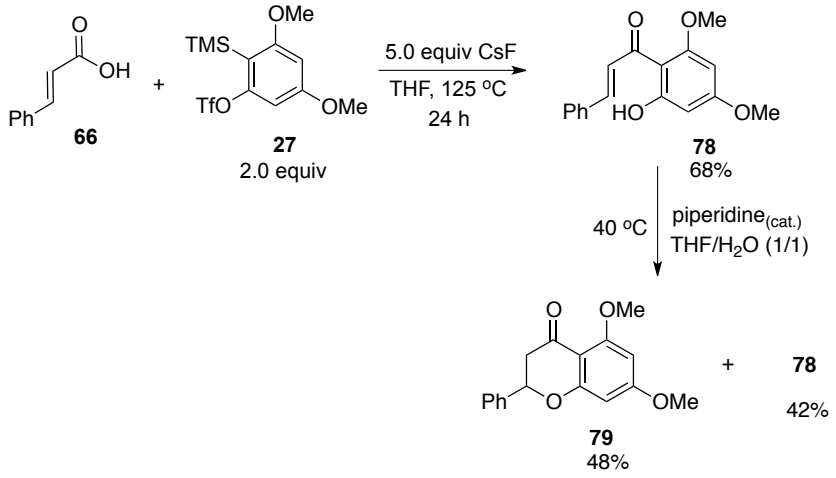
Scheme 14. Examples of Alkenoic Acids that Failed to Provide Chromanones.

We have also examined the reaction of alkenoic acids with other benzyne precursors. The symmetrical dimethoxy-substituted aryne precursor **76**, when allowed to react with 3,3-dimethylacrylic acid, provided the cyclized product **77** in a 53% yield (Scheme 15).[35] It is noteworthy that the dehydrated analogue of this compound, precocene 2, exhibits significant anti-juvenile hormone activity in insects.[36]



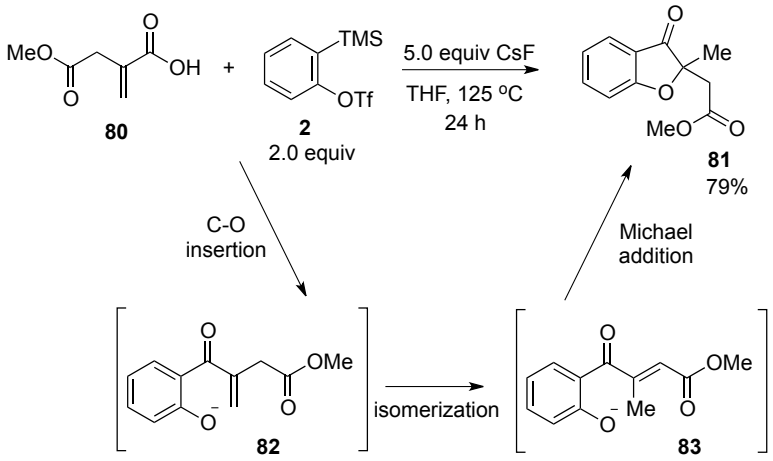
Scheme 15. Reaction of an Alkenoic Acid with a Dimethoxy-substituted Benzyne.

When cinnamic acid (**66**) was allowed to react with the unsymmetrical dimethoxy-benzyne precursor **27**, the uncyclized *o*-hydroxychalcone **78** was isolated in a 65% yield (Scheme 16). Subjecting the latter compound to a piperidine-promoted intramolecular Michael addition reaction resulted in the formation of the desired chromanone **79** in a 48% yield, along with 42% of the unreacted starting material. A chiral version of compound **79** is a natural product found in *Caesalpinia pulcherrima*,[37] and the monodemethylated version of the latter, known as pinostrobin, is reported to be an effective aromatase inhibitor.[38]



Scheme 16. Reaction of Cinnamic Acid with a Dimethoxy-substituted Benzyne.

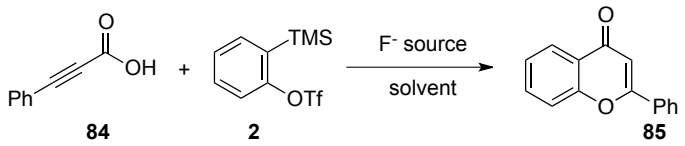
The reaction of itaconic acid methyl ester **80** with benzyne under our optimized conditions did not result in formation of the expected flavanone. Instead, the 3-coumaranone derivative **81** was isolated in a 79% yield (Scheme 17). Since monomethyl fumarate did not provide any isolable product under identical reaction conditions (Table 5, entry 13), this reaction is best explained mechanistally as follows: a) the carboxylic acid undergoes the expected insertion with benzyne to provide intermediate **82**; b) the latter isomerizes to a more stable isomer **83** under the reaction conditions; c) intramolecular Michael addition in the substrate **83** results in formation of the more kinetically favorable 5-membered ring product **81**.



Scheme 17. Mechanism for the Formation of Coumaranone **81** from a Monomethyl Ester of Itaconic Acid.

We have also examined the reaction of phenylpropiolic acid (**84**) with benzyne in THF under our optimized reaction conditions. Unfortunately, due to the high temperature of the reaction, the major product observed was the decarboxylated starting material. The desired flavone **85** could be isolated in only a 31% yield (Table 6, entry 1).

Table 6. Optimization of Benzyne Insertion into the C-O Bond of an Alkynoic Acid.[a]



84 2 85

entry	equiv of **2**	fluoride source (equiv)	solvent, mL	temp. (°C)	% yield[b]
1	1.5 + 0.5	CsF (4 + 1)	THF, 15	120	31
2	1.5 + 0.5	CsF (4 + 1)	THF, 15	90	48
3	1.5	TBAT (2)	THF, 15	65	49
4	1.5	TBAT (2)	Tol, 5	60	56
5	1.2	TBAT (2)	Tol, 5	60	50
6	2.0	TBAT (2)	Tol, 5	60	56

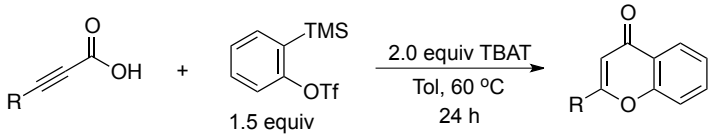
[a] All reactions were carried out on a 0.25 mmol scale in 5 mL of solvent during a 24 h period. [b] Isolated yields.

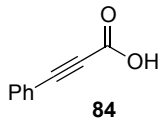
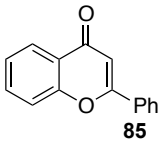
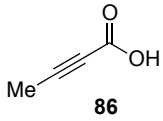
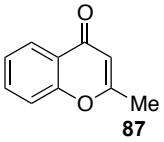
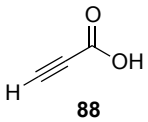
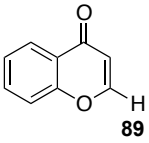
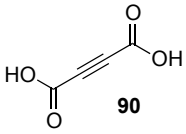
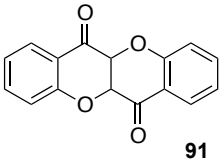
To minimize the side reaction observed in the reaction of phenylpropiolic acid, we attempted to decrease the temperature to 90 °C. Gratifyingly, the yield of the product increased to 48% (entry 2). If we employed tetrabutylammonium triphenyldifluorosilicate (TBAT), the desired product **85** could be isolated in a similar 49% yield, while running the reaction at only 65 °C (entry 3). We then replaced THF with toluene, essentially employing reaction conditions analogous to those reported by Greaney's group using amides.[1b] Running the reaction in toluene at 60 °C allowed us to obtain the flavone **85** in 50-56% yields, with the optimal conditions employing 1.5 equiv of the benzyne precursor (56% yield, entry 6).

Using these optimized reaction conditions, we have examined the reaction of several 2-alkynoic acids with benzyne. 2-Butynoic acid provided the chromone **87** in a 64% yield

(Table 7, entry 2). The reaction of the unsubstituted propiolic acid (**88**) with CsF in THF did not provide any recognizable products. However, running the reaction in the presence of TBAT (see the reaction conditions of Table 6, entry 3) provided the desired chromone **89** in a 71% yield (Table 7, entry 3). Unfortunately, acetylenedicarboxylic acid (**90**) provided messy mixtures of unidentified products under both the CsF- and TBAT-mediated protocols (entry 4).

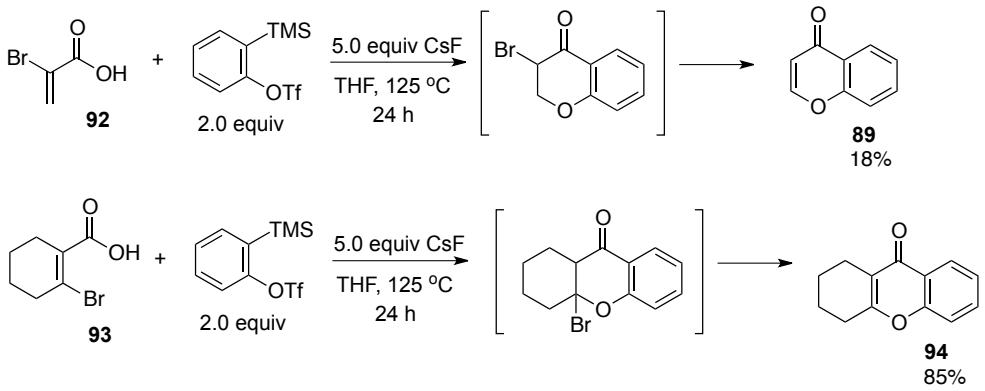
Table 7. Reaction of 2-Alkynoic Acids with Arynes.[a]



entry	acid	product	yield[b] (%)
1	 **84**	 **85**	84
2	 **86**	 **87**	64
3	 **88**	 **89**	71[c]
4	 **90**	 **91**	0

[a] Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the aryne precursor and 2.0 equiv of TBAT in 5 mL of toluene were heated at 60 °C for 24 h.[b] Isolated yield. [c] Reaction conditions: 0.25 mmol of the carboxylic acid, 1.5 equiv of the aryne precursor and 2.0 equiv of TBAT in 15 mL of THF were heated at 65 °C for 24 h.

It is noteworthy that we can also obtain chromones in the reaction of 2- and 3-haloalkenoic acids with benzyne. Apparently, the chromanones produced with 2-bromoacrylic and 2-bromocyclohexenoic acids undergo an elimination reaction furnishing the chromones **89** and **94** in 18% and 85% yields respectively (Scheme 18). The low yield of the former product might be due to an unfavorable configuration for the final dehydrohalogenation reaction, as well as the possible low stability of the starting material under the reaction conditions we have employed. It is possible that further optimization of this reaction could afford far better results, although we have not done that.

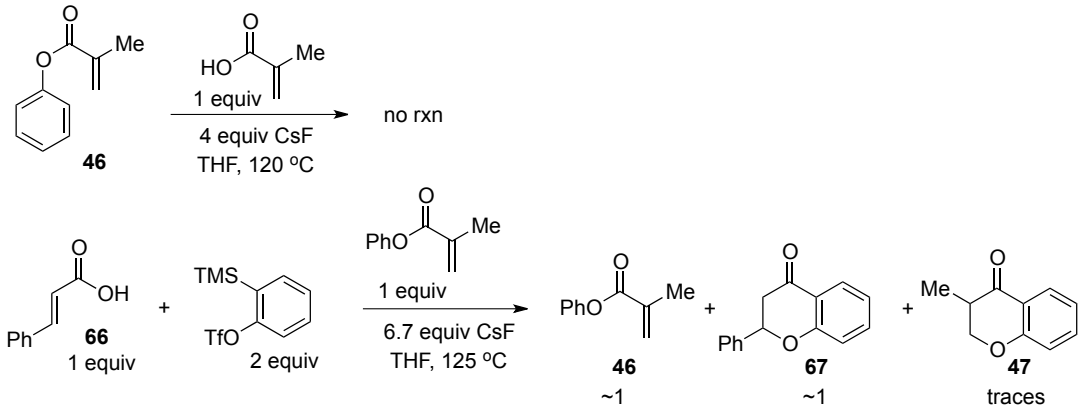


Scheme 18. Reaction of Haloalkenoic Acids with Benzyne.

4.3.4. Final Mechanistic Considerations

Some further mechanistic considerations need to be discussed. An acid-catalyzed Fries rearrangement leading from ester **4** (see Scheme 2) to an *o*-hydroxyaryl ketone (analogous to compound **3**) has been considered as a mechanistic possibility for our overall transformation. Based on literature accounts, however, strong acidic media is absolutely necessary for such a rearrangement to occur.[39] Nevertheless, we allowed phenyl methacrylate

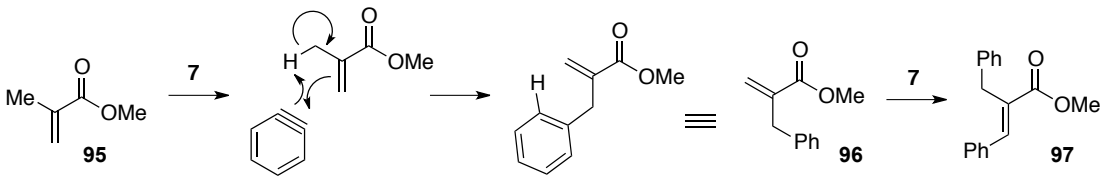
(**46**) to react with methacrylic acid in THF in the presence of CsF at 120 °C (Scheme 19). As expected, no 4-chromanone was detected under these reaction conditions. Replacing the basic CsF media with 1 equiv of $BF_3 \cdot Et_2O$ did not result in the formation of the target compound **47** either. However, the benzyne intermediate or molecules that result from its generation might play the role of a Lewis acid in this transformation. In a crossover experiment, we have allowed cinnamic acid (**66**) to react with 2 equiv of the benzyne precursor in the presence of CsF and phenyl methacrylate at 120 °C. Unexpectedly, the chromanone **47**, that could only be formed from the ester **46**, was detected in the crude NMR spectrum of the reaction mixture, albeit in only trace amounts. This suggests that the cationic Fries mechanism is, at the most, a very minor pathway for the transformation of acrylic acids into the corresponding chromanones.



Scheme 19. Mechanistic Investigation of the Possible Cationic Fries Rearrangement.

We have also examined the possibility that methyl esters can engage in a similar C-O insertion process with a benzyne. While no traces of any reaction were observed in the case of methyl benzoate, methyl methacrylate unexpectedly resulted in the formation of two stable products in ~10% yields. Once the structures of these products were established, it became

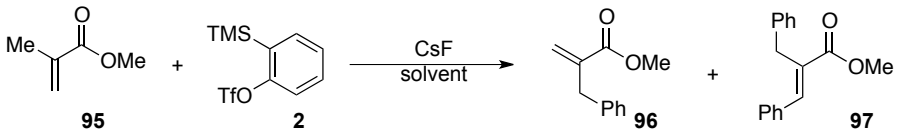
evident that no C-O insertion had taken place in the starting ester **95**. Instead, because of the favorable structural composition of the methacrylate unit, a set of two ene-reactions apparently occurs to produce the two ester products **96** and **97** (Scheme 20).



Scheme 20. Mechanism of the Double Ene Reaction.

After optimization studies, it was found that running the methyl methacrylate reaction in acetonitrile at room temperature in the presence of an excess of the benzyne (3 equiv), the diarylated product **97** can be isolated in an 80% yield (Table 8).

Table 8. Optimization of the Reaction Between Methyl Methacrylate and *o*-(Trimethylsilyl)-phenyl Triflate.[a]

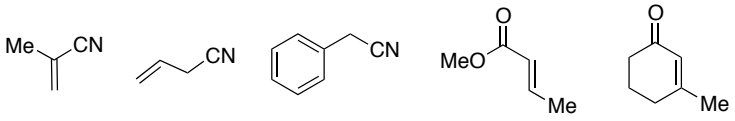


entry	equiv of **2**	fluoride source (equiv)	solvent, mL	temp. (°C)	% yield of **96**[b]	% yield of **97**[b]
1	3.0	CsF (6)	THF, 5	65	10	12
2	2.1	CsF (5)	MeCN, 5	rt	21	40
3	**3.0**	**CsF (6)**	**MeCN, 5**	**rt**	**11**	**80**

[a] Reaction conditions: 0.25 mmol of the substrate, 18 h. [b] Isolated yields.

Other methods leading to stereodefined trisubstituted alkenes usually utilize multiple synthetic steps and require the use of expensive rhodium catalysts.[40] We therefore examined the scope of our aryne ene reaction. Unfortunately, allylic systems similar to methyl

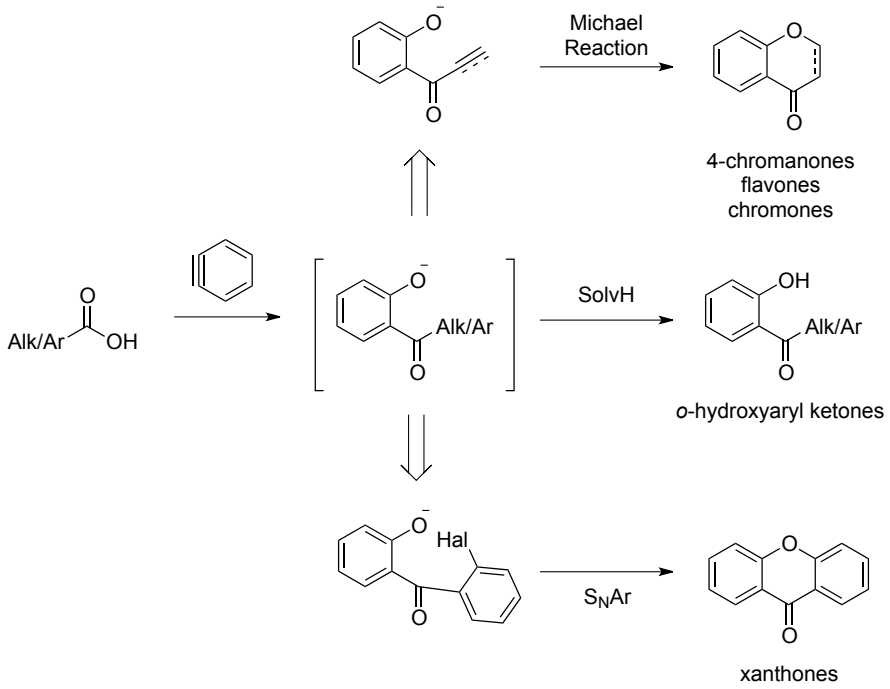
methacrylate resulted in only a very low conversion of the starting material or in the formation of mixtures of unidentified products (Scheme 21). While a few ene reactions with a benzyne intermediate have been observed before,[40] our reaction of methyl methacrylate proceeds under very mild conditions (MeCN, room temperature) and allows one to obtain the diarylated product **97** in a high yield. This synthesis is far more convenient than other current syntheses of ester **97** described in the literature.



Scheme 21. Failed Substrates for an Ene Reaction with Benzyne.

4.4. Conclusions

In summary, we have developed a novel, efficient and expedient route to *o*-hydroxyaryl ketones, xanthones, 4-chromanones, flavones and their analogues by aryne insertion into the C-O bond of readily available carboxylic acids and subsequent rearrangements (Scheme 22). A variety of functional groups are compatible with the reaction conditions. The method should prove useful for the preparation of these biologically and pharmaceutically important structures.



Scheme 22. Summary of the Reactions of Carboxylic Acids and Benzyne.

4.5. Acknowledgement

We thank the National Science Foundation, the National Institute of General Medical Sciences (GM079593) 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 also thank Dr. Feng Shi while at Iowa State University for the preparation of some aryne precursors.

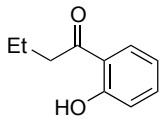
4.6. Experimental

General Information. 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 60 mesh silica gel plates, and visualization was effected by short wavelength UV light (254 nm). All melting points are uncorrected. All high resolution mass spectra were recorded using EI at 70

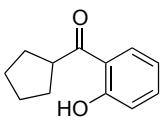
eV or using Agilent QTOF 6540 mass spectrometer (APCI at a voltage of 70 eV). All reagents were used directly as obtained commercially, unless otherwise noted.

General procedure for the reaction of carboxylic acids with arynes.

The aryne precursor (1.5 equiv) was added to a mixture of the carboxylic acid (0.25 mmol) and CsF (4.0 equiv) in 15 mL of freshly distilled THF, and the reaction mixture was then stirred in a closed vial at 125 ºC for 18 h. After the reaction mixture was allowed to cool to room temperature, it was eluted through a plug of silica gel with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired *o*-hydroxyaryl ketone.

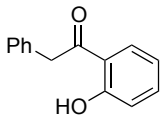


1-(2-Hydroxyphenyl)-1-butanone (3). This compound was obtained as a pale yellow oil in a 77% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.4 Hz, 3H), 1.72-1.82 (m, 2H), 2.95 (t, J = 7.3 Hz, 2H), 6.88 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 12.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.2, 40.4, 118.7, 119.0, 119.6, 130.2, 136.4, 162.7, 207.0; HRMS (EI) calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0839. The ^{1}H NMR spectral data are in good agreement with the literature data.[41]

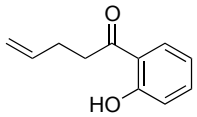


Cyclopentyl(2-hydroxyphenyl)methanone (13). This compound was obtained as a pale yellow oil in a 68% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66-1.74 (m, 4H),

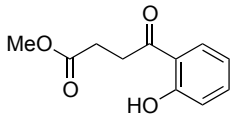
1.89-1.96 (m, 4H), 3.73 (m, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.96 (t, J = 8.4 Hz, 1H), 7.44 (t, J = 7.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 12.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 30.5, 46.2, 118.7, 118.9, 119.2, 130.4, 136.2, 163.1, 209.4; HRMS (EI) calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0993.



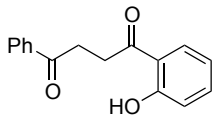
1-(2-Hydroxyphenyl)-2-phenylethanone (15). This compound was obtained as a pale yellow oil in a 62% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 2H), 6.91 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 7.26-7.30 (m, 3H), 7.34-7.37 (m, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 12.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.4, 118.9, 119.2, 127.4, 129.0, 129.6, 130.6, 134.1, 136.8, 163.0, 204.1; HRMS (EI) calcd for $C_{14}H_{12}O_2$ 212.0837, found 212.0842. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[42]



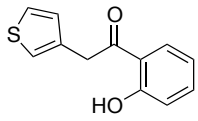
1-(2-Hydroxyphenyl)-4-penten-1-one (17). This compound was obtained as a pale yellow oil in a 72% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43-2.52 (m, 2H), 3.09 (t, J = 7.4 Hz, 2H), 5.02 (dd, J = 17.1, 1.3 Hz, 1H), 5.09 (dd, J = 10.2, <1 Hz, 1H), 5.82-5.94 (m, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 12.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 37.6, 115.9, 118.7, 119.1, 119.5, 130.0, 136.5, 137.0, 162.6, 205.8; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0840. The ^{1}H NMR spectral data are in good agreement with the literature data.[41]



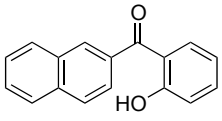
Methyl 4-(2-hydroxyphenyl)-4-oxobutanoate (19). This compound was obtained as a pale yellow semisolid in a 58% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (t, J = 7.4 Hz, 2H), 3.36 (t, J = 7.4 Hz, 2H), 3.70 (s, 3H), 6.90 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 7.1 Hz, 1H), 7.78 (d, J = 7.1 Hz, 1H), 12.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 33.3, 52.2, 118.7, 119.2, 119.4, 129.9, 136.7, 162.5, 173.2, 204.1; HRMS (EI) calcd for $C_{11}H_{12}O_4$ 208.0736, found 208.0740.



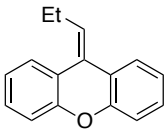
1-(2-Hydroxyphenyl)-4-phenylbutane-1,4-dione (21). This compound was obtained as a pale yellow semisolid in a 39% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43-3.54 (m, 4H), 6.94 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.46-7.53 (m, 3H), 7.60 (t, J = 7.3 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 7.5 Hz, 2H), 12.12 (s, 1H).



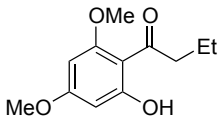
1-(2-Hydroxyphenyl)-2-(thiophen-3-yl)ethanone (23). This compound was obtained as a yellow semisolid in a 30% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (s, 2H), 6.91 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 5.7 Hz, 1H), 7.15 (s, 1H), 7.33 (dd, J = 4.9, 3.0 Hz, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 12.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 118.7, 118.9, 119.0, 123.1, 126.1, 128.5, 130.3, 133.4, 136.6, 162.9, 203.3; HRMS (EI) calcd for $C_{12}H_{10}O_2S$ 218.0396, found 218.0391.



2-Hydroxyphenyl 2-naphthyl ketone (25). This compound was obtained as a pale yellow semisolid in a 44% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.49-7.64 (m, 3H), 7.66 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.90-7.97 (m, 3H), 8.17 (s, 1H), 12.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.7, 118.9, 119.6, 125.5, 127.2, 128.1, 128.4, 128.6, 129.4, 130.7, 132.4, 133.9, 135.1, 135.3, 136.5, 163.4, 201.7; HRMS (EI) calcd for $C_{17}H_{12}O_2$ 248.0837, found 248.0834. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[43]

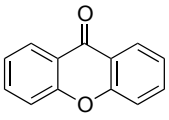


9-Propylidene-9*H*-xanthene (26). This compound was obtained as a pale white amorphous solid in a 50% yield using 3 equiv of the benzyne precursor and 6 equiv of CsF in 5 mL of DME: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.4 Hz, 3H), 2.56 (m, 2H), 5.87 (t, J = 7.2 Hz, 1H), 7.07-7.18 (m, 4H), 7.21-7.32 (m, 2H), 7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 23.4, 116.6, 116.8, 122.8, 123.1, 123.6, 123.9, 125.9, 126.1, 128.1, 128.2, 128.6, 128.9, 151.5, 153.1; HRMS (EI) calcd for $C_{16}H_{14}O$ 222.1045, found 222.1048.

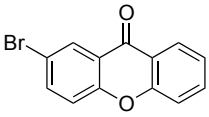


1-(2-Hydroxy-4,6-dimethoxyphenyl)butan-1-one (28). This compound was obtained as a white solid in a 49% yield: mp 69-72 ^{o}C (lit.[44] mp 70 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H), 1.69 (h, J = 7.4 Hz, 2H), 2.96 (t, J = 7.3 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 5.92 (d, J = 2.4 Hz, 1H), 6.06 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100

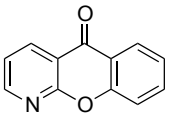
MHz, $CDCl_3$) δ 14.0, 18.1, 46.1, 55.5, 90.7, 93.6, 105.8, 162.7, 165.7, 167.6, 205.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{12}H_{17}O_4$ 225.1121, found 225.1122.



Xanthone (30). This compound was obtained as white crystals in an 80% yield: mp 176-177 ºC (lit.[45] mp 176-177 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.1, 122.0, 124.1, 126.9, 135.0, 156.3, 177.4; HRMS (EI) calcd for $C_{13}H_8O_2$ 196.0524, found 196.0527. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[45]

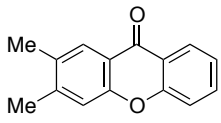


2-Bromoxanthone (32). This compound was obtained as a white solid in a 79% yield: mp 148-150 ºC (lit.[46] mp 150 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.42 (m, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.69-7.79 (m, 2H), 8.29 (dd, J = 7.9, 1.7 Hz, 1H), 8.42 (d, J = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.3, 118.3, 120.2, 121.7, 123.3, 124.5, 127.0, 129.4, 135.4, 137.9, 155.1, 156.2, 176.2; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_8BrO_2$ 274.9702, found 274.9706. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[Error! Bookmark not defined.]

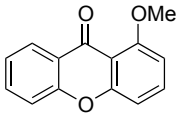


4-Azaxanthone (34). This compound was obtained as a light brown solid in a 22% yield: mp 177-181 ºC (lit.[47] mp 178-182 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.48 (m, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 8.31 (t, J = 7.9 Hz, 1H), 8.72 (t, J

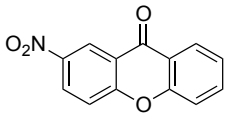
= 7.7 Hz, 1H), 8.75 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.0, 118.7, 121.3, 121.7, 124.9, 126.9, 135.9, 137.6, 154.4, 155.9, 160.5, 177.8; HRMS (EI) calcd for $C_{12}H_7NO_2$ 197.0477, found 197.0479. The ^{1}H NMR spectral data are in good agreement with the literature data.[48]



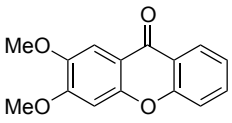
2,3-Dimethylxanthone (42). This compound was obtained as a white solid in a 47% yield: mp 156-158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.38 (s, 3H), 7.24 (s, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 8.04 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 20.8, 118.1, 118.3, 119.9, 122.1, 123.8, 126.5, 126.9, 133.3, 134.6, 145.7, 154.9, 156.3, 177.3. HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{13}O_2$ 225.0910, found 225.0911. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.**Error! Bookmark not defined.**



1-Methoxyxanthone (44). This compound was obtained as white crystals in a 71% yield: mp 128-129 ºC (lit.[49] mp 128.5 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 6.78 (d, J = 8.3 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 105.6, 110.2, 112.8, 117.5, 123.2, 124.0, 127.0, 134.4, 135.1, 155.2, 158.3, 160.9, 176.7; HRMS (APCI) calcd for $[M+H]^+$ $C_{14}H_{11}O_3$ 227.0703, found 227.0705. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[23]

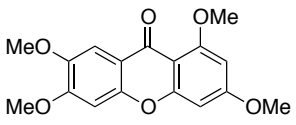


Synthesis of 2-nitroxanthone (36). *o*-(Trimethylsilyl)phenyl triflate (1.5 equiv) was added to a mixture of 2-chloro-5-nitrobenzoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 ºC for 24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL × 2) from the brine solution (40 mL), the organic fractions were combined, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **36** as a pale brown solid in an 87% yield: mp 203-205 ºC (lit. mp[50] 202-203 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.81 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 8.33 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.54 (dd, *J* = 9.2, 2.8 Hz, 1H), 9.19 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.2, 119.7, 121.3, 121.6, 123.5, 125.3, 126.9, 129.0, 135.9, 155.8, 159.1, 175.7; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_8NO_4$ 242.0448, found 242.0452. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[51]



Synthesis of 2,3-dimethoxyxanthone (38). *o*-(Trimethylsilyl)phenyl triflate (1.5 equiv) was added to a mixture of the 2-bromo-4,5-dimethoxybenzoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 ºC for 24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL × 2) from the brine solution (40 mL), the organic fractions

were combined, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the corresponding hydroxyaryl ketone. The latter was dissolved in 4 mL of MeCN and heated in the presence of K_2CO_3 (2 equiv) at 100 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **38** as a light brown solid in a 59% yield: mp 161-162 °C (lit.[52] mp 163-164 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.01 (s, 3H), 6.90 (s, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.63-7.70 (m, 2H), 8.30-8.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.3, 56.5, 99.6, 105.3, 114.9, 117.6, 121.5, 123.7, 126.5, 133.9, 146.7, 152.4, 155.4, 156.0, 176.0; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{13}O_4$ 257.0808, found 257.0809. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[Error! Bookmark not defined.]

