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Palladium-catalyzed and electrophilic cyclization approaches to important heterocycles and carbocycles

Saurabh Mehta
Iowa State University

Palladium-catalyzed and electrophilic cyclization approaches to important heterocycles and carbocycles

by

Saurabh Mehta

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Program of Study Committee:
Richard C. Larock, Major Professor
George A. Kraus
Nicola L. Pohl
Klaus Schmidt-Rohr
John G. Verkade

Iowa State University

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To my parents, my family and my teachers

TABLE OF CONTENTS

LIST OF ABBREVATIONS

Ac	acetyl
aq	aqueous
Ar	argon
Bn	benzyl
Bu	butyl
t-Bu	*tert*-butyl
^{o}C	degrees celsius
calcd	calculated
cat.	catalytic
CO	carbon monoxide
δ	chemical shift
d	doublet
dba	dibenzylideneacetone
DCM	dichloromethane
dd	doublet of doublets
DIPA	diisopropylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq	equation

equiv	equivalent
E	electrophile
EtOAc	ethyl acetate
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectroscopy
Hz	hertz
HPLC	high performance liquid chromatography
IR	infrared
LAH	lithium aluminum hydride
m	multiplet
m	meta
Me	methyl
mg	milligram
mL	milliliter(s)
mol	mole(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
o	ortho

OTf	trifluoromethanesulfonate
p	para
Ph	phenyl
q	quartet
s	singlet
satd	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
td	triplet of doublets
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

GENERAL INTRODUCTION

Heterocyclic and carbocyclic compounds are of immense importance and find applications in a variety of areas, *e.g.* agricultural chemicals, materials, pharmaceuticals, *etc*. The establishment of innovative and efficient synthetic methods for obtaining important heterocycles and carbocycles is an area of active research in synthetic organic chemistry. Over the years, the Larock group has investigated several palladium-catalyzed transformations and electrophilic cyclization reactions for the synthesis of these important classes of compounds. This thesis describes the development of several new and useful approaches for the synthesis of important heterocyclic and carbocyclic ring systems, which take advantage of very efficient and versatile palladium-catalyzed and electrophilic cyclization reactions.

Dissertation organization

This dissertation is organized into four chapters. Each of the first three chapters presented herein is written following the American Chemical Society guidelines for a full paper in the *Journal of Organic Chemistry*, while the fourth chapter is written following the guidelines for a full paper in the *Journal of Combinatorial Chemistry*. Each chapter is composed of an abstract, introduction, results and discussion, conclusions, experimental section, acknowledgments, and references.

Chapter 1 describes the results of competitive electrophilic cyclizations where the relative reactivity of various functional groups towards alkyne electrophilic cyclization reactions has been studied. The required diarylalkynes have been prepared by consecutive Sonogashira reactions of appropriately substituted aryl halides and the competitive cyclizations have been performed using I_2, ICl, NBS and PhSeCl as electrophiles. The results

of these competition studies indicate that various factors, *e.g.* the nucleophilicity of the competing functional groups, polarization of the alkyne triple bond, and the cationic nature of the intermediate, influence the outcome of these reactions.

Chapter 2 describes various strategies for the synthesis of linear and fused polyheterocyclic compounds (PHCs). The general method to prepare linked polyheterocyclic compounds involves iterative cycles of palladium-catalyzed Sonogashira coupling, followed by iodocyclization using I_2 or ICl. A variety of heterocyclic units, including benzofurans, benzothiophenes, indoles and isocoumarins, can be efficiently incorporated under mild reaction conditions. Several variations of this methodology have been combined with other efficient transformations, *e.g.* click chemistry, palladium-catalyzed Ullmann reaction, alkyne annulation reaction *etc.*, to generate interesting linked and fused ring polyheterocyclic systems.

A simple and mild method for the preparation of a variety of iodoheterocyclic ethers, *e.g.* isochromenes, dihydroisobenzofurans, *etc.*, by the iodocyclization of easily accessible 2-(1-alkynyl)benzylic alcohols is described in Chapter 3. The regiochemistry of the reaction products has been studied and it has been found to be dependent upon the substitution pattern of the starting material.

Synthesis of a good sized library of potential pharmacophores is desirable for their biological evaluation. Chapter 4 describes the solution-phase parallel synthesis of a 71-member library of highly-substituted cyclic imidates with four diversity points. The 3-iodomethylene cyclic imidates are readily prepared in good to excellent yields by the palladium/copper-catalyzed cross-coupling of various *o*-iodobenzamides and terminal alkynes, followed by electrophilic cyclization with I_2. Diversification of these 3-

iodomethylene cyclic imidates has been accomplished by palladium-catalyzed Sonogashira, Suzuki, carbonylative amidation and Heck coupling reactions using commercially available building block sublibraries.

Finally, all of the ^{1}H and ^{13}C NMR spectra for all previously unknown starting materials and products are compiled in appendices A-D, following a general conclusion for this dissertation.

CHAPTER 1. Competition Studies in Alkyne Electrophilic Cyclization Reactions

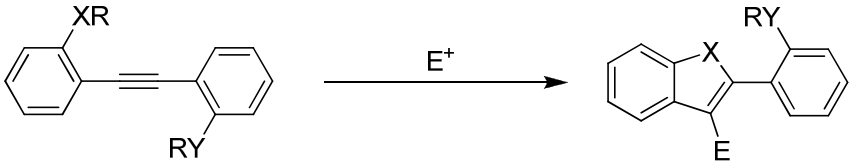
Based on a paper published in the *Journal of Organic Chemistry*[41]

*Saurabh Mehta, Jesse P. Waldo and Richard C. Larock**

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

larock@iastate.edu

Abstract



XR, YR = CHN-*t*-Bu, CHO, COMe, $CONH_2$, CONHPh, CO_2Me, NMe_2, OAc, OBn, OMe, Ph, SMe, SeMe
E = I_2, ICl, NBS, PhSeCl

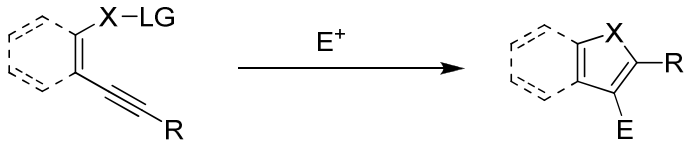
The relative reactivity of various functional groups towards alkyne electrophilic cyclization reactions has been studied. The required diarylalkynes have been prepared by consecutive Sonogashira reactions of appropriately substituted aryl halides and competitive cyclizations have been performed using I_2, ICl, NBS and PhSeCl as electrophiles. The results indicate that the nucleophilicity of the competing functional groups, polarization of the alkyne triple bond, and the cationic nature of the intermediate are the most important factors in determining the outcome of these reactions.

Introduction

Alkynes are versatile building blocks in organic synthesis. A wide range of carbocycles and heterocycles have been prepared by the electrophilic cyclization of functionally-substituted alkynes[1] and by transition metal-catalyzed annulations.[2] Recently, we and others have reported that the electrophilic cyclization of alkynes using halogen, sulfur

and selenium electrophiles can be a very powerful tool for the preparation of a wide variety of interesting carbocyclic and heterocyclic compounds (Scheme 1), including benzofurans,[3] furans,[4] benzothiophenes,[5] thiophenes,[6] benzopyrans,[7] benzoselenophenes,[8] selenophenes,[9] naphthols,[10] indoles,[11] quinolines,[12] isoquinolines,[13] α-pyrones,[14] isocoumarins,[14] isochromenes,[15] cyclic imidates,[16] naphthalenes[17] and polycyclic aromatics,[18] isoxazoles,[19] chromones,[20] bicyclic β-lactams,[21] cyclic carbonates,[22] pyrroles,[23] furopyridines,[24] spiro[4.5]trienones,[25] coumestrol and coumestans,[26] furanones,[27] benzothiazine-1,1-dioxides,[28] *etc*.[29]

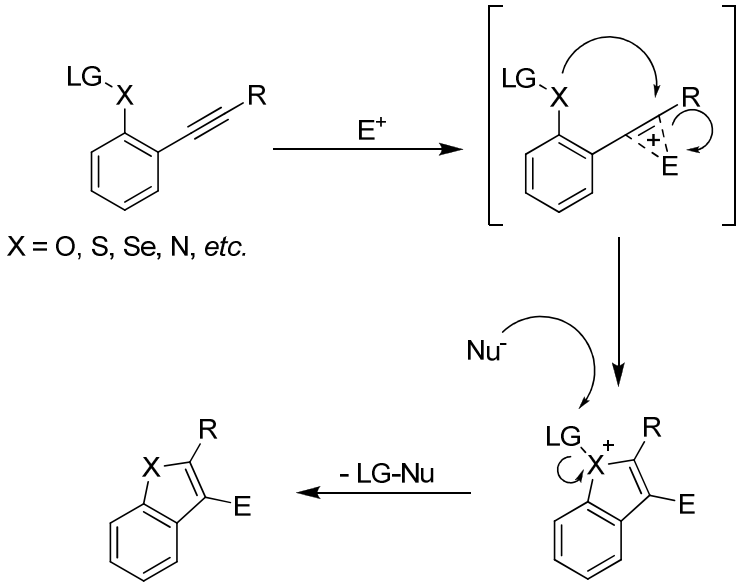
Scheme 1. Electrophilic Cyclization



LG = leaving group
X = O, N, S, *etc.*
R = alkyl, aryl, vinylic
E = I, Br, SAr, SeAr

In general, these electrophilic cyclization reactions are very efficient, afford clean reactions, proceed under very mild reaction conditions in short reaction times, and tolerate almost all important functional groups. Furthermore, the iodine-containing products can be further elaborated to a wide range of functionally-substituted derivatives using subsequent palladium-catalyzed processes. These reactions are generally believed to proceed by a stepwise mechanism involving electrophilic activation of the alkyne carbon-carbon triple bond, intramolecular nucleophilic attack on the cationic intermediate, and subsequent dealkylation (Scheme 2).

Scheme 2. General Mechanism



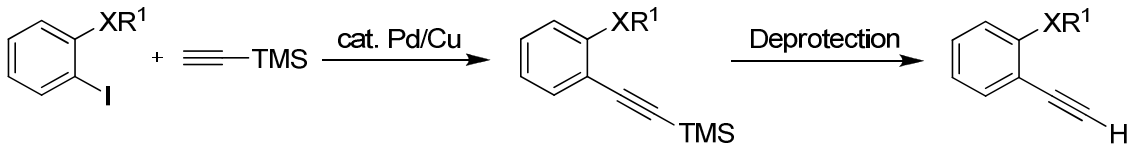
The success of this reaction prompted us to establish the relative reactivity of various functional groups towards cyclization. This has been accomplished by studying competitive cyclizations using halogen and selenium electrophiles.

Results and Discussion

This electrophilic cyclization methodology has been applied to a variety of unsymmetrical functionally-substituted diarylalkynes and the resulting products characterized in order to determine the relative reactivities of various functional groups towards electrophilic cyclization. The required diarylalkynes are readily prepared by consecutive Sonogashira reactions[30] of appropriately substituted aryl halides. Thus, Sonogashira substitution with trimethylsilyl acetylene, removal of the TMS group, followed by a second Sonogashira reaction, generally affords moderate to excellent yields of the

desired diarylalkynes. The results for the preparation of the intermediate terminal alkynes and the subsequent diarylalkynes are summarized in Tables 1 and 2 respectively.

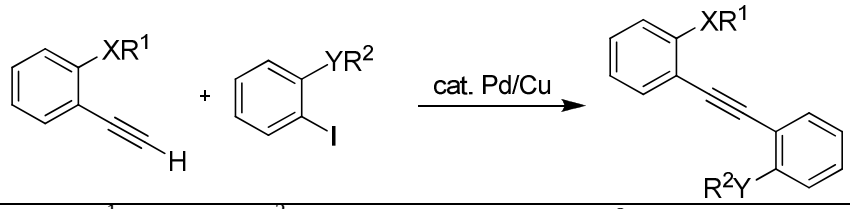
Table 1. Preparation of the Requisite Terminal Alkynes[a]



entry	XR^1	coupling conditions[b]	TMS-alkyne (% yield)	deprotection conditions[c]	terminal alkyne (% overall yield)
1	SMe	A	**1** (97)	aq KOH/MeOH 0.5 h/25 °C	**5** (83)
2	CO_2Me	A	**2** (100)	$KF{\cdot}2H_2O$/MeOH 36 h/25 °C	**6** (82)
3	Ph	A	-[d]	-	-
4	CONHPh	B	**3** (80)	$KF{\cdot}2H_2O$/MeOH 0.5 h/25 °C	**7** (71)
5	NMe_2	C	**4** (74)	aq NaOH/MeOH/ether 0.16 h/25 °C	**8** (48)

[a]All reactions have been run with 5 mmol of *o*-iodoarene. [b]Reaction conditions: (A) 1.2 equiv of alkyne, 2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI, 20 mL of Et_3N, 25 °C. (B) 1.3 equiv of alkyne, 3 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, 4 equiv of DIPA, DMF, 65 °C. (C) 1.2 equiv. of alkyne, 1 mol % $PdCl_2(PPh_3)_2$, 3 mol % CuI, 0.9 equiv of Et_3N, DMF, 25 °C. [c]See the Experimental Section for the experimental details. [d]A complex reaction mixture was obtained.

Table 2. Preparation of the Diarylalkynes[a]



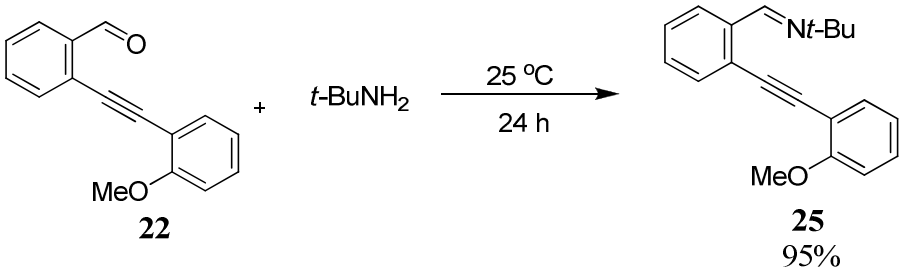
entry	XR^1	YR^2	time (h)	temp (^oC)	product	yield (%)
1	SMe	SeMe	24	25	**9**	80
2	SMe	OMe	6	60	**10**	90
3	SMe	CO_2Me	14	25	**11**	98
4	SMe	CONHPh	1	25	-	-[b]
5	SMe	NMe_2	24	25	-	-[c]
6	CO_2Me	SeMe	10	60	**12**	87
7	CO_2Me	$CONH_2$	2	25	**13**	83
8	CO_2Me	CONHPh	4	60	**14**	62[d]
9	CO_2Me	NMe_2	8	25	**15**	78
10	CO_2Me	OMe	4	25	**16**	74
11	CO_2Me	CHO	14	25	**17**	84
12	CO_2Me	COMe	4	25	**18**	88
13	CO_2Me	Ph	2	25	**19**	70
14	CONHPh	SMe	3	65	-	-[b,e]
15	CONHPh	SeMe	18	65	-	-[c,e]
16	NMe_2	Ph	3	75	**20**	35
17	NMe_2	Ph	2	110	**20**	74[f]

18	OMe	NMe_2	24	25	**21**	70
19	OMe	CHO	7	25	**22**	80
20	OMe	OBn	8	60	**23**	72
21	OMe	Ph	2	25	**24**	94
22	CHO	NMe_2	6	60	-	-[b]

[a]All reactions were run using 1 mmol of iodoarene and 1.2 equiv of alkyne, 2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI, and 5 mL of Et_3N. [b]An inseparable mixture was obtained. [c]The desired compound was not observed. [d]Four mol % of CuI was used. [e]Two mililiters of DMF were used to dissolve the alkyne. [f]The reaction was carried out in toluene using a modified procedure; see the Experimental Section.

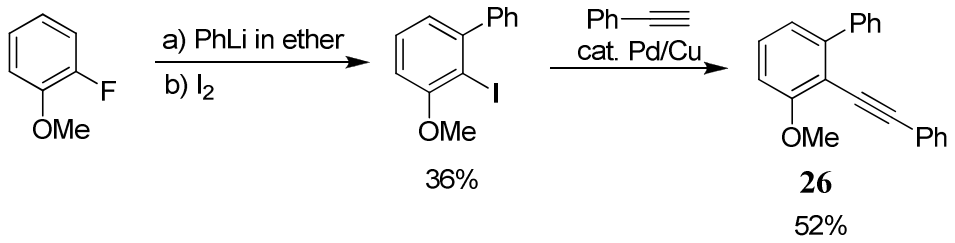
The diarylalkyne **25** containing *t*-butyl imine functionality was prepared by further derivatization of diarylalkyne **22** using a known procedure[13] (Scheme 3). However, similar derivatization starting with the diarylalkyne **17** resulted in a complex reaction mixture.