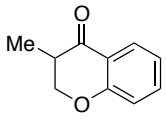


Synthesis of 1,3,6,7-tetramethoxyxanthone (40). The corresponding dimethoxyaryne precursor (1.5 equiv) was added to a mixture of 2-bromo-4,5-dimethoxybenzoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of toluene, and the reaction mixture was then stirred at 60 ºC for 24 h. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL × 2) from the brine solution (40 mL), the organic fractions were combined and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using

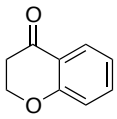
hexanes/EtOAc as the eluent to afford the corresponding hydroxyaryl ketone. The latter was dissolved in 4 mL of MeCN and heated in the presence of K_2CO_3 (2 equiv) at 100 ^oC for 24 h. After allowing the reaction mixture to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired xanthone **40** as a light brown solid in a 49%: mp 202-203 ^oC (lit.[53] mp 202 ^oC); ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.92-3.95 (m, 9H), 6.29 (d, J = 2.1 Hz, 1H), 6.40 (d, J = 2.1 Hz, 1H), 6.74 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 56.2, 56.3, 56.3, 92.5, 95.0, 98.9, 105.7, 106.9, 116.0, 146.4, 150.7, 154.3, 159.7, 161.8, 164.2, 174.6; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{17}O_6$ 317.1020, found 317.1023. The ^1H and ^{13}C NMR spectral data are in good agreement with the literature data.[54]

General procedure for the reaction of 2-alkenoic acids with arynes.

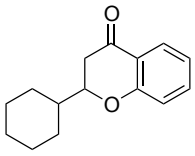
The aryne precursor (1.5 equiv) was added to a mixture of the 2-alkenoic acid (0.25 mmol) and CsF (4.0 equiv) in 15 mL of freshly distilled THF, and the reaction mixture was then stirred in a closed vial at 125 ºC for 18 h. After allowing the reaction mixture to cool, additional aryne precursor (0.5 equiv) and CsF (1.0 equiv) were quickly added and heating was continued at 125 ºC for 6 h. After the reaction mixture was allowed to cool to room temperature, it was eluted through a plug of silica gel with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired 4-chromanones.



3-Methylchroman-4-one (47). This compound was obtained as a colorless oil in an 84% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 7.0 Hz, 3H), 2.75-2.95 (m, 1H), 4.13 (t, J = 11.1 Hz, 1H), 4.48 (dd, J = 11.3, 5.0 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 41.0, 72.4, 117.9, 120.8, 121.5, 127.6, 135.9, 161.9, 195.0; HRMS (EI) calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0683. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[55]

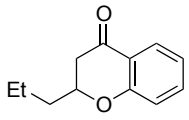


Chroman-4-one (53). This compound was obtained as a yellow oil in a 13% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (t, J = 6.4 Hz, 2H), 4.54 (t, J = 6.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.90 (d, J = 7.7 Hz, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[56]

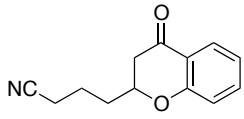


2-Cyclohexylchroman-4-one (55). This compound was obtained as a pale yellow oil in an 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06-1.34 (m, 5H), 1.64-1.85 (m, 5H), 1.98 (d, J = 12.3 Hz, 1H), 2.60-2.77 (m, 2H), 4.14-4.24 (m, 1H), 6.94-7.01 (m, 2H), 7.46 (ddd, J = 8.7, 7.2, 1.8 Hz, 1H), 7.86 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.9, 26.0, 26.3, 28.2, 28.3, 40.3, 41.8, 82.0, 117.9, 121.0, 126.9, 135.9, 161.9,

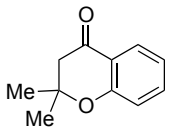
193.2; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{19}O_2$ 231.1380, found 231.1382. The ^1H and ^{13}C NMR spectral data are in good agreement with the literature data.[57]



2-Propylchroman-4-one (57). This compound was obtained as a pale yellow oil in an 82% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.42-1.73 (m, 3H), 1.78-1.96 (m, 1H), 2.66 (d, J = 8.2 Hz, 2H), 4.39-4.47 (m, 1H), 6.93-7.05 (m, 2H), 7.44 (td, J = 8.9, 1.8 Hz, 1H), 7.85 (dd, J = 7.8, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.4, 37.2, 43.2, 77.9, 118.1, 121.2, 121.3, 127.1, 136.1, 161.9, 192.9; HRMS (EI) calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0992.

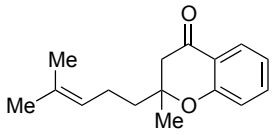


4-(4-Oxochroman-2-yl)butanenitrile (59). This compound was obtained as a pale yellow oil in a 71% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 1.82-2.08 (m, 4H), 2.48 (t, J = 6.6 Hz, 2H), 2.63-2.78 (m, 2H), 4.41-4.51 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.1, 21.3, 33.7, 42.9, 76.9, 117.9, 119.2, 120.9, 121.6, 127.1, 136.2, 161.2, 191.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_{14}NO_2$ 216.1019, found 216.1021.

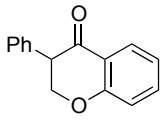


2,2-Dimethylchroman-4-one (61). This compound was obtained as white crystals in a 77% yield: mp 87-89 ºC (lit.[58] mp 86-88 ºC); ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 6H), 2.70 (s, 2H), 6.90 (d, J = 8.3 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 49.1, 79.4, 118.5, 120.4,

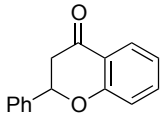
120.9, 126.7, 136.3, 160.1, 192.8; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0833. The ^1H and ^{13}C NMR spectral data are in good agreement with the literature data.[59]



2-Methyl-2-(4-methylpent-3-en-1-yl)chroman-4-one (63). This compound was obtained as a colorless oil in a 64% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.57 (s, 3H), 1.63-1.73 (m, 4H), 1.75-1.85 (m, 1H), 2.05-2.17 (m, 2H), 2.66 (d, J = 16.4 Hz, 1H), 2.79 (d, J = 16.4 Hz, 1H), 5.02-5.10 (m, 1H), 6.89-7.01 (m, 2H), 7.46 (ddd, J = 8.6, 7.2, 1.8 Hz, 1H), 7.84 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 22.5, 24.2, 25.9, 39.5, 47.7, 81.3, 118.5, 120.6, 120.8, 123.5, 126.6, 132.5, 136.3, 160.0, 192.9; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{21}O_2$ 245.1536, found 245.1541.

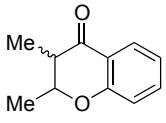


Isoflavanone (65). This compound was obtained as a yellow solid in a 56% yield: mp 67-70 ºC (lit.[60] mp 72 ºC); ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (t, J = 7.2 Hz, 1H), 4.67-4.69 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.26-7.39 (m, 5H), 7.51 (td, J = 6.8, 2.0 Hz, 1H), 7.97 (dd, J = 7.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 71.7, 118.1, 121.3, 121.8, 128.0, 128.8, 129.1, 135.2, 136.2, 161.8, 192.3; HRMS (EI) calcd for $C_{15}H_{12}O_2$ 224.0837, found 224.0844. The ^1H and ^{13}C NMR spectral data are in good agreement with the literature data.[61]

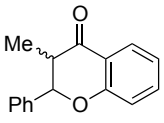


Flavanone (67). Flash chromatography on silica gel using hexanes/EtOAc as the eluent afforded the desired flavanone as a yellow solid in a 54% yield and a mixture

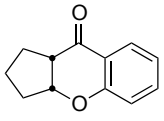
which primarily contained the uncyclized *o*-hydroxyaryl ketone. The latter was dissolved in 5 mL of THF, then 10 mL of water and 10 μL of piperidine were added, and the mixture was stirred for 2 h at 40 ºC. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL × 2), the organic fractions were combined and the solvent was evaporated under reduced pressure. Flash chromatography on silica gel using hexanes/EtOAc as the eluent afforded an additional 20% of the desired flavanone: mp 69-72 ºC (lit.[62] mp 72-73 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (dd, J = 16.9, 2.9 Hz, 1H), 3.07 (dd, J = 16.9, 13.4 Hz, 1H), 5.46 (dd, J = 13.3, 2.8 Hz, 1H), 7.00-7.08 (m, 2H), 7.35-7.54 (m, 6H), 7.93 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.9, 79.8, 118.3, 121.1, 121.8, 126.3, 127.3, 129.0, 129.1, 136.4, 138.9, 161.8, 192.1; HRMS (EI) calcd for $C_{15}H_{12}O_2$ 224.0837, found 224.0842. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[61]



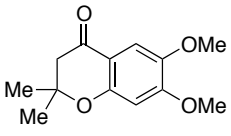
2,3-Dimethylchroman-4-one (69). This compound was obtained in a 76% yield as a mixture of isomers (*E*/*Z* = 1.8). The *E* isomer was further purified and isolated as a colorless semisolid using flash chromatography (hexanes/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.4 Hz, 3H), 1.50 (t, J = 7.4 Hz, 3H), 2.51-2.60 (m, 1H), 4.19-4.27 (m, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.44 (td, J = 7.6, 1.6 Hz, 1H), 7.85 (td, J = 7.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 20.0, 47.1, 79.4, 117.9, 120.5, 121.3, 127.4, 135.9, 161.4, 194.9; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0841.



3-Methyl-2-phenylchroman-4-one (71). This compound was obtained in a 67% yield as a mixture of isomers (*E*/*Z* = ~5.1). The *E* isomer was further purified and isolated as a pale yellow solid using flash chromatography (hexanes/EtOAc): mp 68-70 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.9 Hz, 3H), 2.99-3.08 (m, 1H), 5.06 (d, J = 12.4 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.38-7.52 (m, 6H), 7.94 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 46.6, 85.9, 115.6, 118.1, 120.6, 121.7, 127.5, 127.6, 129.0, 136.1, 138.2, 161.5, 194.6; HRMS (EI) calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0998.

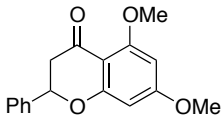


***cis*-2,3,3a,9a-Tetrahydrocyclopenta[*b*][1]benzopyran-9(1*H*)-one (73).** This compound was obtained as a pale yellow solid in a 68% yield: mp 48-49 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-2.20 (m, 6H), 2.66-2.74 (m, 1H), 4.91 (s, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 27.8, 33.2, 51.3, 83.5, 118.2, 119.3, 121.4, 127.2, 136.2, 160.8, 194.7; HRMS (EI) calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0841. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[63]



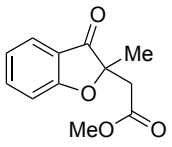
6,7-Dimethoxy-2,2-dimethylchroman-4-one (77). This compound was obtained as a pale yellow solid in a 53% yield: mp 97-100 ºC (lit.[64] mp 98-100 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 6H), 2.63 (s, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 6.37 (s, 1H), 7.23

(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 48.6, 56.4, 56.4, 79.8, 100.7, 106.5, 112.5, 144.2, 156.5, 156.5, 191.2; HRMS (EI) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1048. The ^{13}C NMR spectral data are in good agreement with the literature data.[65]



Synthesis of 5,7-dimethoxy-2-phenylchroman-4-one (79). After the reaction between cinnamic acid (**66**) and the unsymmetrical dimethoxy-substituted benzyne precursor (**27**), the uncyclized *o*-hydroxyaryl ketone **78** was isolated in a 68% yield as a yellow solid: mp 71-74 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.92 (s, 3H), 5.96 (s, 1H), 6.11 (s, 1H), 7.33-7.47 (m, 4H), 7.58-7.65 (m, 3H), 7.78 (d, J = 15.6 Hz, 1H), 7.91 (d, J = 15.6 Hz, 1H); HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{17}O_4$ 285.1121, found 285.1129. The latter was dissolved in 5 mL of THF, then 10 mL of water and 10 µL of piperidine were added, and the mixture was stirred for 2 h at 40 ºC. After allowing the reaction mixture to cool to room temperature, the mixture was extracted with EtOAc (20 mL × 2), the organic fractions were combined, and the solvent was evaporated under reduced pressure. Flash chromatography on silica gel using hexanes/EtOAc as the eluent afforded 42% of the unreacted starting material and 48% of the desired 4-chromanone **79** as a white solid: mp 144-146 °C (lit.[66] mp 145-146 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (dd, J = 16.4, 2.7 Hz, 1H), 2.97-3.07 (m, 1H), 3.82 (s, 3H), 3.90 (s, 3H), 5.41 (d, J = 14.8 Hz, 1H), 6.10 (s, 1H), 6.16 (s, 1H), 7.31-7.49 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 45.6, 55.6, 56.2, 79.3, 93.2, 93.6, 106.0, 126.1, 128.7, 128.8, 138.8, 162.3, 165.0, 166.0, 189.2; HRMS (APCI) calcd for

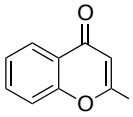
$[M+H]^+$ $C_{17}H_{17}O_4$ 285.1121, found 285.1124. The ^1H and ^3C NMR spectral data are in good agreement with the literature data.[66]



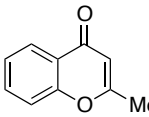
Methyl 2-(2-methyl-3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (81). This compound was obtained as a yellow solid in a 79% yield starting from the monomethyl ester of itaconic acid (**80**): mp 127-130 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 3H), 2.93 (d, *J* = 16.4 Hz, 1H), 3.02 (d, *J* = 16.4 Hz, 1H), 3.53 (s, 3H), 7.08 (t, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 41.5, 52.1, 86.5, 113.5, 120.6, 122.2, 124.8, 138.0, 169.3, 171.1, 202.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{12}H_{13}O_4$ 221.0808, found 221.0809.

Procedure for the reaction of 2-alkynoic acids with arynes.

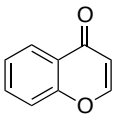
The aryne precursor (1.5 equiv) was added to a mixture of the 2-alkynoic acid (0.25 mmol) and TBAT (2.0 equiv) in 5 mL of anhydrous toluene, and the reaction mixture was then stirred in a closed vial at 60 ºC for 24 h. After the reaction mixture was allowed to cool to room temperature, the reaction mixture was then poured into brine (15 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the organic layers were combined and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired chromone derivatives.



Flavone (85). This compound was obtained as a yellow solid in a 56% yield: mp 96-97 ºC (lit.[67] mp 96-97 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.46-7.58 (m, 4H), 7.68 (t, J = 7.0 Hz, 1H), 7.87-7.94 (m, 2H), 8.22 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.8, 118.3, 124.2, 125.4, 125.9, 126.5, 129.2, 131.8, 132.0, 134.0, 156.5, 163.6, 178.6; HRMS (EI) calcd for $C_{15}H_{10}O_2$ 222.0681, found 222.0686. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[68]

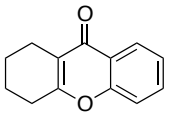


2-Methylchromone (87). This compound was obtained as a pale yellow solid in a 64% yield: mp 69-71 ºC (lit.[68] mp 69-70 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 6.14 (s, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.61 (td, J = 8.1, 1.7 Hz, 1H), 8.15 (dd, J = 7.9, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 110.7, 118.0, 123.7, 125.1, 125.8, 133.6, 156.6, 166.3, 178.4; HRMS (EI) calcd for $C_{10}H_8O_2$ 160.0524, found 160.0548. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[69]

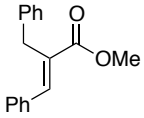


Chromone (89). This compound was obtained as a yellow semisolid in a 71% yield running the reaction in 15 mL of THF at 65 ^{o}C, instead of toluene at 60 ^{o}C. The same compound was also obtained in an 18% yield starting from 2-bromoacrylic acid (**92**) using the CsF/THF protocol at 125 ^{o}C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 6.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.85 (d, J = 6.0 Hz,

1H), 8.20 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 118.4, 125.1, 125.5, 126.0, 134.0, 155.5, 156.7, 177.8; HRMS (EI) calcd for $C_9H_6O_2$ 146.0368, found 146.0370. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[70]



3,4-Dihydro-1*H*-xanthen-9(2*H*)-one (94). This compound was obtained as a white solid in an 85% yield: 87-88 °C (lit.[71] mp 91-92 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.91 (m, 4H), 2.62 (dt, J = 35.8, 6.2 Hz, 4H), 7.29-7.39 (m, 2H), 7.59 (ddd, J = 8.6, 7.1, 1.7 Hz, 1H), 8.19 (dd, J = 8.0, 1.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0, 21.7, 21.9, 28.2, 117.6, 118.4, 123.2, 124.4, 125.7, 132.9, 155.9, 163.9, 177.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_{13}O_2$ 201.0910, found 201.0916. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[72]



Synthesis of methyl (*E*)-2-benzyl-3-phenylacrylate (96). *o*-(Trimethylsilyl)phenyl triflate (3.0 equiv) was added to a mixture of methyl methacrylate (0.25 mmol) and CsF (6.0 equiv) in 5 mL of MeCN, and the reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was then eluted through a plug of silica gel with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired diarylated product **96** as a colorless oil in an 80% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.97 (s, 2H), 7.17-7.41 (m, 10H), 7.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 52.3, 126.3, 128.1, 128.7, 128.8, 129.0, 129.4, 130.9, 135.6, 139.6, 141.2,

168.8; HRMS (EI) calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1170. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[40b]

4.7. References

(1) (a) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (b) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2009**, *12*, 168.

(2) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.

(3) Sato, Y.; Kobayashi, Y.; Sugiura, M.; Shirai, H. *J. Org. Chem.* **1978**, *43*, 199.

(4) Yoshida, H.; Honda, Y.; Shirakawa, E.; Hiyama, T. *Chem. Commun.* **2001**, 1880.

(5) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405.

(6) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049.

(7) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99.

(8) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(9) Slana, G. B. C. A.; Azevedo, M. S. de; Lopes, R. S. C.; Lopes, C. C.; Cardoso, J. N. *Beilstein J. Org. Chem.* **2006**, *2*, 1.

(10) For a related transformation, see: Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.

(11) Kotali, A.; Harris, P. A. *Org. Prep. Proc. Int.* **1994**, *26*, 159.

(12) (a) Zhang, L.; Zhang, J. Y. *J. Comb. Chem.* **2006**, *8*, 361. (b) Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* **1986**, *42*, 885.

(13) Rozenberg, V.; Danilova, T.; Sergeeva, E.; Vorontsov, E.; Starikova, Z.; Lysenko, K.; Belokon', Y. *Eur. J. Org. Chem.* **2000**, 3295.

(14) See Katritzky, A. R.; Le, Khanh, N. B.; Mohapatra, P. P. *Synthesis* **2007**, 3141 and references therein for the biological activity of *o*-hydroxyaryl ketones.

(15) (a) Merza, J.; Aumond, M.-C.; Rondeau, D.; Dumontet, V.; Ray, A.-M. Le; Séraphin, D.; Richomme, P. *Phytochemistry* **2004**, *65*, 2915. (b) Mors, W. B.; Gottlieb, O. R.; Djerassi, C. *J. Am. Chem. Soc.* **1957**, *79*, 4507. (c) Nanda, B.; Patwardhan, S. A.; Gupta, A. S. *Ind. J. Chem., Sec. B* **1983**, *22*, 185.

(16) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169.

(17) Wu, C.-P.; Schalkwyk, D. A. van; Taylor, D.; Smith, P. J.; Chibale, K. *Int. J. Antimicrob. Agents* **2005**, *26*, 170.

(18) Chibale, K.; Visser, M.; Schalkwyk, D. van; Smith, P. J.; Saravanamuthu, A.; Fairlamb, A. H. *Tetrahedron* **2003**, *59*, 2289.

(19) Burmester, J. K. US Patent WO 2006102102, **2006**.

(20) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

(21) Joshi, B. S.; Ravindranath, K. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 433.

(22) (a) Na, Y. *J. Pharm. Pharmacol.* **2009**, *61*, 707. (b) El-Seedi, H. R.; El-Ghorab, D. M. H.; El-Barbary, M. A.; Zayed, M. F.; Goeransson, U.; Larsson, S.; Verpoorte, R. *Curr. Med. Chem.* **2009**, *16*, 2581. (c) Diderot, N. T.; Silvere, N.; Etienne, T. *Adv. Phytomed.* **2006**, *2*, 273.

(23) Zhao, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.

(24) (a) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem. Asian J.* **2010**, *5*, 153. (b) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2743.

(25) Pedro, M.; Cerqueira, F.; Sousa, M. E.; Nascimento, M. S. J.; Pinto, M. *Bioorg. Med. Chem.* **2002**, *10*, 3725.

(26) See Peres, V.; Nagem, T. J.; de Oliveira, F. F. *Phytochem.* **2000**, *55*, 683 and references therein.

(27) Chen, C.-H.; Lin, J.-Y.; Lin, C.-N.; Hsu, S.-Y. *J. Nat. Prod.* **1992**, *55*, 691.

(28) Wang, J.-P.; Raung, S.-L.; Lin, C.-N.; Teng, C.-M. *Eur. J. Pharmacol.* **1994**, *251*, 35.

(29) Gnerre, C.; Thull, U.; Gaillard, P.; Carrupt, P.-A.; Testa, B.; Fernandes, E.; Silva, F.; Pinto, M.; Pinto, M. M. M.; Wolfender, J.-L.; Hostettmann, K.; Cruciani, G. *Helv. Chim. Acta* **2001**, *84*, 552.

(30) For a related reactivity of 3-methoxybenzyne, see: Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180.

(31) (a) Brahmachari, G. *Nat. Prod. Comm.* **2008**, *3*, 1337. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Birt, D. F.; Hendrich, S.; Wang, W. *Pharm. Ther.* **2001**, *90*, 157. (d) Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. *J. Pharmacol. Sci.* **2004**, *96*, 229.

(32) Running the reaction with TBAT in THF ensures the complete conversion of the acid, but also results in higher yields of undesired overarylated products (analogous to products **5** and **6**).

(33) Apparently, an excess of the benzyne intermediate is more likely to engage in the reaction with intermediate **51**, rather than with the starting less reactive carboxylic acid. Ideally, the slow addition technique could be beneficial to the yield of the reaction. However, an overheated solvent in a pressurized vial make this hypothesis difficult to test.

(34) Tanaka, K.; Sugino, T. *Green Chem.* **2001**, *3*, 133.

(35) The only detected by-product was the *O*-monoarylation product.

(36) Bowers, W.; Ohta, T.; Cleere, J.; Marsella, P. *Science* **1976**, *193*, 542.

(37) Rao, Y. K.; Fang, S.-H.; Tzeng, Y.-M. *J. Ethnopharm.* **2005**, *100*, 249.

(38) Le Bail, J.-C.; Aubourg, L.; Habrioux, G. *Cancer Lett.* **2000**, *156*, 37.

(39) Martin, R. *Org. Prep. Proced. Int.* **1992**, *24*, 369.

(40) (a) Navarre, L.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2006**, *348*, 317. (b) Kantam, M. L.; Kumar, K. B. S.; Sreedhar, B. *J. Org. Chem.* **2008**, *73*, 320.

(41) Palmieri, G.; Cimarelli, C. *Tetrahedron* **1998**, *54*, 15711.

(42) Park, J. Y.; Ullapu, P. R.; Choo, H.; Lee, J. K.; Min, S.-J.; Pae, A. N.; Kim, Y.; Baek, D.-J.; Cho, Y. S. *Eur. J. Org. Chem.* **2008**, 5461.

(43) Sandulache, A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron* **2002**, *58*, 105.

(44) Canter, F. W.; Curd, F. H.; Robertson, A. *J. Chem. Soc.* **1931**, 1245.

(45) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2008**, *73*, 7365.

(46) Dhar, S. N. *J. Chem. Soc.* **1920**, *117*, 1053.

(47) Villani, F. J.; Mann, T. A.; Wefer, E. A.; Hannon, J.; Larca, L. L.; Landon, M. J.; Spivak, W.; Vashi, D.; Tozzi, S. *J. Med. Chem.* **1975**, *18*, 1.

(48) Trécourt, F.; Marsais, F.; Güngör, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409.

(49) Charlton, J. L.; Sayeed, V. A.; Koh, K.; Lau, W. F.; Lai, H. K.; Bell, A. R. *J. Agric. Food Chem.* **1990**, *38*, 1719.

(50) Wang, Z.; Zhou, L.-J.; Wang, Y.-L.; Weng, Y.-B.; He, J.; Nie, K. *J. Chem. Res.* **2011**, *35*, 373.

(51) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

(52) Hassall, C. H.; Lewis, J. R. *J. Chem. Soc.* **1961**, 2312.

(53) Ueda, S.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 193.

(54) Hu, H.; Liao, H.; Zhang, J.; Wu, W.; Yan, J.; Yan, Y.; Zhao, Q.; Zou, Y.; Chai, X.; Yu, S.; Wu, Q. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3094.

(55) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190.

(56) He, J.; Zheng, J.; Liu, J.; She, X.; Pan, X. *Org. Lett.* **2006**, *8*, 4637.

(57) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830.

(58) Banerji, A.; Goomer, N. C. *Tetrahedron Lett.* **1979**, 3685.

(59) Deagostino, A.; Farina, V.; Prandi, C.; Zavattaro, C.; Venturello, P. *Eur. J. Org. Chem.* **2006**, 3451.

(60) Ferrinń, S. A.; Maldonado, L. A. *Synth. Commun.* **1980**, *10*, 717.

(61) Ibrahim, A. R.; Abul-Hajj, Y. J. *J. Nat. Prod.* **1990**, *53*, 644.

(62) Litkei, G. *Acta Chim. Hungarica* **1983**, *114*, 47.

(63) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1999**, *64*, 6380.

(64) Ayoub, M. T. *J. Iraqi Chem. Soc.* **1985**, *10*, 131.

(65) Brown, P. E.; Lewis, R. A.; Waring, M. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2979.

(66) Yenjai, C.; Wanich, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2821.

(67) Jin, C.; He, F.; Wu, H.; Chen, J.; Su, W. *J. Chem. Res.* **2009**, 27.

(68) Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076.

(69) (a) Shaw, A. Y.; Chang, C.-Y.; Liau, H.-H.; Lu, P.-J.; Chen, H.-L.; Yang, C.-N.; (b) Li, H.-Y. *Eur. J. Med. Chem.* **2009**, *44*, 2552.

(70) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822.

(71) Watanabe, T.; Katayama, S.; Nakashita, Y.; Yamauchi, M. *Chem. Pharm. Bull.* **1977**, *25*, 2778.

(72) Turner, P. A.; Griffin, E. M.; Whatmore, J. L.; Shipman, M. *Org. Lett.* **2011**, *13*, 1056.

CHAPTER 5

SYNTHESIS OF *o*-(DIMETHYLAMINO)ARYL KETONES, ACRIDONES, ACRIDINIUM SALTS, AND 1*H*-INDAZOLES BY THE REACTION OF HYDRAZONES AND ARYNES.[†]

Anton V. Dubrovskiy and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

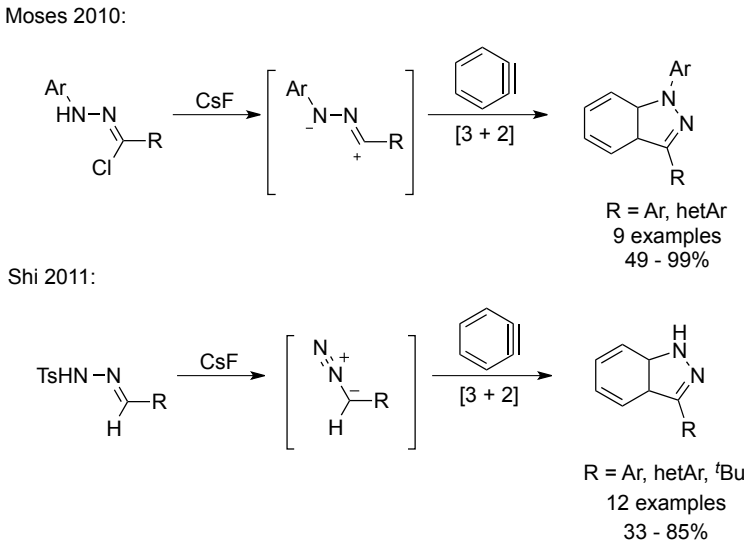
5.1. Abstract

A novel, efficient route to biologically and pharmaceutically important *o*-(dimethylamino)aryl ketones, acridones, acridinium salts, and 1*H*-indazoles has been developed starting from readily available hydrazones of aldehydes and *o*-(trimethylsilyl)aryl triflates. The reaction proceeds through arynes under mild conditions, tolerates a wide range of functional groups, and provides the final products in good to excellent yields.

5.2. Introduction

A number of nitrogen-based nucleophiles have been shown to react with arynes: aryl and alkyl amines,[1,2] enamines,[3] sulfonamides,[1] amides,[4] enamides,[5] nitrogen-containing heterocycles,[6,7] and imines.[8] Two recent approaches to 1*H*-indazoles involve a [3 + 2] cycloaddition between arynes and 1,3-dipoles generated *in situ* from *N*-tosylhydrazones[9] and hydrazonoyl chlorides.[10] (Scheme 1).

[†] Adapted from *Org. Lett.* **2011**, *13*(15), 4136, with permission from the American Chemical Society © 2011, and from *Org. Biomol. Chem.* (co-authorship with Nataliya A. Markina) **2012**, *10*(12), 2409, with permission from the Royal Society of Chemistry © 2012.



Scheme 1. Known Couplings of Hydrazone-derived Dipoles and Benzyne

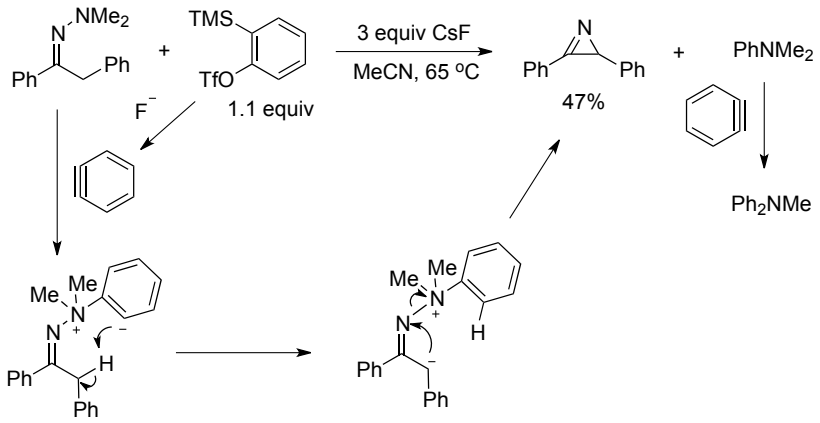
While there has been considerable recent interest in aryne-based methodologies, no reaction of arynes and readily available 1,1-dialkylhydrazones has ever been reported. We wish to report that the reaction of 1,1-dialkylhydrazones and arynes provides easy and efficient access to *o*-(dialkylamino)aryl ketimines, subsequent transformations of which can lead to various biologically and pharmaceutically important products.

5.3. Results and Discussion

5.3.1. Ketimine Generation and Subsequent Transformations

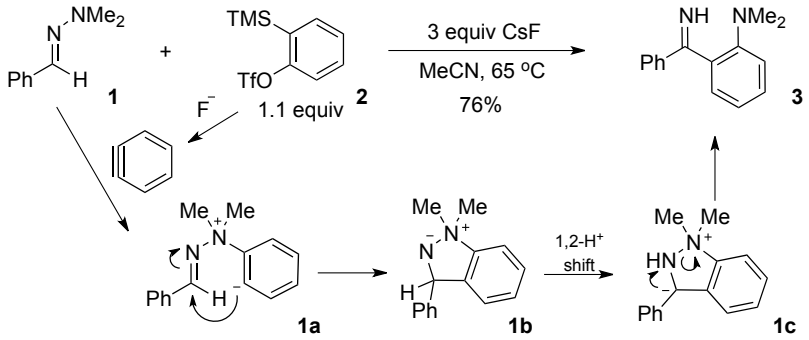
In a preliminary study, it was observed that the reaction of the *N*,*N*-dimethylhydrazone derived from benzyl phenyl ketone and *o*-(trimethylsilyl)phenyl triflate[11] plus CsF at 65 °C in MeCN yielded 2,3-diphenyl-2*H*-azirine in a 47% yield and diphenylmethylamine, along with unreacted starting material. It appears that these products are formed by initial reaction of the hydrazone nitrogen with the very electrophilic aryne to generate a highly basic aryl anion, which deprotonates one of the methylene protons next to

the hydrazone functionality (Scheme 2). An intramolecular S_N2 reaction follows, which leads to formation of the azirine and phenyldimethylamine, which is further converted into diphenylmethylamine by reaction with the benzyne. Although this route to an azirine is not described in the literature, more facile ways of synthesizing azirines have been previously reported.[12]



Scheme 2. Azirine Formation from a Ketone-derived Hydrazone.

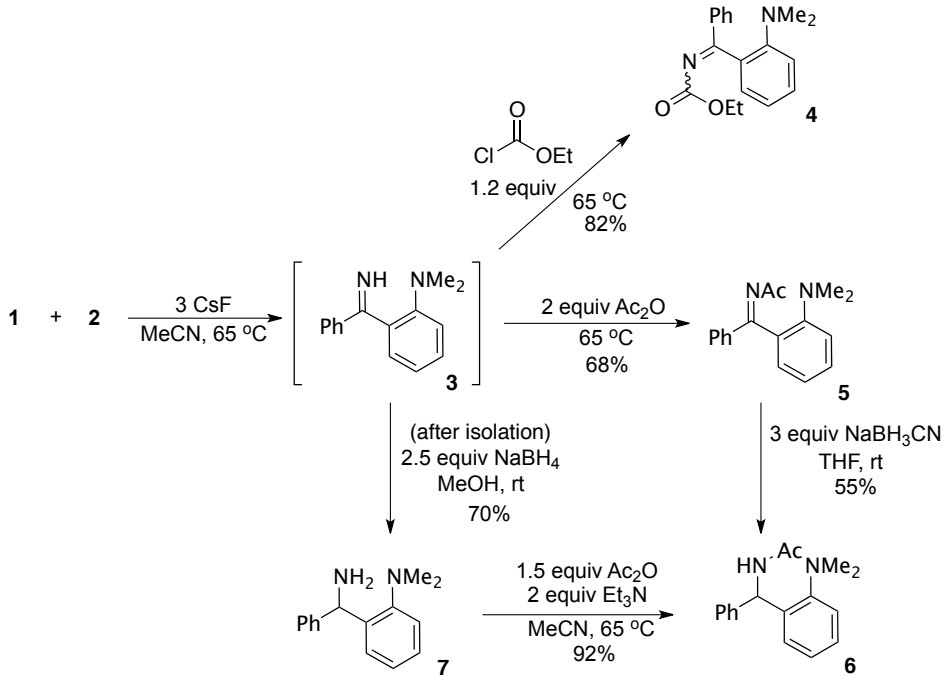
We felt that if the possibility for proton abstraction in the hydrazone substrate could be eliminated, attack of the aryl anion on the activated imine might afford a five-membered ring dinitrogen heterocycle. To our surprise, the reaction between benzaldehyde *N,N*-dimethylhydrazone (**1**) and the benzyne precursor **2** under reaction conditions identical to those used in the reaction of the ketone hydrazone did not yield the expected 1,2-dihydroindazole. Instead, the *o*-(dimethylamino)phenyl imine **3** was obtained in a 76% yield (Scheme 3).



Scheme 3. Imine Formation from an Aldehyde-derived Hydrazone.

Formation of the acyclic product **3** can be rationalized as follows (Scheme 3). After formation of the dinitrogen-containing five-membered ring heterocycle **1b**, a proton shift occurs from the benzylic position to the highly basic amide anion. The resulting dipole **1c** can undergo ring opening to afford the final product **3**. It is possible that the proton shift from **1b** to **1c** occurs without any participation of the solvent, since the reaction also proceeds in less acidic THF,[13] although the yield of the final product drops to 43%.

The imine **3** can be acetylated without isolation by adding ethyl chloroformate to the reaction to yield the corresponding ethyl carbamate **4** in an 82% yield (Scheme 4). An analogous reaction of the imine **3** with Ac_2O provides the *N*-acetylimine derivative **5** in a 68% yield. Reduction of the latter with $NaBH_3CN$ in THF leads to formation of the reduced *N*-acetylamine **6** in a 55% yield. The same compound **6** can be obtained after $NaBH_4$ reduction of the imine **3** to the amine **7** (70%), followed by acetylation of the amino group with Ac_2O (92% yield).



Scheme 4. One-pot Transformations of the Generated Imine **3**.

5.3.2. Synthesis of Aminoaryl Ketones

As expected, the imine formed can also be easily hydrolyzed to the corresponding ketone under aqueous HCl conditions. Running the aryne coupling and hydrolysis reaction in the same vessel, *o*-(dimethylamino)phenyl ketone **8** was isolated in a 93% yield (Table 1, entry 1). Running the reaction at room temperature slightly lowers its yield (from 93% to 84%). The high efficiency and mild reaction conditions for this overall transformation are of great importance, since *o*-(dimethylamino)aryl ketones are generally prepared through pathways involving harsh and not regiospecific Friedel-Crafts reaction conditions[14] or nucleophilic aromatic substitutions of *o*-fluoroaryl ketones, which are not readily available, by amino or proamino nucleophiles.[15,16]

o-(Dimethylamino)aryl ketones are quite important from a biological standpoint. Compound D-205 (**9**) has shown significant anti-inflammatory activity[14b] (Figure 1). The quinolinyl and isoquinolinyl ketones **10** and **11** have been found to be very efficient agonists of the cannabinoid CB2 receptor.[17] Some aminoaryl ketones are found in nature,[18] and some are employed as starting materials in the preparation of chiral 1,3-diamine based reagents and ligands,[15] and in recently reported ruthenium-catalyzed derivatization processes.[19]

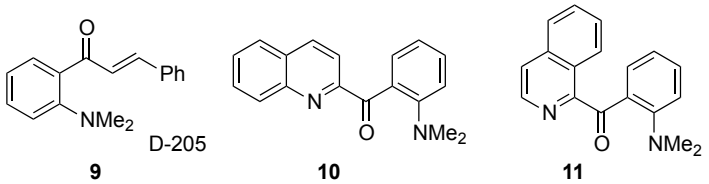
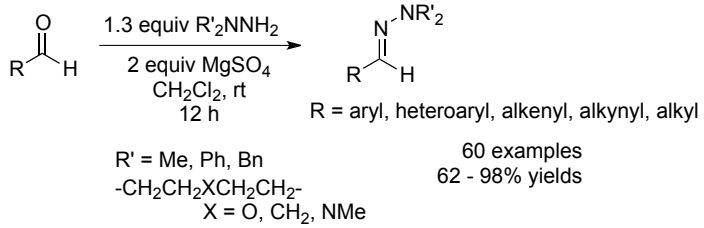


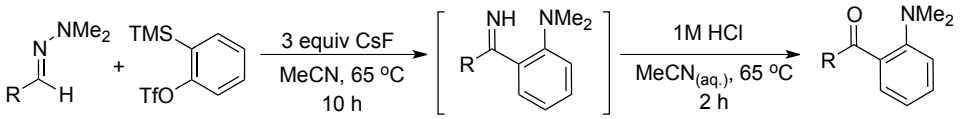
Figure 1. Pharmaceutically Important *o*-(Dimethylamino)aryl Ketones.

The importance of *o*-(dimethylamino)aryl ketones encouraged us to evaluate the scope of this novel aryne coupling reaction. Various hydrazones have been prepared by reacting the corresponding aldehydes with 1,1-disubstituted hydrazines in CH_2Cl_2 in the presence of $MgSO_4$ (Scheme 5).[20] The yields of the hydrazones have ranged from 62% to 98%.



Scheme 5. Preparation of 1,1-Disubstituted Hydrazones.

Table 1. Reaction of 1,1-Dimethylhydrazones with Arynes:[a] Substrate Scope.



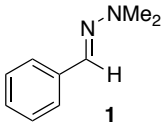
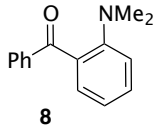
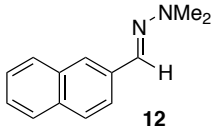
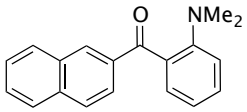
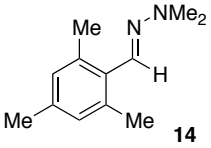
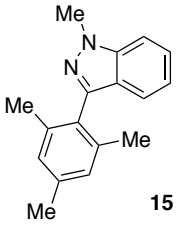
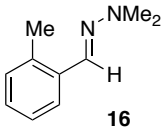
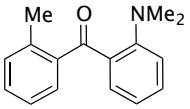
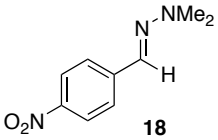
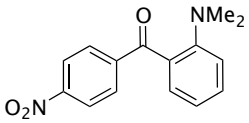
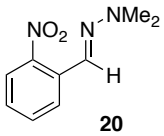
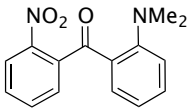
entry	starting hydrazone	product	yield[b] (%)
1	 **1**	 **8**	93
2	 **12**	 **13**	91
3	 **14**	 **15**	33
4	 **16**	 **17**	78
5	 **18**	 **19**	88
6	 **20**	 **21**	0[c]

Table 1 continued.

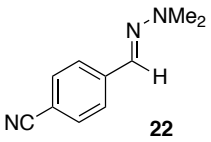
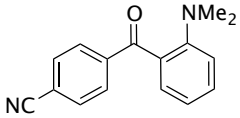
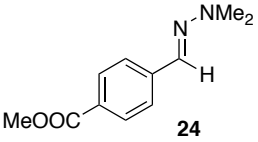
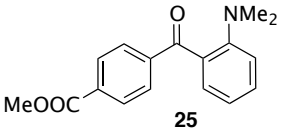
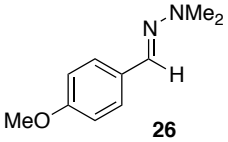
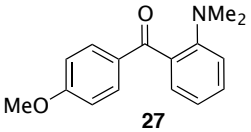
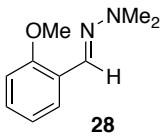
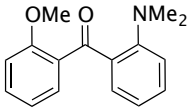
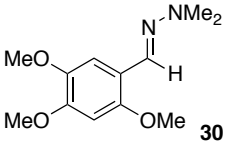
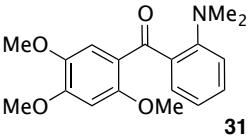
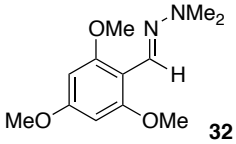
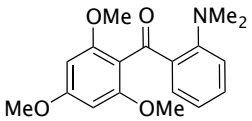
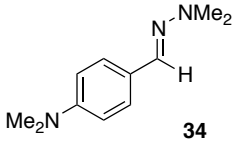
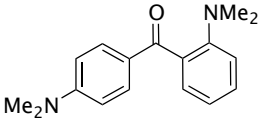
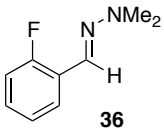
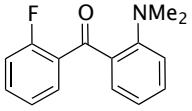
7	 **22**	 **23**	92
8	 **24**	 **25**	94
9	 **26**	 **27**	91
10	 **28**	 **29**	74
11	 **30**	 **31**	67
12	 **32**	 **33**	0^d
13	 **34**	 **35**	45
14	 **36**	 **37**	61

Table 1 continued.

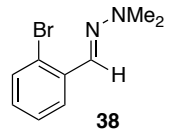
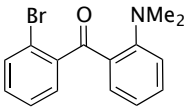
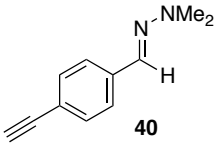
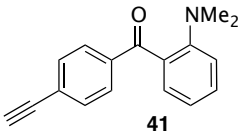
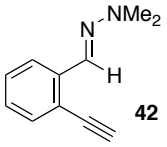
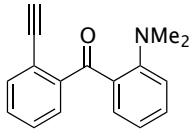
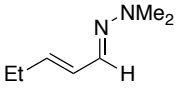
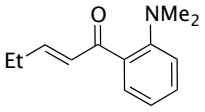
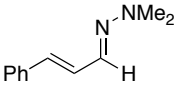
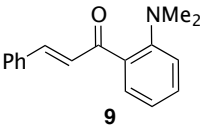
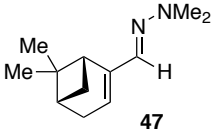
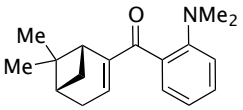
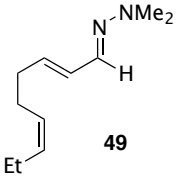
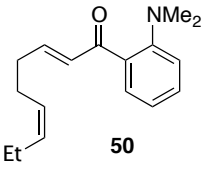
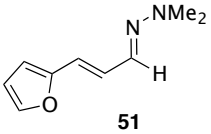
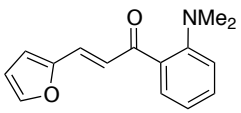
15	 **38**	 **39**	85
16	 **40**	 **41**	100
17	 **42**	 **43**	0[c]
18	 **44**	 **45**	77
19	 **46**	 **9**	91
20	 **47**	 **48**	63
21	 **49**	 **50**	82
22	 **51**	 **52**	85

Table 1 continued.

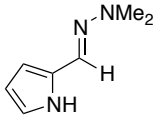
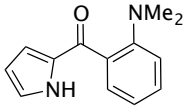
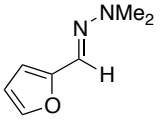
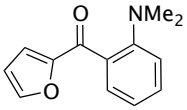
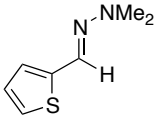
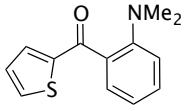
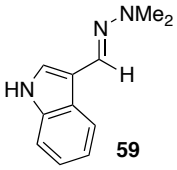
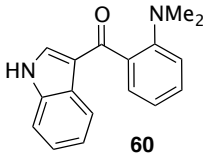
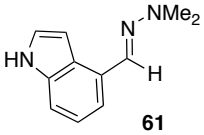
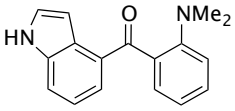
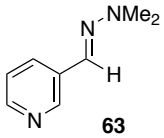
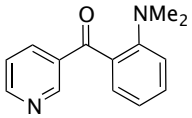
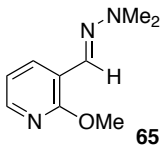
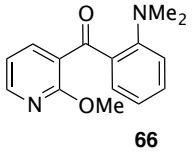
23	 **53**	 **54**	81
24	 **55**	 **56**	90
25	 **57**	 **58**	85
26	 **59**	 **60**	21
27	 **61**	 **62**	84
28	 **63**	 **64**	55
29	 **65**	 **66**	78

Table 1 continued.

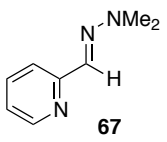
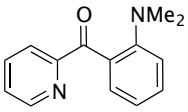
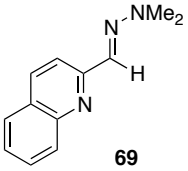
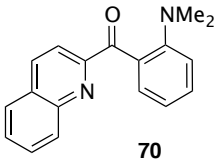
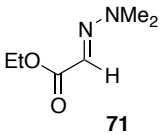
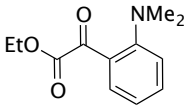
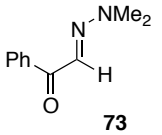
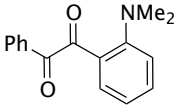
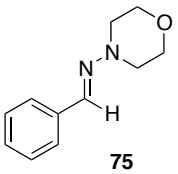
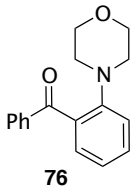
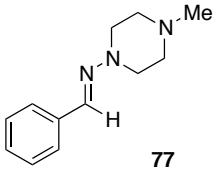
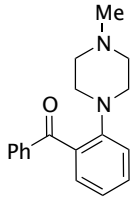
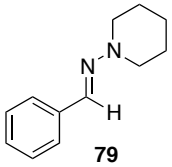
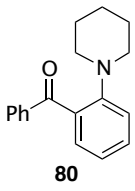
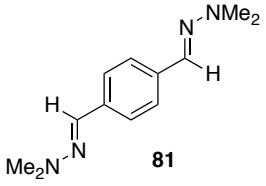
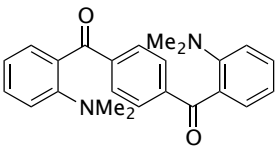
30	 **67**	 **68**	82
31	 **69**	 **70**	84
32	 **71**	 **72**	32
33	 **73**	 **74**	66
34	 **75**	 **76**	89
35	 **77**	 **78**	0[c]
36	 **79**	 **80**	85

Table 1 continued.

37	 **81**	 **82**	84[e]

[a] Reaction conditions: 0.25 mmol of substrate, 1.1 equiv of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then 3 mL of 1M HCl was added and the mixture was heated at 65 °C for 2 h. [b] Isolated yield. [c] A mixture of unidentified products was produced. [d] One of the major products was very polar, presumably a cyclic intermediate analogous to intermediate **1b**. [e] 2.2 Equiv of benzyne precursor and 5.0 equiv of CsF were used.

We first examined other 1,1-dimethylhydrazones. The 2-naphthyl-substituted substrate **12** provided the corresponding ketone **13** in a 91% yield (Table 1, entry 2). Surprisingly, the mesityl hydrazone **14** did not provide the expected product (entry 3). Presumably due to steric hindrance, the presumed cyclic intermediate did not undergo a proton shift, but retained its cyclic structure. The oxidized and demethylated product **15** has been obtained in a 33% yield. In contrast, a less hindered hydrazone **16** with only one methyl group in the position *ortho* to the reacting functionality cleanly furnished the expected aminoaryl ketone **17** in a 78% yield (entry 4). The *p*-nitrobenzaldehyde hydrazone **18** provided the corresponding ketone **19** in an 88% yield (entry 5). In a similar manner, the *p*-methoxybenzaldehyde hydrazone **26** provided the product **27** in a 91% yield (entry 9). These results suggest that there is very little electronic effect of the substituents on the efficiency of this transformation. A messy mixture was observed when the *o*-nitrobenzaldehyde substrate **20** (entry 6) was employed, presumably due to the instability

of the anticipated cyclic intermediate analogous to intermediate **1b**. Other electron-withdrawing substituents, such as cyano and ester groups, resulted in clean formation of the corresponding aminoaryl ketones **23** and **25** in 92% and 94% yields respectively (entries 7 and 8). An electron-donating methoxy group in the *ortho* position leads to aminoaryl ketone **29** in a 74% yield (entry 10, compare with the *o*-nitro substituted substrate **20**). Interestingly, the 2,4,5-trimethoxy-substituted substrate **30** provides the corresponding product **31** in a 67% yield (entry 11), while the 2,4,6-trimethoxy-substituted substrate **32** results in formation of a very polar compound, presumably analogous to intermediate **1b** (entry 12). All of our attempts to open the proposed cyclic structure or to dequaternarize the presumed ammonium fragment of the cyclic intermediate failed to provide any recognizable product. One should note a similarity between entries 3 and 12, where both starting materials have substituents at the 2 and 6 positions of the aromatic ring, which evidently causes some disruption in the corresponding rearrangement of **1b** to **1c**. The *p*-dimethylamino-substituted substrate **34** led to formation of the corresponding ketone **35** in a low 45% yield, likely due to a competing reaction of the nitrogen of the aniline moiety (entry 13). Halides in the *ortho* position of the aryl ring are well tolerated in this methodology, providing the corresponding fluoro- and bromo-containing aminoaryl ketones **37** and **39** in 61% and 85% yields respectively (entries 14 and 15). Alkynyl functionality in the *para* position of the phenyl ring afforded the corresponding product **41** in a quantitative yield (entry 16). It is noteworthy that aminoaryl ketone **41** can potentially be quite useful for further elaboration *via* Sonogashira coupling reactions.[21] In contrast, alkynyl functionality in the *ortho* position is not tolerated in this

transformation (entry 17, compare with the *o*-nitro substrate **20**), providing a mixture of mostly unidentified products.

Unfortunately, 2-alkynal hydrazones did not provide the desired aminoketones, but an inseparable mixture of mostly unidentified products.[22] However, alkenyl functionality is well tolerated in this transformation. Products **45** (entry 18) and **9** (entry 19) have been obtained in 77% and 91% yields respectively from such hydrazones. It is noteworthy that the aminoketone **9** has been previously reported to exhibit significant biological activity.[14b] The chiral (-)-myrtenal-derived hydrazone **47**, the remote alkene-containing hydrazone **49**, and the furan-containing alkenal hydrazone **51** all provided the expected aminoaryl ketones in good yields (63-85%, entries 20-22).

To our delight, despite benzyne's dienophilic nature,[23] the electron-rich pyrrole-, furan-, and thiophene-containing hydrazones have undergone the transformation with good efficiency, providing the 2-pyrrolyl (entry 23), 2-furyl (entry 24), and 2-thienyl (entry 25) ketones **54**, **56**, and **58** in 81%, 90%, and 85% yields respectively. Unfortunately, the indole-derived hydrazone **59** with the substitution at the C-3 position provided the desired aminoaryl ketone **60** in only a 21% yield (entry 26), along with a number of unidentified side products. However, the isomeric hydrazone **61** with the substitution at the C-4 position of the indole system efficiently provided the corresponding product **62** in an 84% yield (entry 27).

Despite the well-documented reactivity of pyridines with arynes,[7,24] a number of substituted pyridines provided the expected aminoaryl ketones in high yields. Thus, hydrazones derived from nicotinaldehyde (**63**), 2-methoxynicotinaldehyde (**65**), and picolinaldehyde (**67**) provided the corresponding products in 55%, 78%, and 82% yields

(entries 28-30). The high efficiency of the transformations for the pyridine-derived hydrazones suggests a significant difference in the nucleophilicities of the NMe_2 groups in the hydrazones and the nitrogen atoms in the pyridine rings towards the benzyne. The 2-quinolinyl-derived hydrazone **69** provided the expected product **70** in an 84% yield (entry 31). It is noteworthy that the aminoketone **70** has been previously reported to exhibit significant biological activity.[17]

Ester- and ketone-containing hydrazones **71** and **73** provided the corresponding aminoaryl 1,2-dicarbonyl compounds in 32% and 66% yields respectively (entries 32 and 33). Unfortunately, our attempts to cyclize the compound **72** into an isatin heterocycle were not successful.

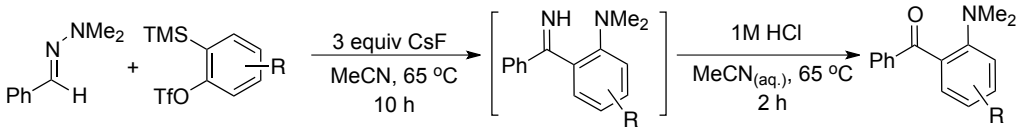
The nature of the hydrazone moiety can be modified as well. The 1-aminomorpholine-derived substrate **75** afforded the corresponding ketone **76** in an 89% yield (entry 34). The apparent high reactivity of the remote NMe unit in the piperazine-derived hydrazone **77** resulted in the formation of unidentified products with none of the expected aminoaryl ketone isolated. However, the piperidine-derived hydrazone **79** cleanly furnished the desired product **80** in an 85% yield (entry 36).

As an interesting application of our method, we were able to obtain a double aryne insertion product **82** from a substrate derived from terephthalaldehyde in an 84% yield (entry 37).

Next, we examined the reactivity of various aryne precursors toward our model substrate **1** (Table 2). The symmetrical naphthalyne precursor **83** afforded the corresponding aminoaryl ketone **84** in a 77% yield (entry 1). The electron-rich symmetrical

dimethoxybenzyne afforded the expected product in a 83% yield (entry 2), while the electron-deficient 4,5-difluorobenzyne afforded the ketone **88** in a lower 62% yield, which is the general case for this highly reactive difluorobenzyne.[25] The unsymmetrical 4-methoxy and 4-methylsilylaryl triflates provided ~1/1 mixtures of regioisomers in 81% and 85% yields respectively (entries 4 and 5). The lack of regiocontrol in these two reactions is good evidence that the transformation being studied indeed occurs *via* benzyne intermediates.

Table 2. Reaction of 1,1-Dimethylhydrazones with Arynes: Aryne Scope.[a]



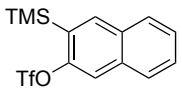
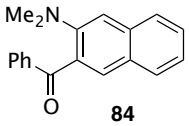
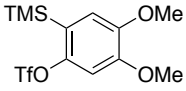
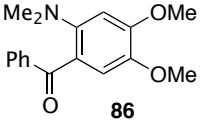
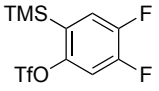
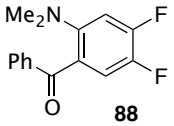
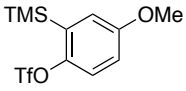
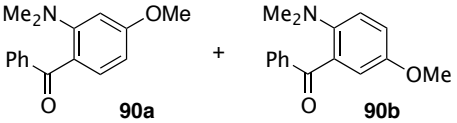
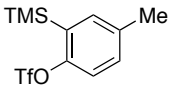
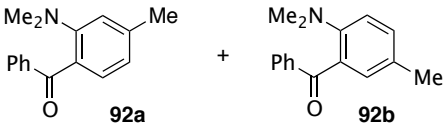
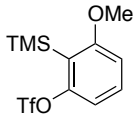
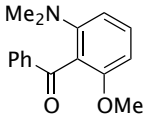
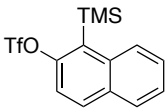
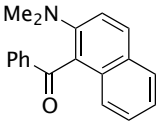
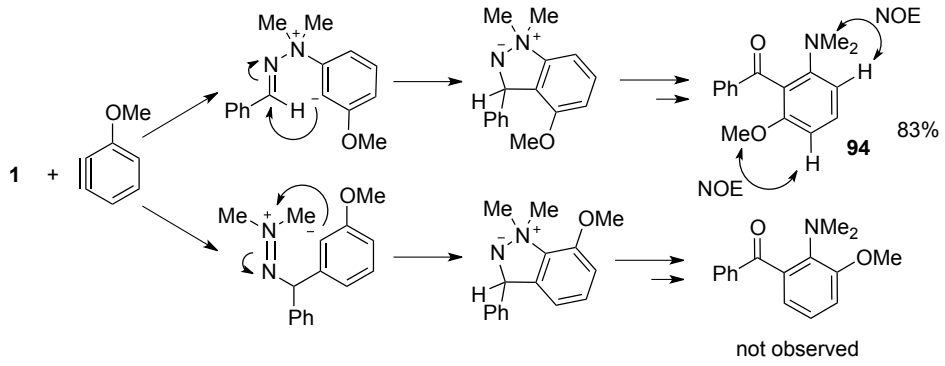
entry	aryne	product	yield[b] (%)
1	 **83**	 **84**	77
2	 **85**	 **86**	83
3	 **87**	 **88**	62
4	 **89**	 **90a** **90b**	81[c]
5	 **91**	 **92a** **92b**	85[d]

Table 2 continued.

6	 **93**	 **94**	83[e]
7	 **95**	 **96**	82[e]

[a] Reaction conditions: 0.25 mmol of benzaldehyde dimethylhydrazone, 1.1 equiv of aryne precursor and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then 3 mL of 1M HCl was added and the mixture was heated at 65 °C for 2 h. [b] Isolated yield. [c] A separable ~1/1 mixture of regioisomers was produced. [d] An inseparable ~1/1 mixture of regioisomers was produced. [e] See the experimental section for the structure determination of this product.

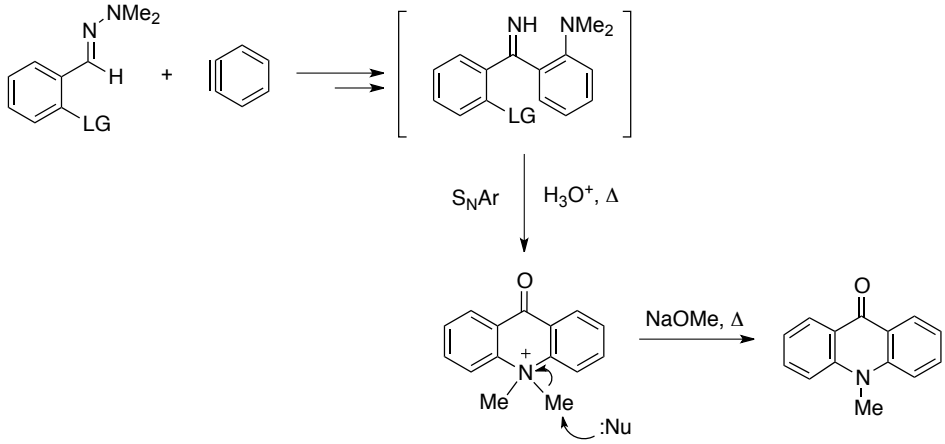
The reaction of the 1,1-dimethylhydrazone derived from benzaldehyde with the unsymmetrical aryne precursor 3-methoxy-2-(trimethylsilyl)phenyl triflate resulted in the formation of a single regioisomer **94** in an 83% yield (entry 6). The regiochemistry of the product affirms that it is the NMe_2 group that initially attacks the benzyne, not the nucleophilic carbon through the substrate's alternative resonance structure as is the case with enamines[3] (Scheme 6).[26] Similar regiocontrol is observed with the unsymmetrical naphthalyne precursor **95**. A single regioisomer **96**, resulting from attack of the dimethylamino group of the hydrazone at the more electrophilic C-2 position of the naphthalyne,[27] was produced in an 82% yield (entry 7).



Scheme 6. Reaction with an Unsymmetrical 3-Methoxyaryne.

5.3.3. Synthesis of *N*-Methylacridones

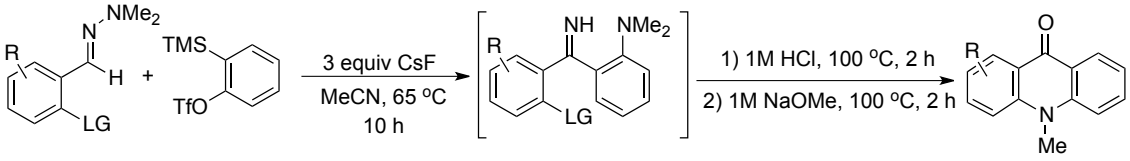
We envisioned that the NMe_2 group of the aminoketones generated by our process could further undergo an intramolecular S_NAr reaction if there were a favorably positioned leaving group *ortho* to the ketone. This would lead to the formation of a cationic *N*,*N*-dimethylacridone, which should undergo *in situ* demethylation to the more stable *N*-methylacridone in the presence of the nucleophilic fluoride media or the addition of a base, such as NaOMe (Scheme 7).[28] The latter is a prominent naturally-occurring scaffold[29] with many of its members exhibiting a wide range of biological activity, including antitumor,[30] antimalarial,[31] and antiplasmodial[32] activities.