Scheme 3. Imine formation



In addition to the above substrates, a different type of diarylalkyne **26** bearing both of the competing groups (OMe and Ph) on the same aromatic ring has been prepared as shown in Scheme 4. The requisite iodoarene was prepared using a previously reported procedure.[31]

Scheme 4. Preparation of diarylalkyne 26 with both competing groups on the same ring



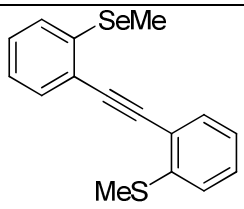
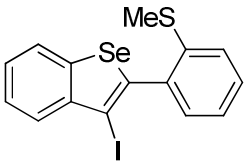
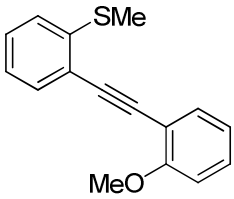
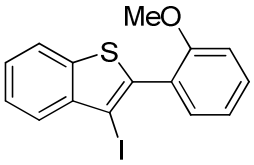
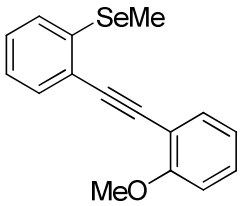
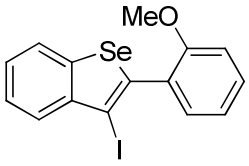
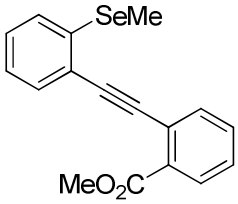
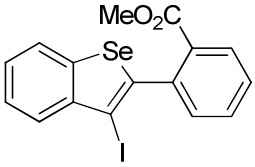
36%

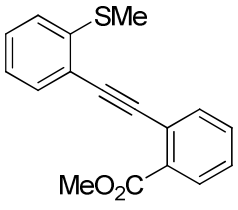
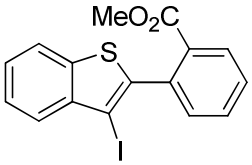
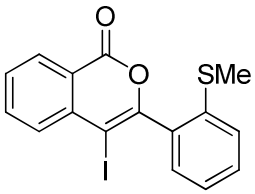
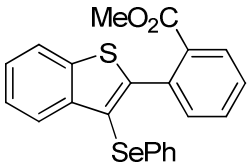
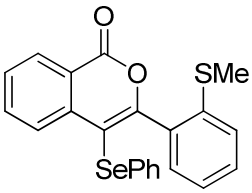
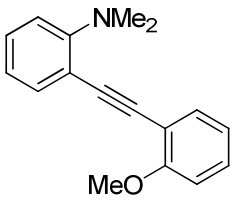
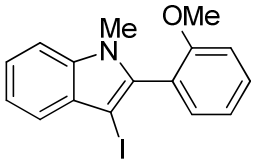
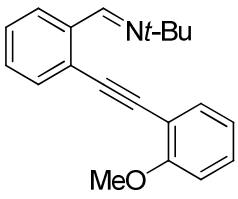
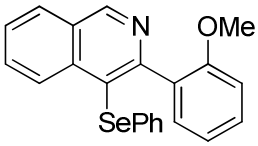
26

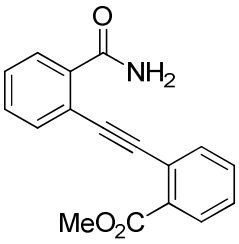
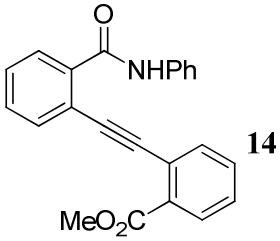
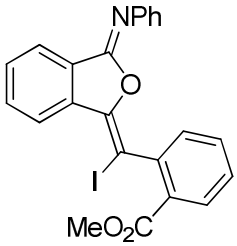
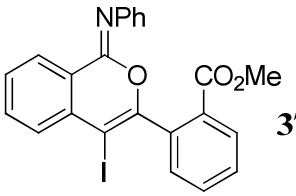
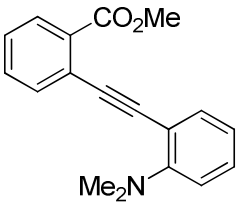
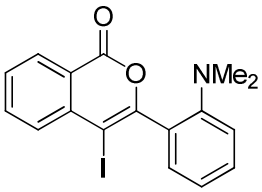
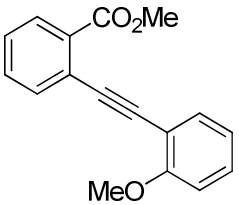
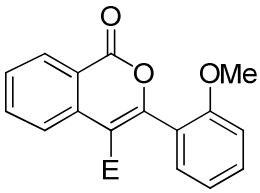
52%

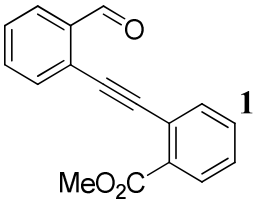
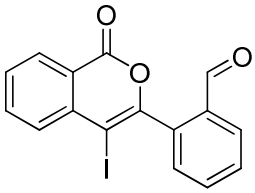
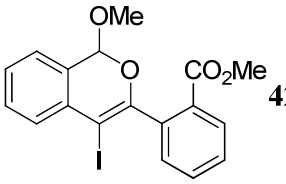
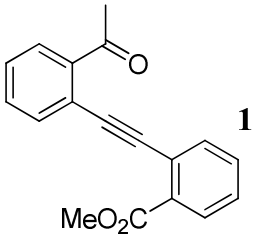
After preparing the desired diarylalkynes, we subjected these compounds to the previously established and already optimized electrophilic cyclization conditions for each class of heterocycle being prepared (Table 3). In most cases, reaction conditions that are appropriate for both of the competing functional groups present in the diarylalkyne in question have been used (entries 1-3). In those cases where common reaction conditions for both functional groups have not been previously reported, more than one set of reaction conditions has been tried in order to allow the functional groups to react under supposedly "optimal" conditions. For example, entries 4 and 5 in Table 3 involve the same diarylalkyne **12**, yet each entry uses varying amounts of different electrophiles in compliance with the previously reported reaction conditions for methylseleno and carbomethoxy functional groups, respectively.[8a,14]

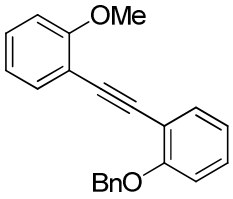
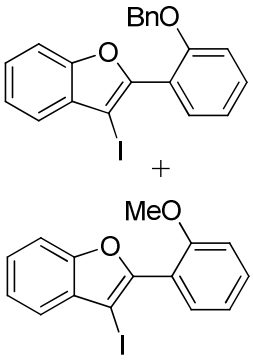
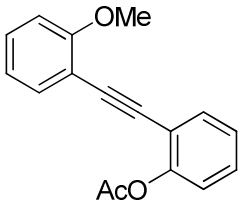
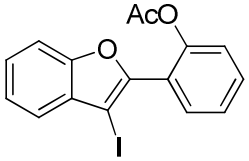
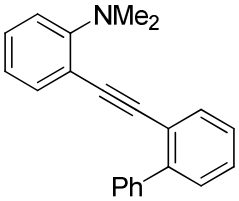
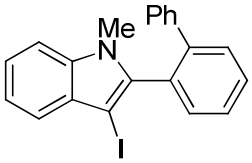
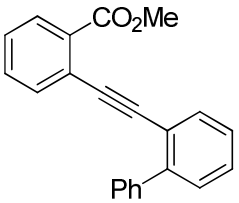
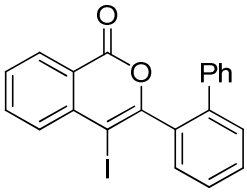
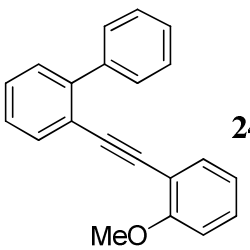
Table 3. Results of the competitive cyclizations[a]

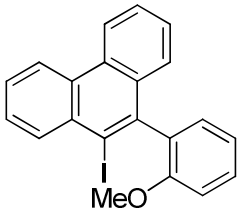
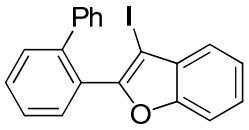
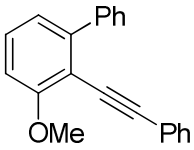
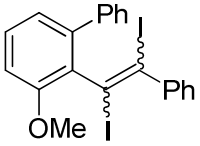
entry	substrate	electrophile	time (h)	product(s)	yield (%)
1	 **9**	1.1 I_2	0.16	 **27**	82[b]
2	 **10**	1.2 I_2	1	 **28**	96
3		1.1 I_2	0.5		91[c]
4	 **12**	1.2 I_2	1	 **29**	98[d]
5	**12**	1.2 ICl		**29**	93[d]

6	 **11**	1.2 I_2	1	 **30**	93
				+	
				 **31**	7
7	**11**	1.2 ICl	0.5	**30**	93
				+	
				31	7
8	**11**	1.5 PhSeCl	1	 **32**	56[e]
				+	
				 **33**	44[e]
9	 **21**	1.2 I_2	1	 **34**	95
10	 **25**	2 PhSeCl	3	 **35**	70

11	 **13**	1.2 I_2	1	-	-[f]
12	**13**	3 I_2	1	-	-[f,g]
13	 **14**	1.2 I_2	1	 **36** +  **37**	45 18
14	**14**	1.2 ICl	1	**36** + **37**	35 30
15	 **15**	1.2 I_2	1.5	 **38**	57[h]
16	 **16**	1.2 I_2	1	 **39** E = I	98

17	**16**	2 ICl	0.5	**39**	96
18	**16**	1.5 PhSeCl	0.5	E = SePh **40**	95
19	 **17**	1.2 I_2	2	-	-[i]
20	**17**	1.2 ICl	0.5	 **41**	25[j]
21	**17**	1.2 I_2, 1.2 K_2CO_3 MeOH/1.0	10	 **42** + **41**	82[k] 12
22	 **18**	1.2 I_2	1	-	-[f]
23	**18**	1.2 ICl	0.5	-	-[f]
24	**18**	1.2 I_2, 1.2 K_2CO_3 MeOH/1.0	2	-	-[f]

25		**23**	2 I_2	3		4:1[l]
26	**23**		1.2 ICl	3	**43** + **44**	6:1[l]
27			2 I_2	3		95[m]
28		**20**	2 I_2	2		78
29	**20**		1.2 ICl	0.5	-	-[f]
30	**20**		1.2 NBS	1	-	-[f]
31		**19**	2 ICl	3		90
32		**24**	2 I_2	3	-	-[f]

33	**24**	1.2 ICl	0.5	 + 	**47** **48**	49[e] 33[e]
34	 **26**	6 I_2	2		**49**	89[d]
35	**26**	1.2 ICl	1	-		-[d,n]

[a]Unless otherwise stated, all reactions have been carried out on a 0.25 mmol scale in 5 ml of methylene chloride at room temperature. All yields are isolated yields after column chromatography. [b]A small amount of the corresponding benzothiophene product (~7%) was observed by GC-MS analysis; however, it could not be isolated. [c]This result has previously been reported in the literature (see reference 8a). [d]This reaction hasf been carried out on a 0.10 mmol scale. [e]The reported yield is the average of two runs. [f]This reaction resulted in a complex mixture of unidentifiable products. [g]MeCN was used as the reaction solvent and 3 equiv of $NaHCO_3$ were added as a base. [h]The corresponding indole (~8%) was also observed by GC-MS analysis. However, it could not be isolated. [i]No reaction occurred; the starting material was recovered. A complex mixture was obtained upon longer reaction. [j]This was the only isolated product. The rest of the product mixture was complex and inseparable. [k]This product decomposed quickly; see the Experimental Section for details. [l]An inseparable complex mixture was obtained. This ratio is based on GC-MS data. [m]This result has previously been reported in the literature (see reference 3b). [n]An alkyne ICl addition product whose structure is similar to compound **49** in entry 34 was obtained.

The results of the competition studies are summarized in Table 3. Before discussing individual results, it should be noted that a close examination of the results suggests that a number of factors affect the cyclization. These include electronic (relative nucleophilicity of the functional groups, polarization of the carbon-carbon triple bond, and the cationic nature of the intermediate) and steric factors (hindrance and geometrical alignment of the functional groups), as well as the nature of the electrophile. Three kinds of results have been observed for these competitive cyclizations. (1) Only one of the two possible products has been

obtained. This is most common, indicating that there is a hierarchy of functional group reactivity toward the electrophilic cyclizations. Assuming that the various factors mentioned above may affect the cyclization, the dominance of one functional group over another can be attributed to any one or a combination of two or more factors operating in favor of the one functional group over the other. (2) A mixture of both possible products has been observed. This occurs less commonly, but even in these cases, one product is often obtained in a significantly higher yield than the other, indicating that one group is usually significantly more reactive towards cyclization. (3) A complex reaction mixture is obtained. Although this does not provide any substantial information about the relative reactivity, it points to the fact that either the more reactive functional group is not compatible with the particular reaction conditions or neither of the two functional groups involved has a dominant reactivity, thus resulting in a complex reaction mixture.

It also should be noted that since these reactions are very fast in general, and may involve multiple steps and intermediates, it is quite difficult to strictly assign the reactivity of any particular functional group to any one factor mentioned above. Indeed, we assume that in some cases one or more factors are operating in opposition to each other, resulting in a mixture of products. However, in the following discussion, we will attempt to ascribe the relative reactivity of various functional groups to what we believe to be the most important factors.

With regard to the results of individual experiments, entry 1 (Table 3) demonstrates the competitive cyclization of a methylsulfanyl group versus a methylseleno group. Benzoselenophene **27** was isolated as the major product of the reaction using I_2 as the electrophile. In another experiment (not shown in Table 3 as the product could not be

purified completely), when PhSeCl was used as the electrophile, the corresponding benzoselenophene was again formed as the major product in high yield. These results can be attributed to the higher nucleophilicity of selenium compared to sulfur, due to its lower electronegativity and higher polarizability. Similarly, in entry 2, when diarylalkyne **10** (containing methylsulfanyl and methoxy as competing functional groups) was subjected to electrophilic cyclization, benzothiophene **28** was formed exclusively in an excellent yield. It is a general observation that the nucleophilicity increases as one descends a column in the periodic table.[32] This trend is also observed when examining the results of entries 3-14, where the nucleophilicity of the competing functional groups governs the resulting cyclization. Thus, methylseleno is more reactive than methoxy (entry 3) and carbomethoxy functional groups (entries 4 and 5).

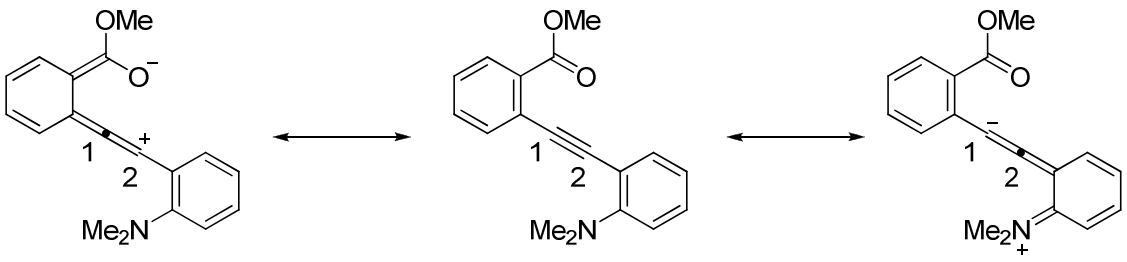
Entries 6-8 involve the competition between a methylsulfanyl group and a carbomethoxy group under different conditions. In all three cases, benzothiophene derivatives are the major but not exclusive products, again suggesting that the greater nucleophilicity of sulfur over oxygen controls the reaction. It is noteworthy, however, that changing the electrophile to PhSeCl in entry 8 significantly affects the product distribution, presumably because of the nature of the electrophile.

When competing nucleophilic atoms are in the same row in the periodic table, the results show that the nucleophilicity still governs the outcome of the cyclization. Thus, nitrogen nucleophiles are more reactive than oxygen nucleophiles. This is exemplified by the cyclization of diarylalkyne **21** bearing an NMe_2 group and a methoxy group (entry 9), which leads to exclusive formation of the corresponding indole **34** in an excellent yield. Similarly, a *t*-butyl imine group was found to be more reactive than a methoxy functional group (entry

10). Cyclization reactions involving diarylalkyne **13** (entries 11 and 12) resulted in complex reaction mixtures. It has been observed previously by us that a primary amide does not afford the desired cyclized product and generally results in a complex reaction mixture.[16] On the other hand, the related diarylalkyne **14** containing an *N*-phenyl amide undergoes cyclization cleanly with I_2, affording two regioisomeric products, both resulting from cyclization by the CONHPh group (entry 13). Using ICl (entry 14) also resulted in the same set of products, although with reduced regioselectivity in accordance to our previously reported results.[16]

Entry 15 involving a competition between a carbomethoxy group and an *N*,*N*-dimethylamino group represents a special case where the corresponding isocoumarin **38** was isolated as the major product of the cyclization. Formation of the isocoumarin product is presumably the result of one (or a combination) of the two factors working in favor of the carbomethoxy group: (1) The electronics of the two substituents polarize[33] the carbon-carbon triple bond in a way that leads to a more cationic C2 and anionic C1, thus facilitating nucleophilic attack at the more electrophilic C2 position (Figure 1), and/or (2) there seems to be a more favorable geometrical alignment of the ester functionality when compared to the *N*,*N*-dimethylamino group.

Figure 1. Carbomethoxy versus an *N*,*N*-dimethylamino group



Entries 16-27 involve competitions among various oxygen nucleophiles. In a competition between a methoxy group and a carbomethoxy group (entries 16-18) using I_2, ICl and PhSeCl as the electrophiles, the corresponding isocoumarin derivatives are formed exclusively in excellent yields. Analogous to the previous case (entry 15 and Figure 1), formation of the isocoumarin products is again presumably due to the electronic polarization of the triple bond, which increases the electrophilicity of the carbon being attacked by the carbomethoxy group, and also a more favorable geometrical alignment of the ester functionality when compared to the methoxy group.

Entries 19-21 involve the competitive cyclization of an aldehyde and an ester group under different reaction conditions. When iodine is used as the electrophile (entry 19), the starting material was recovered after 2 h. If the reaction was allowed to stir for a longer time, a complex reaction mixture was obtained. Using ICl as the electrophile (entry 20), a complex mixture was obtained and only isocoumarin derivative **41** was isolable in a 25% yield. It should be noted that the aldehyde group after nucleophilic attack becomes cationic and needs an external nucleophile to neutralize the positive charge. Thus, the same reaction was performed with methanol as an external nucleophile (entry 21). This time, isochromene derivative **42** was isolated as the major product, indicating the impact of an external nucleophile on the cyclization. Similar reactions involving a methyl ketone and a carbomethoxy group as competing entities resulted in complex mixtures of unidentifiable products (entries 22-24).