Scheme 7. Plausible Pathway of the Formation of *N*-Methylacridones.

To our delight, a closer examination of the reaction of the *o*-bromobenzaldehyde hydrazone (Table 1, entry 15) indicated that along with the 85% yield of the aminoketone **39**, *N*-methylacridone was generated in a 7% yield. Upon heating the *o*-aminoketone **39** in MeCN at 100 °C, the ketone quantitatively cyclized to the desired acridone. After optimizing the reaction conditions, we found that *N*-methylacridone (**97**) could be obtained in one-pot in a 95% yield (Table 3, entry 1) by reacting the *o*-bromobenzaldehyde hydrazone **38** with the benzyne precursor **2** in the presence of CsF and subsequently hydrolyzing the imine and at the same time inducing the cyclization in the presence of aqueous HCl at 100 °C. Further addition of a solution of NaOMe and heating the mixture at 100 °C presumably assists in dequaternarizing the initially formed *N*,*N*-dimethylacridone.

Table 3. Synthesis of *N*-Methylacridones[a]



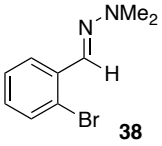
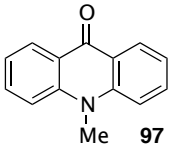
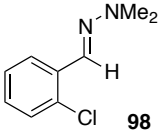
entry	starting hydrazone	product	yield[b] (%)
1	 **38**	 **97**	95
2	 **98**	**97**	91

Table 3 continued.

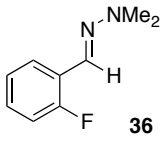
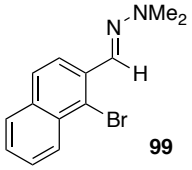
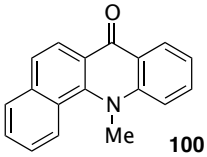
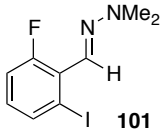
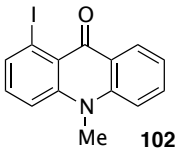
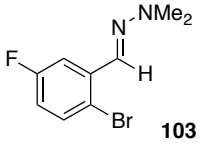
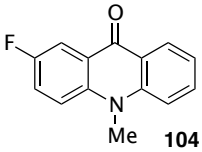
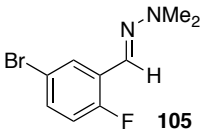
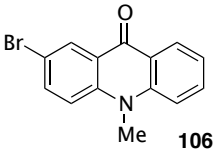
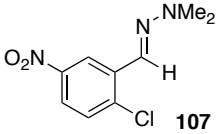
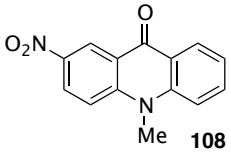
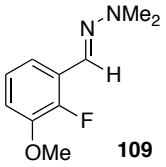
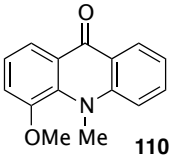
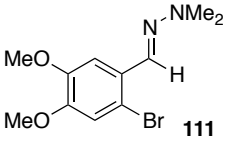
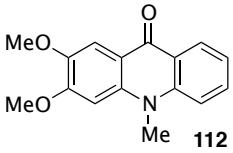
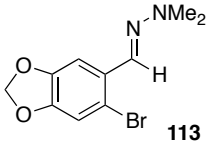
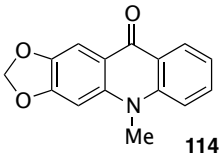
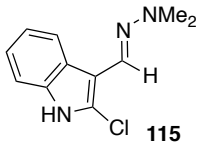
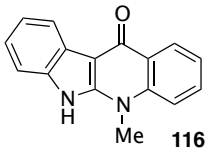
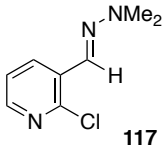
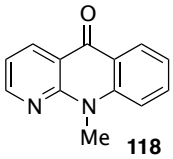
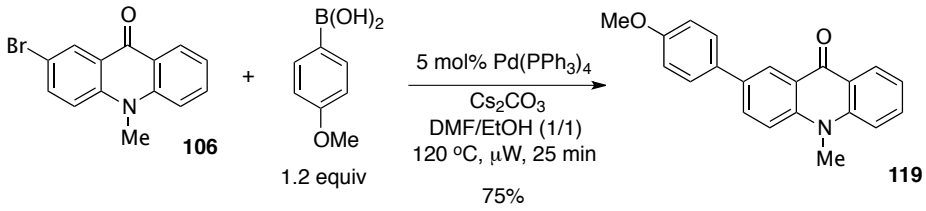
3	 **36**	**97**	94
4	 **99**	 **100**	45
5	 **101**	 **102**	0
6	 **103**	 **104**	84
7	 **105**	 **106**	79
8	 **107**	 **108**	59
9	 **109**	 **110**	87
10	 **111**	 **112**	77
11	 **113**	 **114**	38

Table 3 continued.

12	 **115**	 **116**	0
13	 **117**	 **118**	48

[a] Reaction conditions: 0.25 mmol of substrate, 1.1 equiv of benzyne precursor and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then 3 mL of 1 M HCl was added and the mixture was heated at 100 °C for 2 h. Then 5 mL of 1 M NaOMe was added and the mixture was heated at 100 °C for 2 h. [b] Isolated yield.

Excellent yields (91% and 94%) have also been observed using the corresponding *o*-chloro- and *o*-fluorobenzaldehyde hydrazones **98** (entry 2) and **36** (entry 3). The 1-bromo-2-naphthaldehyde-derived hydrazone provided the polycyclic acridone **100** in a 45% yield (entry 4). Unfortunately, the reaction of 2-fluoro-6-iodobenzaldehyde dimethylhydrazone with benzyne resulted in the formation of a mixture of unidentified products, likely due to a competitive S_NAr reaction with the iodo- and fluoro-substituents (entry 5). The dihalogenated substrates **103** and **105** provided the corresponding acridones **104** and **106** in 84% and 79% yields respectively (entries 6 and 7). It is noteworthy that the presence of the halide moiety at the C-2 position of the acridone **106** generated allows further elaboration of this heterocyclic structure by various, well known Pd-catalyzed processes. As a representative example of such methodologies, we have successfully obtained the Suzuki-Miyaura coupling product **119** in a 75% yield (Scheme 8).[33]



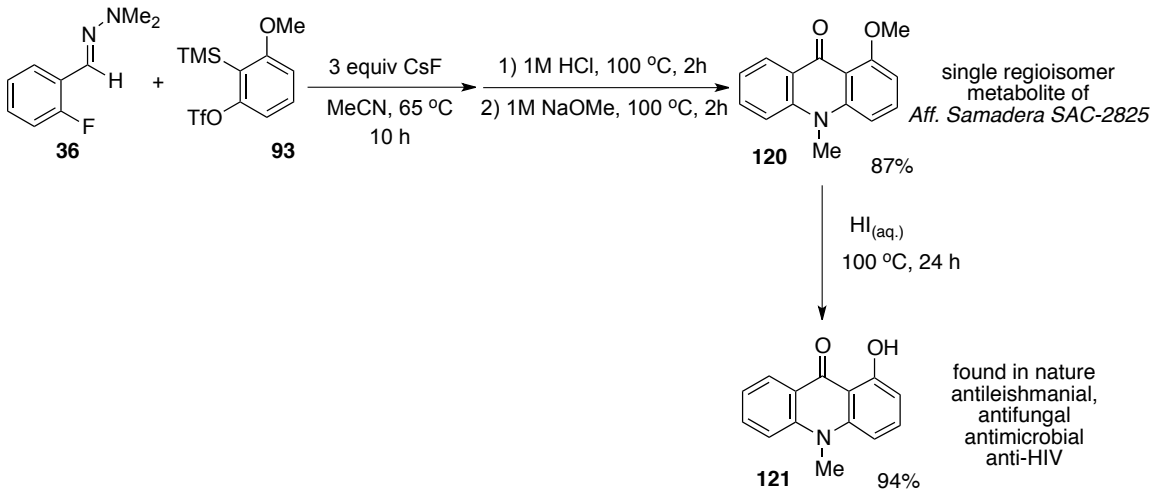
Scheme 8. Suzuki-Miyaura Coupling from an Acridone.

The nitro-substituted acridone **108** was obtained using our aryne methodology, but the limited solubility of the product produced only a modest 59% yield of this acridone (entry 8). The mono- and dimethoxy-substituted *o*-halobenzaldehyde hydrazones **109** and **111** successfully provided the corresponding *N*-methylacridones in 87% and 77% yields respectively (entries 9 and 10). Despite similarities between the oxygenated substrates **111** and **113**, the final S_NAr step in the latter case was rather sluggish and the desired product **114** was obtained in only a 38% yield (entry 11).

Unfortunately, applying our methodology to an indole system was not successful; none of the desired product was formed under our optimized conditions when hydrazone **115** was employed (entry 12). However, the pyridine-derived hydrazone **117** led to formation of the desired aza-acridone derivative **118** in a 48% yield (entry 13). The latter compound is a type of benzonaphthyridinone, some of which have shown antimicrobial,[34] trypanocidal,[35] and anticancer[36] activities. They have also been shown to reverse the multidrug resistance of tumor cells.[37]

A number of naturally-occurring acridones have been synthesized utilizing our methodology. The use of the unsymmetrical 3-methoxy-2-(trimethylsilyl)phenyl triflate **93** in the above transformation resulted in the formation of a single regioisomer **120** in an 87%

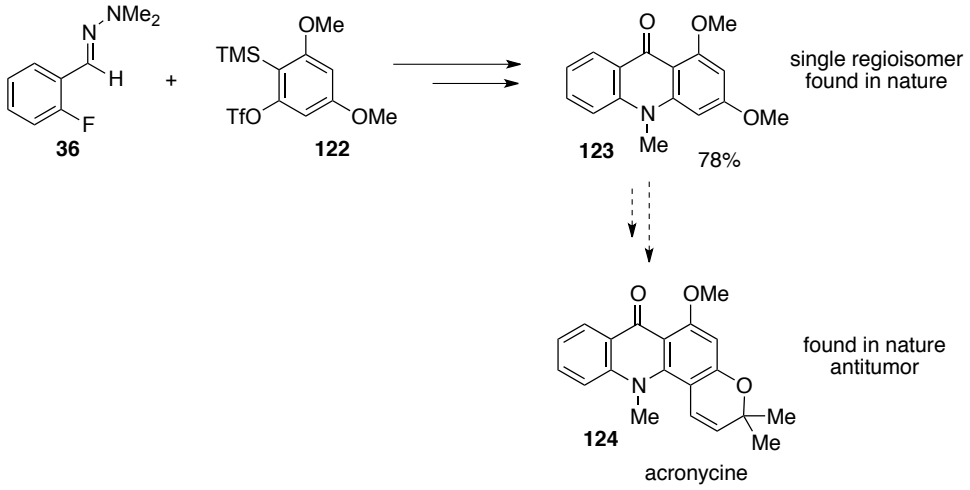
yield with regioselectivity analogous to that described above (Table 2, entry 6). It is noteworthy that compound **120** is a naturally-occurring acridone[38] and its demethylated derivative **121** has been shown to exhibit anti-HIV activity.[39] We obtained the latter pharmaceutically important product in a 94% yield after HI-induced demethylation of the acridone **120** (*i.e.* in a 75% overall yield *via* 3 steps starting from *o*-fluorobenzaldehyde) (Scheme 9).



Scheme 9. Synthesis of a Naturally-occurring Acridone.

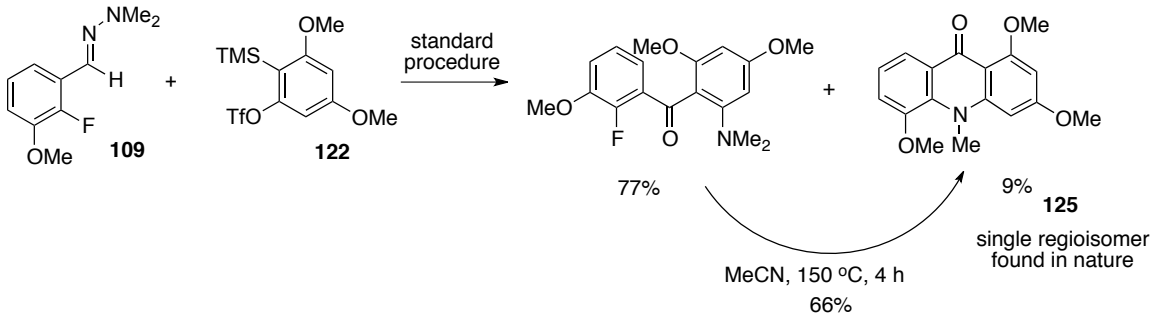
The use of the unsymmetrical 3,5-dimethoxy-2-(trimethylsilyl)phenyl triflate **122**[40] in a reaction with *o*-fluorobenzaldehyde dimethylhydrazone resulted in the formation of compound **123** in a 78% yield as a single regioisomer (Scheme 10). Compound **123** is found in nature,[41] as well as its 1-demethylated[42] and 1,3-bisdemethylated[43] derivatives. The latter has also been shown to have significant antipsoriatic activity[44] and has been previously made from compound **123** using an HBr-mediated ether cleavage.[45] It is also noteworthy that the

compound **123** has been previously used as a precursor to acronycine (**124**),[46] an alkaloid long known for its antitumor properties.[47]



Scheme 10. Synthesis of a Naturally-occurring Acridone.

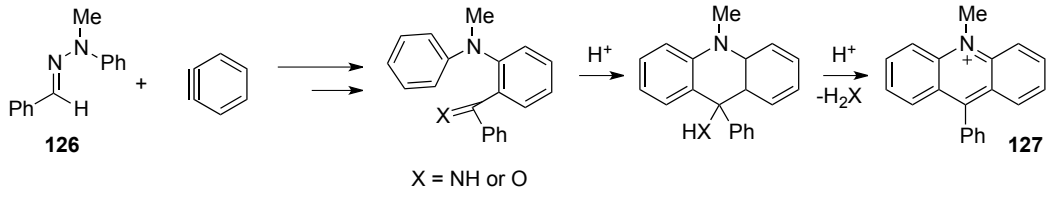
The analogous reaction of the unsymmetrical 3,5-dimethoxy-2-(trimethylsilyl)phenyl triflate with the methoxy-analog of **36** resulted in the formation of acridone **125** after additional exposure of the unreacted, uncyclized aminoaryl ketone to elevated temperatures, because of incomplete cyclization under our standard S_NAr reaction conditions. The acridone **125** was isolated in a combined 60% yield as a single isomer. The compound **125** is found in nature.[48] Synthesis of its 1,3,6-trisdemethylated derivative by HBr-mediated demethylation is described in the literature.[49] The latter is an immediate precursor to the natural product acrimarine-G.[49,50]



Scheme 11. Synthesis of a Naturally-occurring Acridone.

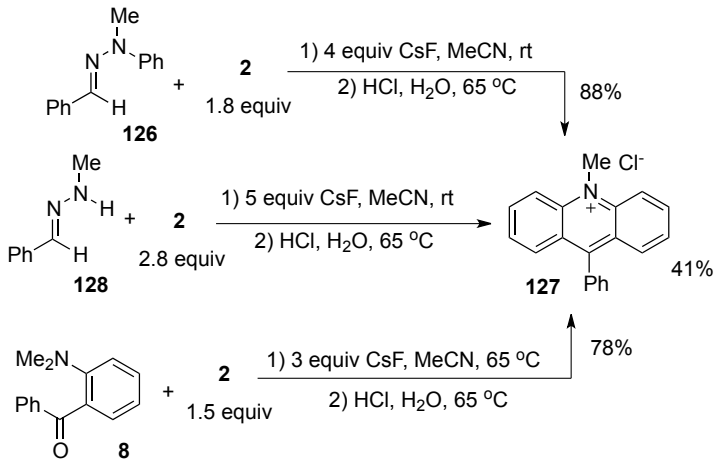
5.3.4. Synthesis of Acridinium Salts

To further extend the scope of our methodology, we reacted the *N*-methyl-*N*-phenyl hydrazone of benzaldehyde (**126**) with benzyne under our optimized reactions conditions for the synthesis of aminoaryl ketones (Scheme 12). To our surprise, instead of the expected ketone, a very polar compound **127** was obtained with its spectrum identical to that reported in the literature.[51] The formation of the *N*-methylacridinium salt **127** can be rationalized in the following way (Scheme 12). After ketimine formation, the acid added to the reaction mixture apparently catalyzes an intramolecular Friedel-Crafts reaction of the imine (or of the previously hydrolyzed ketone) with the neighboring phenyl group leading to the formation of a 6-membered ring heterocycle.[52] Subsequent deamination (or dehydration) of the intermediate leads to formation of the acridinium salt **127**.



Scheme 12. Plausible Pathway for Acridinium Salt Formation.

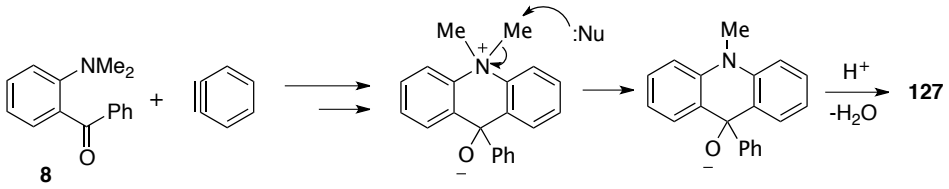
A related finding has been recently reported by Greaney's group, where the cyclization of a secondary amine derivative with simultaneous dehydration leads to formation of an acridine.[4] It has been found that reacting the hydrazone with 1.8 equiv of the aryne precursor in the presence of 4 equiv of CsF in acetonitrile at room temperature affords, after HCl-catalyzed cyclization and aromatization, the desired product **127** in an 88% yield (Scheme 13).



Scheme 13. Various Routes to Acridinium Salt Formation.

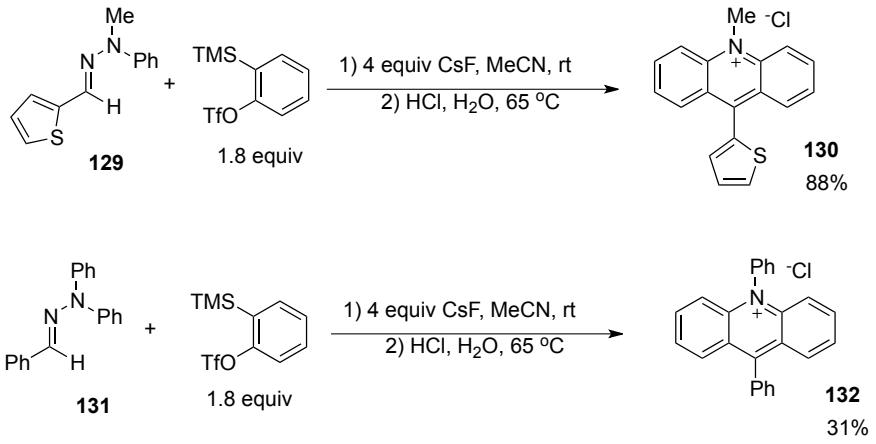
The same product **127** can be formed in a 41% yield starting from the *N*-methyl hydrazone **128**. Presumably, the first equivalent of benzyne arylates the hydrazone nitrogen, [53] essentially forming the starting substrate for the subsequent benzyne insertion/Friedel-Crafts cyclization/aromatization sequence. Also, it has been found that the reaction of dimethylaminoaryl ketone **8** (obtained from benzaldehyde dimethylhydrazone and benzyne as reported in Table 1, entry 1) with benzyne leads to formation of the same acridinium salt **127**. This result can be rationalized in the following way (Scheme 14). After nucleophilic attack of the dimethylamino group onto the benzyne, the expected annulation

reaction occurs,[54] and dequaternarization of the diaryldimethylammonium fragment follows (presumably assisted by the fluoride). Following the addition of hydrochloric acid to the reaction mixture, loss of the hydroxyl group (as water) from the molecule results in formation of the stable aromatic acridinium salt **127**, which was formed in a 78% yield using this approach.



Scheme 14. Plausible Pathway for Acridinium Salt Formation.

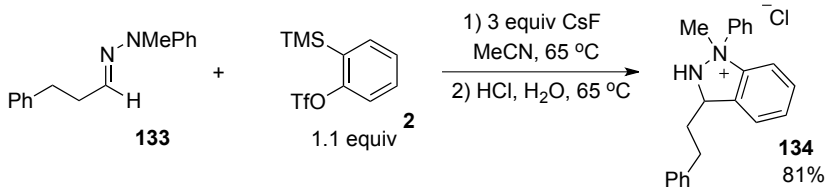
Acridinium salts are an intriguing class of compounds used for DNA intercalation studies[51] and as NAD^+ analogues.[55] Recently, their analogues, quinolinium salts, have been shown to be effective photocatalysts for the direct oxygenation of benzene to phenol.[56] Our methodology provides a convenient approach to the synthesis of derivatized acridinium salts. Using the 2-thienaldehyde-derived substrate **129** in place of the model hydrazone **126** in our chemistry afforded the thiophene-containing acridinium chloride **130** in an 88% yield (Scheme 15). The *N*,*N*-diphenylhydrazone **131** afforded the *N*-phenyl acridinium salt **132** in a 31% yield. The lower yield is presumably due to difficulties in removing the phenyl group during the dequaternization step.



Scheme 15. Synthesis of Substituted Acridinium Salts.

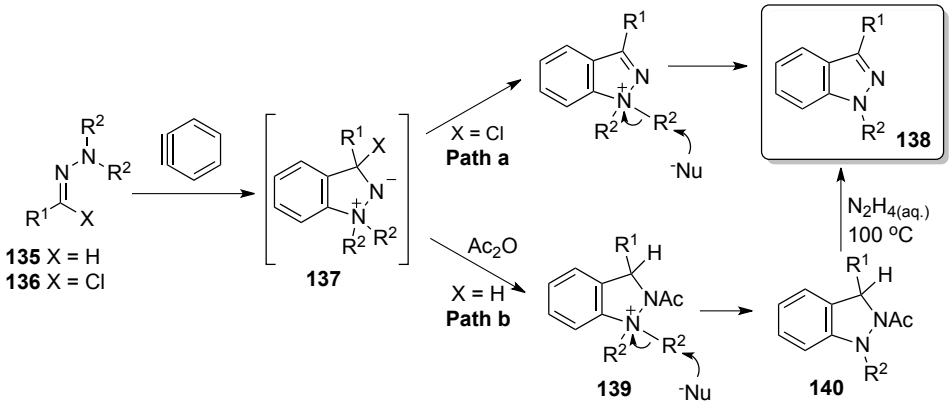
5.3.5. Synthesis of 1*H*-Indazoles from Hydrazones

During our study of the scope of the reaction of hydrazones and arynes, we discovered that hydrazones possessing a hydrogen atom at the α-position of the hydrazone functionality, when reacted with an aryne under our standard reaction conditions, formed highly polar products related to intermediate **1b**. For example, reaction of the dihydrocinnamaldehyde dimethylhydrazone **133** with benzyne resulted in formation of the corresponding cyclic product **134** in an 81% yield (Scheme 16).[57] You will also recall that we earlier found that a mesityl-substituted hydrazone afforded the indazole **15**, albeit in only a 33% yield (Table 1, entry 3).



Scheme 16. Reaction of Hydrazones Derived from Aliphatic Aldehydes.

In order to improve the scope and efficiency of this process, we envisioned that one can retain the cyclic nature of the intermediate **137** in two complementary ways (Scheme 17), namely by having either a nearby leaving group (path a) or by trapping the amide **137** with a trapping agent (path b). In the latter case, further deprotection of the *N*-acetyl group and subsequent aromatization should lead to the formation of 1*H*-indazoles **138**.



Scheme 17. Two Complementary Pathways Leading to an Indazole Structure.

1*H*-Indazoles constitute an important class of heterocyclic compounds that exhibit a wide range of biological and pharmaceutical activities,[58] including anti-inflammatory,[59] antitumor, [60] and anti-HIV [61] activity among others. Selected examples of 1-alkyl-1*H*-indazoles with notable pharmacological activities include granisetron, a serotonin 5-HT3 receptor antagonist, used to treat nausea and vomiting after chemotherapy;[62] lonidamine, used for the treatment of brain tumors;[63] and CL-958, an antitumor agent, which is currently in clinical evaluation (Figure 2).[64]

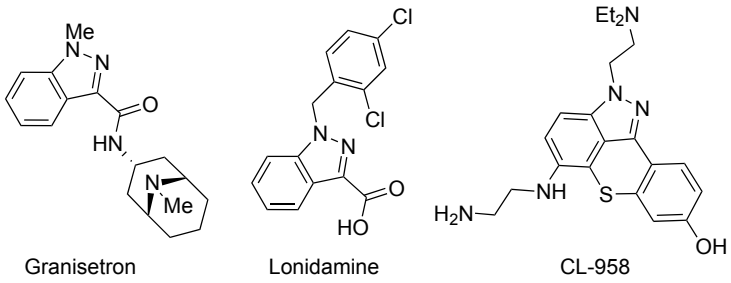


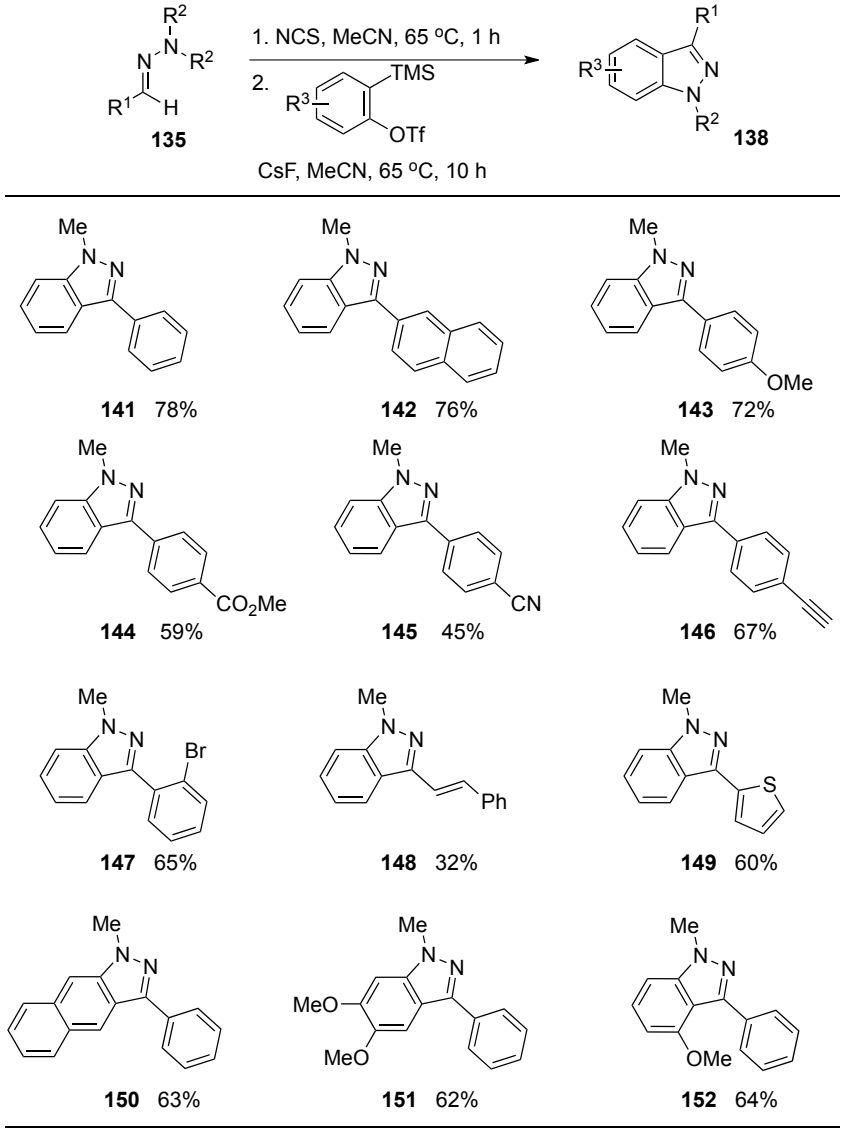
Figure 2. Biologically Active 1-Alkyl-1*H*-indazoles.

Various methods for the synthesis of the 1*H*-indazole core have been developed.[65] However, most of them employ harsh reaction conditions, which have limited their scope and applicability. Recently, several methodologies have been reported that involve aryne intermediates in [3 + 2] cycloaddition reactions with diazo compounds,[66] *N*-tosyl-hydrazones,[9,67] and *in situ* generated nitrile imines.[10] 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.

The NCS-mediated synthesis of 1*H*-indazoles (Scheme 17, path a) has been developed by Nataliya A. Markina. She found that the reaction of *N,N*-dimethylhydrazone chloride **136** (R^1 = Ph, R^2 = Me) with benzyne proceeds smoothly to afford the indazole **138** in an 81% yield. However, it proved difficult to purify and isolate the labile starting materials **136**. The possibility of a one-pot procedure was investigated wherein the chlorine-containing hydrazones are not isolated, but generated *in situ* from 1,1-dialkylhydrazones **135** and NCS and further reacted with the *o*-(trimethylsilyl)phenyl triflate **2** in the presence of a fluoride source.[68]

To our delight, the desired indazole **138** (R^1 = Ph, R^2 = Me) was obtained in a 78% yield (Scheme 18). The optimal reaction conditions were found to be 1.1 equiv of NCS per 1 equiv of the hydrazone **135**, and a slight excess of the substrate **136** (1.2 equiv) per 1 equiv of the aryne precursor. Both steps in this process conveniently proceed in acetonitrile at 65 °C.

With the optimal conditions in hand, we next examined the scope and limitations of this method (Scheme 18). A range of hydrazones was studied first. Aryl, alkenyl and heteroaryl-containing hydrazones afforded the corresponding indazoles **141-149** in 32-78% yields. Electron-poor aryl hydrazones afforded the corresponding indazoles **144** and **145** 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 **150** and **151** in good 63% and 62% yields respectively. The unsymmetrical 3-methoxybenzyne precursor provided exclusively the 4-OMe regioisomer **152** in a 64% yield. The structure of the product **152** is consistent with the proposed mechanism (Scheme 2, path a).[26]

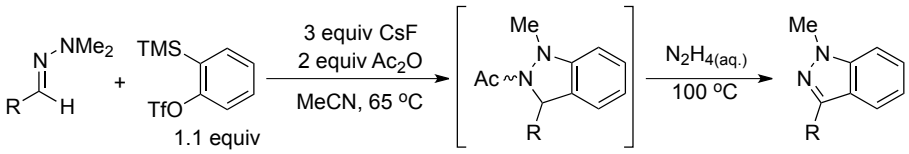


Scheme 18. Synthesis of 1*H*-Indazoles by the Chlorination Route.

In order to overcome some limitations of the methodology using NCS, we have studied the reaction between hydrazone **135** (R^1 = Ph, R^2 = Me) and the benzyne precursor **2** in the presence of acetic anhydride (Scheme 17, path b). We were pleased to observe formation of the corresponding trapped product **140** (R^1 = Ph, R^2 = Me) in an 83% yield, which could also be subsequently deacetylated and aromatized *in situ* to produce the indazole

141 (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 **140** (Table 4, entry 1). The scope of this process is summarized in Table 4.

Table 4. Synthesis of 1*H*-Indazoles: Scope of the Reaction.



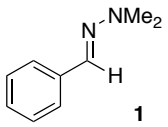
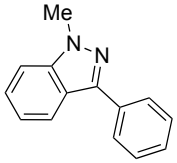
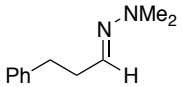
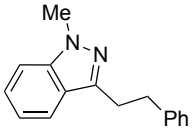
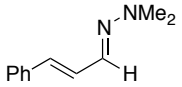
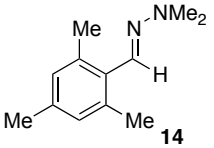
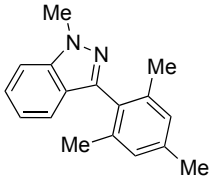
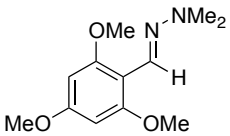
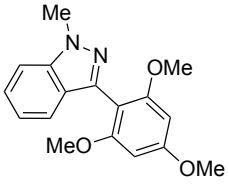
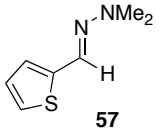
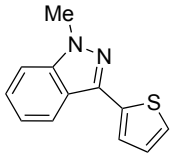
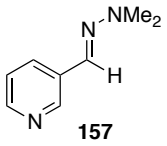
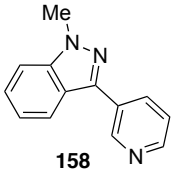
entry	starting material	product	yield[b] (%)
1	 **1**	 **141**	83
2	 **153**	 **154**	80
3	 **46**	**154**	41
4	 **14**	 **15**	91
5	 **155**	 **156**	76

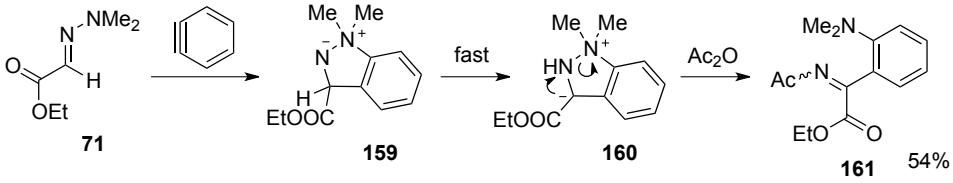
Table 4 continued.

6	 **57**	 **149**	39 (56)[c]
7	 **157**	 **158**	29

[a] Reaction conditions: 0.25 mmol of dimethylhydrazone, 1.1 equiv of aryne precursor, 2.0 equiv of Ac_2O and 3.0 equiv of CsF in 5 mL of MeCN were heated in a closed vial at 65 °C for 10 h. Then the solvent was evaporated, 3 mL of $N_2H_4 \cdot H_2O$ (85% solution, w/w) was added and the mixture was heated at 100 °C for an additional 10 h. [b] Isolated yield. [c] Using the Boc_2O/HCl procedure (see the experimental section for details).

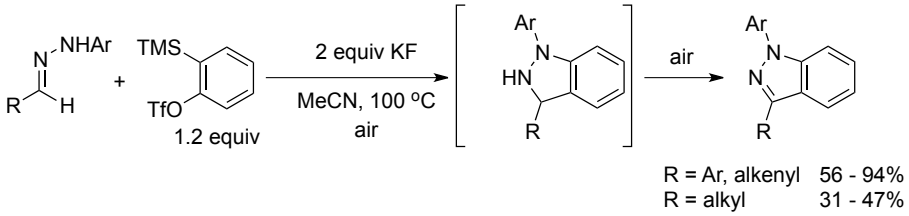
Gratifyingly, a variety of substituents in the R^1 position of the hydrazone are well tolerated. For example, the 3-alkylindazole **154** is obtained in an 80% yield (entry 2), whereas the corresponding reaction under NCS conditions completely failed. Unexpectantly, the alkenyl-containing substrate **46** provided the reduced alkyl indazole **154** in a 41% yield, which can be rationalized by the presence of the strong reducing media (N_2H_4) during the final deprotection step of the sequence (entry 3). The electron-rich hydrazones, that failed to react efficiently under the NCS-mediated protocol, have afforded the corresponding indazoles **15** and **156** in excellent yields (91% and 76% respectively), despite their steric encumbrance (entries 4 and 5). On the other hand, electron-deficient hydrazones, such as 2-thiophenyl and 3-pyridyl hydrazones, provided the corresponding products **149** and **158** in only 39% and 29% yields respectively (entries 5 and 6). In the case of an even stronger

electron-withdrawing CO_2Et group, *N*-acyl imine **161** was isolated in a 54% yield, instead of the desired indazole (Scheme 19). This result can be rationalized by considering the proposed intermediate **159**, in which the acidic C-3 hydrogen can be easily transferred to the negatively charged nitrogen atom. Subsequent ring-opening results in formation of the acyclic product **161**.



Scheme 19. Reaction with an Ester-containing Hydrazone.

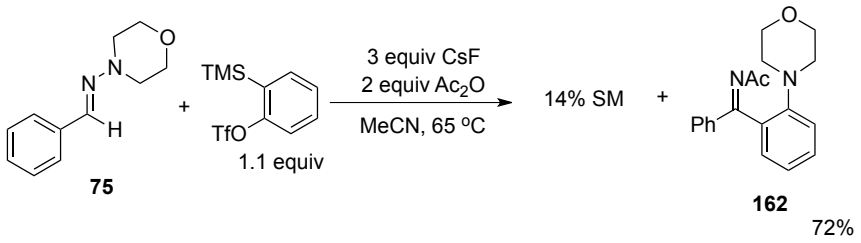
N-Methyl-*N*-phenyl hydrazone **126** resulted in the formation of the expected *N*-phenyl indazole, albeit in only a low 30-40% yield.[69] Fortunately, it has been recently reported by Shi[70] that *N*-aryl hydrazones of aromatic and alkenyl aldehydes (hydrazones of alkyl aldehydes react less efficiently) react with benzyne with the formation of *N*-aryl indazoles in 56-94% yields, following an annulation/dehydration sequence (Scheme 20).



Scheme 20. Alternative Reported Route to 1-Arylindazoles.

The morpoline-derived hydrazone **75**, when subjected to our indazole reaction conditions, retained its morpholine ring, suggesting that the proton-transfer leading to the aminoaryl ketimine product (that gets acetylated eventually to form the final product **162**) is

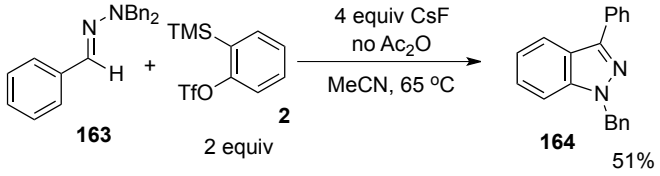
a faster step than acetylation of the amide with a neighboring *gem*-disubstituted nitrogen (Scheme 21).



Scheme 21. Reaction of a Morpholine-derived Hydrazone.

Alternatively, Boc_2O has been tested as a trapping source (with subsequent deprotection with aqueous HCl), but in most cases similar or lower yields of the indazoles have been obtained, except for the 2-thiophenyl product **149**, for which the yield improved from 39% to 56% (Table 4, entry 6).

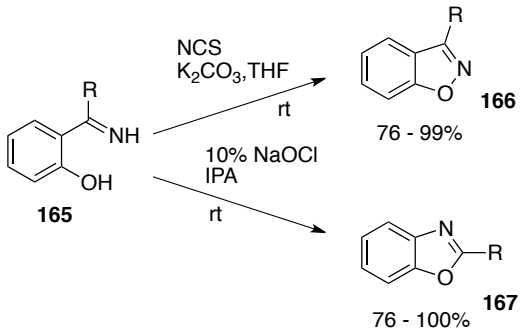
Surprisingly, the *N*,*N*-dibenzyl-substituted hydrazone **163** provided the corresponding indazole **164** without even employing either a trapping agent or NCS (Scheme 22). The product was isolated in a higher (51%) yield when a two fold-excess of the benzyne precursor **2** was used.[71] All attempts to obtain this indazole through the optimized NCS or Ac_2O routes have proved to be inferior to the one illustrated below.



Scheme 22. Reaction of a Dibenzyl Hydrazone.

5.3.6. Synthesis of 1*H*-Indazoles by the Chlorination and Subsequent Cyclization of *ortho*-Aminoaryl Ketimines

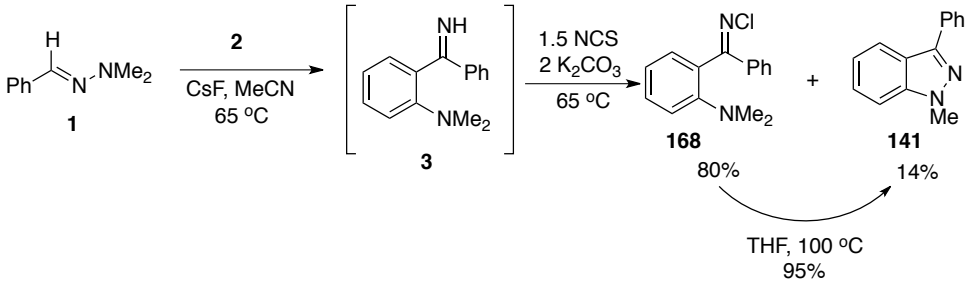
Recently, a convenient method for the preparation of isomeric benzoxazoles was described by Chen and co-workers (Scheme 23).[72] In that process, *o*-hydroxyaryl ketimines **165** are intramolecularly cyclized to benzisoxazoles **166** or benzoxazoles **167** upon exposure to chlorinating conditions involving respectively a) NCS in the presence of K_2CO_3 or b) 10% NaOCl.



Scheme 23. Synthesis of Isomeric Benzoxazoles by the Chen group.

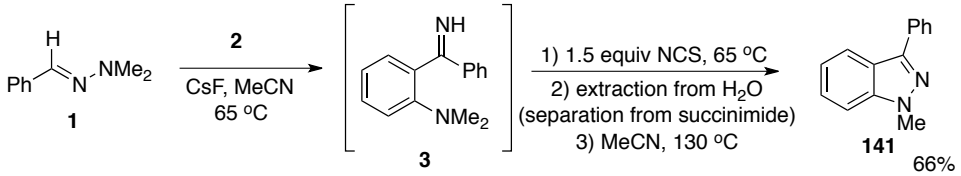
Due to the similar nature of *o*-hydroxyaryl ketimines and our *o*-aminoaryl ketimines **3**, we attempted to induce a similar cyclization to 1*H*-indazoles through a one-pot synthesis of aminoaryl ketimines by the reaction of hydrazones with arynes, followed by chlorination with NCS (Scheme 24).[73] When the reaction mixture containing ketimine **3** was subjected to NCS/K_2CO_3 at 65 ^oC, only 14% of the desired indazole was isolated. The major product of the reaction, *N*-chloroketimine **168**, was isolated in an 80% yield. The latter cyclized to the desired indazole **141** upon exposure to elevated temperatures (100 ^oC) in THF in a 90% yield. We noticed that the key cyclization is more facile in THF (as compared to MeCN). However, running the first step (the reaction with the benzyne) in acetonitrile, followed by

evaporation and immediate addition of THF, unavoidably causes some hydrolysis of the labile ketimine **3** to the corresponding ketone. We could obtain the indazole **141** in only a 50% yield using the procedure with the two different solvents.



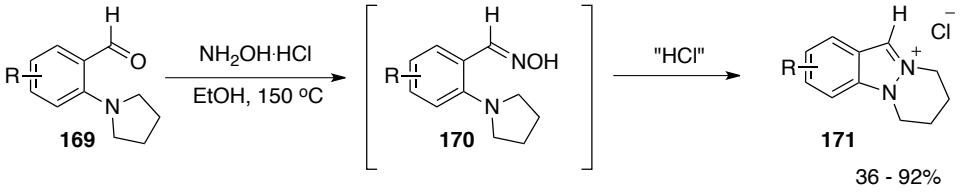
Scheme 24. Attempts to Develop a One-Pot Synthesis of 1*H*-Indazoles.

Subjecting the original reaction mixture of the ketimine **3** to the NCS-chlorinating conditions and, after a complete imine-to-chloroimine conversion (as detected by TLC), heating at 130 °C resulted in only a 34% isolated yield of the desired product **141**. This result suggests interference of the constituents of the reaction mixture with the intramolecular cyclization step. If one extracts the reaction mixture after the NCS-chlorination step (performed at 65 °C with no K_2CO_3) from water (thus, separating the desired products from all possible water-soluble constituents) and subsequently exposes the reaction mixture to 130 °C in acetonitrile, the desired indazole **141** is formed in a 66% yield in a pseudo-one-pot fashion (Scheme 25).



Scheme 25. Optimized of the Synthesis of Indazoles from Ketimines.

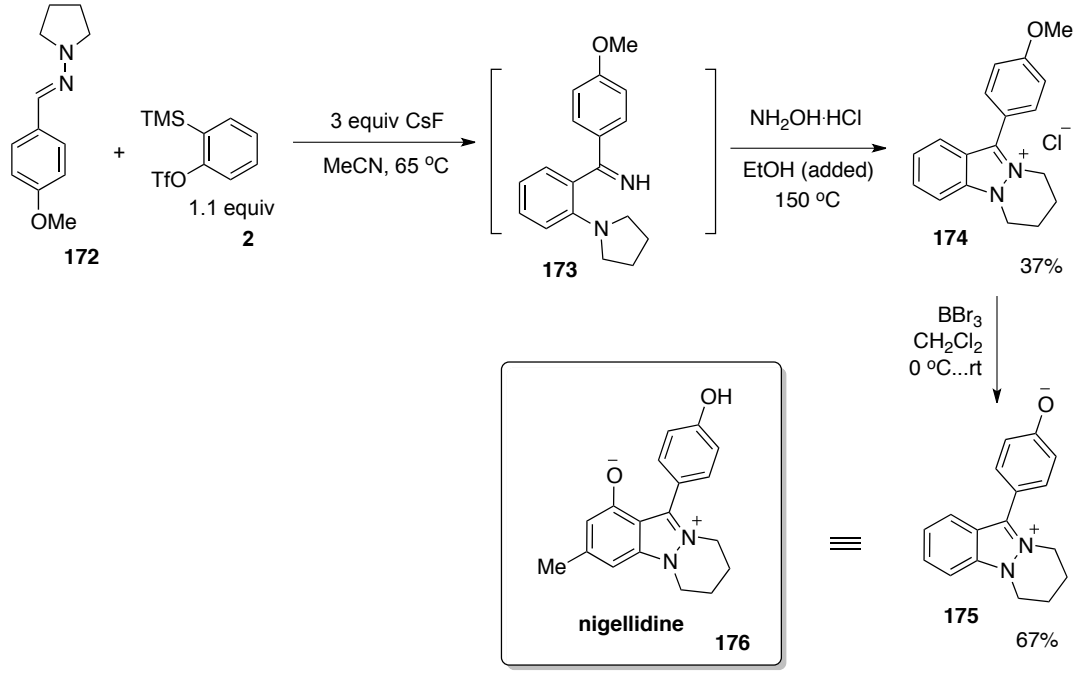
An alternative route to indazoles from *o*-aminoaryl aldehydes **169** has been recently described by Rebek Jr. (Scheme 26).[74] When reacting the latter compounds with hydroxylamine hydrochloride at elevated temperatures, the hydroxyl group of the *o*-aminoaryl aldoximes **170** formed *in situ* is intramolecularly replaced by the neighboring amino group (after activation by the HCl present in the reaction media), thus leading to the desired indazole moiety **171**.



Scheme 26. Synthesis of Indazoles by Rebek.

Although no attempts to run this transformation on analogous ketones have been reported, we decided to use this approach for the synthesis of an analogue of the natural alkaloid nigellidine (**176**). Nigellidine and its sulfated analogue have been isolated[75] from the seeds of the common spice *Nigella sativa*.

After the reaction of the pyrrolidine-derived hydrazone **172** with the silylaryl triflate **2** in the presence of CsF in MeCN at 65 °C, hydroxylamine hydrochloride was added to the imine formed *in situ* and the reaction was kept at 150 °C for an additional 24 h. As a result, we could succesfully isolate the tricyclic compound **174**, albeit in a low 37% yield (Scheme 27). Subsequent BBr_3-mediated demethylation[76] furnished the desired nigellidine analogue **175** in a 67% yield. Further optimization studies on the synthesis of the product **175**, as well as nigellidine (**176**) are underway.



Scheme 27. Synthesis of the Nigellidine Analogue.

In summary, an alternative pathway (complementing to those reported in section 4.3.5) leading to 1*H*-indazoles has been discovered. After the benzyne-induced cyclization and subsequent ring-opening has occurred, the resulting *o*-aminoaryl ketimine can be cyclized to an 1*H*-indazole by chlorination of the imine by NCS, followed by intramolecular displacement of the chloride. Additionally, an analogue of nigellidine **175** has been synthesized in only two steps from the starting hydrazone **172** and the commercially available benzyne precursor **2**.

5.4. Conclusions

In summary, we have developed a novel, efficient route to *o*-(dimethylamino)aryl ketones, acridones, acridinium salts, and 1*H*-indazoles starting from readily available aldehydes, 1,1-dimethylhydrazine and *o*-(trimethylsilyl)aryl triflates. In the formation of

o-(dimethylamino)aryl ketones, the reaction proceeds through a cyclization-ring opening pathway with intermediate formation of a dihydroindazole. In the case of acridones, the initial transformation is followed by an additional intramolecular S_NAr reaction and demethylation. In the case of acridinium salts, the initial transformation is followed by an intramolecular acid-catalyzed Friedel-Crafts cyclization. In the case of indazoles, the cyclic dihydroindazole intermediate is trapped *in situ* with acetic anhydride, followed by N_2H_4-mediated acyl cleavage and aromatization. This array of methods should prove useful for the preparation of a variety of biologically and pharmaceutically important structures. A representative number of naturally-occurring and medicinally-relevant compounds have been obtained using our methodology. A variety of functional groups are compatible with the reaction conditions.

5.5. 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. We also thank Dr. Feng Shi while at Iowa State University for the preparation of some of the non-commercially available aryne precursors.

5.6. Experimental

General Information.

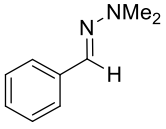
The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Chemical shifts are reported in δ units (ppm) by assigning the TMS resonance in the ^1H NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C NMR spectrum as

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 (APCI 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.

Synthesis of the Hydrazones

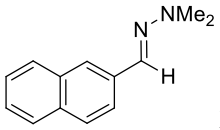
General procedure for synthesis of the starting hydrazones.[77]

A mixture of the aldehyde (1.5 mmol), anhydrous magnesium sulfate (3.0 mmol, 2 equiv), and the 1,1-disubstituted hydrazine (2.0 mmol, 1.3 equiv) was stirred for 10 h at room temperature in dichloromethane (5 mL). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired hydrazones.

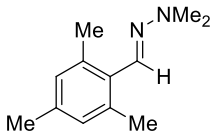


Benzaldehyde dimethylhydrazone (1). This compound was obtained as a pale yellow liquid in an 89% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 7.22 (t, J = 7.3

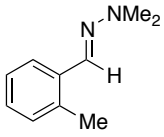
Hz, 1H), 7.25 (s, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[77]



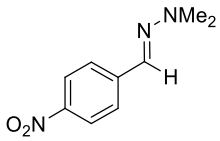
2-Naphthaldehyde dimethylhydrazone (12). This compound was obtained as a white solid in a 97% yield: mp 69-70 ^{o}C (lit.[78] mp 67 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (s, 6H), 7.42-7.48 (m, 3H), 7.79-7.82 (m, 4H), 7.93 (d, J = 7.5 Hz, 1H).



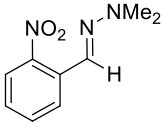
2,4,6-Trimethylbenzaldehyde dimethylhydrazone (14). This compound was obtained as a colorless liquid in an 84% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.41 (s, 6H), 2.96 (s, 6H), 6.88 (s, 2H), 7.47 (s, 1H).



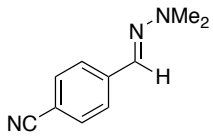
***o*-Tolylaldehyde dimethylhydrazone (16).** This compound was obtained as a light yellow liquid in an 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.00 (s, 6H), 7.10-7.23 (m, 3H), 7.44 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 43.2, 125.2, 126.3, 127.4, 130.7, 131.5, 134.9.



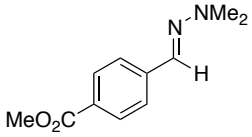
4-Nitrobenzaldehyde dimethylhydrazone (18). This compound was obtained as bright orange crystals in a 96% yield: mp 113-114 ^{o}C (lit.[79] mp 113-114 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 6H), 7.10 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.9 Hz, 2H).



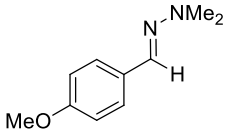
2-Nitrobenzaldehyde dimethylhydrazone (20). This compound was obtained as a bright red liquid in a 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 6H), 7.27 (t, J = 7.7 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.68 (s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 7.3 Hz, 1H).



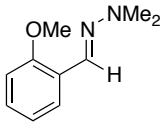
4-Cyanobenzaldehyde dimethylhydrazone (22). This compound was obtained as a colorless solid in a 92% yield: mp 141-143 °C (lit.[80] mp 139-140 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 6H), 7.05 (s, 1H), 7.50-7.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.6, 109.4, 119.6, 125.5, 128.1, 132.4, 141.8; MS (EI) *m/z* (%) 173 (M^+, 100%), 158 (24%), 128 (67%), 42 (21%); IR (CH_2Cl_2, cm^{-1}) 2866 (w), 2223 (s), 1576 (s), 1545 (s), 1054 (s).



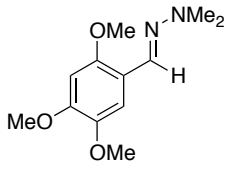
Methyl 4-[(2,2-dimethylhydrazono)methyl]benzoate (24). This compound was obtained as a colorless solid in a 96% yield: mp 65-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 3.85 (s, 3H), 7.09 (s, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.6, 51.9, 125.0, 128.0, 129.6, 129.8, 141.6, 167.0; MS (EI) *m/z* (%) 206 (M^+, 97%), 163 (59%), 130 (100%), 102 (46%), 76 (23%), 44 (21%); IR (CH_2Cl_2, cm^{-1}) 2953 (w), 1716 (s), 1581 (m), 1550 (m).



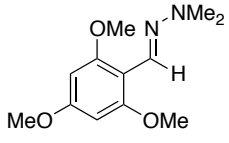
4-Methoxybenzaldehyde dimethylhydrazone (26). This compound was obtained as a pale yellow liquid in a 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 (s, 6H), 3.81 (s, 3H), 6.87 (d, J = 8.8 Hz, 2H), 7.26 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H).



2-Methoxybenzaldehyde dimethylhydrazone (28). This compound was obtained as a light yellow liquid in a 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 3.85 (s, 3H), 6.86 (d, J = 8.2 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.20 (td, J = 8.3, 1.7 Hz, 1H), 7.61 (s, 1H), 7.85 (dd, J = 7.7, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.3, 55.7, 111.0, 121.1, 125.2, 125.6, 128.5, 129.1, 156.7.

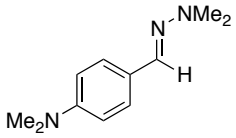


2,4,5-Trimethoxybenzaldehyde dimethylhydrazone (30). This compound was obtained as a pale brown solid in a 95% yield: mp 60-63 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (s, 6H), 3.76 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 6.42 (s, 1H), 7.36 (s, 1H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 56.2, 56.4, 56.8, 97.6, 107.8, 117.6, 129.7, 143.8, 149.6, 151.5.



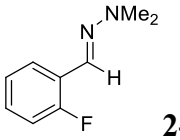
2,4,6-Trimethoxybenzaldehyde dimethylhydrazone (32). This compound was obtained as a light brown liquid in a 94% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (s, 6H), 3.76 (s, 3H), 3.83 (d, J = 5.1 Hz, 6H), 6.42 (s, 1H), 7.37 (s, 1H), 7.53 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 55.9, 56.2, 56.6, 97.3, 107.5, 117.4, 129.4, 143.5, 149.4, 151.2; MS (EI) *m/z* (%) 238 (M^+, 81%), 193 (93%), 179 (100%), 164 (25%), 151 (34%), 121 (23%), 44 (49%); HRMS (APCI) calcd for $[M+H]^+$ $C_{12}H_{19}N_2O_3$ 239.139, found 238.1317; IR (neat, cm^{-1}) 3005 (w), 2941 (m), 2839 (m), 1676 (w), 1592 (s), 1468 (m), 1126 (s).

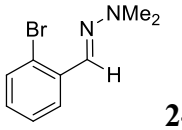


4-(*N*,*N*-dimethylamino)benzaldehyde dimethylhydrazone (34)

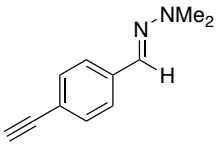
This compound was obtained as a red solid in an 88% yield: mp 67-68 °C (lit.[81] mp 65-67 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (s, 6H), 2.97 (s, 6H), 6.70 (d, J = 8.8 Hz, 2H), 7.32 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8, 43.6, 112.6, 125.5, 127.2, 135.9, 150.5.



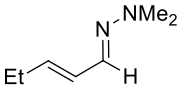
2-Fluorobenzaldehyde dimethylhydrazone (36). This compound was obtained as a colorless liquid in a 92% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 6H), 6.98-7.03 (m, 1H), 7.09 (t, J = 7.3 Hz, 1H), 7.15-7.19 (m, 1H), 7.39 (s, 1H), 7.86 (t, J = 7.6 Hz, 1H).



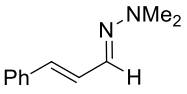
2-Bromobenzaldehyde dimethylhydrazone (38). This compound was obtained as a pale yellow liquid in an 86% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 6H), 7.06 (t, J = 7.7 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.46 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H).



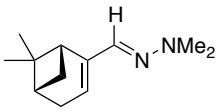
4-Ethynylbenzaldehyde dimethylhydrazone (40). This compound was obtained as a light yellow solid in a 94% yield: mp 79-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 6H), 3.10 (s, 1H), 7.16 (s, 1H), 7.40-7.47 (m, 2H), 7.47-7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 77.6, 84.3, 120.5, 125.4, 131.1, 132.5, 137.7; MS (EI) *m/z* (%) 172 (M^+, 100%); HRMS (ESI) calcd for $[M+H]^+$ $C_{11}H_{13}N_2$ 173.1073, found 172.1000; IR (CH_2Cl_2, cm^{-1}) 3295 (s), 2863 (w), 2105 (w), 1578 (s), 1546 (m), 1040 (s).



(*E*)-Pent-2-enal dimethylhydrazone (44). This compound was obtained as a dark yellow liquid in a 60% yield (caution: the compound is volatile under a moderate vacuum): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3H), 2.08-2.18 (m, 2H), 2.78 (s, 6H), 5.84 (dt, J = 15.5, 6.4 Hz, 1H), 6.16 (dd, J = 8.9, 15.6 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H).

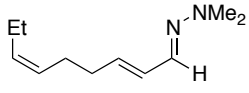


Cinnamaldehyde dimethylhydrazone (46). This compound was obtained as a yellow liquid in a 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (s, 6H), 6.61 (d, J = 15.9 Hz, 1H), 6.91-6.97 (m, 1H), 7.14 (d, J = 9.0 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.4 Hz, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[77]

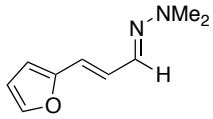


(-)-Myrtenal dimethylhydrazone (47). This compound was obtained as a pale yellow liquid in a 79% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.14 (d, J =

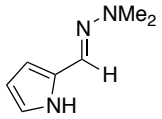
8.8 Hz, 1H), 1.32 (s, 3H), 2.07-2.16 (m, 1H), 2.34-2.47 (m, 3H), 2.81 (s, 6H), 2.97 (t, J = 5.4 Hz, 1H), 5.61 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 26.4, 31.6, 32.3, 37.9, 40.4, 41.3, 43.3, 124.6, 136.8, 146.8.



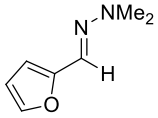
(2*E*,6*Z*)-Nonadienal dimethylhydrazone (49). This compound was obtained as a red-brown liquid in a 76% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 2.02 (quintet, J = 7.3, 2H), 2.13-2.19 (m, 4H), 2.81 (s, 6H), 5.27-5.42 (m, 2H), 5.77-5.84 (m, 1H), 6.17-6.23 (m, 1H), 6.99 (d, J = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.8, 27.0, 33.0, 43.2, 128.3, 129.5, 132.5, 135.2, 137.0.



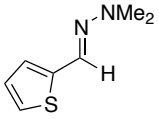
(*E*)-3-(2-Furyl)-2-propenal dimethylhydrazone (51). This compound was obtained as a black solid in a 93% yield: mp 37-39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (s, 6H), 6.26 (d, J = 3.3 Hz, 1H), 6.35-6.43 (m, 2H), 6.82 (dd, J = 15.8, 9.1 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 108.0, 111.8, 119.3, 126.5, 134.7, 142.3, 153.6.



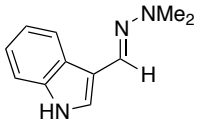
2-Pyrrolecarbaldehyde dimethylhydrazone (53). This compound was obtained as a black solid in a 98% yield: mp 43-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 6H), 6.22 (d, J = 12.5 Hz, 2H), 6.76 (s, 1H), 7.28 (s, 1H), 9.03 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 109.1, 109.4, 119.1, 127.8, 130.3.



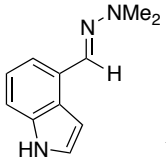
Furan-2-carbaldehyde dimethylhydrazone (55). This compound was obtained as a dark brown liquid in a 67% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (s, 6H), 6.37 (d, J = 13.5 Hz, 2H), 7.12 (s, 1H), 7.38 (s, 1H).



Thiophene-2-carbaldehyde dimethylhydrazone (57). This compound was obtained as a green liquid in a 99% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (s, 6H), 6.94-7.02 (m, 2H), 7.13 (d, J = 4.9 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 124.3, 124.7, 127.2, 128.0, 142.8; MS (EI) *m/z* (%) 154 (M^+, 100%), 109 (27%); IR (neat, cm^{-1}) 3084 (doublet, w), 2854 (m), 1570 (m), 1034 (m), 699 (m).

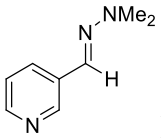


Indole-3-carbaldehyde dimethylhydrazone (59). This compound was obtained as a brown solid in an 84% yield using 2 mL of MeOH as a co-solvent: mp 90-93 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 7.18 (d, J = 2.7 Hz, 1H), 7.23-7.29 (m, 3H), 7.74 (s, 1H), 8.35-8.40 (m, 1H), 8.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 111.5, 114.6, 120.8, 122.1, 123.0, 125.0, 125.2, 133.1, 137.0.

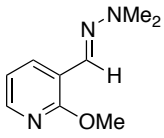


Indole-4-carbaldehyde dimethylhydrazone (61). This compound was obtained as a black oil in a 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 6H), 7.09-7.30 (m, 5H),

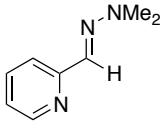
7.62 (s, 1H), 8.31 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.0, 103.1, 110.5, 119.1, 121.8, 124.2, 124.5, 128.6, 134.6, 136.4.