The cyclizations reported in entries 25 and 26 involving methoxy and benzyloxy functional groups resulted in inseparable complex mixtures. However, the GC-MS analyses of the product mixtures indicated the presence of two benzofuran products **43** and **44** in

varying ratios, the major product resulting from cyclization by the OMe group. These results are presumably a consequence of the greater steric hindrance of the benzyloxy group.

Entry 27 involves a competition between a methoxy group and a relatively electron-poor acetoxy group. As the reaction outcome, the methoxy cyclization product is formed exclusively in high yield. The result of this reaction again suggests that electronic factors play a crucial role in these cyclization reactions. We have taken advantage of this high selectivity and subsequent palladium-catalyzed carbonylation to prepare coumestrol and a variety of related coumestans.[26]

Entries 28-35 involve competition of an aryl ring versus nitrogen and different oxygen nucleophiles. In the cyclization of diarylalkyne **20** containing an NMe_2 group and a phenyl ring (entries 28-30), the corresponding indole **45** is obtained when I_2 is used as the electrophile, presumably due to the more nucleophilic NMe_2 group. The reaction of diarylalkyne **20** with ICl or NBS resulted in complex reaction mixtures. However, mass spectral analysis of the mixture resulting from the NBS cyclization (entry 30) indicated the presence of the corresponding indole, an observation that is in accord with that of entry 28. In a competition between a carbomethoxy group and a phenyl group (entry 31), the exclusive formation of isocoumarin derivative **46** can be explained based on the greater nucleophilicity of the carbomethoxy group when compared to the electron-poor phenyl ring.

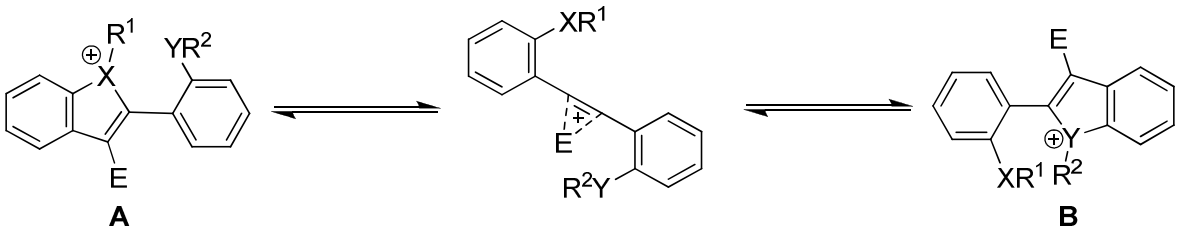
The cyclization of diarylalkyne **24** bearing a phenyl ring and an *o*-methoxy group has also been studied (entries 32 and 33). Using iodine as the electrophile resulted in a complex mixture of inseparable products, but analysis of the crude ^1H NMR and mass spectral data suggested preferential cyclization on the phenyl ring. Aromatic rings have previously been observed by us to give complex reaction mixtures upon reaction with iodine.[17] Using ICl as

the electrophile (entry 33) resulted in a mixture of products resulting from participation by both the phenyl ring and the methoxy group, with the phenyl cyclized phenanthrene derivative **47** being the major product. Presumably, the cationic character of the intermediate and/or the higher nucleophilicity of the phenyl ring when compared to the methoxy group account for this observation. In competition studies employing diarylalkyne substrate **26** containing both of the competing functional groups (Ph and methoxy) on the same phenyl ring (entries 34 and 35), the only products observed using either I_2 or ICl were products of addition of the iodine-containing reagent to the carbon-carbon triple bond. These results can again be rationalized by assuming the cationic nature and the electronics of the intermediates involved in these reactions.

Conclusions

The results of competitive electrophilic cyclizations using halogen and selenium electrophiles on a wide variety of functionally-substituted diarylalkynes have been reported. The results suggest that a number of factors affect the cyclization. These include electronic (the relative nucleophilicity of the functional groups, and the cationic nature of the intermediate) and steric factors (hindrance and geometrical alignment of the functional groups), and the nature of the electrophile. It should be noted that although the nucleophilicity of the participating functional groups, the polarization of the carbon-carbon triple bond, and the cationic nature of the intermediate seem to be the crucial factors determining the outcome of these reactions, the possibility of some reactions being reversible (Figure 2) before the loss of R^1 or R^2 cannot be ruled out. Thus in such cases, the selectivity might also be controlled by the relative stability of the cyclized intermediate ions (A and B).

Figure 2. Possible equilibrium among reaction intermediates



The following pattern has been observed for the relative reactivity of various functional groups (Figure 3).

Figure 3. Relative reactivity of the functional groups towards cyclization

SeMe > SMe > CO_2Me > NMe_2 > Aryl (Ph) > OMe > OBn

CH=N-*t*-Bu > OMe > OAc

CONHPh > CO_2Me < CHO

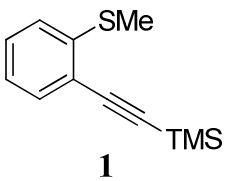
Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm). DCM was distilled over CaH_2. Anhydrous MeCN was used as received. Purification of the compounds has been performed by column chromatography. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

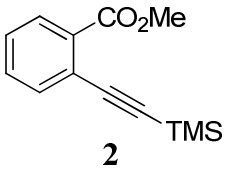
Preparation of the non-commercial aryl iodides. 2-Iodophenyl methyl selenide was prepared using a modified literature procedure.[8a] In a 100 ml round bottom flask, 8.0 mmol of the 2-iodoaniline was dissolved in 5 ml of HBF_4 (48% solution) and the mixture was stirred for 15 min and then allowed to cool to 0 ^oC. To this solution, an aqueous solution of $NaNO_2$ (8.0 mmol in 3 mL of water) was added dropwise to the reaction mixture. The mixture was allowed to warm to room temperature, filtered and washed with cold ethanol. The diazonium salt was dried under vacuum and used for the next step without purification. A suspension of 8.0 mmol of the crude diazonium salt in 25 mL of $CHCl_3$ containing 10 mol % of 18-crown-6 and 9.0 mmol of dimethyl diselenide was stirred at 0 ^oC. To this mixture, 16 mmol of KOAc was added in small portions over a period of 10 min and the resulting solution was allowed to stir for 4 h and then filtered. The solid residue was washed with chloroform and the resulting filtrate was washed with water (2 x 5 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product obtained was then purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent. The product was obtained as a yellow oil (yield = 35%) with spectral properties identical to those previously reported.[8a] *N*-Phenyl-2-iodobenzamide[34] and *N,N*-dimethyl-2-iodoaniline[35] were prepared according to literature procedures.

Preparation of the TMS-protected alkynes.



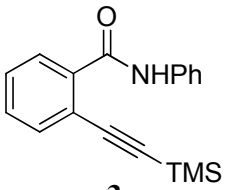
1

***o*-(Trimethylsilylethynyl)thioanisole (1).** This compound was prepared according to a modified literature procedure.[5b] To a solution of *o*-iodothioanisole (5.0 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 2 mol %), and CuI (0.01 g, 1 mol %) in TEA (20 mL) (stirring for 5 min beforehand), 6.0 mmol of trimethylsilylacetylene (1.2 equiv) in 5 mL of TEA was added dropwise over 15 min. The reaction flask was flushed with argon and the mixture was stirred at room temperature for 20 h. The resulting solution was filtered, washed with brine, and extracted with diethyl ether (2 x 10 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under vacuum to yield the crude product. Purification by flash chromatography afforded the product (yield = 97%) as a yellow oil with spectral properties identical to those previously reported.[5b]



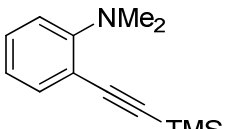
2

Methyl 2-(trimethylsilylethynyl)benzoate (2). This compound was prepared using the procedure (reaction time: 15 h) used for compound **1**. After flash chromatography, the compound was isolated as a colorless oil (yield = 100%) with spectral properties identical to those previously reported.[36]



3

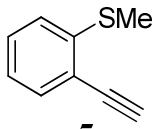
***N*-Phenyl 2-(trimethylsilylethynyl)benzamide (3).** To a solution of the iodobenzamide (5.0 mmol) in DMF (20 ml) were added $PdCl_2(PPh3)_2$ (3 mol %), CuI (2 mol%) and DIPA (4 equiv). A solution of trimethylsilylacetylene (1.3 equiv) in 5 ml of DMF was added dropwise and the resulting mixture was then heated under an N_2 atm at 65 ^oC. After 4 h of stirring, the mixture was allowed to cool to room temperature and 25 ml of satd aq NH_4Cl and 25 ml of ethyl acetate were added. The organic layer was separated and the aqueous layer was back extracted with ethyl acetate. The combined organic layers were washed with brine and water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the product (80%) as a colorless solid with spectral properties identical to those previously reported:[37] mp 96-97 ºC (lit. mp[37] 95-96 ºC).



4

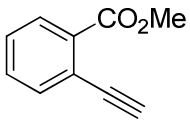
***N*,*N*-Dimethyl-2-(trimethylsilylethynyl)aniline (4).** This compound was prepared according to a literature procedure.[38] Purification by flash chromatography afforded the product as a yellow oil (yield = 74%) with spectral properties identical to those previously reported.[38]

Preparation of the terminal alkynes.



5

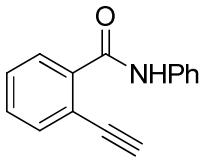
2-Ethynylthioanisole (5). A modified literature procedure[39] was used to prepare this compound. A solution of KOH (0.45 g, 8.0 mmol, 2 equiv) in 2 mL of water was added dropwise to *o*-(trimethylsilylethynyl)thioanisole (0.88 g, 4.0 mmol) in 20 mL of CH_3OH under an argon atmosphere at 25 ^oC. The mixture was stirred for another 0.5 h at 25 ^oC, and the CH_3OH was removed under vacuum. The residue was added to 20 mL of brine, and the mixture was extracted with EtOAc (3 x 20 mL), dried (Na_2SO_4), filtered, and the solvent removed under vacuum. Purification by flash chromatography afforded the product (yield = 86%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.47 (s, 1H), 7.08 (td, J = 0.8, 7.2 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.31 (td, J = 1.2, 7.6 Hz, 1H), 7.46 (dd, J = 1.2, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ15.3, 81.2, 83.7, 120.3, 124.38, 124.41, 129.5, 133.3, 142.0; IR (in CH_2Cl_2, cm^{-1}) 3288, 3049, 2922, 2102, 1436; HRMS Calcd for C_9H_8S: 148.0347. Found: 148.0334.



6

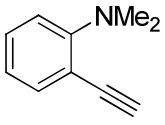
Methyl 2-ethynylbenzoate (6). A modified literature procedure was used.[36] To a solution of compound **2** (4.0 mmol) in methanol (20 mL), $KF{\cdot}2H_2O$ (2.26 g, 24 mmol, 6 equiv) was added and the reaction mixture was stirred for 36 h at 25 ^oC. After the reaction was over,

methanol was removed under vacuum and the residue was extracted with EtOAc (3 x 20 mL), washed with 0.1M HCl and brine, dried (Na_2SO_4), filtered, and the solvent removed under vacuum. Purification by flash chromatography afforded the product (yield = 82%) as a colorless oil with spectral properties identical to those previously reported.[36]



7

***N*-Phenyl-2-ethynylbenzamide (7).** This compound was prepared according to the modified literature procedure used for compound **6** above, except that the reaction time was 0.5 h.[36] Purification by flash chromatography afforded the product (yield = 89%) as a yellow solid: mp 95-98 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (s, 1H), 7.11-7.16 (t, J = 7.2 Hz, 1H), 7.24-7.46 (m, 4H), 7.55-7.58 (m, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.96-7.99 (m, 1H), 9.02 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.0, 84.4, 118.6, 120.1, 124.7, 129.2, 129.7, 130.0, 130.9, 134.2, 136.9, 138.1, 164.4; IR (in CH_2Cl_2, cm^{-1}) 3295, 3054, 2305, 1672, 1265; HRMS Calcd for $C_{15}H_{11}NO$: 221.08406. Found: 221.08437.

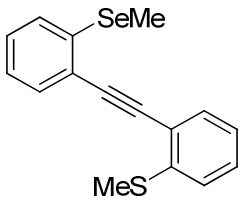


8

***N,N*-Dimethyl-2-ethynylaniline (8).** This compound was prepared according to a literature procedure.[38] Purification by flash chromatography afforded the product as a yellow oil (yield = 65%) with spectral properties identical to those previously reported.[38]

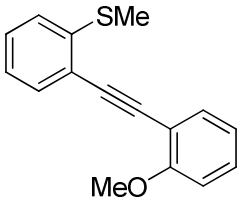
Preparation of the diarylalkynes.

General procedure used for the Sonogashira Coupling. The following procedure has been used for the preparation of all of the diarylalkynes. Slight modifications were made wherever required (Table 2). To a solution of iodoarene (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 2 mol %), and CuI (0.002 g, 1 mol %) in TEA (4 mL) (stirring for 5 min beforehand), 1.2 mmol of trimethylsilylacetylene (1.2 equiv) in 1 mL of TEA was added dropwise over 10 min. The reaction flask was flushed with argon and the mixture was stirred at the indicated temperature for the indicated time (Table 2). After the reaction was over, the resulting solution was filtered, washed with brine, and extracted with EtOAc (2 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. Purification was performed by flash chromatography.



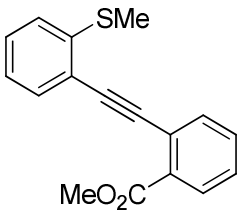
9

2-[(2-(Methylselenyl)phenyl)ethynyl]thioanisole (9). The product was obtained as a white solid: mp 105-107 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.52 (s, 3H), 7.10-7.19 (m, 3H), 7.24-7.33 (m, 3H), 7.54 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.5, 15.5, 92.6, 94.2, 121.4, 123.7, 124.3, 124.4, 125.3, 127.5, 129.10, 129.11, 132.77, 132.81, 136.5, 141.8; IR (in CH_2Cl_2, cm^{-1}) 3053, 2986, 2305, 1266; HRMS Calcd for $C_{16}H_{14}SSe$: 317.99814. Found: 317.99874.



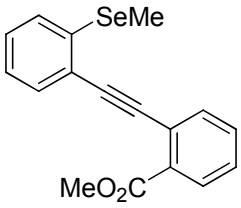
10

2-[(2-Methoxyphenyl)ethynyl]thioanisole (10). The product was obtained as a white solid: mp 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.93 (s, 3H), 6.89-6.96 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.26-7.33 (m, 2H), 7.51-7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ15.4, 56.1, 91.1, 92.5, 110.9, 112.6, 120.6, 122.0, 124.41, 124.43, 128.7, 130.1, 132.5, 133.8, 141.7, 160.1; IR (in CH_2Cl_2, cm^{-1}) 3053, 2986, 2305, 1265; HRMS Calcd for $C_{16}H_{14}OS$: 254.07654. Found: 254.07689.



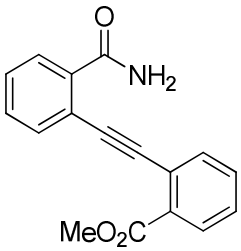
11

Methyl 2-[(2-(methylthio)phenyl)ethynyl]benzoate (11). The product was obtained as a colorless solid: mp 73-75 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.96 (s, 3H), 7.11 (t, J = 7.2 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ15.2, 52.4, 91.9, 94.6, 121.4, 123.6, 124.1, 124.3, 128.1, 129.1, 130.5, 131.6, 131.8, 132.8, 134.4, 141.9, 166.8; IR (in CH_2Cl_2, cm^{-1}) 3054, 2986, 2305, 1727, 1265; HRMS Calcd for $C_{17}H_{14}O_2S$: 282.07145. Found: 282.07178.



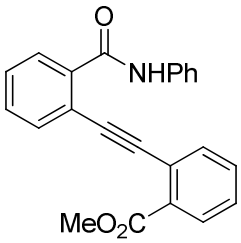
12

Methyl 2-[(2-(methylselenyl)phenyl)ethynyl]benzoate (12). The product was obtained as a yellow gel: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.97 (s, 3H), 7.14-7.20 (m, 1H), 7.24-7.32 (m, 2H), 7.36-7.42 (m, 1H), 7.48-7.55 (m, 2H), 7.73 (dd, J = 0.9, 7.8 Hz, 1H), 7.98 (dd, J = 0.9, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.3, 52.5, 92.9, 93.9, 123.7, 123.9, 125.4, 127.6, 128.3, 129.3, 130.6, 131.8, 131.9, 132.9, 134.5, 136.7, 166.9; IR (in CH_2Cl_2, cm^{-1}) 3053, 2928, 2305, 1729, 1262; HRMS Calcd for $C_{17}H_{14}O_2Se$: 330.01590. Found: 330.01629.



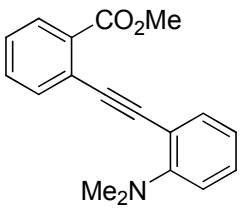
13

Methyl 2-[(2-carbamoylphenyl)ethynyl]benzoate (13). The product was obtained as a colorless solid: mp 122-124 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.48 (br s, 1H), 7.39-7.57 (m, 4H), 7.65-7.70 (m, 2H), 8.03 (dt, J = 0.9, 8.1 Hz, 1H), 8.21-8.24 (m, 1H), 8.37 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.6, 92.7, 94.6, 120.3, 123.2, 128.8, 129.2, 130.75, 130.82, 130.9, 131.0, 132.3, 134.2, 134.3, 134.7, 166.3, 167.8; IR (in CH_2Cl_2, cm^{-1}) 3486, 3370, 3054, 2987, 2305, 1722, 1670; HRMS Calcd for $C_{17}H_{13}NO_3$: 279.08954. Found: 279.08994.