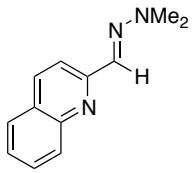
Nicotinaldehyde dimethylhydrazone (63). This compound was obtained as a yellow liquid in an 88% yield: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.94 (s, 6H), 7.08 (s, 1H), 7.16 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 4.7 Hz, 1H), 8.64 (s, 1H).



2-Methoxy-3-pyridinecarboxaldehyde dimethylhydrazone (65). This compound was obtained as a colorless liquid in an 83% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 6H), 3.97 (s, 3H), 6.85 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.38 (s, 1H), 7.98-8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 53.5, 117.4, 120.2, 126.6, 132.8, 145.3, 160.7.

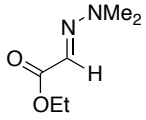


2-Pyridinecarboxaldehyde dimethylhydrazone (67). This compound was obtained as a pale brown liquid in a 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 6H), 7.03 (ddd, *J* = 7.2, 4.8, 1.3 Hz, 1H), 7.24 (s, 1H), 7.56 (t, *J* = 7.7, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.8, 118.9, 121.6, 131.8, 136.3, 149.2, 156.1.

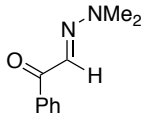


2-Quinolinecarboxaldehyde dimethylhydrazone (69). This compound was obtained as a brown-red semisolid in a 93% yield: mp 67-68 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$)

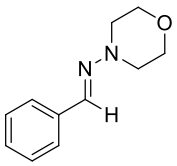
δ 2.92 (s, 6H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 7.51 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.80-7.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7, 117.6, 125.7, 127.5, 127.7, 128.7, 129.5, 131.3, 135.8, 148.1, 156.5.



Ethyl 2-(2,2-dimethylhydrazono)acetate (71). This compound was obtained as a yellow liquid in a 69% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.09 (s, 6H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 42.5, 60.2, 117.4, 165.1; MS (EI) *m/z* (%) 144 (M^+, 77%), 99 (34%), 71 (45%), 44 (100%); IR (neat, cm^{-1}) 2981 (m), 1720 (s), 1545 (s), 1273 (s), 1184 (s), 1083 (s), 837 (m).

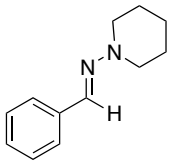


2-Oxo-2-phenylacetaldehyde aldehyde(dimethylhydrazone) (73). This compound was obtained as a pale yellow solid in a 78% yield from phenylglyoxal monohydrate using 3 equiv (instead of 2) of $MgSO_4$: mp 41-42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 6H), 7.05 (s, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.96 (dd, *J* = 8.3, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.8, 126.3, 128.1, 129.8, 131.7, 138.5, 189.7.

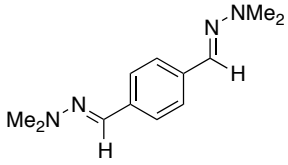


(*E*)-*N*-Benzylidenemorpholin-4-amine (75). This compound was obtained as white crystals in a 71% yield: mp 90-91 °C (lit.[81] mp 89 °C); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*

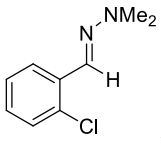
3.17-3.19 (m, 4H), 3.88-3.90 (m, 4H), 7.29 (d, J = 7.1 Hz, 1H), 7.35 (t, J = 7.3 Hz, 2H), 7.60-7.61 (m, 3H).



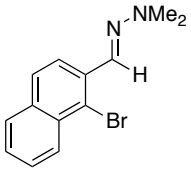
(*E*)-*N*-Benzylidenepiperidin-1-amine (79). This compound was obtained as a colorless solid in a 72% yield: mp 69-70 °C (lit.[82] mp 70-71 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (ddt, J = 11.7, 8.4, 4.8 Hz, 2H), 1.78 (p, J = 5.9 Hz, 4H), 3.10-3.30 (m, 4H), 7.28 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.57 (s, 1H), 7.59-7.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.2, 52.0, 125.9, 127.7, 128.4, 134.3, 136.7; MS (EI) *m/z* (%) 188 (M^+, 100%), 131 (22%), 103 (26%), 77 (18%); IR (CH_2Cl_2, cm^{-1}) 2939 (m), 2856 (m), 1592 (m), 1565 (m), 1363 (m), 1087 (m), 992 (m).



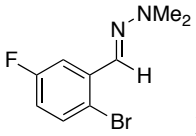
1,4-Benzenedicarboxaldehyde bis(dimethylhydrazone) (81). This compound was obtained as a pale yellow solid in a 97% yield: mp 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (s, 12H), 7.22 (s, 2H), 7.53 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 127.0, 133.0, 136.1.



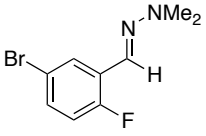
2-Chlorobenzaldehyde dimethylhydrazone (98). This compound was obtained as a pale yellow liquid in a 92% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 6H), 7.13 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.93 (d, J = 7.8 Hz, 1H).



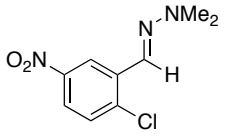
1-Bromo-2-naphthaldehyde dimethylhydrazone (99). This compound was obtained as a white solid in a 94% yield: mp 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 6H), 7.48 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.78-7.80 (m, 2H), 8.13 (d, J = 8.6 Hz, 1H), 8.36 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 122.2, 124.2, 126.4, 127.3, 127.6, 127.7, 128.4, 131.6, 132.9, 133.9, 134.1.



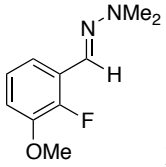
2-Bromo-5-fluorobenzaldehyde dimethylhydrazone (103). This compound was obtained as a colorless liquid in a 93% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 6H), 6.77 (ddd, J = 8.7, 7.7, 3.2 Hz, 1H), 7.33 (s, 1H), 7.43 (dd, J = 8.8, 5.3 Hz, 1H), 7.61 (dd, J = 10.3, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 112.5 ($^{2}J_{CF}$ = 24.4 Hz), 115.4 ($^{2}J_{CF}$ = 23.6 Hz), 116.3 ($^{4}J_{CF}$ = 2.9 Hz), 128.8 ($^{4}J_{CF}$ = 2.7 Hz), 134.1 ($^{3}J_{CF}$ = 8.2 Hz), 137.8 ($^{3}J_{CF}$ = 8.1 Hz), 162.3 ($^{1}J_{CF}$ = 244.9 Hz).



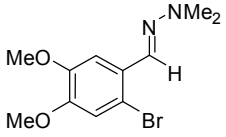
5-Bromo-2-fluorobenzaldehyde dimethylhydrazone (105). This compound was obtained as a colorless liquid in a 79% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (s, 6H), 6.88 (dd, J = 10.3, 8.7 Hz, 1H), 7.19-7.25 (m, 2H), 7.98 (dd, J = 6.6, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 117.3 (J_{CF} = 3.0 Hz), 117.3 (J_{CF} = 22.9 Hz), 122.3, 127.0 (J_{CF} = 11.7 Hz), 128.0 (J_{CF} = 3.8 Hz), 130.6 (J_{CF} = 8.4 Hz), 159.1 ($^{1}J_{CF}$ = 247.8 Hz).



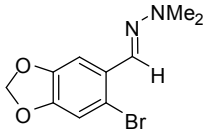
2-Chloro-5-nitrobenzaldehyde dimethylhydrazone (107). This compound was obtained as an orange solid in a 97% yield: mp 87-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 6H), 7.25 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 8.8, 2.7 Hz, 1H), 8.69 (d, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.8, 120.5, 121.2, 123.6, 130.6, 136.3, 137.2, 147.1.



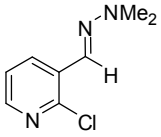
2-Fluoro-3-methoxybenzaldehyde dimethylhydrazone (109). This compound was obtained as a colorless liquid in a 94% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 6H), 3.86 (s, 3H), 6.79 (td, J = 8.2, 1.6 Hz, 1H), 7.00 (td, J = 8.1, 1.5 Hz, 1H), 7.38 (s, 1H), 7.44 (ddd, J = 8.0, 6.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 56.4, 111.5, 116.9, 123.9 (J_{CF} = 4.7 Hz), 124.5 (J_{CF} = 6.4 Hz), 125.8 (J_{CF} = 7.6 Hz), 148.0 (J_{CF} = 10.6 Hz), 150.3 ($^1J_{CF}$ = 247.9 Hz) (extra signals due to C-F coupling).



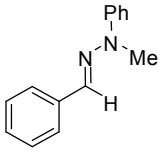
2-Bromo-4,5-dimethoxybenzaldehyde dimethylhydrazone (111). This compound was obtained as a white solid in a 90% yield: mp 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 6.88 (s, 1H), 7.33 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 56.1, 56.3, 108.1, 113.3, 115.1, 128.2, 131.6, 148.7, 149.2.



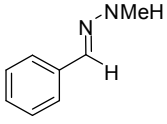
6-Bromopiperonal dimethylhydrazone (113). This compound was obtained as a white solid in a 96% yield: mp 55-57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 6H), 5.92 (s, 2H), 6.93 (s, 1H), 7.38 (s, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.1, 101.9, 105.7, 112.5, 113.7, 129.7, 131.4, 147.9.



2-Chloro-3-pyridinecarboxaldehyde dimethylhydrazone (117). This compound was obtained as a pale yellow liquid in a 96% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (s, 6H), 7.14-7.19 (m, 1H), 7.29 (s, 1H), 8.15-8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 122.9, 125.3, 131.5, 133.9, 147.4, 148.5.

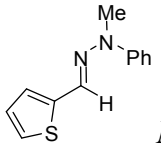


***N*-Methyl-*N*-phenylbenzaldehyde hydrazone (126).** This compound was obtained as a white solid in a 62% yield: mp 105-106 °C (lit.[83] mp 107-109 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H), 6.95 (tt, J = 7.0, 1.3 Hz, 1H), 7.23-7.44 (m, 7H), 7.51 (s, 1H), 7.72 (d, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.3, 115.5, 120.8, 126.3, 127.9, 128.8, 129.3, 132.1, 137.0, 148.1. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[84]

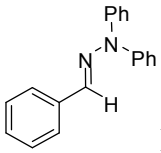


Benzaldehyde methylhydrazone (128). This compound was obtained as a colorless liquid in an 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 3H), 7.23-7.29 (m,

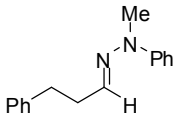
1H), 7.34 (t, 2H, J = 8.0 Hz, 5H), 7.53 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7, 125.7, 127.8, 128.5, 135.4, 136.2.



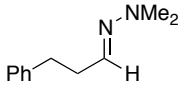
***N*-Methyl-*N*-phenyl-2-thienaldehyde hydrazone (129)** This compound was obtained as a pale yellow solid in a 90% yield: mp 82-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 6.94 (t, J = 6.3 Hz, 1H), 7.02 (t, J = 4.1 Hz, 1H), 7.11 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 7.31-7.36 (m, 4H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 115.4, 120.9, 125.1, 125.6, 127.1, 127.4, 129.3, 142.9, 147.7.



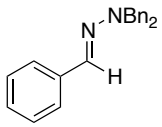
Benzaldehyde diphenylhydrazone (131). This compound was obtained as a colorless solid in an 87% yield: mp 124-125 °C (lit.[85] mp 125-126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.33 (m, 8H), 7.38 (t, J = 7.4 Hz, 2H), 7.47 (d, J = 7.0 Hz, 4H), 7.66 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.8, 124.8, 126.6, 128.4, 128.8, 130.1, 135.7, 136.4, 143.9.



***N*-Methyl-*N*-phenyl-dihydrocinnamaldehyde hydrazone (133).** This compound was obtained as an orange oil in a 72% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69-2.78 (m, 2H), 2.95 (t, J = 7.9 Hz, 2H), 3.23 (s, 3H), 6.85-6.93 (m, 2H), 7.21-7.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 34.2, 35.0, 115.1, 120.1, 126.2, 128.7, 128.7, 129.2, 134.8, 141.9, 148.5.

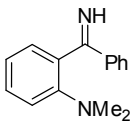


Dihydrocinnamaldehyde dimethylhydrazone (153). This compound was obtained as a light yellow liquid in a 74% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (q, J = 7.2, 6.6 Hz, 2H), 2.73 (s, 6H), 2.82 (t, J = 7.8 Hz, 2H), 6.67 (d, J = 5.5 Hz, 1H), 7.20 (dd, J = 12.4, 6.5 Hz, 3H), 7.29 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3, 35.0, 43.5, 126.1, 128.5, 128.6, 138.3, 141.6; MS (EI) *m/z* (%) 176 (M^+, 15%), 91 (30%), 85 (100%), 44 (19%); IR (neat, cm^{-1}) 3061 (w), 2952 (s), 2852 (s), 1603 (m), 1496 (s), 1029 (s), 699 (s). The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[86]



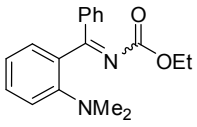
Benzaldehyde dibenzylhydrazone (163). This compound was obtained as a colorless solid in an 85% yield: mp 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 4H), 6.61-7.49 (m, 14H), 7.55 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.1, 125.7, 127.4, 127.8, 128.6, 128.7, 128.7, 132.0, 137.1, 137.8; MS (EI) *m/z* (%) 300 (M^+, 47%), 181 (14%), 166 (13%), 103 (15%), 91 (100%); IR (CH_2Cl_2, cm^{-1}) 3086 (w), 3029 (m), 2845 (w), 1589 (s), 1562 (s), 1494 (s), 1452 (s), 1129 (m).

Synthesis of Aminoaryl Ketimines and Derivatives



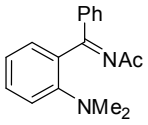
***N,N*-Dimethyl-2-[imino(phenyl)methyl]aniline (3).** To a mixture of benzaldehyde dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was

added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired ketamine **3** as a yellow oil in a 76% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 6H), 6.94 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.30-7.46 (m, 4H), 7.72 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 117.7, 120.6, 128.3, 128.4, 130.3, 130.4, 130.6, 131.5, 139.1, 151.5, 178.4; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{17}N_2$ 225.1386, found 225.1385.



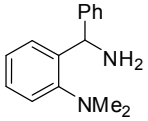
Ethyl [(2-(dimethylamino)phenyl)(phenyl)methylene]carbamate (4). To a mixture of benzaldehyde dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. After cooling to room temperature, ethyl chloroformate (0.3 mmol, 1.2 equiv) was added and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product **4** as a yellow oil in an 82% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J =

7.1 Hz, 3H), 2.66 (s, 6H), 4.14 (q, J = 7.1 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.33-7.38 (m, 3H), 7.46 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 43.2, 62.3, 117.6, 120.0, 127.4, 128.3, 129.4, 130.4, 131.1, 131.8, 137.2, 151.5, 163.1, 173.3; HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{21}N_2O_2$ 297.1598, found 297.1595.

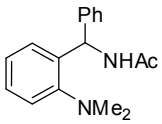


***N*-[(2-(Dimethylamino)phenyl)(phenyl)methylene]acetamide (5).** To a mixture of benzaldehyde dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. After cooling to room temperature, acetic anhydride (0.5 mmol, 2 equiv) was added and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product **5** as a yellow oil in a 68% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.68 (s, 6H), 6.92 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.12 (dd, J = 7.6, 1.6 Hz, 1H), 7.31-7.42 (m, 3H), 7.43-7.50 (m, 1H), 7.70-7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2,

43.2, 117.8, 120.1, 127.1, 128.4, 129.5, 130.4, 131.0, 131.6, 137.5, 151.3, 165.7, 185.2; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{19}N_2O$ 267.1492, found 267.1489.



***N,N*-Dimethyl-2-[amino(phenyl)methyl]aniline (7).** To a solution of imine **3** (0.20 mmol) in MeOH (4 mL) in a 10 mL vial, $NaBH_4$ (0.50 mmol, 2.5 equiv) was added portionwise. The reaction mixture was allowed to stir for 10 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product as a yellow oil in a 70% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (br s, 2H, NH_2), 2.63 (s, 6H), 5.75 (s, 1H), 7.09 (t, J = 7.1 Hz, 1H), 7.19-7.24 (m, 3H), 7.28-7.33 (m, 3H), 7.41 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.1, 54.3, 121.4, 124.8, 126.8, 127.2, 128.1, 128.2, 128.5, 141.0, 144.7, 152.7; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{19}N_2$ 227.1543, found 227.1545.



***N*-[(2-(Dimethylamino)phenyl)(phenyl)methyl]acetamide (6).**

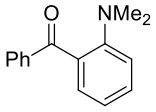
Method A. To a solution of *N*-acetylimine **5** (0.20 mmol) in THF (4 mL) in a 10 mL vial, $NaBH_3CN$ (0.50 mmol, 2.5 equiv) was added portionwise. The reaction mixture was allowed to stir for 10 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product in a 55% yield.

Method B. To a solution of amine **7** (0.20 mmol) in CH_3CN (4 mL) in a 10 mL vial, Ac_2O (0.40 mmol, 2.0 equiv) and Et_3N (0.40 mmol, 2.0 equiv) were added. The reaction mixture was allowed to stir for 2 h at 65 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product in a 92% yield as a pale brown solid: mp 97-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.50 (s, 6H), 6.56 (d, J = 8.6 Hz, 1H), 7.11-7.19 (m, 4H), 7.22-7.35 (m, 5H), 7.58 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 45.9, 54.6, 122.8, 125.3, 126.7, 126.9, 128.4, 128.8, 129.9, 137.5, 142.7, 152.9, 169.3; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{21}N_2O$ 269.1648, found 269.1653.

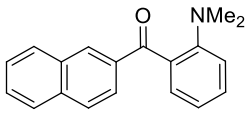
Synthesis of the Aminoaryl Ketones

General procedure for synthesis of the o-(dimethylamino)aryl ketones

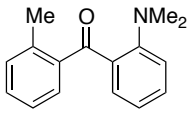
To a mixture of the appropriate dialkylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, the silylaryl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then 3 mL of 1M HCl was added and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired *o*-(dimethylamino)aryl ketone.



2-(Dimethylamino)benzophenone (8). This compound was obtained as a yellow oil in a 93% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 6H), 6.90 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.37-7.44 (m, 3H), 7.54 (t, J = 7.4 Hz, 1H), 7.83 (d, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.6, 116.6, 119.0, 128.3, 129.2, 130.1, 130.9, 131.6, 132.8, 137.9, 151.8, 198.4; HRMS (APCI) calcd for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found 226.1230. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[15]

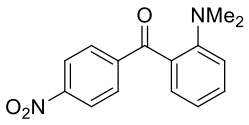


[2-(Dimethylamino)phenyl](naphthalen-2-yl)methanone (13). This compound was obtained as a yellow oil in a 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 6H), 6.95 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.40-7.47 (m, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.59 (t, J = 7.3 Hz, 1H), 7.87-7.90 (m, 3H), 7.99 (d, J = 8.7 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 116.6, 119.0, 125.7, 126.7, 127.9, 128.0, 128.4, 129.3, 129.7, 131.0, 131.6, 132.0, 132.6, 135.1, 135.6, 151.8, 198.2; HRMS (APCI) calcd for $C_{19}H_{18}NO$ $[M+H]^+$ 276.1383, found 276.1384.

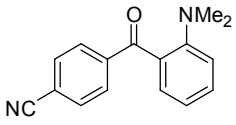


2-(Dimethylamino)-2'-methylbenzophenone (17). This compound was obtained as a pale yellow oil in a 78% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 2.77 (s, 6H), 6.83 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.31-7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 43.8, 116.6, 118.5,

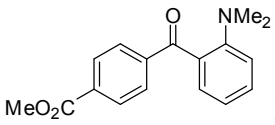
125.3, 129.3, 130.8, 131.1, 131.7, 132.4, 132.5, 138.8, 139.0, 152.3, 199.2; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{18}NO$ 240.1383, found 240.1386.



2-(Dimethylamino)-4'-nitrobenzophenone (19). This compound was obtained as a dark red oil in an 88% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 6H), 6.98 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.90 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 117.3, 120.2, 123.4, 128.8, 130.6, 131.1, 132.7, 143.1, 150.1, 152.3, 196.4; HRMS (APCI) calcd for $C_{15}H_{15}N_2O_3$ $[M+H]^+$ 271.1077, found 271.1079.

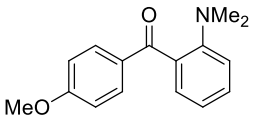


4-[2-(Dimethylamino)benzoyl]benzonitrile (23). This compound was obtained as light orange crystals in a 92% yield: mp 99-102 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 6H), 6.95 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.44 (ddd, J = 8.6, 7.3, 1.7 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 115.8, 117.2, 118.5, 120.0, 128.6, 130.2, 131.1, 132.1, 132.7, 141.5, 152.2, 196.7; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{15}N_2O$ 251.1179, found 251.1186.

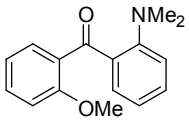


Methyl 4-[2-(dimethylamino)benzoyl]benzoate (25). This compound was obtained as a light orange oil in a 94% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 6H), 3.92 (s, 3H), 6.92 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.41

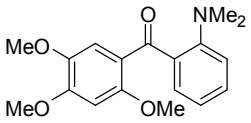
(t, J = 8.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 52.6, 116.9, 119.6, 129.0, 129.5, 129.8, 131.1, 132.2, 133.5, 141.6, 152.1, 166.6, 197.7; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{18}NO_3$ 284.1281, found 284.1289.



2-(Dimethylamino)-4'-methoxybenzophenone (27). This compound was obtained as a yellow amorphous solid in a 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 6H), 3.86 (s, 3H), 6.87-6.91 (m, 3H), 6.97 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.6, 55.6, 113.5, 116.5, 119.1, 129.8, 130.5, 130.6, 131.2, 132.5, 151.4, 163.5, 197.2; HRMS (APCI) calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332, found 256.1336.

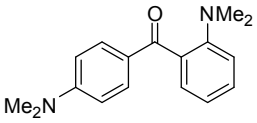


2-(Dimethylamino)-2'-methoxybenzophenone (29). This compound was obtained as yellow crystals in a 74% yield: mp 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 6H), 3.68 (s, 3H), 6.77 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 2H), 6.99 (t, J = 7.5 Hz, 1H), 7.32-7.36 (m, 2H), 7.44 (ddd, J = 9.3, 7.6, 1.9 Hz, 1H), 7.52 (dd, J = 7.6, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 55.9, 111.7, 116.1, 118.1, 120.5, 129.7, 129.9, 131.2, 131.9, 132.1, 132.7, 151.9, 158.5, 196.6; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{18}NO_2$ 256.1332, found 256.1335.

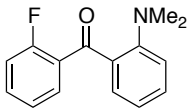


2-(Dimethylamino)-2',4',5'-trimethoxybenzophenone (31). This compound was obtained as a pale brown solid in a 67% yield: mp 106-110 °C; ^{1}H NMR (400

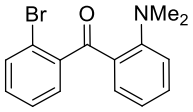
MHz, $CDCl_3$) δ 2.75 (s, 6H), 3.58 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 6.46 (s, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.20-7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 56.3, 56.6, 56.7, 97.3, 114.1, 116.0, 118.4, 120.4, 130.5, 131.2, 131.8, 143.2, 151.3, 153.5, 154.9, 195.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{22}NO_4$ 316.1543, found 316.1550.



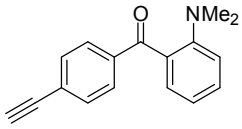
2-(Dimethylamino)-4'-(dimethylamino)benzophenone (35). This compound was obtained as a pale yellow oil in a 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 6H), 3.06 (s, 6H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.3, 43.7, 110.6, 116.5, 119.0, 125.4, 130.3, 130.6, 130.8, 132.7, 151.3, 153.6, 197.0; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{21}N_2O$ 269.1648, found 269.1650.



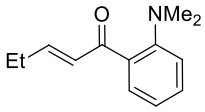
2-(Dimethylamino)-2'-fluorobenzophenone (37). This compound was obtained as a yellow oil in a 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 6H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 7.04-7.10 (m, 1H), 7.20 (td, *J* = 7.6, 1.1 Hz, 1H), 7.37-7.43 (m, 2H), 7.45-7.51 (m, 1H), 7.68 (td, *J* = 7.4, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 115.9, 116.1, 116.5, 118.9, 120.1, 123.6, 123.9, 124.0, 127.7, 127.8, 127.9, 129.7, 131.2, 131.3, 132.4, 133.3, 133.4, 152.1, 159.7, 162.3, 193.8 (extra peaks due to C-F coupling); HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{15}FNO$ 244.1132, found 244.1129.



2'-Bromo-2-(dimethylamino)benzophenone (39). This compound was obtained as a yellow amorphous solid in an 85% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (s, 6H), 6.81 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 7.26-7.29 (m, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.38-7.42 (m, 3H), 7.62 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 116.8, 118.4, 120.7, 126.8, 127.2, 130.9, 131.5, 133.4, 133.6, 133.7, 141.2, 152.9, 195.3; HRMS (APCI) calcd for $C_{15}H_{15}BrNO$ $[M+H]^+$ 304.0332, found 304.0334.

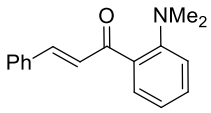


2-(Dimethylamino)-4'-ethynylbenzophenone (41). This compound was obtained as a light orange oil in a quantitative yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 6H), 3.23 (s, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 80.3, 83.3, 116.8, 119.5, 126.5, 129.2, 129.9, 130.9, 132.0, 132.1, 137.8, 151.9, 197.5; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{16}NO$ 250.1226, found 250.1229.

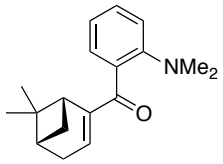


(*E*)-1-[2-(Dimethylamino)phenyl]pent-2-en-1-one (45). This compound was obtained as a dark orange liquid in a 77% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3H), 2.27 (quintet, J = 6.4 Hz, 2H), 2.78 (s, 6H), 6.66 (d, J = 15.7 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.95-7.01 (m, 2H), 7.34 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H); ^{13}C

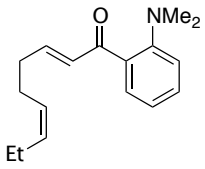
NMR (100 MHz, $CDCl_3$) δ 43.8, 117.3, 120.2, 123.4, 128.8, 130.6, 131.1, 132.7, 143.1, 150.1, 152.3, 196.4; HRMS (APCI) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1385.



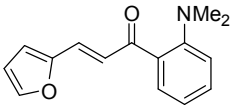
(*E*)-1-[2-(Dimethylamino)phenyl]-3-phenylprop-2-en-1-one (9). This compound was obtained as a red amorphous solid in a 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 6H), 6.97 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.36-7.44 (m, 5H), 7.53-7.60 (m, 3H), 7.73 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.5, 117.0, 120.2, 126.3, 128.4, 129.1, 130.3, 130.7, 131.8, 132.1, 135.4, 142.6, 152.4, 195.2; HRMS (APCI) calcd for $C_{17}H_{18}NO$ $[M+H]^+$ 251.1383, found 251.1310. The ^{1}H NMR spectral data are in good agreement with the literature data.[87]



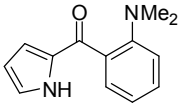
[2-(Dimethylamino)phenyl][(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methanone (48). This compound was obtained as a yellow oil in a 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.13 (d, J = 9.1 Hz, 1H), 1.36 (s, 3H), 2.44 (dt, J = 10.7, 3.1 Hz, 1H), 2.51 (dt, J = 9.1, 5.8 Hz, 1H), 2.73 (s, 1H), 3.00-3.05 (m, 6H), 6.44 (s, 1H), 6.86 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 7.18 (dd, J = 7.5, 1.7 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 26.2, 31.7, 32.9, 38.0, 40.4, 40.7, 43.8, 116.8, 119.1, 130.0, 130.5, 130.7, 140.9, 149.6, 151.3, 197.6; HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{24}NO$ 270.1852, found 270.1857.



(2*E*,6*Z*)-1-[2-(Dimethylamino)phenyl]nona-2,6-dien-1-one (50). This compound was obtained as a brown oil in an 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.5 Hz, 3H), 2.03 (p, *J* = 7.4 Hz, 2H), 2.18-2.34 (m, 4H), 2.78 (s, 6H), 5.28-5.46 (m, 2H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.86-6.97 (m, 3H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 20.8, 26.1, 32.8, 44.4, 116.8, 119.9, 127.7, 130.1, 130.6, 131.3, 131.8, 133.0, 147.5, 152.1, 195.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{24}NO$ 258.1852, found 258.1848.

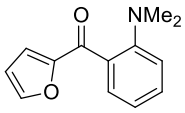


(*E*)-1-[2-(Dimethylamino)phenyl]-3-(furan-2-yl)prop-2-en-1-one (52). This compound was obtained as a dark red solid in an 85% yield: mp 80-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 6H), 6.45-6.49 (m, 1H), 6.64 (d, *J* = 3.4 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 15.7 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.45-7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.6, 112.7, 115.4, 117.0, 120.1, 124.0, 129.1, 130.6, 131.6, 132.1, 144.8, 152.1, 152.4, 194.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{16}NO_2$ 242.1176, found 242.1180.

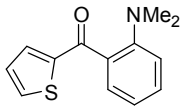


[2-(Dimethylamino)phenyl](1*H*-pyrrol-2-yl)methanone (54). This compound was obtained as a gray green solid in an 81% yield: mp 96-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 6H), 6.24-6.31 (m, 1H), 6.75 (s, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 7.10 (s, 1H), 7.36 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.7

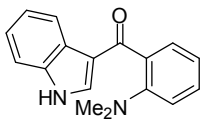
Hz, 1H), 10.23 (s, NH, broad, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 111.0, 116.6, 118.4, 119.5, 125.5, 128.9, 130.9, 131.3, 132.6, 151.3, 187.3; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_{15}N_2O$ 215.1179, found 215.1180.



[2-(Dimethylamino)phenyl](furan-2-yl)methanone (56). This compound was obtained as a dark yellow amorphous solid in a 90% yield: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.78 (s, 6H), 6.52 (s, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 7.34-7.40 (m, 2H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 43.7, 112.3, 116.7, 118.5, 120.2, 128.0, 130.7, 131.9, 147.2, 151.6, 153.1, 185.2; HRMS (APCI) calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1019, found 216.1023.

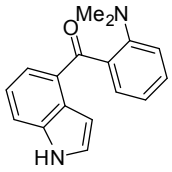


[2-(Dimethylamino)phenyl](thiophen-2-yl)methanone (58). This compound was obtained as a yellow solid in an 85% yield: mp 49-51°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 6H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 7.09 (t, *J* = 4.4 Hz, 1H), 7.35-7.39 (t, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 3.8 Hz, 1H), 7.66 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 116.7, 118.7, 128.1, 129.1, 130.5, 131.7, 134.3, 134.7, 145.0, 151.2, 190.4; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_{14}NOS$ 232.0791, found 232.0797.

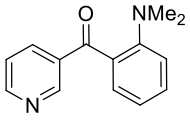


[2-(Dimethylamino)phenyl](1*H*-indol-3-yl)methanone (60). This compound was obtained as a red oil in a 21% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 6H), 6.87-6.91 (m, 3H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 7.7 Hz,

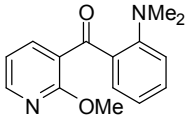
1H), 7.40-7.45 (m, 2H), 7.70 (d, J = 7.4 Hz, 1H), 8.58 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 110.7, 111.9, 118.6, 120.0, 122.0, 123.1, 125.1, 128.5, 129.9, 133.6, 135.7, 136.2, 150.8, 152.8, 187.0; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$ 256.1335, found 256.1339.