14

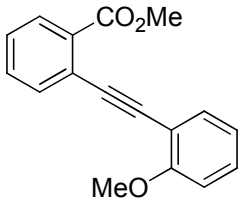
Methyl 2-[(2-(phenylcarbamoyl)phenyl)ethynyl]benzoate (14). The product was obtained as a yellow solid: mp 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 7.10-7.14 (m, 1H), 7.28-7.32 (m, 2H), 7.44 (td, J = 1.2, 7.6 Hz, 1H), 7.49-7.53 (m, 3H), 7.60-7.63 (m, 3H), 7.69-7.71 (m, 1H), 8.03-8.05 (m, 1H), 8.16-8.19 (m, 1H), 9.45 (br s, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 52.5, 92.1, 95.2, 119.8, 121.4, 123.0, 124.7, 128.96, 129.03, 129.4, 130.8, 131.0, 131.1, 131.5, 132.4, 133.9, 134.3, 135.9, 138.2, 164.7, 166.2; IR (in CH_2Cl_2, cm^{-1}) 3350, 3053, 2985, 2306, 1719, 1665, 1265; HRMS Calcd for $C_{23}H_{17}NO_3$: 355.12084. Found: 355.12145.



15

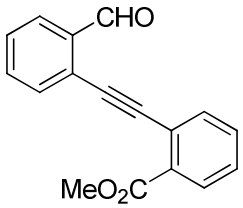
Methyl 2-[(2-(dimethylamino)phenyl)ethynyl]benzoate (15). The product was obtained as a yellow oil (strongly fluorescent under UV): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 6H), 3.93 (s, 3H), 6.86-6.91 (m, 2H), 7.21-7.27 (m, 1H), 7.32 (td, J = 1.5, 7.8 Hz, 1H), 7.45 (td, J = 1.5, 7.5 Hz, 1H), 7.55 (dd, J = 1.8, 6.9 Hz, 1H), 7.64 (dt, J = 0.6, 7.8 Hz, 1H), 7.95 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 43.6, 52.2, 93.6, 94.1, 114.9, 116.8, 120.4,

124.4, 127.6, 129.6, 130.5, 131.5, 131.7, 133.7, 134.9, 154.7, 166.9; IR (in CH_2Cl_2, cm^{-1}) 2948, 2835, 2207, 1728, 1251; HRMS Calcd for $C_{18}H_{17}NO_2$: 279.12593. Found: 279.12658.



16

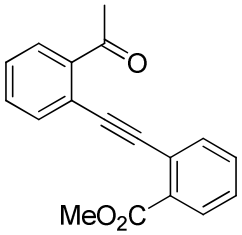
Methyl 2-[(2-methoxyphenyl)ethynyl]benzoate (16). The product was obtained as a light brown solid: mp 62-64 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.94 (s, 3H), 6.86-6.96 (m, 2H), 7.26-7.36 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 52.3, 56.0, 91.2, 92.5, 111.0, 112.8, 120.7, 124.2, 128.0, 130.3, 130.6, 131.8, 131.9, 134.1, 134.3, 160.3, 167.1; IR (in CH_2Cl_2, cm^{-1}) 3054, 2951, 2838, 2306, 2216, 1716, 1270; HRMS Calcd for $C_{17}H_{14}O_3$: 266.09429. Found: 266.09468.



17

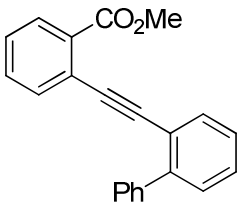
Methyl 2-[(2-formylphenyl)ethynyl]benzoate (17). The product was obtained as a white solid that turned gray upon exposure to air: mp 87-89 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.40-7.61 (m, 4H), 7.67-7.71 (m, 2H), 7.95-8.03 (m, 2H), 10.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ52.6, 90.1, 95.1, 123.1, 127.16, 127.24, 128.9, 129.0, 130.9, 131.9,

132.1, 133.6, 133.9, 134.5, 136.5, 166.4, 192.6; IR (in CH_2Cl_2, cm^{-1}) 3054, 2987, 2306, 1727, 1696, 1264; HRMS Calcd for $C_{17}H_{12}O_3$: 264.07864. Found: 264.07909.



18

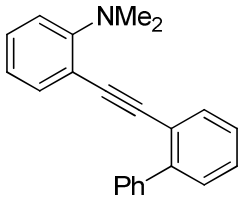
Methyl 2-[(2-acetylphenyl)ethynyl]benzoate (18). The product was obtained as an orange solid: mp 68-70 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H), 3.93 (s, 3H), 7.36-7.40 (m, 2H), 7.46-7.49 (m, 2H), 7.66-7.76 (m, 3H), 7.96 (dd, J = 1.2, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 52.1, 93.2, 93.7, 121.6, 123.3, 128.2, 128.4, 128.6, 130.4, 131.2, 131.5, 131.7, 133.9, 134.1, 140.3, 166.2, 199.9; IR (in CH_2Cl_2, cm^{-1}) 3055, 2952, 2305, 1730, 1678, 1270; HRMS Calcd for $C_{18}H_{14}O_3$: 278.09429. Found: 278.09473.



19

Methyl 2-(biphenyl-2-ylethynyl)benzoate (19). The product was obtained as a colorless solid: mp 67-69 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 7.29-7.47 (m, 9H), 7.68-7.74 (m, 3H), 7.92 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.3, 91.2, 94.5, 121.8, 124.1, 127.3, 127.7, 128.0, 128.2, 129.1, 129.67, 129.73, 130.6, 131.77, 131.82, 133.7, 134.1,

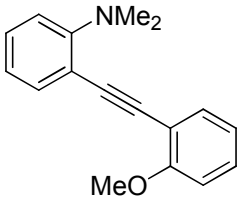
140.7, 144.0, 166.9; IR (in CH_2Cl_2, cm^{-1}) 3053, 2987, 2303, 2212, 1727, 1268; HRMS Calcd for $C_{22}H_{16}O_2$: 312.11503. Found: 312.11564.



20

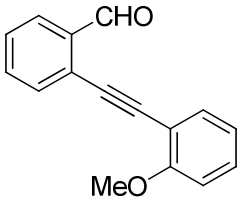
***N,N*-Dimethyl-2-(biphenyl-2-ylethynyl)aniline (20).** This compound was obtained in a 35% yield following the general procedure mentioned above. The following slightly modified literature procedure resulted in a significantly increased yield.[40] *N,N*-Dimethyl-2-iodoaniline (2.0 mmol), 42 mg of $PdCl_2(PPh_3)_2$ (0.06 mmol, 3.0 mol %), and 12 mg of CuI (0.06 mmol, 3.0 mol %) were placed in a dry reaction flask. Next, 5 mL of toluene and 0.6 mL of diisopropylamine were added to the flask, followed by 0.22 g of 2-methyl-3-butyn-2-ol (2.6 mmol, 1.3 equiv). The reaction mixture was stirred at 80 ^oC under argon for 1 h. As monitored by TLC, the first acetylene coupling was complete. The reaction temperature of the oil bath was increased to 110 ^oC, and 96 mg of NaH (120 mg of 80% dispersion, 4.0 mmol, 2.0 equiv) was added slowly to the mixture. After 5 min of stirring, 0.560 g (2.0 mmol, 1.0 equiv) of 2-iodobiphenyl was added to the reaction mixture, and the stirring was continued. After 25 min, 48 mg of NaH (another 60 mg portion of 80% dispersion) (2.0 mmol, 1.0 equiv) was added carefully, and the solution was stirred at 110 ^oC for 1 h. After cooling to room temperature, the suspension was filtered, and the separated amine-hydrochloride was washed with toluene. Evaporation of the combined toluene solution gave a crude product, which was purified by column chromatography using hexane-ethyl acetate

mixtures to afford the product as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (s, 6H), 6.78-6.85 (m, 2H), 7.16-7.45 (m, 9H), 7.66 (d, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 91.8, 94.6, 115.4, 116.9, 120.4, 122.4, 127.2, 127.5, 128.1, 128.4, 129.3, 129.6, 129.7, 132.9, 134.4, 140.9, 143.6, 154.6; IR (in CH_2Cl_2, cm^{-1}) 3051, 2984, 2304, 2207, 1269; HRMS Calcd for $C_{22}H_{19}N$: 297.15175. Found: 297.15210.



21

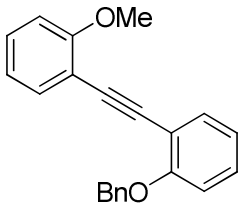
***N,N*-Dimethyl-2-[(2-methoxyphenyl)ethynyl]aniline (21).** The product was obtained as a green liquid (fluorescent under UV): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 6H), 3.88 (s, 3H), 6.86-6.94 (m, 4H), 7.20-7.30 (m, 2H), 7.48-7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 55.9, 91.5, 93.1, 110.8, 113.4, 115.7, 117.1, 120.59, 120.64, 129.3, 129.6, 133.3, 134.6, 154.8, 160.2; IR (in CH_2Cl_2, cm^{-1}) 3054, 2986, 2305, 1265; HRMS Calcd for $C_{17}H_{17}NO$: 251.13101. Found: 251.13138.



22

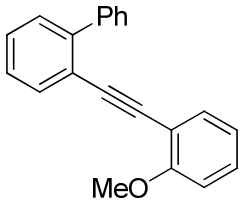
2-[(2-Methoxyphenyl)ethynyl]benzaldehyde (22). The product was obtained as a colorless solid: mp 82-84 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.90-6.98 (m, 2H), 7.31-7.44

(m, 2H), 7.49-7.58 (m, 2H), 7.62-7.65 (m, 1H), 7.94 (dd, J = 1.2, 7.8 Hz, 1H), 10.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 89.2, 93.2, 110.8, 111.7, 120.7, 127.1, 127.5, 128.5, 130.7, 133.1, 133.4, 133.8, 136.0, 160.5, 192.7; IR (in CH_2Cl_2, cm^{-1}) 3053, 2987, 2305, 2215, 1694, 1271; HRMS Calcd for $C_{16}H_{12}O_2$: 236.08373. Found: 236.08409.



23

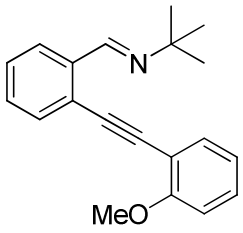
1-Benzyloxy-2-[(2-methoxyphenyl)ethynyl]benzene (23). The product was obtained as a white solid: mp 77-79 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.18 (s, 2H), 6.85-6.95 (m, 4H), 7.22-7.30 (m, 3H), 7.35 (t, J = 7.2 Hz, 2H), 7.49 (d, J = 7.2 Hz, 1H), 7.54-7.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 70.6, 90.1, 90.3, 110.9, 113.0, 113.1, 113.9, 120.6, 121.0, 127.2, 127.8, 128.5, 129.6, 129.7, 133.6, 133.7, 137.3, 159.3, 160.0; IR (in CH_2Cl_2, cm^{-1}) 3052, 2984, 2306, 1266; HRMS Calcd for $C_{22}H_{18}O_2$: 314.13068. Found: 314.13110.



24

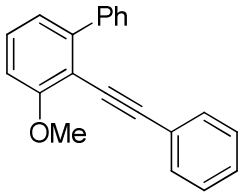
2-[(2-Methoxyphenyl)ethynyl]biphenyl (24). The product was obtained as a white solid: mp 69-71 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.78-6.86 (m, 2H), 7.18-7.45 (m,

8H), 7.66-7.72 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 89.1, 93.6, 111.0, 113.0, 120.7, 122.2, 127.2, 127.6, 128.1, 128.6, 129.7, 129.8, 129.9, 133.4, 133.6, 140.8, 143.9, 160.2; IR (in CH_2Cl_2, cm^{-1}) 3052, 2965, 2304, 2212, 1263; HRMS Calcd for $C_{21}H_{16}O$: 284.12012. Found: 284.12065.



25

***N*-[2-((2-Methoxyphenyl)ethynyl)benzylidene]-2-methylpropan-2-amine (25).** The compound was prepared according to the literature procedure as a yellow oil and the spectral properties were found to be identical to those previously reported.[39]



26

3-Methoxy-2-(phenylethynyl)biphenyl (26). The product was obtained as yellow gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 6.91 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.25-7.26 (m, 3H), 7.31-7.46 (m, 6H), 7.65 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 85.6, 97.1, 109.4, 111.3, 122.1, 124.0, 127.7, 128.0, 128.1, 128.3, 129.3, 129.7, 131.5, 140.7, 146.1, 160.6; IR (in CH_2Cl_2, cm^{-1}) 3052, 2986, 2305, 1265; HRMS Calcd for $C_{21}H_{16}O$: 284.12012. Found: 284.12053.

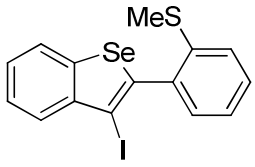
Electrophilic cyclization of the diarylalkynes.

General procedure for iodocyclization. To a solution of 0.25 mmol of the diarylalkyne in 3 mL of CH_2Cl_2 was added gradually the I_2/ICl (amounts as indicated in Table 3) in 2 mL of CH_2Cl_2. The reaction mixture was flushed with argon and allowed to stir at 25 °C for the indicated time (the reaction was monitored by TLC for completion). The excess I_2/ICl was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc or diethyl ether (2 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel with ethyl acetate/hexanes as the eluent.

General procedure for the PhSeCl cyclizations. To a solution of 0.25 mmol of the diarylalkyne in CH_2Cl_2 (3 mL) was added the PhSeCl (amount as indicated in Table 3) in 2 mL of CH_2Cl_2. The mixture was flushed with argon and allowed to stir at 25 °C for the indicated time. The reaction mixture was washed with 20 mL of water and extracted with EtOAc or diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was further purified by flash chromatography on silica gel with ethyl acetate/hexanes as the eluent.

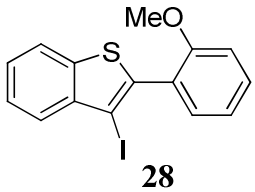
General procedure for bromocyclization. To a solution of 0.25 mmol of the diarylalkyne in 3 mL of CH_2Cl_2 was added gradually 1.2 equiv of NBS dissolved in 2 mL of CH_2Cl_2. The reaction mixture was allowed to stir at 25 °C for 1-4 h. The excess NBS was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by diethyl ether (2 x 10 mL). The combined ether layers were dried over anhydrous $MgSO_4$ and concentrated under

vacuum to yield the crude product, which was purified by flash chromatography on silica gel using ethyl acetate/hexanes as the eluent.



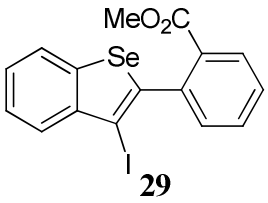
27

3-Iodo-2-(2-methylsulfanylphenyl)benzo[*b*]selenophene (27). The product was obtained as a white solid: mp 116-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.24-7.38 (m, 4H), 7.42-7.50 (m, 2H), 7.85-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 87.2, 124.7, 125.2, 125.6, 125.9, 126.1, 128.8, 129.8, 131.0, 135.6, 139.3, 141.4, 142.9, 143.1; IR (in CH_2Cl_2, cm^{-1}) 3054, 2986, 2925, 1264; HRMS Calcd for $C_{15}H_{11}ISSe$: 429.87914. Found: 429.88004.



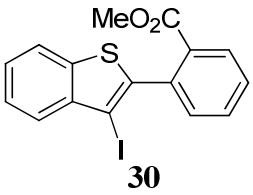
28

3-Iodo-2-(2-methoxyphenyl)benzo[*b*]thiophene (28). The product was obtained as a yellow solid: mp 104-106 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 7.00-7.08 (m, 2H), 7.35-7.40 (m, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.79 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 82.9, 111.6, 120.6, 122.3, 123.7, 125.3, 125.4, 126.1, 130.9, 132.7, 139.6, 139.8, 141.4, 157.3; IR (in CH_2Cl_2, cm^{-1}) 3052, 2980, 1432, 1264; HRMS Calcd for $C_{15}H_{11}IOS$: 365.95764. Found: 365.95825.



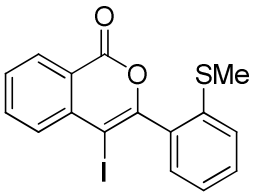
29

Methyl 2-(3-iodobenzo[*b*]selenophen-2-yl)benzoate (29). The product was obtained as a white solid: mp 113-115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 7.32-7.35 (m, 1H), 7.42-7.55 (m, 3H), 7.60 (td, J = 1.2, 7.6 Hz, 1H), 7.85 (t, J = 7.2 Hz, 2H), 8.04 (dd, J = 1.2, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 85.3, 125.3, 125.8, 125.9, 128.6, 129.1, 130.7, 131.2, 131.9, 132.2, 138.2, 140.9, 142.8, 144.2, 167.1; IR (in CH_2Cl_2, cm^{-1}) 3054, 2984, 1727, 1266; HRMS Calcd for $C_{16}H_{11}IO_2Se$: 441.89690. Found: 441.89743.



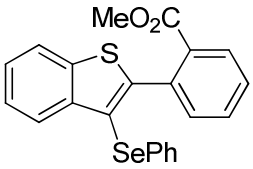
30

Methyl 2-(3-iodobenzo[*b*]thiophen-2-yl)benzoate (30). The product was obtained as a colorless solid: mp 111-115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 7.38-7.39 (m, 3H), 7.53-7.64 (m, 2H), 7.76-7.81 (m, 2H), 8.05 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 82.2, 122.3, 125.5, 125.6, 126.0, 129.4, 130.8, 131.7, 132.0, 132.6, 135.9, 139.4, 141.1, 142.2, 167.1; IR (in CH_2Cl_2, cm^{-1}) 3053, 2952, 1729, 1264; HRMS Calcd for $C_{16}H_{11}IO_2S$: 393.95245. Found: 393.95324.



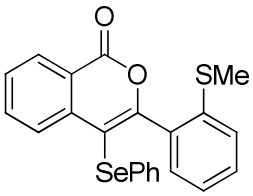
31

4-Iodo-3-[2-(methylthio)phenyl]isocoumarin (31). The product was obtained as a colorless solid: mp 128-130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.28 (t, J = 7.6 Hz, 1H), 7.34-7.40 (m, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.60-7.63 (m, 1H), 7.82-7.85 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ16.7, 80.1, 120.7, 125.4, 127.1, 129.7, 130.1, 130.5, 130.8, 131.3, 135.5, 135.9, 137.8, 138.9, 154.6, 161.9; IR (in CH_2Cl_2, cm^{-1}) 3054, 2987, 1735, 1264; HRMS Calcd for $C_{16}H_{11}IO_2S$: 393.95245. Found: 393.95324.



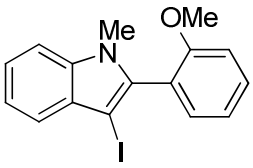
32

Methyl 2-[3-(phenylselenyl)benzo[*b*]thiophen-2-yl]benzoate (32). The product was obtained as a yellow gel: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H), 7.07-7.12 (m, 5H), 7.36-7.39 (m, 3H), 7.48-7.53 (m, 2H), 7.80-7.87 (m, 2H), 7.97-8.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ52.3, 118.0, 122.3, 125.0, 125.16, 125.19, 126.2, 129.07, 129.11, 130.0, 130.05, 131.5, 131.8, 132.2, 132.8, 135.2, 139.7, 141.1, 147.9, 167.2; IR (in CH_2Cl_2, cm^{-1}) 3055, 2987, 1727, 1263; HRMS Calcd for $C_{22}H_{16}O_2SSe$: 424.00362. Found: 424.00442.



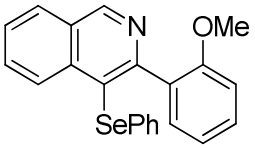
33

3-[2-(Methylthio)phenyl]-4-(phenylselenyl)isocoumarin (33). The product was obtained as a white solid: mp 111-113 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.13-7.23 (m, 6H), 7.29-7.35 (m, 2H), 7.39-7.43 (m, 1H), 7.52-7.56 (m, 1H), 7.68-7.72 (m, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.37 (dd, J = 0.8, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 108.0, 121.4, 125.1, 126.7, 126.9, 128.2, 129.1, 129.4, 129.9, 130.0, 130.2, 130.5, 131.5, 134.2, 135.5, 137.9, 139.1, 158.3, 162.1; IR (in CH_2Cl_2, cm^{-1}) 3056, 2987, 1743, 1262; HRMS Calcd for $C_{22}H_{16}O_2SSe$: 424.00362. Found: 424.00442.



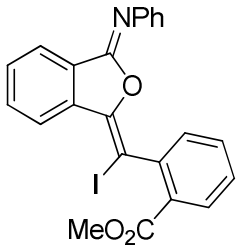
34

3-Iodo-2-(2-methoxyphenyl)-1-methylindole (34). The product was obtained as a white oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.79 (s, 3H), 7.04 (d, J = 8.4 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.19-7.36 (m, 4H), 7.46-7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ31.8, 55.8, 59.4, 109.8, 111.4, 120.4, 120.77, 120.79, 121.5, 122.7, 130.4, 131.1, 133.6, 137.6, 139.5, 158.0; IR (in CH_2Cl_2, cm^{-1}) 3053, 2939, 1465, 1265; HRMS Calcd for $C_{16}H_{14}INO$: 363.01202. Found: 363.01255.



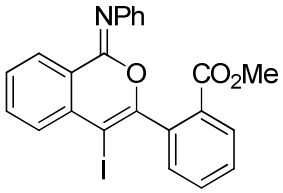
35

3-(2-Methoxyphenyl)-4-(phenylselenyl)isoquinoline (35). The product was obtained as a yellow gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 6.94 (d, J = 8.0 Hz, 1H), 7.02-7.05 (m, 6H), 7.35-7.40 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.67 (td, J = 1.2, 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 110.6, 120.6, 124.0, 126.1, 127.5, 128.3, 128.46, 128.49, 129.1, 129.8, 130.2, 130.8, 131.6, 131.7, 133.3, 138.1, 153.5, 156.1, 156.9; IR (in CH_2Cl_2, cm^{-1}) 3053, 2985, 1265; HRMS Calcd for $C_{22}H_{17}NOSe$: 391.04753. Found: 391.04826.

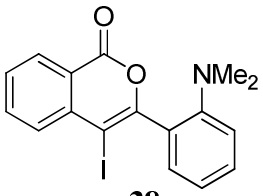


36

Methyl 2-((1*E*)-iodo(3-(phenylimino)isobenzofuran-1(3*H*)-ylidene)methyl)benzoate (36). The product was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 7.02 (t, J = 7.1 Hz, 1H), 7.10-7.18 (m, 4H), 7.37-7.43 (m, 2H), 7.54-7.62 (m, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.97-8.02 (m, 2H), 8.81 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 71.2, 124.0, 124.7, 125.1, 125.2, 128.5, 128.6, 129.3, 130.7, 130.8, 131.0, 132.0, 132.2, 132.9, 135.1, 141.8, 144.7, 147.5, 151.9, 166.8; IR (in CH_2Cl_2, cm^{-1}) 3054, 2986, 1726, 1689, 1265; HRMS Calcd for $C_{23}H_{16}INO_3$: 481.01750. Found: 481.01876.

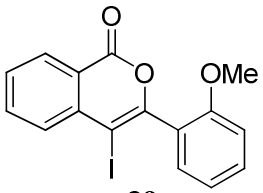


methyl 2-(4-iodo-1-(phenylimino)-1*H*-isochromen-3-yl)benzoate (37). The product was obtained as a white solid: mp 112-114 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.98 (t, J = 7.3 Hz, 1H), 7.09-7.11 (m, 2H), 7.21 (t, J = 7.7 Hz, 2H), 7.46-7.52 (m, 3H), 7.57-7.68 (m, 3H), 8.04 (d, J = 7.7 Hz, 1H), 8.39 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ52.7, 76.6, 123.0, 123.9, 124.1, 127.8, 128.7, 129.2, 130.0, 130.1, 130.7, 130.9, 132.1, 132.4, 133.1, 134.5, 137.1, 145.9, 148.7, 153.8, 166.1; IR (in CH_2Cl_2, cm^{-1}) 3052, 2985, 1725, 1664, 1263; HRMS Calcd for $C_{23}H_{16}INO_3$: 481.01750. Found: 481.01876.



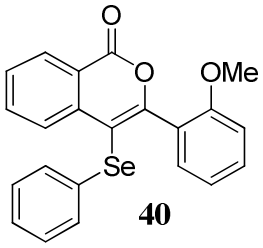
38

3-[2-(Dimethylamino)phenyl]-4-iodoisocoumarin (38). The product was obtained as a light green solid: mp 103-105 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 6H), 6.95-7.02 (m, 2H), 7.32-7.40 (m, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.79-7.87 (m, 2H), 8.31 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ43.4, 79.5, 117.8, 120.0, 120.2, 126.7, 129.2, 129.9, 131.16, 131.21, 132.2, 135.8, 138.6, 152.0, 156.2, 162.3; IR (in CH_2Cl_2, cm^{-1}) 3056, 2989, 1731, 1265; HRMS Calcd for $C_{17}H_{14}INO_2$: 391.00693. Found: 391.00772.



39

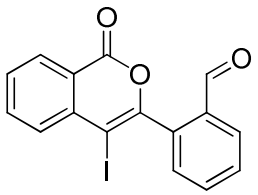
4-Iodo-3-(2-methoxyphenyl)isocoumarin (39). The product was obtained as a white solid: mp 166-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.96-6.98 (m, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.56-7.60 (m, 1H), 7.79-7.85 (m, 2H), 8.31 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ55.8, 79.8, 111.5, 120.5, 120.6, 125.1, 129.3, 129.9, 131.2, 131.4, 132.0, 135.7, 138.2, 153.8, 157.2, 162.2; IR (in CH_2Cl_2, cm^{-1}) 3054, 2928, 1735, 1265; HRMS Calcd for $C_{16}H_{11}IO_3$: 377.97530. Found: 377.97601.



40

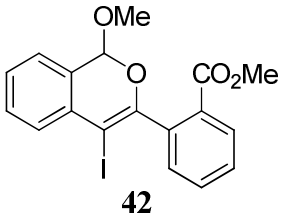
3-(2-Methoxyphenyl)-4-(phenylselenyl)isocoumarin (40). The product was obtained as a yellow solid: mp 113-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 6.92 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.12-7.15 (m, 3H), 7.19-7.21 (m, 2H), 7.35-7.43 (m, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ55.5, 107.7, 111.0, 120.2, 121.2, 123.9, 126.5, 128.0, 128.7, 129.3, 129.6, 129.9, 131.0, 131.6, 131.8, 135.3, 138.2, 157.27, 157.35, 162.4; IR (in

CH_2Cl_2, cm^{-1}) 3057, 2985, 1735, 1265; HRMS Calcd for $C_{22}H_{16}O_3Se$: 408.02647. Found: 408.02699.



41

3-(2-Formylphenyl)-4-iodoisocoumarin (41). The product was obtained as a white solid: mp 146-148 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.2 Hz, 1H), 7.62-7.77 (m, 3H), 7.82-7.88 (m, 2H), 8.04 (dd, J = 1.2, 7.6 Hz, 1H), 8.34 (d, J = 7.6 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ79.6, 120.7, 129.9, 130.2, 130.4, 131.0, 131.3, 131.6, 134.1, 134.2, 136.1, 137.3, 137.5, 152.9, 161.3, 190.2; IR (in CH_2Cl_2, cm^{-1}) 3054, 2985, 1740, 1706, 1265; HRMS Calcd for $C_{16}H_9IO_3$: 375.95965. Found: 375.96067.

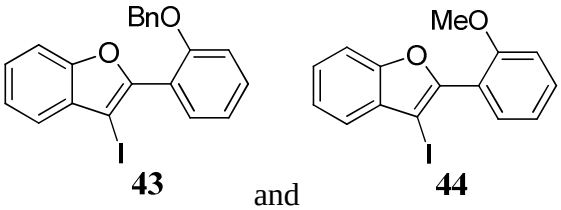


42

Methyl 2-(4-iodo-1-methoxy-1*H*-isochromen-3-yl)benzoate (42).

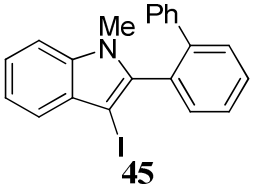
A modified literature procedure was used to prepare this compound.[15c] To a solution of the diarylalkyne **15** (0.25 mmol), K_2CO_3 (0.25 mmol, 1.0 equiv) and methanol (0.3 mmol, 1.2 equiv) in CH_2Cl_2 (5.0 mL), iodine (0.3 mmol, 1.2 equiv) was added and the solution was stirred at room temperature for 10 h. The reaction mixture was then quenched with satd aq $Na_2S_2O_3$, extracted using EtOAc and washed with water. The combined organic extracts

were dried over anhydrous $MgSO_4$ and concentrated under vacuum. Following flash column chromatography, compound **36** was isolated as the major product. The compound was unstable and decomposed during rotary evaporation (in order to remove the trace amounts of solvent). The NMR data showing the presence of the compound (note that the attached spectrum shows extra peaks because of the solvent and a slight impurity) is provided here: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 3H), 3.80 (s, 3H), 6.06 (s, 1H), 7.21 (dt, J = 0.8, 7.2 Hz, 1H), 7.31 (td, J = 1.2, 7.2 Hz, 1H), 7.40-7.45 (m, 2H), 7.48-7.52 (m, 2H), 7.61 (td, J = 1.6, 7.6 Hz, 1H), 8.05 (dt, J = 0.8, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 56.0, 74.9, 100.5, 125.7, 127.1, 127.8, 129.0, 129.4, 130.0, 130.4, 130.5, 131.0, 131.3, 132.4, 138.8, 152.3, 166.7.



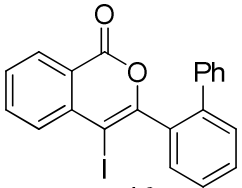
43 and **44**

2-[2-(Benzyloxy)phenyl]-3-iodobenzofuran (43) and 3-iodo-2-(2-methoxyphenyl)benzofuran (44). The reaction resulted in a complex inseparable mixture. However, these two products were observed by GC-MS analysis.



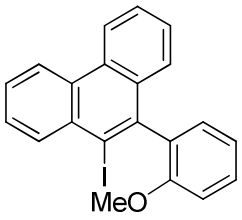
45

2-(Biphenyl-2-yl)-3-iodo-1-methylindole (45). The product was obtained as a yellow gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 7.07-7.09 (m, 1H), 7.13-7.23 (m, 7H), 7.46-7.48 (m, 3H), 7.55-7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 60.4, 109.8, 120.6, 121.3, 122.6, 127.3, 127.5, 128.4, 128.8, 130.0, 130.2, 130.3, 130.4, 133.4, 137.1, 140.6, 141.7, 142.8; IR (in CH_2Cl_2, cm^{-1}) 3052, 2984, 1463, 1265; HRMS Calcd for $C_{21}H_{16}IN$: 409.03275. Found: 409.03326.



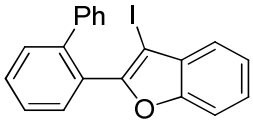
46

3-(Biphenyl-2-yl)-4-iodoisocoumarin (46). The product was obtained as a white solid: mp 132-134 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.28 (m, 3H), 7.38-7.39 (m, 2H), 7.44-7.57 (m, 5H), 7.67-7.75 (m, 2H), 8.22 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.8, 120.2, 127.4, 127.6, 128.4, 128.8, 129.4, 129.9, 130.3, 130.5, 130.8, 131.0, 134.6, 135.8, 137.8, 140.2, 142.2, 155.7, 161.5; IR (in CH_2Cl_2, cm^{-1}) 3055, 2985, 1736, 1266; HRMS Calcd for $C_{21}H_{13}IO_2$: 423.99603. Found: 423.99687.



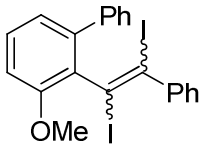
47

9-Iodo-10-(2-methoxyphenyl)phenanthrene (47). The product was obtained as a colorless solid: mp 135-137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 7.09 (d, J = 8.4 Hz, 1H), 7.14-7.15 (m, 2H), 7.40-7.42 (m, 2H), 7.49-7.53 (m, 1H), 7.62-7.70 (m, 3H), 8.44-8.46 (m, 1H), 8.66-8.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ55.9, 107.5, 111.6, 121.0, 122.8, 122.9, 127.2, 127.3, 127.5, 128.0, 128.3, 129.8, 130.5, 130.8, 131.6, 132.4, 132.8, 134.3, 134.7, 142.8, 157.0; IR (in CH_2Cl_2, cm^{-1}) 3052, 2985, 1492, 1266; HRMS Calcd for $C_{21}H_{15}IO$: 410.01677. Found: 410.01757.



48

2-(Biphenyl-2-yl)-3-iodobenzofuran (48). The product was obtained as a yellow gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.39 (m, 8H), 7.48-7.51 (m, 1H), 7.54-7.58 (m, 1H), 7.64-7.66 (m, 2H), 7.82 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ65.7, 111.4, 121.6, 123.4, 125.4, 127.17, 127.21, 128.3, 128.5, 128.8, 130.3, 130.6, 131.5, 132.0, 140.9, 142.7, 154.3, 156.0; IR (in CH_2Cl_2, cm^{-1}) 3053, 2984, 1449, 1263; HRMS Calcd for $C_{20}H_{13}IO$: 396.00112. Found: 396.00172.



49

2-(1,2-Diiodo-2-phenylvinyl)-3-methoxybiphenyl (49). The product was obtained as a dark yellow solid: mp 102-104 ^{o}C; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 4.00 (s, 3H), 6.98-7.01 (m,

2H), 7.10 (d, *J* = 7.2 Hz, 2H), 7.28-7.35 (m, 3H), 7.43-7.50 (m, 4H), 7.63 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ56.4, 95.5, 101.2, 110.7, 123.0, 127.7, 127.9, 128.0, 128.3, 128.5, 129.7, 130.1, 140.5, 141.6, 147.4, 155.6; IR (in CH_2Cl_2, cm^{-1}) 3053, 2986, 1422, 1265; HRMS Calcd for $C_{21}H_{16}I_2O$: 537.92907. Found: 537.92995.