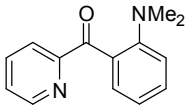
[2-(Dimethylamino)phenyl](1*H*-indol-4-yl)methanone (62). This compound was obtained as a yellow solid in an 84% yield: mp 173-176 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (s, 6H), 6.79 (m, 1H), 6.88 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.09-7.17 (m, 2H), 7.27 (d, J = 7.4 Hz, 1H), 7.37 (ddd, J = 8.7, 7.4, 1.6 Hz, 1H), 7.51 (t, J = 2.7 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 11.47 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.8, 102.7, 117.2, 117.4, 119.3, 120.7, 125.0, 127.2, 128.8, 129.1, 130.2, 131.3, 131.6, 137.5, 151.4, 198.9; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$ 265.1335, found 265.1337.



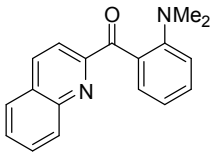
[2-(Dimethylamino)phenyl](pyridin-3-yl)methanone (64). This compound was obtained as a dark yellow oil in a 55% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 6H), 6.96 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 7.34-7.39 (m, 2H), 7.43 (t, J = 8.6 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.72 (d, J = 4.9 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.7, 117.0, 120.0, 123.3, 128.8, 131.0, 132.5, 133.1, 136.9, 151.5, 152.1, 152.9, 196.7; HRMS (APCI) calcd for $C_{14}H_{14}N_2O$ $[M+H]^+$ 227.1179, found 227.1177.



[2-(Dimethylamino)phenyl](2-methoxypyridin-3-yl)methanone (66). This compound was obtained as a yellow solid in a 78% yield: mp 69-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 6H), 3.80 (s, 3H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.92-6.95 (m, 2H), 7.35-7.39 (m, 2H), 7.84 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.25 (dd, *J* = 5.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1, 53.8, 116.6, 116.7, 119.3, 123.5, 130.1, 131.5, 132.5, 140.1, 149.7, 152.5, 161.9, 195.4; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{17}N_2O_2$ 257.1285, found 257.1287.

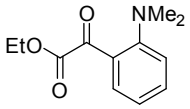


[2-(Dimethylamino)phenyl](pyridin-2-yl)methanone (68). This compound was obtained as a red oil in an 82% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 6H), 6.89 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 7.34-7.44 (m, 3H), 7.81 (t, *J* = 6.9 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 8.66 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 117.0, 119.1, 124.2, 126.2, 128.6, 131.4, 132.3, 136.8, 149.3, 152.6, 155.8, 197.1; HRMS (APCI) calcd for $[M+H]^+$ $C_{14}H_{15}N_2O$ 227.1179, found 227.1179.

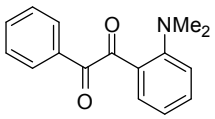


[2-(Dimethylamino)phenyl](quinolin-2-yl)methanone (70). This compound was obtained as yellow crystals in an 84% yield: mp 111-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 6H), 6.92 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.72 (t, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 117.0, 119.0, 120.8, 127.7, 128.3, 128.5, 129.2,

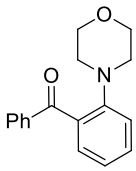
130.0, 130.9, 132.2, 132.5, 136.7, 147.5, 153.0, 155.6, 197.0; HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{17}N_2O$ 277.1335, found 277.1343. The ^1H and ^{13}C NMR spectral data are in good agreement with the literature data.[17]



Ethyl 2-[2-(dimethylamino)phenyl]-2-oxoacetate (72). This compound was obtained as a yellow oil in a 32% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 2.71 (s, 6H), 4.33 (q, J = 7.1 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 45.8, 61.8, 120.1, 123.7, 129.8, 130.9, 134.9, 155.7, 165.3, 189.1; HRMS (APCI) calcd for $[M+H]^+$ $C_{12}H_{16}NO_3$ 222.1125, found 222.1124.

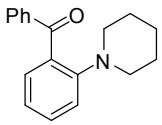


1-[2-(Dimethylamino)phenyl]-2-phenylethane-1,2-dione (74). This compound was obtained as a light brown solid in a 66% yield: mp 92-93 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 7.27 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.61 (td, J = 7.7, 1.7 Hz, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.97 (dd, J = 7.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.0, 122.9, 126.1, 128.1, 128.7, 130.3, 133.0, 133.2, 134.3, 135.6, 155.8, 189.3, 196.5; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{16}NO_2$ 254.1176, found 254.1176.

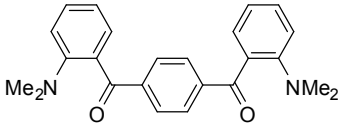


2-(Morpholino)benzophenone (76). This compound was obtained as a light yellow amorphous solid in an 89% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 2.86-2.89 (m, 4H),

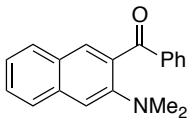
3.25-3.27 (m, 4H), 7.05 (d, J = 8.1 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.38-7.49 (m, 4H), 7.54 (t, J = 7.4 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 66.7, 118.7, 123.0, 128.2, 129.9, 130.4, 131.9, 133.0, 133.6, 137.6, 151.1, 198.8; HRMS (APCI) calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$ 268.1332, found 268.1333.



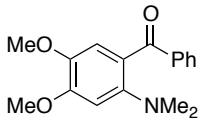
2-(Piperidin-1-yl)benzophenone (80). This compound was obtained as a light brown solid in an 80% yield: mp 94-95 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.17 (m, 4H), 1.24-1.30 (m, 2H), 2.83 (t, J = 5.3 Hz, 4H), 7.01-7.09 (m, 2H), 7.35-7.46 (m, 4H), 7.51 (t, J = 7.4 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 25.8, 53.7, 118.9, 122.0, 128.0, 130.1, 130.4, 131.8, 132.7, 133.4, 137.7, 152.7, 199.1; HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{20}NO$ 266.1539, found 266.1540.



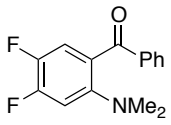
1,4-*Bis*(2-dimethylaminobenzoyl)benzene (82). 2.2 Equiv of the benzyne precursor and 5.0 equiv of CsF were used in this synthesis. The compound **82** was obtained as an orange solid in an 84% yield: mp 130-131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 12H), 6.93 (t, J = 7.4 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.9 Hz, 2H), 7.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 116.9, 119.5, 129.1, 129.6, 131.1, 132.2, 141.1, 152.1, 197.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{24}H_{25}N_2O_2$ 373.1911, found 373.1914.



[3-(Dimethylamino)naphthalen-2-yl](phenyl)methanone (84). This compound was obtained as a light orange oil in a 77% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 6H), 7.27 (s, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.75 (dd, *J* = 8.2, 3.8 Hz, 2H), 7.83 (s, 1H), 7.87 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 112.7, 124.3, 126.7, 127.9, 128.1, 128.4, 128.6, 130.3, 130.9, 133.0, 133.2, 135.6, 137.7, 149.3, 198.2; HRMS (APCI) calcd for $[M+H]^+$ $C_{19}H_{18}NO$ 276.1383, found 276.1386.



2-(Dimethylamino)-4,5-dimethoxybenzophenone (86). This compound was obtained as yellow crystals in an 83% yield: mp 101-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 6H), 3.80 (s, 3H), 3.93 (s, 3H), 6.55 (s, 1H), 6.94 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.3, 56.1, 56.6, 101.6, 114.1, 122.2, 128.1, 129.9, 132.5, 138.6, 143.1, 147.8, 152.1, 197.6; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{20}NO_3$ 286.1438, found 286.1441.

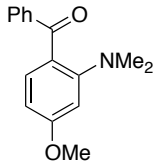


2-(Dimethylamino)-4,5-difluorobenzophenone (88). This compound was obtained as a pale yellow oil in a 62% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 6H), 6.77 (dd, *J* = 12.9, 6.6 Hz, 1H), 7.17 (dd, *J* = 10.3, 9.1 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 105.7, 105.9, 115.6, 119.4, 119.6, 124.9, 128.5, 130.0, 133.3, 137.3, 142.5, 142.6, 144.9, 145.0, 149.3,

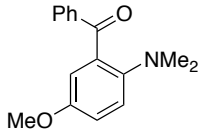
149.4, 150.9, 151.0, 153.4, 153.5, 195.9 (extra signals due to C-F coupling); HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{14}F_2NO$ 262.1038, found 262.1041.

Mixture of (2-(Dimethylamino)-4-methoxyphenyl)(phenyl)methanone (90a) and (2-(Dimethylamino)-5-methoxyphenyl)(phenyl)methanone (90b) (~1/1 ratio).

The mixture can be separated using preparative TLC. The mixture was isolated in an 81% yield.



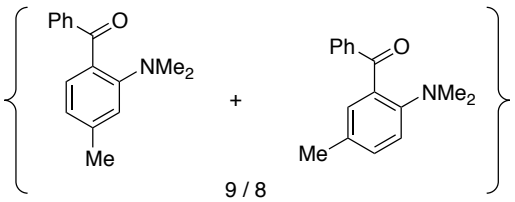
2-(Dimethylamino)-4-methoxybenzophenone (90a). This compound was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 6H), 3.85 (s, 3H), 6.40 (d, *J* = 8.5 Hz, 1H), 6.45 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5, 55.5, 102.1, 103.5, 121.6, 128.2, 130.1, 132.5, 133.9, 138.8, 154.0, 162.9, 197.1; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{18}NO_2$ 256.1332, found 256.1333.



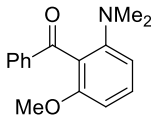
2-(Dimethylamino)-5-methoxybenzophenone (90b).

This compound was obtained as a yellow solid: mp 58-59 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 6H), 3.77 (s, 3H), 6.87 (d, *J* = 2.8 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 7.3 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 44.8, 55.9, 114.4, 117.5, 119.7, 128.3, 130.0, 133.0, 133.6, 137.6, 146.1, 154.4, 198.5; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{18}NO_2$ 256.1332, found 256.1334

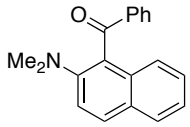


Mixture of 2-(Dimethylamino)-4-methoxy-benzophenone (92a) and 2-(dimethylamino)-5-methoxybenzophenone (92b) (~1/1 ratio). This mixture was obtained as a pale yellow oil in an 85% yield: ^{1}H NMR of the mixture (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, minor isomer), 2.38 (s, 3H, major isomer), 2.63 (s, 6H, minor), 2.70 (s, 6H, major), 6.71 (d, J = 7.7 Hz, 1H, major), 6.79 (s, 1H, major), 6.93 (d, J = 8.3 Hz, 1H, minor), 7.13 (s, 1H, minor), 7.18-7.26 (m, 2H), 7.41 (t, J = 7.7 Hz, 4H), 7.48-7.57 (m, 2H), 7.78-7.86 (m, 4H); ^{13}C NMR of the mixture (100 MHz, $CDCl_3$) δ 20.6, 22.2, 43.7, 44.1, 117.1, 117.2 (×2), 119.8 (×2), 126.4, 128.3, 129.3, 130.1, 130.5, 130.8, 131.4, 132.2, 132.7, 132.9, 137.9, 138.3, 142.2, 149.8, 152.0, 198.2, 198.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{18}NO$ 240.1383, found 240.1384.



2-(Dimethylamino)-6-methoxybenzophenone (94). This compound was obtained as a pale yellow solid in an 83% yield: mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 6H), 3.66 (s, 3H), 6.60 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 7.32 (t, J = 8.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.82 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.5, 55.9, 104.5, 111.1, 121.9, 128.4, 129.4, 130.7, 133.0, 138.1, 152.9, 157.8, 197.5; HRMS (APCI) calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332, found 256.1334.

Note: in the 1D-NOE experiment a correlation of 6.71 (d, 1H) – 2.63 (s, 6H) and of 6.59 (d, 1H) – 3.66 (s, 3H) is observed. This would not be the case if compound **94** were the other regioisomer.



[2-(Dimethylamino)naphthalen-1-yl](phenyl)methanone (96). This compound was obtained as a light orange oil in an 82% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 6H), 7.33-7.43 (m, 5H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.61-7.66 (m, 1H), 7.78-7.84 (m, 3H), 7.91 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.7, 119.3, 124.3, 124.5, 127.3, 127.6, 128.3, 128.6, 129.6, 129.9, 130.8, 131.9, 133.3, 138.6, 149.6, 199.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{19}H_{18}NO$ 276.1383, found 276.1386.

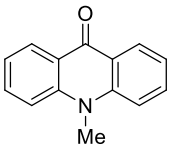
Note: in a 1D-NOE experiment a correlation of 7.42 (1H) – 2.72 (s, 6H) and in a ^{1}H-^{1}H COSY experiment a coupling of 7.42 (1H) to 7.91 (d, 1H) is observed. Were the other regioisomer formed, the latter coupling would be a triplet.

Synthesis of the Acridones

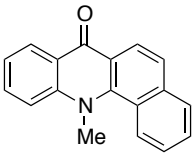
General procedure for synthesis of the acridones

To a mixture of the appropriate dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial, the silylaryl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then 3 mL of 1M HCl was added and the mixture was heated at 65 °C for 2 h. Then 5 mL of 1M NaOMe was added and the mixture was heated at 100 °C for an additional 2 h. After

cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired acridone.

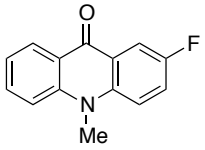


***N*-Methyl-9-acridone (97).** This compound was obtained as light brown crystals in a 95% yield starting from the substrate **38**, a 91% yield starting from the substrate **98**, and a 94% yield starting from the substrate **36**: mp 201-203 °C (lit.[88] mp 201-202 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 7.26 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 7.68 (t, J = 7.8 Hz, 2H), 8.53 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 114.9, 121.4, 122.6, 127.8, 133.9, 142.7, 178.2; HRMS (APCI) calcd for $C_{14}H_{12}NO$ $[M+H]^+$ 210.0913, found 210.0917. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[54]

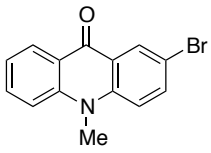


12-Methylbenz[*c*]acridin-7(12*H*)-one (100). This compound was obtained as a red brown solid in a 45% yield: mp 142-145 °C (lit.[89] mp 143-144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 3H), 7.36 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.60-7.67 (m, 2H), 7.76 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.44 (d, J =

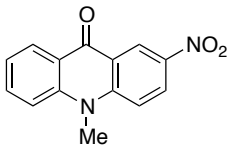
8.7 Hz, 1H), 8.53 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.1, 117.4, 121.7, 122.6, 122.8, 123.5, 124.3, 124.9, 125.0, 127.2, 127.5, 128.4, 129.1, 133.6, 137.6, 144.3, 145.9, 178.0; HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{14}NO$ 260.1070, found 260.1070.



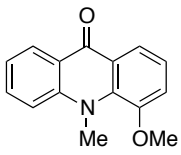
2-Fluoro-*N*-methylacridone (104). This compound was obtained as orange crystals in an 84% yield: mp 173-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.29-7.40 (m, 3H), 7.63 (ddd, *J* = 8.7, 7.0, 1.8 Hz, 1H), 8.05 (dd, *J* = 8.8, 2.9 Hz, 1H), 8.41 (dd, *J* = 8.1, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.1, 111.9, 112.1, 114.9, 117.1, 117.1, 121.5, 121.7, 122.1, 122.3, 123.3, 123.4, 127.7, 134.1, 139.1, 142.4, 156.4, 158.8, 177.3 (extra peaks due to C-F coupling); HRMS (APCI) calcd for $[M+H]^+$ $C_{14}H_{11}FNO$ 228.0819, found 228.0823.



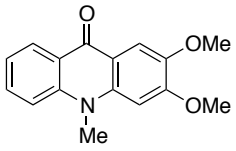
2-Bromo-*N*-methylacridone (106). This compound was obtained as brown crystals in a 79% yield: mp 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 7.17-7.27 (m, 2H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.58-7.68 (m, 2H), 8.40 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.50 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 114.7, 115.1, 117.0, 121.8, 122.4, 123.6, 127.8, 130.0, 134.2, 136.5, 141.2, 142.3, 176.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{14}H_{10}BrNO$ 288.0019, found 288.0020. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[54]



2-Nitro-*N*-methylacridone (108). This compound was obtained as an orange solid in a 59% yield: mp 284-286 °C (decomp.) (lit.[90] mp 287 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.82 (t, *J* = 8.2 Hz, 1H), 8.52 (dd, *J* = 17.8, 9.2 Hz, 2H), 9.39 (s, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 34.1, 116.4, 117.3, 121.4, 122.8, 123.3, 127.0, 127.4, 134.7, 141.3, 141.4, 142.9, 146.4, 176.4; HRMS (APCI) calcd for $[M+H]^+$ $C_{14}H_{11}N_2O_3$ 255.0764, found 255.0773. The ^{1}H NMR spectral data are in good agreement with the literature data.[91]

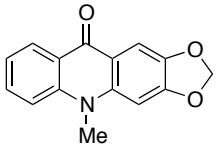


4-Methoxy-*N*-methylacridone (110). This compound was obtained as a red-yellow solid in an 87% yield: mp 89-91 °C (lit.[92] mp 90 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.95 (s, 3H), 7.11-7.27 (m, 3H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.66 (ddd, *J* = 8.5, 6.8, 1.7 Hz, 1H), 8.09 (dd, *J* = 7.7, 1.8 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.6, 56.6, 115.7, 116.3, 119.3, 121.5, 122.1, 122.9, 125.6, 127.3, 133.8, 135.8, 145.8, 150.1, 178.6; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{14}NO_2$ 240.1019, found 240.1022.

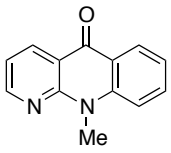


2,3-Dimethoxy-*N*-methylacridone (112). This compound was obtained as light brown needles in a 77% yield: mp 193-196 °C (lit.[93] mp 192-195 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 6.72 (s, 1H), 7.22-7.27 (m, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 8.52 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz,

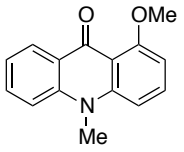
$CDCl_3$) δ 34.0, 56.4, 56.4, 96.7, 107.0, 114.8, 116.4, 121.2, 122.2, 127.6, 133.1, 138.9, 142.1, 145.4, 154.9, 176.5; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{16}NO_3$ 270.1125, found 270.1132. The ^1H NMR spectral data are in good agreement with the literature data.[93]



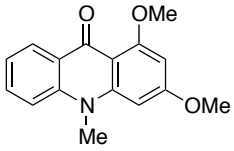
1,3-Dioxolo[4,5-*b*]-5-methyl-acridan-10-one (114). This compound was obtained as a light brown solid in a 38% yield: mp 258-260 °C (lit.[93] mp 260-263 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.01 (s, 2H), 6.88 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.74 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5, 94.8, 102.3, 104.2, 115.0, 117.5, 121.6, 121.8, 127.4, 133.4, 140.7, 142.0, 144.0, 154.0, 176.8; HRMS (APCI) calcd for $[M+H]^+$ $C_{15}H_{12}NO_3$ 254.0812, found 254.0821. The ^1H NMR spectral data are in good agreement with the literature data.[93]



10-Methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (118). This compound was obtained as a gray brown solid in a 48% yield: mp 220-221°C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.20-7.27 (m, 1H), 7.33 (dd, J = 7.9, 7.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.77 (ddd, J = 8.7, 6.9, 1.7 Hz, 1H), 8.52 (dd, J = 8.0, 1.8 Hz, 1H), 8.73-8.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 115.6, 117.4, 117.6, 122.1, 122.8, 127.8, 134.6, 137.0, 142.6, 151.3, 153.5, 178.6; HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_{11}N_2O$ 211.0866, found 211.0867.



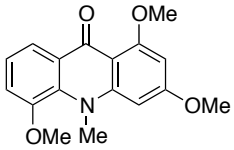
***N*-Methyl-1-methoxy-9-acridone (120).** This compound was obtained as a pale brown solid in an 87% yield: mp 164-165 °C (lit.[94] mp 162-164 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.95 (s, 3H), 6.60 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.45 (t, J = 8.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.7, 56.3, 102.7, 107.0, 113.2, 114.3, 121.2, 124.4, 127.6, 133.0, 133.8, 141.7, 145.2, 161.5, 177.9; HRMS (APCI) calcd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1024. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[54]



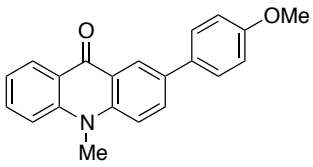
1,3-Dimethoxy-*N*-methylacridone (123). This compound was obtained as a pale yellow solid in a 78% yield: mp 158-160 °C (lit.[89] mp 162-163 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 6.08 (s, 1H), 6.11 (s, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.43 (t, J = 8.6 Hz, 1H), 8.34 (d, J = 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.7, 55.5, 56.1, 90.2, 92.4, 108.2, 114.4, 121.3, 124.3, 127.4, 132.8, 141.7, 146.7, 163.1, 164.1, 176.9; HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{16}NO_3$ 270.1125, found 270.1129. The ^{13}C NMR spectral data are in good agreement with the literature data.[95]

Note: in a 1D-NOE experiment a correlation of 3.48 (s, 3H) – 7.13 (d, 1H) and 6.11 (s, 1H) is observed. If the other regioisomer had been obtained, a correlation of 3.48 (s, 3H) to one of

the OMe groups (3.86 or 3.77 ppm) and lack of 3.48 (s, 3H) – 6.11 (s, 1H) would be expected.

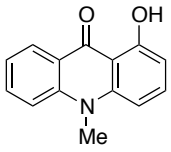


1,3,5-Trimethoxy-10-methylacridone (125). The standard procedure yielded the desired acridone (9%) and the uncyclized aminoaryl ketone (77%). The latter compound was exposed to 150 ^{o}C in 5 mL MeCN for 4 h while stirring. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford an additional 51% of the desired product **125**. Thus, the acridone **125** was obtained in a 60% overall yield as a brown red solid: mp 128-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 6.16 (d, J = 2.1 Hz, 1H), 6.28 (d, J = 2.2 Hz, 1H), 7.00 (dd, J = 7.9, 1.5 Hz, 1H), 7.02-7.26 (m, 1H), 7.93 (dd, J = 7.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.4, 55.4, 56.1, 56.3, 91.0, 92.5, 108.9, 114.6, 119.0, 121.9, 127.8, 134.5, 149.4, 149.8, 162.4, 163.9, 177.1; HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{18}NO_4$ 300.1230, found 300.1239.



Suzuki-Miyaura procedure [96] *for the preparation of* **2-(4-methoxyphenyl)-10-methylacridin-9(10*H*)-one (119).** To a 2 mL microwave vial was added the bromoacridone **106** (0.28 mmol), *p*-methoxyphenyl boronic acid (1.2 equiv), 1M Cs_2CO_3 (0.2 mL), and 5 mol % $Pd(PPh_3)_4$ in 1/1 DMF/EtOH (1 mL). The solution was

vigorously stirred for 5 min at room temperature, flushed with argon, and then heated to 120 ^{o}C under microwave irradiation for 20 min. Upon cooling to room temperature, the resulting reaction mixture was diluted with a saturated solution of Na_2SO_4 and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired product as yellow needles in a 75% yield: mp 218-220 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.86 (s, 3H), 6.99 (d, J = 8.8 Hz, 2H), 7.26 (ddd, J = 7.9, 5.9, 1.0 Hz, 1H), 7.48 (dd, J = 13.7, 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.68 (ddd, J = 8.8, 7.0, 1.7 Hz, 1H), 7.88 (dd, J = 9.0, 2.4 Hz, 1H), 8.55 (dd, J = 8.0, 1.7 Hz, 1H), 8.72 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 55.6, 114.6, 115.0, 115.6, 121.4, 122.6, 122.8, 124.8, 128.0, 128.1, 132.3, 132.4, 133.7, 133.9, 141.5, 142.5, 159.4, 178.3; HRMS (APCI) calcd for $[M+H]^+$ $C_{21}H_{18}NO_2$ 316.1332, found 316.1335.



Synthesis of the natural product ***N*-methyl-1-hydroxy-9-acridone (121).** A mixture of *N*-methyl-1-methoxy-9-acridone (**120**) (62 mg, 27.5 mmol) and HI (47% aqueous solution, 3 mL) was stirred for 24 h at 100 ^{o}C in a closed vial. After cooling to room temperature, 15 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 15 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc (3/1) as the

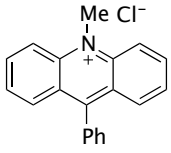
eluent to afford the desired *N*-methyl-1-hydroxy-9-acridone as yellow needles in a 94% yield: mp 189-190 °C (lit.[97] mp 190 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 6.56 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 103.8, 107.6, 109.8, 114.8, 120.9, 121.5, 126.6, 134.5, 136.0, 142.2, 143.2, 163.5, 182.1; ^{13}C NMR (100 MHz, DMSO + $CDCl_3$) δ 33.9, 104.2, 106.4, 108.8, 115.4, 119.8, 121.1, 125.4, 134.3, 135.7, 141.7, 142.7, 162.4, 181.0; HRMS (APCI) calcd for $C_{14}H_{12}NO_2$ $[M+H]^+$ 226.0863, found 226.0862.

Synthesis of Acridinium Salts

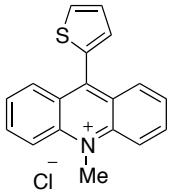
Method A. To a mixture of the appropriate *N*,*N*-disubstituted hydrazone (0.25 mmol), CsF (4 equiv) and 5 mL of acetonitrile in a 10 mL vial, the silylaryl triflate (1.8 equiv) was added. The reaction mixture was allowed to stir for 10 h at room temperature. Then 3 mL of 1M HCl was added and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 25 ml of brine in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was eluted with hexanes/EtOAc (1/2) using a preparative thin-layer chromatography plate with silica gel. The bright yellow spot of high polarity was collected and put on a short plug of silica gel. CH_2Cl_2/MeOH (1/1, 15 mL) was run through the plug, the solvent was evaporated to afford the desired acridinium salt.

Method B. The silylaryl triflate (2.8 equiv) was added a mixture of benzaldehyde *N*-methylhydrazone (0.25 mmol), CsF (5 equiv) and 5 mL of acetonitrile in a 10 mL vial. The reaction mixture was allowed to stir for 10 h at room temperature. The rest of the procedure follows Method A.

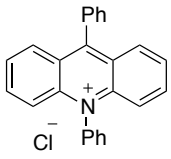
Method C. The silylaryl triflate (1.5 equiv) was added to a mixture of the aminoaryl ketone **8** (0.25 mmol), CsF (3 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. The rest of the procedure follows Method A.



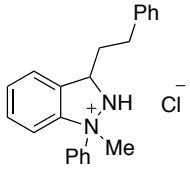
10-Methyl-9-phenylacridin-10-ium chloride (127). This compound was obtained as a dark yellow-green solid in an 88% yield (Method A), in a 41% yield (Method B), and in a 78% yield (Method C): 201-203 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (s, 3H), 7.44-7.51 (m, 2H), 7.66-7.76 (m, 3H), 7.79 (dd, *J* = 8.7, 6.7 Hz, 2H), 8.00 (dd, *J* = 8.7, 1.6 Hz, 2H), 8.38 (ddd, *J* = 9.0, 6.8, 1.6 Hz, 2H), 8.75 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 119.1, 126.3, 128.1, 129.3, 130.0, 130.4, 130.7, 133.2, 139.4, 141.8, 161.7; HRMS (APCI) calcd for $[M]^+$ $C_{20}H_{16}N$ 270.1277, found 270.1278. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[51]



10-Methyl-9-(thiophen-2-yl)acridin-10-ium chloride (130). This compound was obtained as a dark green solid in an 88% yield: mp 136-138 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (s, 3H), 7.34-7.41 (m, 2H), 7.72-7.80 (m, 2H), 7.82 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 8.7 Hz, 2H), 8.31 (dd, J = 8.9, 7.1 Hz, 2H), 8.66 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.5, 118.9, 127.0, 128.2, 128.3, 129.9, 130.8, 131.6, 132.9, 139.3, 141.4, 154.7; HRMS (APCI) calcd for $[M]^+$ $C_{18}H_{14}NS$ 276.0841, found 276.0849.



9,10-Diphenylacridin-10-ium chloride (132). This compound was obtained as a yellow solid in a 31% yield: mp 259-263 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 9.2 Hz, 2H), 7.66-7.70 (m, 2H), 7.71-7.79 (m, 7H), 7.85-7.92 (m, 3H), 8.03-8.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.6, 126.2, 127.8, 128.0, 128.9, 130.1, 130.2, 130.5, 131.6, 131.8, 133.0, 137.1, 138.4, 142.1, 163.4; HRMS (APCI) calcd for $[M]^+$ $C_{25}H_{18}N$ 332.1434, found 332.1443.



Synthesis of **1-Methyl-3-phenethyl-1-phenyl-2,3-dihydro-1*H*-indazol-1-ium chloride (134).** To a mixture of the dihydrocinnamyl *N*-methyl-*N*-phenylhydrazone **133** (0.25 mmol), CsF (0.75 mmol, 3 equiv), and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added. The vial was capped and

the reaction mixture was allowed to stir for 10 h at 65 °C. The rest of the procedure follows Method A described for the preparation of the acridinium salts. The final compound was obtained in an 81% yield as a dark brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69-1.81 (m, 1H), 2.02-2.11 (m, 1H), 2.75 (t, J = 8.5 Hz, 2H), 4.12 (s, 3H), 4.99-5.04 (m, 1H), 7.08 (d, J = 7.2 Hz, 2H), 7.14-7.19 (m, 1H), 7.21-7.29 (m, 3H), 7.41-7.47 (m, 2H), 7.48-7.61 (m, 5H), 7.72-7.78 (m, 2H), 8.27 (d, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.5, 36.4, 58.3, 61.3, 118.7, 121.5, 124.9, 126.4, 128.6, 128.8, 130.1, 130.4, 131.3, 132.2, 136.7, 141.0, 145.6, 149.2; HRMS (APCI) calcd for $[M]^+$ $C_{22}H_{23}N_2$ 315.1856, found 315.1852.

Synthesis of 1*H*-Indazoles

General procedures for the one-pot synthesis of the indazoles

Method A (Ac_2O/N_2H_4)

o-(Trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added to a mixture of the appropriate dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv), acetic anhydride (0.50 mmol, 2 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then the solvent was evaporated under reduced pressure, 3 mL of $N_2H_4{\cdot}H_2O$ (85% solution, w/w) was added and the mixture was heated at 100 ^{o}C for an additional 10 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 50 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 15 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired indazole.

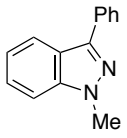
Method B (Boc_2O/HCl)

o-(Trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added to a mixture of the appropriate dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv), di-*tert*-butyl dicarbonate (1.50 mmol, 6 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then 3 mL of 1M HCl was added and the mixture was heated at 75 °C for an additional 3 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired indazole.