Acknowledgements

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CHAPTER 2. Iodine/Palladium Approaches to the Synthesis of Polyheterocyclic Compounds

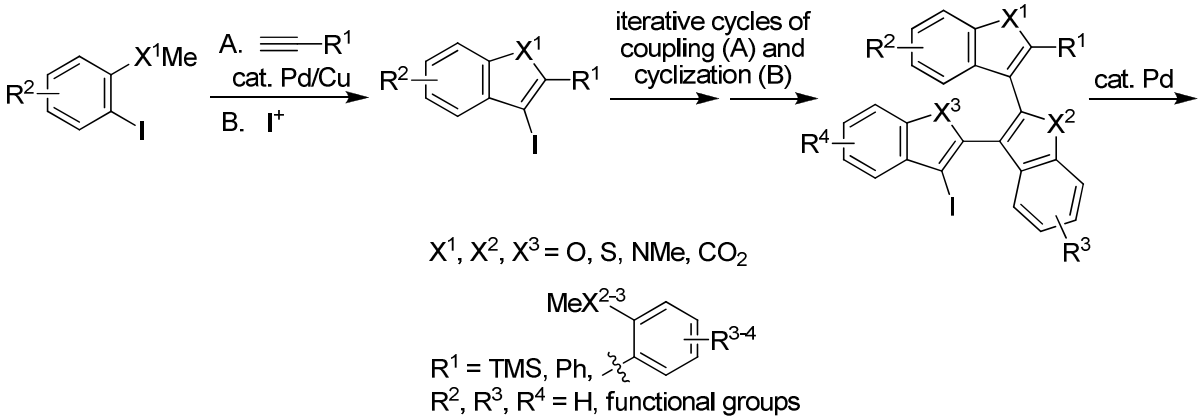
Based on a paper to be published in the *Journal of Organic Chemistry*[49]

*Saurabh Mehta and Richard C. Larock**

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

larock@iastate.edu

Abstract

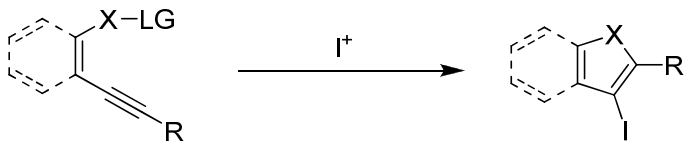


A simple, straightforward strategy for the synthesis of polyheterocyclic compounds (PHCs) is reported, which involves iterative cycles of palladium-catalyzed Sonogashira coupling, followed by iodocyclization using I_2 or ICl. A variety of heterocyclic units, including benzofurans, benzothiophenes, indoles and isocoumarins, can be efficiently incorporated under mild reaction conditions. In addition, variations of this strategy afford a variety of linked and fused PHCs.

Introduction

The iodocyclization of alkynes has emerged as an efficient tool for the synthesis of important heterocycles and carbocycles.[1] We and others have utilized this methodology (Scheme 1) for the synthesis of benzofurans,[2] furans,[3] benzothiophenes,[4] thiophenes,[5] benzopyrans,[6] benzoselenophenes,[7] selenophenes,[8] naphthols,[9] indoles,[10] quinolines,[11] isoquinolines,[12] α-pyrones,[13] isocoumarins,[13] naphthalenes[14] and polycyclic aromatics,[15] isoxazoles,[16] chromones,[17] bicyclic β-lactams,[18] cyclic carbonates,[19] pyrroles,[20] furopyridines,[21] spiro[4.5]trienones,[22] coumestrol and coumestans,[23] furanones,[24] benzothiazine-1,1-dioxides,[25] isochromenes,[26] *etc*.[27]

SCHEME 1. Iodocyclization Reaction



LG = leaving group
X = O, NMe, S, CO_2, CONHR, C=N *etc.*
R = alkyl, aryl, vinylic, TMS

In general, iodocyclization is a very efficient reaction, proceeds under very mild reaction conditions and exhibits a very broad scope in terms of the functional group/substituent compatibility. As iodine is known to be an excellent handle for further elaboration through transition metal-catalyzed cross-couplings, especially palladium-catalyzed transformations,[28] the iodocyclization products are ideal substrates for further functionalization and a rapid increase in molecular diversity. These features prompted us to

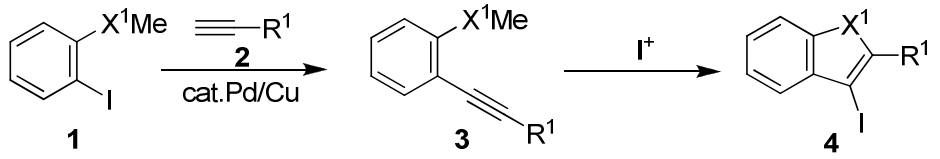
test the applicability of this strategy for building more complex systems containing multiple heterocyclic units. Polyheterocyclic compounds (PHCs) of this type have found applications in biological,[29] as well as materials chemistry.[30] We here present several versatile synthetic strategies involving iodocyclization and subsequent palladium-catalyzed transformations for the synthesis of PHCs.

Results and Discussion

The general scheme employed by us for polyheterocycle synthesis involves the Sonogashira coupling[31] of a functionally-substituted haloarene with a functionalized alkyne (Scheme 2). The alkyne is then subjected to iodocyclization and the resulting 3-iodoheterocycle is generally isolated in good to excellent yields as reported previously. The resulting iodine-containing heterocycle is then used as the starting material for further iterative cycles of Sonogashira coupling and iodocyclization to generate the desired polyheterocyclic molecule.

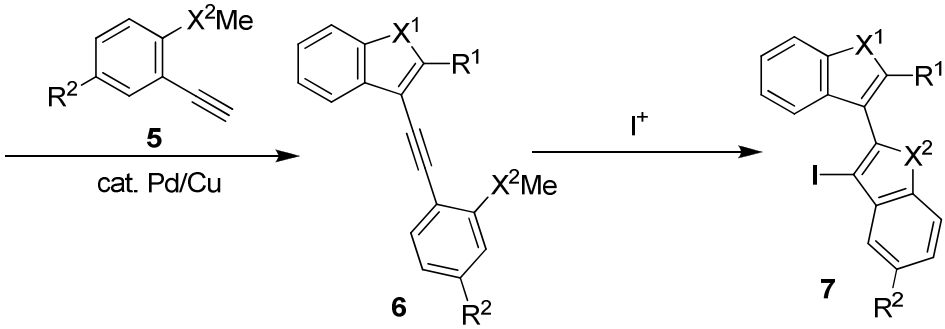
Repetitive cycles of Sonogashira coupling, followed by iodocyclization, have proven quite efficient and lead to PHCs bearing 2 or 3 linked heterocycles in moderate to good yields. Representative heterocycles and the corresponding intermediates prepared by this general strategy are listed in Scheme 2. For preparation of the intermediate alkynes, the usual Sonogashira coupling conditions have been somewhat modified, as they have generally been performed in DMF (see the Experimental Section). The intermediate alkynes have generally been prepared in good to excellent yields (Scheme 2). The iodocyclization reactions have been performed using our previously published procedures for the corresponding heterocycles.

SCHEME 2. Generation of Polyheterocyclic Compounds by the General Strategy[a]



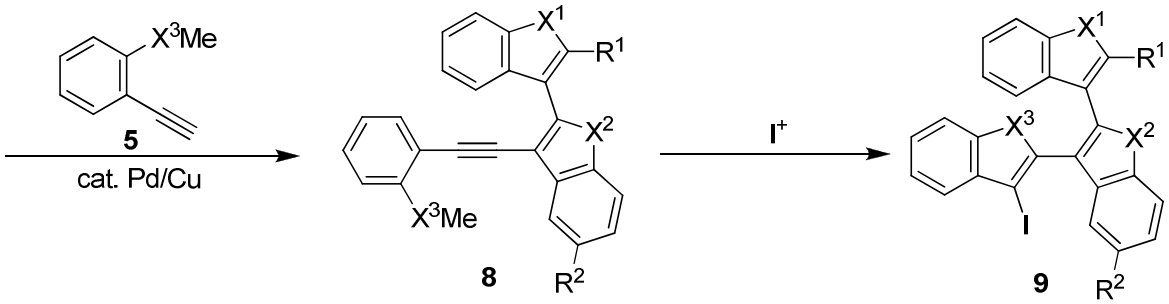
	X^1	R^1	yield (%)
3a	O	Ph	72
3b	S	Ph	100
3c	S	TMS	97

	X^1	R^1	yield (%)
4a	O	Ph	81
4b	S	Ph	99
4c	S	TMS	99
4d	S	H	95[b]



	X^1	R^1	X^2	R^2	yield (%)
6a	O	Ph	CO_2	H	98
6b	O	Ph	S	H	84
6c	O	Ph	NMe	H	81
6d	S	Ph	O	H	65
6e	S	H	O	OMe	95
6f	S	TMS	CO_2	H	79

	X^1	R^1	X^2	R^2	yield (%)
7a	O	Ph	CO_2	H	91
7b	O	Ph	S	H	98
7c	O	Ph	NMe	H	96
7d	S	Ph	O	H	67
7e	S	H	O	OMe	66



	X^1	R^1	X^2	R^2	X^3	yield (%)
8a	O	Ph	CO_2	H	NMe	79
8b	O	Ph	CO_2	H	O	75
8c	O	Ph	CO_2	H	S	55
8d	O	Ph	S	H	CO_2	89
8e	S	H	O	OMe	CO_2	81

	X^1	R^1	X^2	R^2	X^3	yield (%)
9a	O	Ph	CO_2	H	NMe	91
9b	O	Ph	CO_2	H	O	70
9c	O	Ph	CO_2	H	S	96
9d	O	Ph	S	H	CO_2	63
9e	S	H	O	OMe	CO_2	71

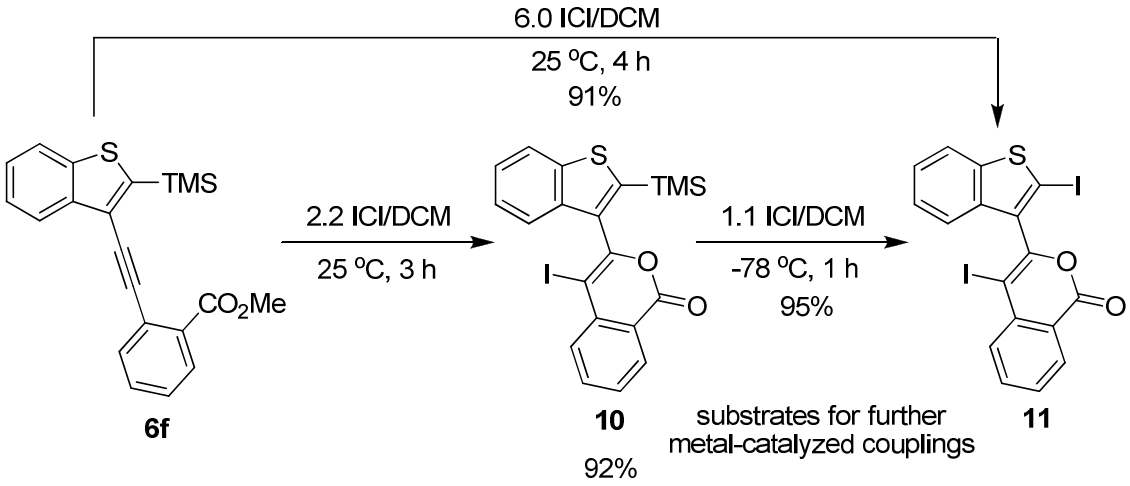
Conditions: [a]All Sonogashira reactions were carried out on a 0.25-5.0 mmol scale and the iodocyclization reactions were carried out on a 0.10-0.25 mmol scale using I_2 or ICl (see the Experimental Section). [b]This compound was prepared from **4c** by desilylation.

Various 5- and 6-membered ring heterocycles linked through different positions have been conveniently synthesized by this general strategy. We believe that this basic methodology can be extended to all other functional groups and substituents that have previously been shown to undergo facile iodocyclization.[1-27] An interesting feature of this approach is the fact that after starting the reaction sequence using an *o*-haloarene, only one other type of building block, namely a readily available functionalized terminal alkyne **5**, is required for polyheterocycle generation and different heterocyclic units can be successfully inserted at the desired positions in the PHC by simply changing the sequence of functionalized alkyne building blocks. The iterative nature of this approach to linked PHCs lends itself well to the automated synthesis of large heterocyclic sequences of varying complexity. The solubility issues in larger heterocyclic systems should be resolved by adjusting the polarity of the individual alkyne building blocks.

After successful implementation of this general strategy for the efficient synthesis of PHCs, several variations in the approach have been explored that further highlight the versatility and scope of this methodology. First, iodocyclization can be carried out quite selectively affording a variety of intermediates, which should prove quite versatile for further elaboration (Scheme 3). For example, 2-silyl-3-alkynylbenzothiophene derivative **6f** can be converted to the benzothiophene-isocoumarin di-heterocycle **11** in one step in excellent yield

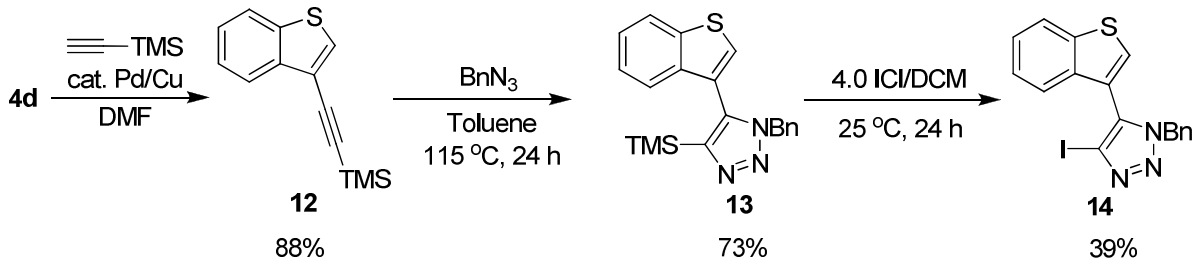
or **6f** can be very efficiently cyclized to the corresponding silicon-containing iodoisocoumarin **10**, allowing for further selective functionalization and/or iodocyclization.

SCHEME 3. Simultaneous and Stepwise Diiodination



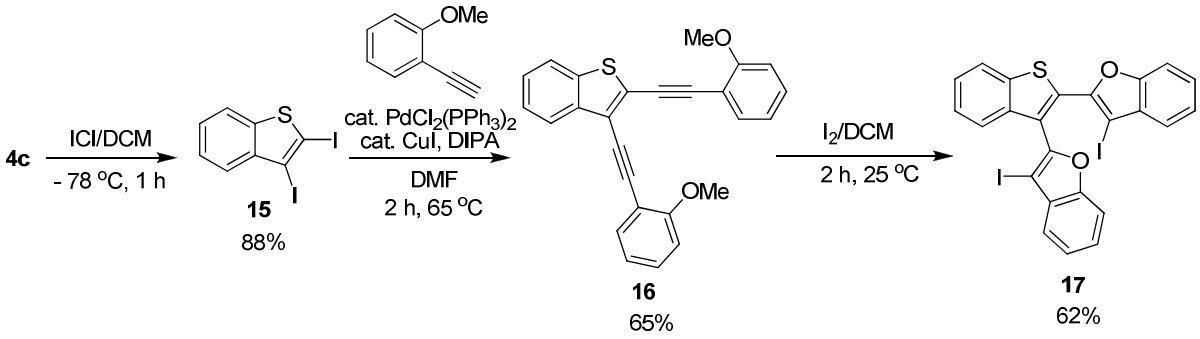
As noted earlier, a variety of heterocyclic units are readily accessible by this iodocyclization strategy. This approach can be combined with other efficient transformations to broaden the scope of the methodology and allow easy access to heterocycles that are not presently accessible by iodocyclization. For example, alkyne **12** has been subjected to well known click chemistry using benzyl azide and the desired triazole **13** was obtained in good yield (Scheme 4).[32] Upon iodo-desilylation, the iodotriazole **14** was obtained, providing avenues for the further introduction of heterocycles using our Sonogashira coupling/iodocyclization methodology or other coupling reactions, such as Suzuki-Miyaura couplings.[33]

SCHEME 4. Click Chemistry Followed by Iodo-desilylation



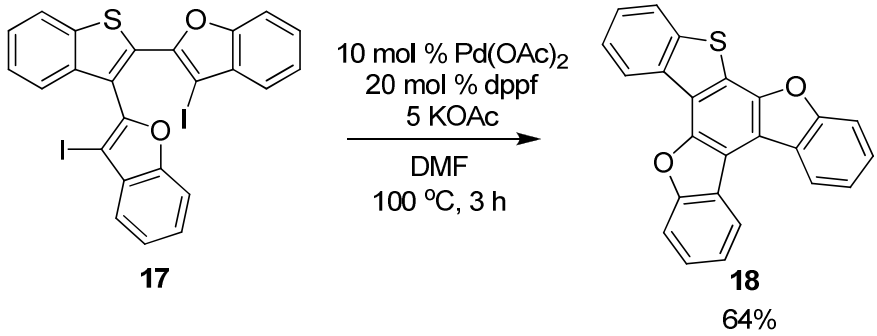
In an effort to synthesize fused polyheterocyclic compounds, the benzothiophene derivative **4c** was subjected to silyl-iodine exchange (Scheme 5). The resulting 2,3-diiodobenzothiophene (**15**) on double Sonogashira coupling with an appropriate *o*-functionalized terminal alkyne, followed by double cyclization, quickly leads to a compound **17**, having three linked heterocyclic units and two iodine handles.

SCHEME 5. Double Sonogashira Coupling, Followed by Double Iodocyclization



The diiodo compound **17** was then subjected to a palladium-catalyzed Ullmann reaction leading to the formation of fused heterocycle **18** (Scheme 6).[34] Similar fused heterocyclic systems have been shown to exhibit interesting electronic and luminescent properties.[35] This approach can be conveniently extended to the synthesis of symmetrical fused heterocycles as well. PHCs such as these should prove useful as ligands in coordination and organometallic chemistry.

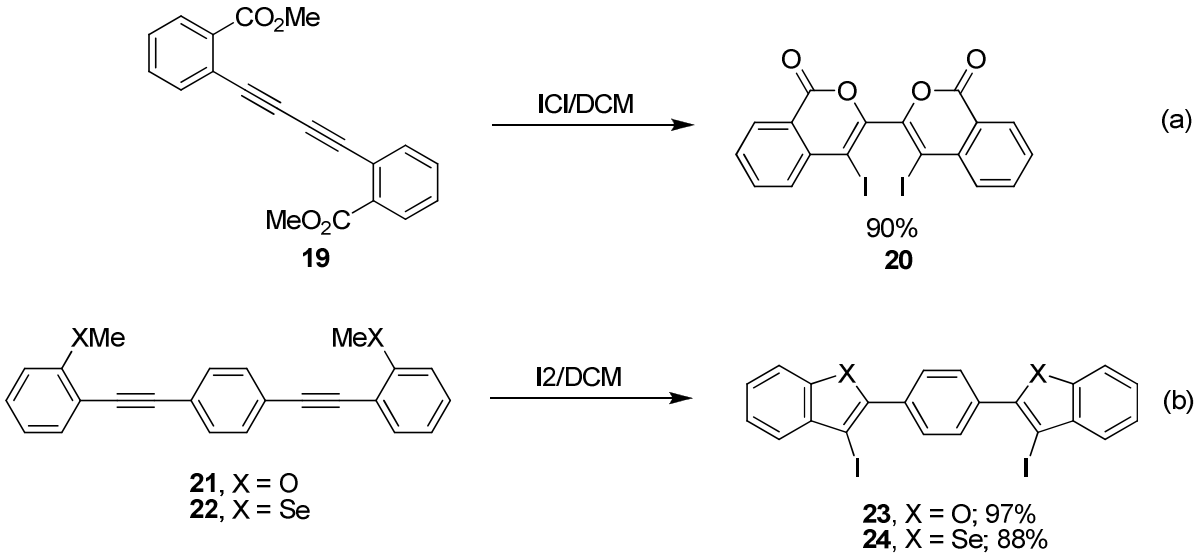
SCHEME 6. Palladium-catalyzed Ullmann Reaction



17 **18**
64%

The above variations in our basic strategy (Schemes 4 and 6) highlight the ability to couple our methodology with other efficient methodologies to synthesize molecules with diverse functionalities quickly and efficiently. In another variation, the cyclization of 1,3-diynes has been explored. Efficient examples of homo 1,3-diyne cyclization have been reported (Scheme 7) previously by us and others.[2b,3h,7a,13,36]

SCHEME 7. Previously Reported Examples of 1,3-Diyne Cyclization

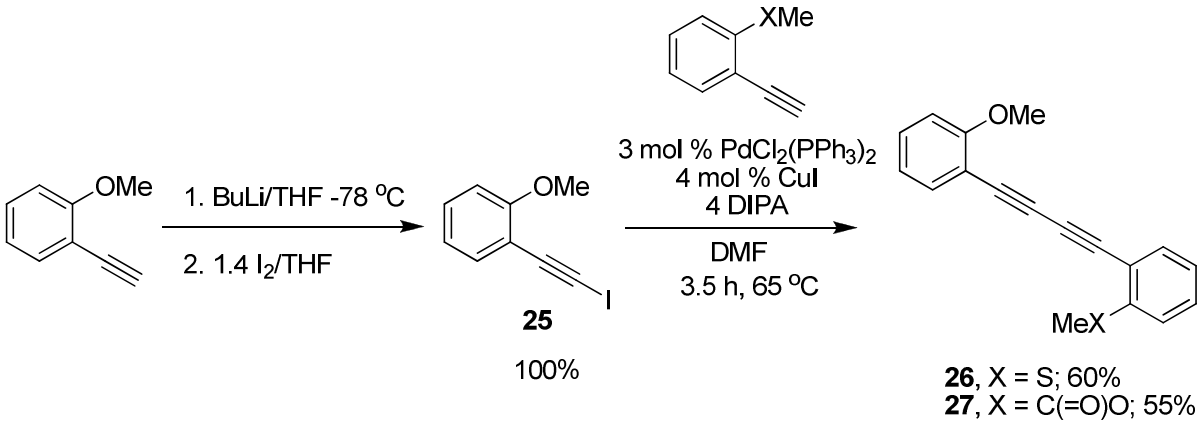


19 **20**
21, X = O
22, X = Se
23, X = O; 97%
24, X = Se; 88%

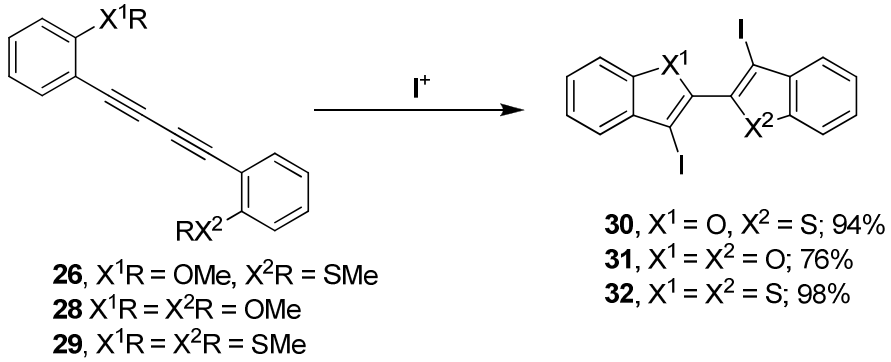
In an effort to cover other functional groups and heteroatom-containing diynes, several additional 1,3-diynes have been synthesized using our optimized Sonogashira conditions (Scheme 8). The hetero-1,3-diynes were obtained in only moderate yields as the

cross-coupling suffers from formation of homocoupling by-products. Nonetheless, the homo- and hetero-1,3-diynes were subjected to iodocyclization and the double cyclized products **30-32** were obtained in good to excellent yields (Scheme 9). Furthermore, in the case of hetero-1,3-diyne **27**, the reaction conditions were tuned to achieve single or double cyclization (Scheme 10). Thus, symmetrical, as well as unsymmetrical, bisheterocyclic units with dihalide functionality are readily accessible using our methodology. Recently, similar dihalo compounds have been used as precursors for the synthesis of more complex fused heterocycles exhibiting potential applications as organic field effect transistors (OFETs).[37]

SCHEME 8. Preparation of 1,3-Diynes



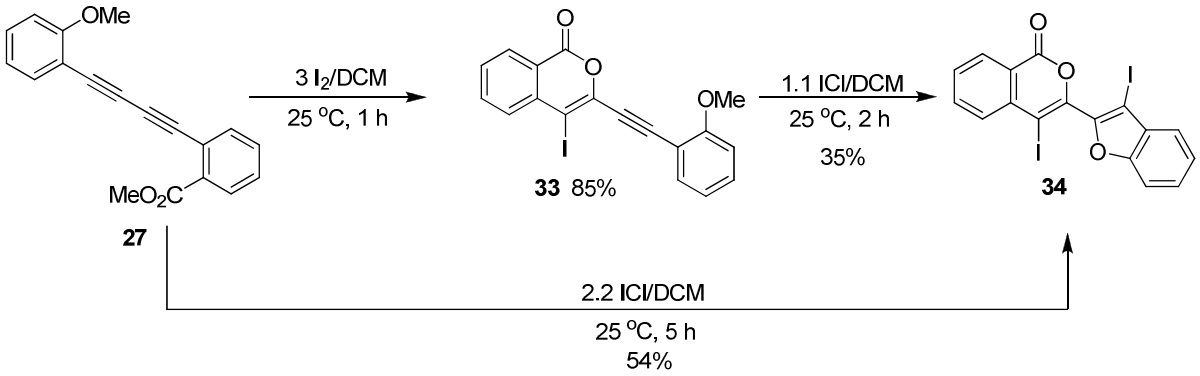
SCHEME 9. Iodocyclization of Homo- and Hetero-1,3-diynes



26, X^1R = OMe, X^2R = SMe
28 $X^1R = X^2R$ = OMe
29, $X^1R = X^2R$ = SMe

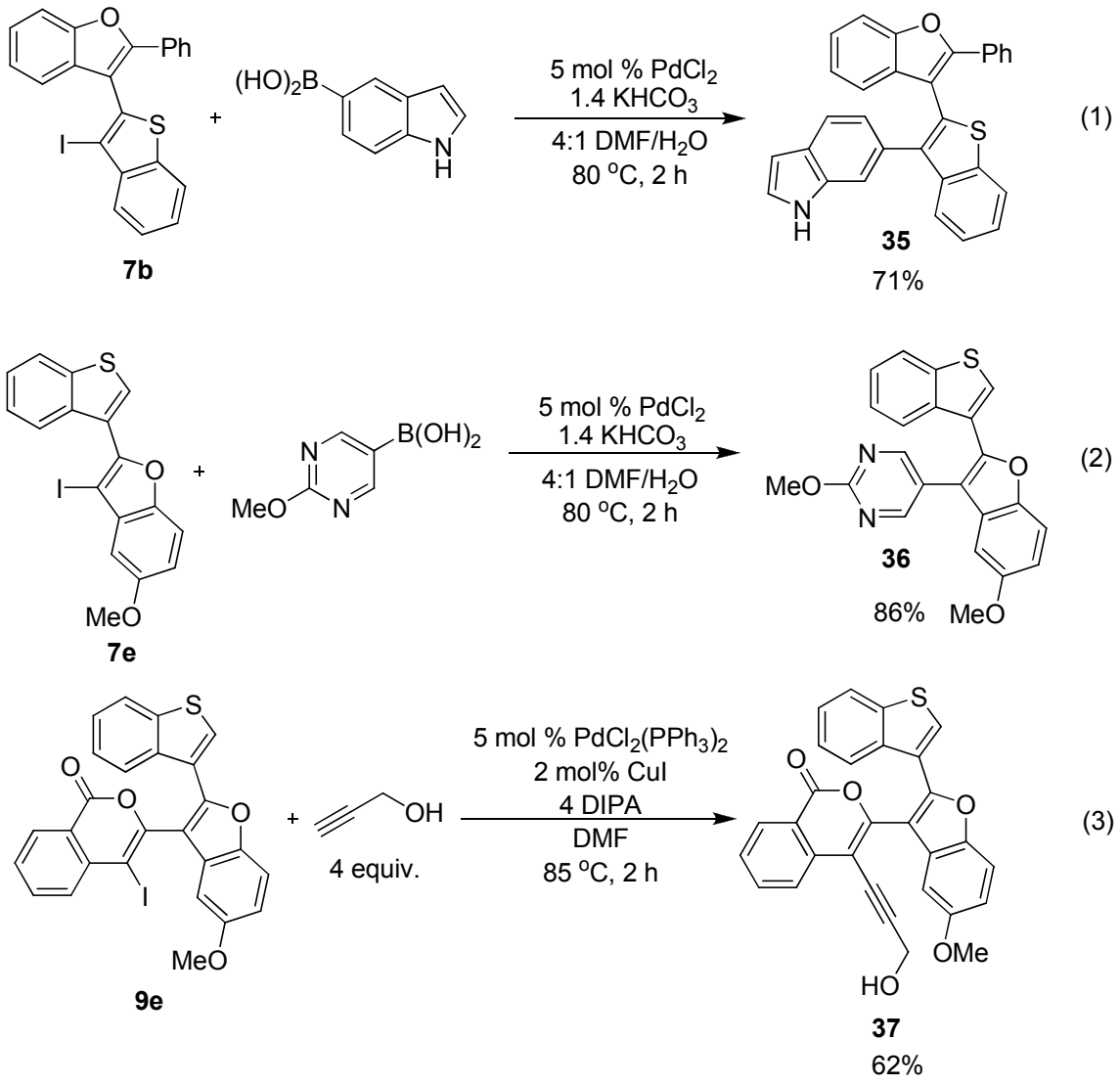
30, X^1 = O, X^2 = S; 94%
31, $X^1 = X^2$ = O; 76%
32, $X^1 = X^2$ = S; 98%

SCHEME 10. Tuning of Reaction Conditions for Single or Double Cyclization



As observed in all of the processes outlined above, the end products contain iodine, an important handle for further modifications. Thus, these heterocyclic iodides can either be subjected to reductive hydrodehalogenation,[38] or they can be used to introduce further diversity and polarity into the molecules using conventional palladium-catalyzed transformations (Scheme 11), for example Suzuki-Miyaura couplings (eqs 1 and 2) and Sonogashira alkynylation (eq 3).

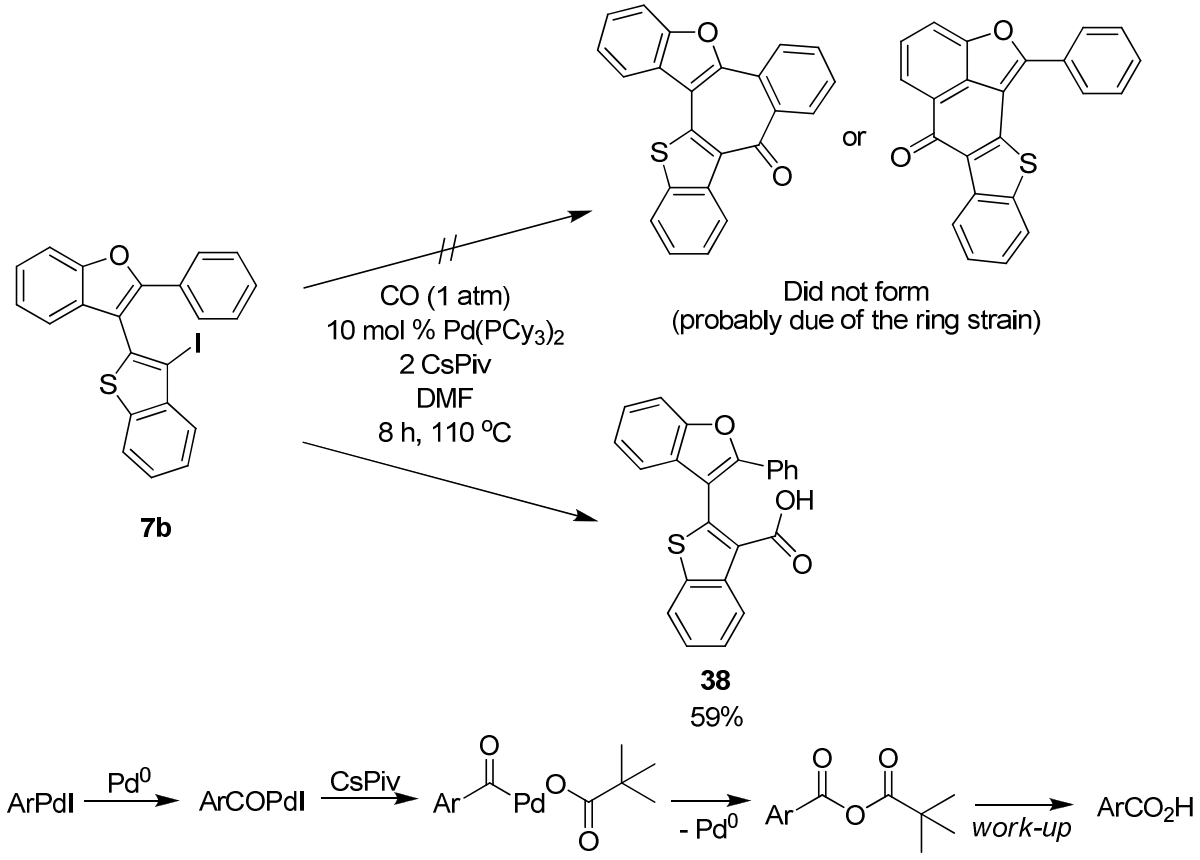
SCHEME 11. Elaboration of the Iodine-containing Products



Finally, palladium-catalyzed annulations have been examined in order to extend the scope of this methodology for the generation of complex fused PHCs. For example, in an attempt to perform the cyclocarbonylation reaction, bisheterocyclic compound **7b** was subjected to our previously published conditions (Scheme 12).[39] However, neither of the two expected regioisomeric annulated products was formed presumably due to the ring strain. Instead, the reaction led to the corresponding carboxylic acid **38**, whose structure was

confirmed by single crystal X-ray analysis, in 61% yield. Carboxylic acid formation probably happens because of nucleophilic attack by the pivalate anion on the initially formed acylpalladium intermediate, which leads to the corresponding anhydride, followed by hydrolysis during aqueous work up of the reaction mixture (Scheme 12).

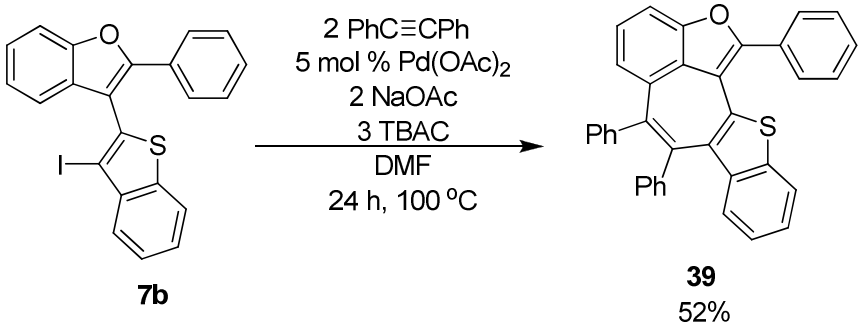
SCHEME 12. Cyclocarbonylation Attempt



On the other hand, the alkyne annulation of polyheterocyclic compound **7b** affords the fused ring heterocycle **39** in 52% yield (Scheme 13).[40] The regioisomeric assignment is based on X-ray crystallographic data. Such annulation processes provide considerable scope

in terms of the types of heterocycles that can be included in different positions, the ring size, *etc*., allowing one to introduce a wide variety of heterocycles in desired positions.

SCHEME 13. Alkyne Annulation Reaction Leading to a Fused PHC



7b **39** 52%

Conclusions

Several iodocyclization/palladium-catalyzed approaches have been reported for the generation of linked and fused polyheterocyclic compounds. The ability to quickly put together multiple heterocyclic rings and accommodate various other subsequent transformations adds to the synthetic utility and scope of the methodology, making this a very practical approach for PHC synthesis. In some cases, the potential exists for combinatorial automated synthesis. Considering the broad scope and considerable flexibility of this methodology and the widespread potential applications of the resulting products, rapid advances in this area of research are anticipated.