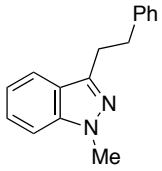
Method C (via NCS chlorination/cyclization of the ketimine system)

The silylaryl triflate (0.28 mmol, 1.1 equiv) was added to a mixture of the appropriate dialkylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then NCS (1.5 equiv) was added and the mixture was heated at 65 °C for an additional 2 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 40 ml of water in a separatory funnel. After shaking the

layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was dissolved in 5 mL of acetonitrile and heated at 130 ^{o}C for 10 h. After cooling to room temperature, 25 ml of dichloromethane was added to the residue, and the reaction mixture was poured into 40 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired 1*H*-indazole.

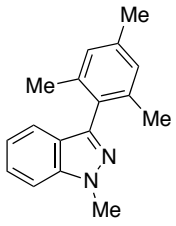


1-Methyl-3-phenyl-1*H*-indazole (141). This compound was obtained as a gray solid in an 83% yield by Method A, and in a 66% yield by Method C: mp 81-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.21 (s, 1H), 7.42 (t, J = 4.3 Hz, 3H), 7.52 (t, J = 7.6 Hz, 2H), 7.99 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.7, 109.4, 121.1, 121.5, 121.8, 126.5, 127.6, 128.0, 129.0, 133.9, 141.6, 143.9; MS (EI) *m/z* (%) 208 (M^+, 100%), 77 (10%); HRMS (APCI) 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). The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[98]

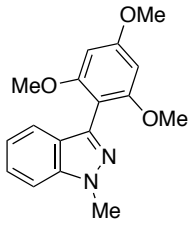


1-Methyl-3-phenethyl-1*H*-indazole (154). This compound was obtained as as

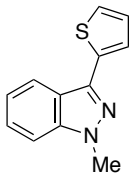
a colorless amorphous solid in an 80% yield by Method A starting from compound **153**, in an 81% yield by Method B starting from compound **153**, and in a 41% yield by Method A starting from compound **46**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (dd, *J* = 10.2, 6.2 Hz, 2H), 3.30 (dd, *J* = 10.1, 6.1 Hz, 2H), 4.04 (s, 3H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.20-7.26 (m, 1H), 7.28-7.50 (m, 6H), 7.63 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 35.4, 36.0, 109.0, 117.5, 119.8, 120.5, 122.8, 126.2, 126.4, 128.6, 141.0, 142.0, 144.8; MS (EI) *m/z* (%) 236 (M^+, 58%), 145 (100%), 91 (21%); HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{17}N_2$ 237.1386, found 237.1393; IR (CH_2Cl_2, cm^{-1}) 2928 (s), 2859 (m), 1616 (s), 1505 (s).



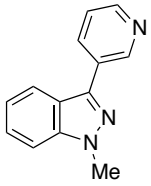
3-Mesityl-1-methyl-1*H*-indazole (15). This compound was obtained as a light yellow amorphous solid in a 91% yield (Method A) and in a 33% yield using the procedure for preparation of aminoaryl ketones (Table 1, entry 3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 2.38 (s, 3H), 4.15 (s, 3H), 7.00 (s, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.38-7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 21.4, 35.7, 109.1, 120.3, 121.3, 123.5, 126.3, 128.3, 129.1, 137.9, 138.3, 140.8, 143.9; MS (EI) *m/z* (%) 250 (M^+, 73%), 249 ($[M-H]^+$, 100%), 235 (13%), 219 (11%); HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{19}N_2$ 251.1543, found 251.1549; IR (CH_2Cl_2, cm^{-1}) 3004 (m), 2921 (s), 2858 (m), 1614 (s), 1492 (s), 1337 (s).



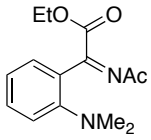
1-Methyl-3-(2,4,6-trimethoxyphenyl)-1*H*-indazole (156). This compound was obtained as a yellow solid in a 76% yield (Method A): mp 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 6H), 3.89 (s, 3H), 4.13 (s, 3H), 6.27 (s, 2H), 7.08 (t, J = 7.2 Hz, 1H), 7.33-7.42 (m, 2H), 7.46 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.7, 55.6, 56.1, 91.0, 109.0, 119.9, 121.9, 124.5, 125.9, 138.2, 140.7, 157.3, 160.1, 161.8; MS (EI) *m/z* (%) 298 (M^+, 100%), 297 ($[M-H]^+$, 39%), 267 (16%); HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{19}N_2O_3$ 299.1390, found 299.1399; IR (CH_2Cl_2, cm^{-1}) 3009 (w), 2940 (m), 2839 (m), 1615 (s), 1587 (s), 1337 (s), 1127 (s).



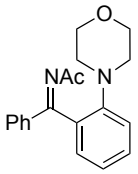
1-Methyl-3-(thiophen-2-yl)-1*H*-indazole (149). This compound was obtained as a yellow-green oil in a 39% yield by Method A and in a 56 % yield by Method B: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 3H), 7.17 (dd, J = 4.9, 3.7 Hz, 2H), 7.20-7.26 (m, 2H), 7.33-7.37 (m, 2H), 7.38-7.46 (m, 3H), 7.63 (d, J = 3.6 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8, 109.4, 121.3, 121.3, 124.5, 124.9, 126.8, 127.8, 136.2, 139.0, 141.5; MS (EI) *m/z* (%) 214 (M^+, 100%), 199 (25%); HRMS (APCI) 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).



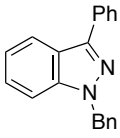
1-Methyl-3-(pyridin-3-yl)-1*H*-indazole (158). This compound was obtained as an orange amorphous solid in a 29% yield (Method A): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 3H), 7.18 (dt, *J* = 8.1, 4.0 Hz, 1H), 7.34 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.37 (d, *J* = 3.6 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 8.17 (dt, *J* = 7.9, 1.8 Hz, 1H), 8.55 (dd, *J* = 4.7, 1.3 Hz, 1H), 9.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9, 109.6, 121.0, 121.7, 121.7, 123.9, 126.8, 130.0, 134.5, 140.8, 141.6, 148.6, 149.0; MS (EI) *m/z* (%) 209 (M^+, 100%), 208 ($[M-H]^+$, 33%), 181 (10%); HRMS (APCI) calcd for $[M+H]^+$ $C_{13}H_{12}N_3$ 210.1026, found 210.1029; IR (CH_2Cl_2, cm^{-1}) 3392 (w, broad), 2939 (m), 1618 (s), 1496 (s), 1153 (s).



(*E*)-Ethyl 2-(acetylimino)-2-[2-(dimethylamino)phenyl]acetate (161). This compound was obtained as an orange amorphous solid in a 54% yield (Method A): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 2.36 (s, 3H), 2.66 (s, 6H), 4.22 (q, *J* = 7.1 Hz, 2H), 7.09-7.21 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 25.1, 45.0, 62.1, 119.8, 124.2, 130.2, 130.4, 132.7, 154.1, 157.3, 163.4, 185.6; MS (EI) *m/z* (%) 262 (M^+, 11%), 203 (82%), 189 (29%), 175 (19%), 158 (84%), 147 (100%), 131 (31%), 43 (26%); HRMS (APCI) calcd for $[M+H]^+$ $C_{14}H_{19}N_2O_3$ 263.1390, found 263.1397; IR (CH_2Cl_2, cm^{-1}) 2942 (m), 2867 (m), 2835 (m). 2792 (m), 1736 (s), 1708 (s), 1652 (s), 1595 (s), 1490 (s).



***N*-[(2-Morpholinophenyl)(phenyl)methylene]acetamide (162).** This compound was obtained as a yellow amorphous solid in a 72% yield (Method A): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.89 (t, *J* = 4.6 Hz, 4H), 3.31 (t, *J* = 4.6 Hz, 4H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.44 (dt, *J* = 15.1, 7.7 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 52.1, 66.9, 120.1, 123.2, 128.3, 129.0, 129.8, 131.4, 131.4, 131.6, 137.4, 150.8, 165.8, 185.4; HRMS (APCI) calcd for $[M+H]^+$ $C_{19}H_{21}N_2O_2$ 309.1598, found 309.1601.

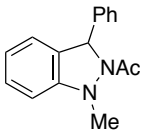


Procedure for the preparation of **1-benzyl-3-phenyl-1*H*-indazole (164).** *o*-(Trimethylsilyl)phenyl triflate (149 mg, 0.50 mmol, 2.0 equiv) was added to a mixture of benzaldehyde dibenzylhydrazone (**163**, 75 mg, 0.25 mmol), CsF (151 mg, 1.00 mmol, 4 equiv), and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford indazole **164** as a yellow amorphous solid in a 51% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 2H), 7.16-7.34 (m, 6H), 7.37 (d, *J* = 4.1 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H),

8.02 (d, J = 7.1 Hz, 2H), 8.05 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 109.8, 121.3, 121.6, 122.3, 126.6, 127.3, 127.7, 127.9, 128.1, 128.9, 129.0, 133.9, 137.1, 141.3, 144.4; MS (EI) *m/z* (%) 284 (M^+, 100%), 91 (79%); HRMS (APCI) calcd for $[M+H]^+$ $C_{20}H_{16}N_2$ 285.1386, found 285.1394; IR (CH_2Cl_2, cm^{-1}) 2927 (m), 2854 (w), 1614 (s), 1493 (s), 1350 (s). The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[99]

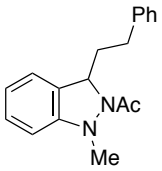
General procedure for the preparation of the 2-acetyl-1-methyl-dihydroindazoles

o-(Trimethylsilyl)phenyl triflate (0.28 mmol, 1.1 equiv) was added to a mixture of the appropriate dimethylhydrazone (0.25 mmol), CsF (0.75 mmol, 3 equiv), acetic anhydride (0.50 mmol, 2 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then the reaction mixture was poured into 25 ml of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 ml). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired *N*-acetylated dihydroindazole.

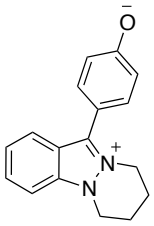


1-(1-Methyl-3-phenyl-1*H*-indazol-2(3*H*)-yl)ethanone (140, R^1 = Ph, R^2 = Me). This compound was obtained as a light brown amorphous solid in an 83% yield as an inseparable mixture of diastereomers (ratio ~5:1): major diastereomer ^{1}H NMR (400 MHz,

$CDCl_3$) δ 2.30 (s, 3H), 3.05 (s, 3H), 6.45 (s, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.19-7.28 (m, 2H), 7.31 (t, *J* = 6.5 Hz, 3H), 7.37 (d, *J* = 6.9 Hz, 3H); minor diastereomer (selected peaks) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (br s, 3H), 3.36 (br s, 3H) 6.06 (br s, 1H) 6.93-6.95 (br m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (all of the peaks listed for the mixture of diastereomers) δ 21.5, 22.9, 45.7, 48.6, 64.2, 64.2, 68.0, 112.7, 113.8, 115.4, 123.3, 124.1, 124.2, 126.4, 127.8, 127.8, 128.7, 129.0, 129.3, 130.8, 142.0, 150.4, 173.7; MS (EI) *m/z* (%) 252 (M^+, 14%), 209 (100%), 194 (15%); HRMS (APCI) calcd for $[M+H]^+$ $C_{16}H_{17}N_2O$ 253.1335, found 253.1332; IR (CH_2Cl_2, cm^{-1}) 2921 (m), 1666 (s), 1610 (m), 1483 (m), 1381 (s).



1-[1-Methyl-3-phenethyl-1*H*-indazol-2(3*H*)-yl]ethanone (140, R^1 = CH_2CH_2Ph, R^2 = Me). This compound was obtained as a light yellow amorphous solid in a 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.09-2.23 (m, 1H), 2.29 (s, 3H), 2.75 (d, *J* = 14.6 Hz, 1H), 2.88 (td, *J* = 12.7, 6.1 Hz, 1H), 3.09 (s, 3H), 5.45 (t, *J* = 5.6 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.15-7.24 (m, 4H), 7.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 32.5, 41.1, 48.6, 61.7, 113.8, 117.5, 123.0, 123.8, 126.0, 128.3, 128.5, 132.4, 141.9, 150.1, 174.5; MS (EI) *m/z* (%) 280 (M^+, 14%), 237 (85%), 175 (24%), 145 (71%), 133 (100%), 104 (33%), 77 (22%); HRMS (APCI) calcd for $[M+H]^+$ $C_{18}H_{21}N_2O$ 281.1648, found 281.1656; IR (CH_2Cl_2, cm^{-1}) 2920 (w), 2863 (w), 1660 (s), 1610 (w), 1385 (s).



Synthesis of **nigellidine analogue 175**. The silylaryl triflate **2** (0.28 mmol, 1.1 equiv) was added to a mixture of the hydrazone **172** (0.25 mmol),[100] CsF (0.75 mmol, 3 equiv) and 5 mL of acetonitrile in a 10 mL vial. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then $NH_2OH{\cdot}HCl$ (2 equiv) and EtOH (3 mL) were added and the mixture was heated at 150 °C for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel using hexanes/EtOAc (1/1) as the eluent to afford the tricyclic product **174** as a dark brown oil (37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26-2.52 (m, 4H), 3.92 (s, 3H), 4.70 (dt, J = 19.5, 6.1 Hz, 4H), 7.16 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.8 Hz, 3H), 7.76-7.83 (m, 2H). BBr_3 (1.0 M solution in CH_2Cl_2, 6 equiv)[101] was added dropwise to a solution of the compound **174** in CH_2Cl_2 (5 mL) at 0 °C and stirred at room temperature for 5 h. The mixture was extracted with 10% methanol in dichloromethane (5 mL × 4) and the organic solution was concentrated under reduced pressure. The residue was washed with hexanes (5 mL × 2), diethyl ether (5 mL × 2), and ethyl acetate (5 mL × 2) and dried *in vacuo* to afford the desired nigellidine analogue **175** as a black oil in a 67% yield: ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD) δ 2.15-2.38 (m, 4H), 4.56 (dt, J = 31.3, 6.1 Hz, 4H), 6.99 (d, J = 8.6 Hz, 2H), 7.35-7.40 (m, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.7 Hz, 1H), 7.68-7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 19.4, 20.3, 47.0, 49.1, 110.2, 113.9, 116.9, 119.4, 122.7, 125.8,

131.5, 133.7, 140.6, 144.8, 160.8. HRMS (APCI) calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$ 265.1335, found 265.1337.

5.7. References

(1) Liu, Z.; Larock R. C. *J. Org. Chem.* **2006**, *71*, 3198.

(2) Cant, A. A.; Bertand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199.

(3) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.

(4) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168.

(5) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.

(6) Rogness, R.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003.

(7) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem. Asian J.* **2010**, *5*, 153.

(8) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040.

(9) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340.

(10) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368.

(11) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(12) Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. *Org. Lett.* **2010**, *12*, 3736.

(13) Switching the solvent to THF had a major impact in our previously reported work: Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.

(14) (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley-Interscience: New York, **1963**. (b) Batt, D. G.; Goodman, J.; Jones, D. G.; Kerr, J. S.; Mantegna, L. R.;

McAllister, C.; Newton, R. C.; Nurnberg, S.; Welch, P. K., Covington, M. B. *J. Med. Chem.* **1993**, *36*, 1434.

(15) Martjuga, M.; Shabashov, D.; Belyakov, S.; Liepinsh, E.; Suna, E. *J. Org. Chem.* **2010**, *75*, 2357.

(16) Gabbutt, C. D.; Heron, B. M.; McCreary, J. M.; Thomas, D. A. *J. Chem. Res.* **2002**, 69.

(17) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorg. Med. Chem.* **2009**, *17*, 4441.

(18) Casey, A. C.; Malhotra, A. *Tetrahedron Lett.* **1975**, 401.

(19) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.

(20) Petroski, R. J. *Synth. Commun.* **2006**, *36*, 1727.

(21) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, **1998**; Chapter 5, pp. 203-229.

(22) One of the identified products appears to be diphenylmethylamine.

(23) Xie, C.; Zhang, Y. *Org. Lett.* **2007**, 9, 781.

(24) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2743.

(25) For a similar observation, see: Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003.

(26) For an explanation of the reactivity of the unsymmetrical monomethoxy benzyne, see: (a) Z. Liu, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 3198. (b) R. Sanz, *Org. Prep. Proced. Int.*

2008, *40*, 215. (c) P. H.-Y. Cheong, R. S Paton, S. M. Bronner, G-Y. J. Im, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267.

(27) For an explanation of the reactivity of the unsymmetrical naphthalyne, see ref. 25.

(28) A similar approach has been recently reported by Greaney, where an *N*-aryl aniline underwent an intramolecular S_NAr reaction under microwave conditions with the formation of *N*-arylacridones: see ref. 4.

(29) Prager, R. H.; Williams, C. M. *Sci. Synth.* **2005**, *15*, 1029.

(30) David-Cordnonnier, M.-H.; Laine, W.; Gaslonde, T.; Michel, S.; Tillequin, F.; Koch, M.; Léonce, S.; Pierré, A.; Bailly, C. *Curr. Med. Chem.: Anti-cancer Agents* **2004**, *4*, 83.

(31) Basco, L. K.; Mitaku, S.; Skaltsounis, A. L.; Ravelomanantsoa, N.; Tillequin, F.; Koch, M.; Le Bras, J. *Antimicrob. Agents Chemother.* **1994**, *38*, 1169.

(32) Kamdem Waffo, A. F.; Coombes, P. H.; Crouch, N. L.; Mulholland, D. A.; El Amin, S. M. M.; Smith, P. J. *Phytochem.* **2007**, *68*, 663.

(33) Markina, N. A.; Mancuso, R.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2011**, *13*, 265.

(34) Mink, K.; Bracher, F. *Arch. Pharm. (Weinheim, Ger.)* **2007**, *340*, 429.

(35) Mefetah, H.; Brouant, P.; Charbit, J.-J.; Placidi, M.; Galy, A. M.; Galy, J. P.; Soyfer, J.-C.; Barbe, J.; Mesavalle, C. *et al. Heterocyclic Commun.* **1994**, *1*, 27.

(36) Koch, M.; Tillequin, F.; Michel, S.; Hickman, J.; Pierre, A.; Leonce, S.; Pfeiffer, B.; Renard, P.; U.S. Patent Appl. Publ. 24, 2005.

(37) Misbahi, H.; Brouant, P.; Hever, A.; Molnar, A. M.; Wolfard, K.; Spengler, G.; Mefetah,

H.; Molnar, J.; Barbe, J. *Anticancer Res.* **2002**, *22*, 2097.

(38) Rosza, Z.; Szendrei, K.; Kovacs, Z.; Novak, I.; Minker, E. *Phytochem.* **1978**, *17*, 169.

(39) Fujiware, M.; Okamoto, M.; Okamoto, M.; Watanabe, M.; Machida, H.; Shigeta, S.; Konno, K.; Yokota, T.; Baba, M. *Antiviral Res.* **1999**, *43*, 189.

(40) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

(41) Lamberton, J. A.; Price, J. R. *Aust. J. Chem.* **1953**, *6*, 66.

(42) Waffo, A. F. K.; Coombes, P. H.; Crouch, N. R.; Mulholland, D. A.; El Amin, S. M. M.; Smith, P. J. *Phytochem.* **2007**, *68*, 663.

(43) Ju-ichi, M.; Inoue, M.; Ito, C.; Matsuoka, M.; Furukawa, H.; Kajiura, I. *Heterocycles* **1987**, *26*, 1873.

(44) Putic, A.; Stecher, L.; Prinz, H.; Müller, K. *Eur. J. Med. Chem.* **2010**, *45*, 5345.

(45) Hughes, G. L.; Ritchie, E. *Aust. J. Scient. Res. (A)* **1951**, *4*, 423.

(46) Horne, S.; Rodrigo, R. *Chem. Commun.* **1991**, 1046.

(47) (a) David-Cordonnier, M.-H.; Laine, W.; Gaslonde, T.; Sylvie, M.; Tillequin, F.; Koch, M.; Leonce, S.; Pierre, A.; Bailly, C. *Curr. Med. Chem. Anticancer Agents* **2004**, *4*, 83. (b) Dorr, R. T.; Liddil, J. D.; Von Hoff, D. D.; Soble, M.; Osborne, C. K. *Cancer Res.* **1989**, *49*, 340.

(48) Vaquette, J.; Cleriot, M. O.; Paris, M. R.; Pousset, J. L.; Cave, A.; Paris, R. R. *Plant Med. Phytother.* **1974**, *8*, 57.

(49) Herath, H. M. T. B.; Müller, K.; Diyabalanage, H. V. K. *J. Heterocyclic Chem.* **2004**, *41*, 23.

(50) Furukawa, H.; Ito, H.; Toyoko, M.; Motoharu, J.; Mami, I.; Ichiro, K.; Mitsuo, O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1593.

(51) Joseph, J.; Kuruvilla, E.; Achuthan, A. T.; Ramaiah, D.; Schuster, G. B. *Bioconjugate Chem.* **2004**, *15*, 1230.

(52) This cyclization was occurring even when trying to purify the imine on silica gel.

(53) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673.

(54) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.

(55) Fukuzumi, S.; Kotani, H.; Lee, Y.-M.; Nam, W. *J. Am. Chem. Soc.* **2008**, *130*, 15134.

(56) Ohkubo, K.; Kobayashi, T.; Fukuzumi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 8652.

(57) All our attempts to ring open the cyclic structure or dequaternarize the ammonium fragment of this product failed.

(58) For a review, see: Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415.

(59) Guglielmotti, A.; De Joannon, A. C.; Cazzolla, N.; Marchetti, M.; Soldo, L.; Cavallo, G.; Pinza, M. *Pharmacol. Res.* **1995**, *32*, 369.

(60) (a) Hartmann, M.; Sommer, M. E.; Keppler, B. K.; Kratz, F.; Einhaüser, Th. J. *J. Inorg. Biochem.* **1995**, *59*, 214. (b) Clarke, M. J. *Coord. Chem. Rev.* **2003**, *236*, 209.

(61) Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers, J. D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627.

(62) For a recent review, see: Hsu, E. S. *Am. J. Ther.* **2010**, *17*, 476.

(63) For a review, see: Di Cosimo, S.; Ferretti, G.; Papaldo, P.; Carlini, P.; Fabi, A.; Cognetti, F. *Drugs of Today* **2003**, *39*, 157.

(64) (a) Krapcho, A. P.; Haydar, S. N. *J. Heterocycl. Chem.* **2001**, *38*, 1153. (b) Dees, E. C.; Whitfield, L. R.; Grove, W. R.; Rummel, S.; Grochow, L. B; Donehower, R. C. *Clin. Cancer Res.* **2000***, 6,* 3885.

(65) For a review, see: Schmidt, A.; Beutler, A.; Snovydovych, B. *Eur. J. Org. Chem.* **2008**, 4073.

(66) (a) Jin, T.; Yamamoto, Y. *Angew. Chem. Intl. Ed.* **2007**, *46*, 3323. (b) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219.

(67) *N*-Tosylhydrazones have been alternatively employed as starting materials for the benzyne Fischer-indole reaction: McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667.

(68) 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 **135** was fully converted to the chlorohydrazone **136** in about 30 minutes. We have also found that upon addition of CsF to the resulting reaction mixture, the chlorohydrazone **136** is instantly converted to its fluoro analogue **136'** (X = F, supported by HRMS).

(69) The product was not separable from the starting hydrazone using flash chromatography.

(70) Li, P.; Wu, C.; Zhao, J.; Rogness, D. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 3149.

(71) The reaction seems to be independent of the amount of oxygen in the reaction media suggesting that the final aromatization step is not an oxygen-induced oxidation of the substrate. This is consistent with ref. 70.

(72) Chen, C.; Andreani, T.; Li, H. *Org. Lett.* **2011**, *13*, 6300.

(73) Due to the different electronic properties of **165** and **2**, exposure of the aminoaryl ketimines to NaOCl did not result in the formation of benzimidazoles; chloroimine and 1*H*-indazole products were detected, albeit in lower yields than when using the procedure involving NCS.

(74) Sather, A. C.; Berryman, O. B.; Rebek, J. *Org. Lett.* **2012**, *14*, 1600.

(75) (a) Malik, S.; Hasan, S. S.; Choudhary, M. I.; Ni, C.-Z.; Clardy, J. *Tetrahedron Lett.* **1995**, *36*, 1993. (b) Ali, Z.; Ferreira, D.; Carvalho, P.; Avery, M. A.; Khan, I. A. *J. Nat. Prod.* **2008**, *71*, 1111.

(76) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695.

(77) Based on ref. 20.

(78) Said, S. B.; Skarżewski, J.; Młochowski, J. *Synthesis* **1989**, *1989*, 223.

(79) Rainer, B. *Chem. Ber.* **1990**, *123*, 2039.

(80) Giurg, M.; Młochowski, J.; Ambrozak, A. *Pol. J. Chem.* **2002**, *76*, 1713.

(81) Perdicchia, D. *Tetrahedron* **2003**, *59*, 7733.

(82) Boehme, H.; Ebel, S. *Chem. Ber.* **1965**, *98*, 1819.

(83) Zhu, M.; Zheng, N. *Synthesis* **2011**, *2011*, 2223.

(84) Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 2191.

(85) Entwistle, I. D. *Tetrahedron* **1982**, *38*, 419.

(86) Denmark, S. E.; Edwards, J. P.; Weber, T.; Piotrowski, D. W. *Tetrahedron Asymmetry* **2010**, *21*, 1278.

(87) Park, P.-H.; Kim, H. S.; Jin, X. Y.; Jin, F.; Hur, J.; Ko, G.; Sohn, D. H. *Eur. J. Pharmacol.* **2009**, *606*, 215.

(88) Wang, C.; Hang, T.; Zhang, H. *Synth. Commun.* **2003,** *33,* 451.

(89) MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, *73*, 9710.

(90) Storoniak, P.; Krzymiński, K.; Boużyk, A.; Koval'chuk, E. P.; Błażejowski, J. *J. Therm. Anal. Calorim.* **2003**, *74*, 443.

(91) Boużyk, A.; Jóźwiak, L.; Błażejowski, J. *J. Mol. Struct.* **2002**, *612*, 29.

(92) Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531.

(93) Coppola, G. M.; Schuster, H. F. *J. Heterocycl. Chem.* **1989**, *26*, 957.

(94) Charlton, J. L.; Sayeed, V. A.; Koh, K.; Lau, W. F.; Lai, H. K.; Bell, A. R. *J. Agric. Food Chem.* **1990,** *38,* 1719.

(95) Bergenthal, D.; Mester, I.; Rózsa, Z.; Reisch, J. *Phytochemistry* **1979**, *18*, 161.

(96) Adapted from ref. 33.

(97) Hormi, O. E. O. *J. Org. Chem.* **1988**, *53*, 880

(98) Viña, D.; del Olmo, E.; López-Pérez, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525.

(99) Collot, V.; Dallemagne, P.; Bovy, P. R.; Rault, S. *Tetrahedron* **1999**, *55*, 6917.

(100) Prepared according to Maekawa, T.; Tomotaki, Y.; Ishikawa, K.; Nabeshima, A.; Furuichi, T. *Eur. Pat. Appl.* **1999**, EP 894788A1.

(101) The demethylation procedure is adapted from ref. 76.

CHAPTER 6. GENERAL CONCLUSIONS

Using readily available substrates, a variety of medicinally and biologically important molecules can now be easily prepared by a one-pot transformation involving a reaction with aryne intermediates. The highly reactive arynes have been generated from commercially available or readily prepared *o*-(trimethylsilyl)aryl triflates and a fluoride source under relatively mild conditions.

Chapter 2 provides a comprehensive overview of the synthesis of 5-membered ring fused heterocycles using aryne chemistry.

Chapter 3 covers the [3 + 2] cycloaddition between highly reactive nitrile oxides and arynes resulting in the formation of medicinally relevant benzisoxazoles. The nitrile oxides were generated *in situ* from readily prepared chlorooximes of aryl, alkyl, and alkenyl aldehydes. Due to a number of side reactions, slow addition was found to be essential for the efficiency of the desired transformation. The reaction's scope and limitations have been thoroughly studied. An ~100 member library of promising benzisoxazole-containing drug candidates is being developed in collaboration with the KU CMLD center for further biological screenings.

Chapter 4 describes a methodology for the synthesis of medicinally relevant *o*-hydroxyaryl ketones, xanthones, 4-chromanones, and flavones from readily available carboxylic acids. The key to the successful transformation is a low pK_a solvent (THF) and elevated temperatures altering the reaction pathway towards formation of a four-membered ring intermediate, which eventually results in the formal insertion of the aryne molecule into the C-O bond of a carboxylic acid. The reaction's scope and limitations have been

thoroughly studied. A number of naturally-occurring products have been preparing utilizing this transformation.

Chapter 5 describes a convenient reaction of readily prepared hydrazones of aldehydes with arynes, resulting in the formation of a cyclic dinitrogen-containing intermediate. Retaining the cyclic nature of the intermediate leads to the formation of pharmaceutically relevant 1*H*-indazoles. Disrupting the cyclic nature of the intermediate leads to the formation of biologically interesting *o*-(dimethylamino)aryl ketones. Further one-pot transformations of the latter lead to the formation of acridones and biologically important acridinium salts prevalent in nature. One more synthetic modification of the *o*-(dimethylamino)aryl ketones allowed us to synthesize an analogue of a natural alkaloid nigellidine.

We believe that the work accomplished will contribute to the rapid development of aryne insertion chemistry and appeal to synthetic organic chemists, medicinal chemists, and heterocyclic chemists.

Harvesting the high reactivity of aryne intermediates allows one to raise the art of organic synthesis to a new level. Arene-condensed structures, so prevalent both in nature and the pharmacy, are now being accessed in a conceptually new way, where the arene moiety, and not the fused portion of the molecule, is a synthon. The versatility of the aryne reactivity (*i.e.* as a soft Lewis acid, as a dienophile, as a dipolarophile, and as a π-donor for Pd-catalyzed processes) ensures that an abundance of new aryne-mediated methodologies are likely to appear in the years to come. Several aspects of aryne chemistry need to be addressed and certain problems solved in the near future: 1) lowering the cost of the aryne precursors,

2) accessing multisubstituted aryne and heteroaryne structures, 3) gaining more control over the rate of generation of the aryne intermediates, and 4) solving issues related to the regio- and stereoselectivity of the aryne-mediated processes.

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude and appreciation to Distinguished Professor Richard C. Larock. It has been a privilege to work under his guidance all these years. I am thankful for his professionalism, thoroughness, patience, and financial support. I am also thankful for his decision to accept me into his research group as a visiting scholar in 2005, and then, as a graduate student in 2007.

I thank my Program of Study Committee: Professors Malika Jeffries-EL, Thomas Greenbowe, Yan Zhao, Aaron Sadow, and Nicola Pohl for their valuable time and assistance throughout my work in graduate school.

I would like to thank former and present Larock group members with whom I have had the privilege to work, particularly Dr. Feng Shi and Dr. Donald Rogness for their valuable "aryne" discussions.

I am grateful to the Iowa State University Chemistry Department, particularly for our indispensable secretary, Patricia Boone, and for our past and present Instrument Services staff for valuable discussions and assistance.

I am thankful for all of my friends, too many to list, that I met during my life in graduate school.

I am grateful to Sergey E. Semenov, who inspired me to be a scientist and a teacher more than 12 years ago.

I would like to acknowledge my family, who provided their love and support from the other side of the world, including my parents Vladimir and Margarita Dubrovskiy, my brother Alex Dubrovskiy, and the rest of my extended family.

Finally, I've been blessed with a loving and caring wife. This dissertation would certainly have not been completed without Nataliya's daily sacrifices for my sake.