Experimental Section

General

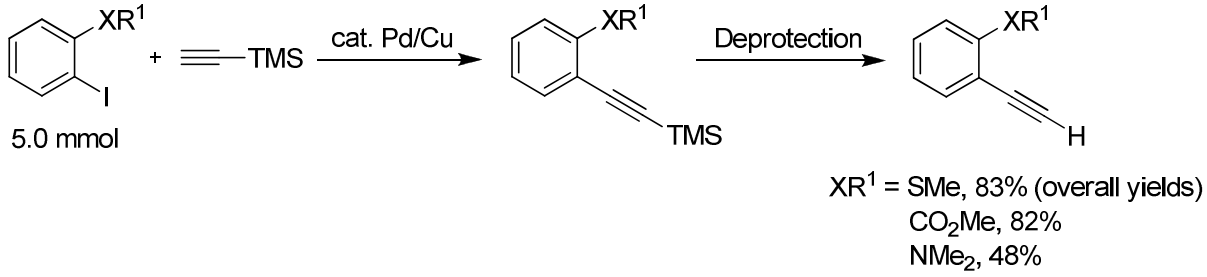
The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 MHz or 400 MHz and 75 MHz or 100 MHz, respectively, with Me_4Si as an internal standard. The chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm). Purification of the compounds has been performed by column chromatography and/or recrystallization. All melting points are uncorrected. HRMS data: the electron impact ionization experiments were performed on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA) fitted with a Finnigan EI/CI ion source. The samples were introduced to the mass spectrometer using a solids probe. The probe was heated gradually from 100 to 400 ^{o}C. The instrument was used as a single quadrupole and scanned from 50 to 1000 daltons. Accurate mass measurements were conducted using a manual peak matching technique with the KRATOS MS50 double focusing mass spectrometer.

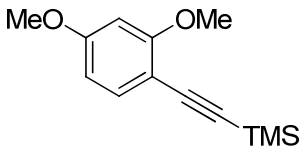
Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

Solvents. All solvents were used directly as obtained commercially except for DCM that was distilled over CaH_2.

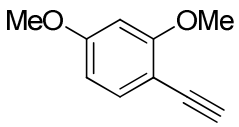
Terminal alkyne building blocks (5). Commercially available terminal alkynes were used as received. Non-commercial terminal alkynes were prepared using the two-step approach, which involves Sonogashira coupling of the commercially available haloarene with trimethylsilyl acetylene, followed by removal of the TMS group (Scheme S1).[1a]

Scheme S1. Preparation of the Requisite Terminal Alkynes





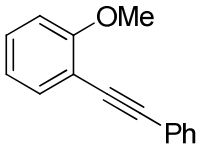
[(2,4-Dimethoxyphenyl)ethynyl]trimethylsilane. To a solution of 1-iodo-2,4-dimethoxybenzene (5.0 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 2 mol %), and CuI (0.02 g, 2 mol %) in TEA (20 mL) (stirring for 5 min beforehand), 6.0 mmol of trimethylsilyl acetylene (1.2 equiv) in 5 mL of TEA was added dropwise over 10 min. The reaction flask was flushed with Ar and the mixture was stirred at room temperature for 1.5 h. The resulting solution was filtered, washed with brine, and extracted with ethyl acetate (2 x 10 mL). The combined fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. Purification by flash chromatography afforded the product (yield = 93%) as a brown solid: mp 45-47 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 3.72 (s, 3H), 3.78 (s, 3H), 6.34 (s, 1H), 6.36 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.16, 55.2, 55.6, 96.3, 98.1, 101.6, 104.6, 104.7, 134.8, 161.2, 161.4; HRMS Calcd for $C_{13}H_{18}O_2Si$: 234.10760. Found: 234.10815.



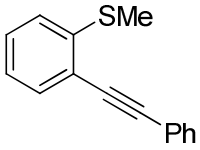
1-Ethynyl-2,4-dimethoxybenzene. A solution of NaOH (24.0 mmol, 6 equiv) in 5 mL of water was added dropwise to [(2,4-dimethoxyphenyl)ethynyl]trimethylsilane (4.0 mmol) in 15 mL of CH_3OH:diethyl ether (1:1). After stirring the reaction mixture for 2 h at 25 ^oC, CH_3OH was removed under vacuum, the reaction mixture was diluted with ether and the excess NaOH was neutralized with 2M HCl. The ether layer was washed with water, dried (Na_2SO_4), filtered, and the solvent removed under vacuum. Purification by flash chromatography afforded the product (yield = 92%) as a clear oil:[41] ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 6.41 (s, 1H), 6.42 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 55.8, 79.7, 80.2, 98.2, 103.6, 104.8, 134.8, 161.5, 161.8; HRMS Calcd for $C_{10}H_{10}O_2$: 162.06808. Found: 162.06848.

Synthesis of Compounds 3-9 by the General Strategy.

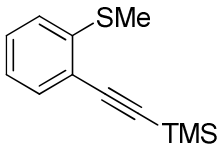
General Sonogashira Coupling Procedure Used for the Preparation of 3a-c. To a solution of *o*-iodoarene **1** (5.0 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 2 mol %), and CuI (0.01 g, 1 mol %) in TEA (20 mL) (stirring for 5 min beforehand), 6.0 mmol of terminal acetylene **2** (1.2 equiv) in 5 mL of TEA was added dropwise over 10 min. The reaction flask was flushed with Ar and the mixture was stirred at room temperature for 3 h. The resulting solution was filtered, washed with brine, and extracted with EtOAc (2 x 10 mL). The combined fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. Purification of the products was performed using flash chromatography.



2-(Phenylethynyl)anisole (3a). This compound was isolated (reaction time: 2 h; yield: 72%) as a yellow oil. The spectral properties were identical to those previously reported.[2b]



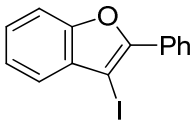
2-(Phenylethynyl)thioanisole (3b). This compound was isolated (yield: 100%) as a yellow oil. The spectral properties were identical to those previously reported.[42]



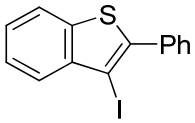
2-(Trimethylsilylethynyl)thioanisole (3c). This compound was isolated (yield: 97%) as a yellow oil. The spectral properties were identical to those previously reported.[4b]

General Iodocyclization Procedure for the Synthesis of 4a-c. The iodocyclization reactions have been performed using our previously published procedures for the corresponding heterocycles.[2b,4b] To a solution of the starting alkyne **3** (4.0 mmol) in DCM (30 mL) was gradually added the I_2 (1.5-2.0 equiv) dissolved in 10 mL of DCM. The reaction mixture was allowed to stir at 25 °C and the reaction was monitored by TLC for completion. The excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then

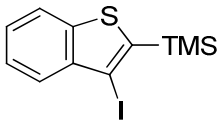
extracted by EtOAc or diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexane-EtOAc as the eluent.



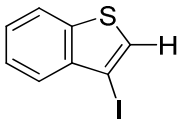
3-Iodo-2-phenylbenzo[*b*]furan (4a). This reaction was performed using 2.0 equiv of iodine. This compound was obtained as a yellow oil (reaction time: 3 h; yield: 81%). The spectral properties were identical to those previously reported.[2b]



3-Iodo-2-phenylbenzo[*b*]thiophene (4b). This reaction was performed using 1.5 equiv of iodine. This compound was obtained as a yellow oil (reaction time: 1 h; yield: 99%). The spectral properties were identical to those previously reported.[39a]

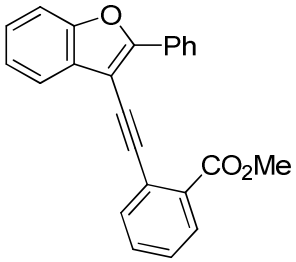


3-Iodo-2-(trimethylsilyl)benzo[*b*]thiophene (4c). This reaction was performed using 1.5 equiv of iodine. This compound was isolated as a yellow oil (reaction time: 0.5 h; yield: 99%). The spectral properties were identical to those previously reported.[4b]



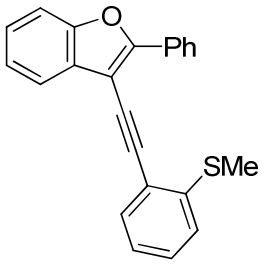
3-Iodobenzo[*b*]thiophene (4d). To a solution of **4c** (4 mmol) in THF (13 mL) was slowly added TBAF (3.0 equiv, 1M solution in THF, 13 mL) and the reaction mixture was allowed to stir at 25 ^{o}C for 3 h. The reaction was worked up using satd aq $NaHCO_3$, washed with brine and water, extracted with ether, and dried with Na_2SO_4. After purification by flash chromatography, the compound was isolated as a yellow liquid (yield: 95%). The spectral properties were identical to those previously reported.[43]

Preparation of 6a-f by Sonogashira Coupling.



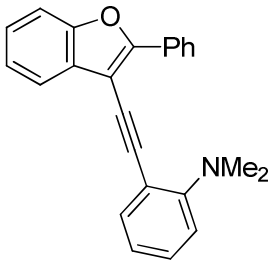
Methyl 2-[(2-phenylbenzofuran-3-yl)ethynyl]benzoate (6a). A solution of **4a** (0.47 g, 1.48 mmol), $PdCl_2(PPh_3)_2$ (0.042 g, 4 mol %), and CuI (0.012 g, 4 mol %) in TEA (15 mL) was stirred for 5 min. The reaction flask was flushed with Ar and a solution of methyl 2-ethynylbenzoate (0.36 g, 2.22 mmol, 1.5 equiv) in 5 mL of TEA was added dropwise over 10 min. The reaction mixture was stirred at 60 ^{o}C for 21 h. The resulting solution was filtered, washed with brine, and extracted with EtOAc (2 x 10 mL). The combined fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. After

purification by flash chromatography, the product (yield = 98%) was obtained as an orange solid: mp 73-76 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.28-7.49 (m, 8H), 7.66 (d, J = 8.0 Hz, 1H), 7.84-7.86 (m, 1H), 7.94-7.96 (m, 1H), 8.40-8.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 86.5, 96.1, 99.4, 111.2, 120.6, 123.5, 123.9, 125.4, 126.2, 127.9, 128.7, 129.3, 130.0, 130.2, 130.6, 131.2, 131.8, 134.1, 153.5, 156.6, 166.3; HRMS Calcd for $C_{24}H_{16}O_3$: 352.10994. Found: 352.11081.

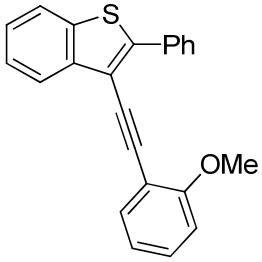


3-[(2-(Methylthio)phenyl)ethynyl]-2-phenylbenzofuran (6b). To a solution of **4a** (1.0 mmol) in DMF (8 mL) were added $PdCl_2(PPh_3)_2$ (21.0 mg, 3 mol %) and CuI (8.0 mg, 4 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (405 mg, 4.0 equiv) was added by syringe. The reaction mixture was then heated to 80 °C. A solution of 2-ethynylthioanisole (1.2 equiv) in DMF (2 mL) was added dropwise over 10 min, and the mixture was allowed to stir at 80 ^{o}C for 3.5 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane-EtOAc as eluent. After purification, the product was obtained (yield: 84%) as a white solid: mp 110-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.14 (td, J = 1.2, 7.6 Hz, 1H), 7.19-7.21 (m, 1H), 7.29-7.41 (m, 4H), 7.47-7.52 (m, 3H), 7.56-7.58 (m, 1H), 7.84-7.86 (m,

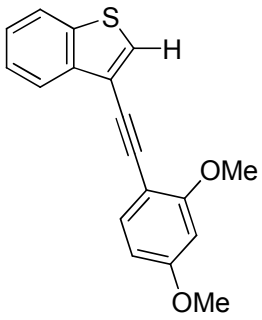
1H), 8.41-8.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 87.7, 94.7, 99.4, 111.3, 120.8, 121.7, 123.6, 124.5, 124.6, 125.5, 126.3, 128.8, 129.0, 129.3, 130.17, 130.22, 132.6, 141.5, 153.6, 156.4; HRMS Calcd for $C_{23}H_{16}OS$: 340.09218. Found: 340.09304.



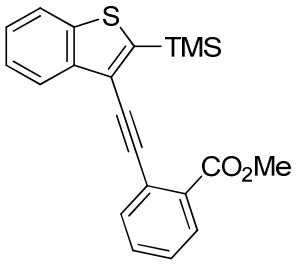
***N*,*N*-Dimethyl-2-[(2-phenylbenzofuran-3-yl)ethynyl]aniline (6c).** Starting with the iodo compound **4a** and the corresponding terminal alkyne, the reaction was run by using the procedure used for the preparation of **6b** above, except that the reaction was run on a 0.5 mmol scale and the reaction time was 2 h. After purification, the product was obtained (yield = 81%) as a yellow solid: mp 66-69 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 3H), 6.91-6.96 (m, 2H), 7.24-7.30 (m, 3H), 7.31-7.37 (m, 1H), 7.43-7.50 (m, 3H), 7.56-7.58 (m, 1H), 7.74-7.76 (m, 1H), 8.41 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1, 86.4, 96.5, 99.9, 111.3, 115.9, 117.4, 120.5, 120.9, 123.5, 125.4, 126.1, 128.7, 129.2, 129.6, 130.2, 130.4, 134.3, 153.6, 154.9, 155.9; HRMS Calcd for $C_{24}H_{19}NO$: 337.14666. Found: 337.14717.



3-[(2-Methoxyphenyl)ethynyl]-2-phenylbenzo[*b*]thiophene (6d). Starting with the iodo compound **4b** and the corresponding terminal alkyne, the reaction was run by using the procedure used for the preparation of **6b**, except that the reaction was run on a 0.5 mmol scale. The product was obtained (yield = 65%) as a white solid: mp 90-92 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.92-6.98 (m, 2H), 7.31-7.41 (m, 3H), 7.45-7.50 (m, 3H), 7.54 (dd, J = 7.6, 2.0 Hz, 1H), 7.81 (d, J = 8.0, 1H), 8.11 (d, J = 8.0, 1H), 8.19 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 88.4, 91.9, 110.9, 112.9, 114.1, 120.7, 122.2, 123.7, 125.1, 125.4, 128.6, 128.76, 128.82, 130.0, 133.4, 134.1, 137.6, 141.5, 145.7, 160.4; HRMS Calcd for $C_{23}H_{16}OS$: 340.09219. Found: 340.09269.

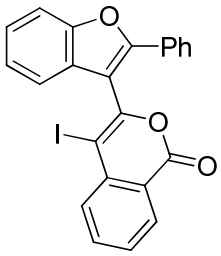


3-[(2,4-Dimethoxyphenyl)ethynyl]benzo[*b*]thiophene (6e). Starting with the iodo compound **4d** and the corresponding terminal alkyne, the reaction was run by using the procedure used for the preparation of **6b**. The product was obtained (yield = 95%) as a yellow gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.95 (s, 3H), 6.52 (s, 1H), 6.54 (d, J = 1.6 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.47-7.53 (m, 2H), 7.68 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 56.0, 85.8, 88.5, 98.6, 105.01, 105.04, 119.1, 122.7, 123.4, 124.7, 125.1, 128.8, 134.4, 138.9, 139.5, 161.40, 161.44; HRMS Calcd for $C_{18}H_{14}O_2S$: 294.07145. Found: 294.07216.

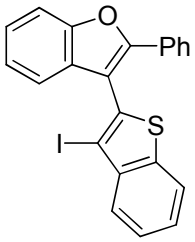


Methyl 2-[(2-(trimethylsilyl)benzo[*b*]thiophen-3-yl)ethynyl]benzoate (6f). Starting with the iodo compound **4c** and the corresponding terminal alkyne, the reaction was run by using the procedure used for the preparation of **6b**. The product was obtained (yield = 79%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (s, 9H), 4.02 (s, 3H), 7.42 (t, J = 7.6 Hz, 2H), 7.51-7.57 (m, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.36, 52.4, 90.2, 92.4, 122.1, 123.4, 124.1, 124.81, 124.83, 125.0, 127.9, 130.7, 131.6, 131.9, 133.8, 141.8, 142.1, 146.4, 166.6; HRMS Calcd for $C_{21}H_{20}O_2SSi$: 364.09532. Found: 364.09634.

General Iodocyclization Procedure for the Synthesis of 7a-e. The iodocyclization reactions have been performed using our previously published procedures for the corresponding heterocycles.[2b,4b,10d,13] The appropriate alkyne starting material **6** (0.25-0.30 mmol) in 4 mL of CH_2Cl_2 was placed in a 4-dram vial and flushed with Ar. I_2 (2 equiv) [ICl (1.2 equiv) in the case of **7a**] in 2 mL CH_2Cl_2 was added and the reaction was stirred at room temperature for the indicated time. After the reaction was over, the reaction mixture was diluted with 30 mL of EtOAc, washed with 25 mL of satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

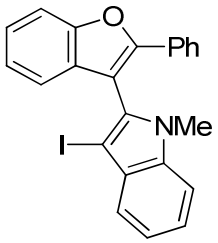


4-Iodo-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (7a). For this reaction, the ICl (1.2 equiv) in 1 mL of CH_2Cl_2 was added dropwise to the reaction vial with a syringe (reaction time: 30 min). After purification, the product was obtained (yield = 91%) as a white solid: mp 204-207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1H), 7.36-7.41 (m, 4H), 7.51 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.64-7.68 (m, 1H), 7.76-7.78 (m, 2H), 7.85-7.86 (m, 2H), 8.37 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.6, 111.7, 112.4, 120.6, 120.9, 123.7, 125.5, 126.75, 126.81, 128.1, 129.2, 129.8, 130.0, 130.2, 131.5, 136.0, 138.0, 149.6, 153.8, 154.4, 161.9; HRMS Calcd for $C_{23}H_{13}IO_3$: 463.99094. Found: 463.99233.

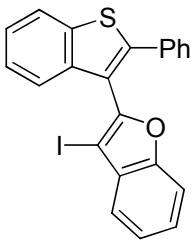


3-(3-Iodobenzo[*b*]thiophen-2-yl)-2-phenylbenzofuran (7b). Reaction time: 30 min. After purification, the product was obtained (yield = 98%) as a white solid: mp 158-161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.52 (m, 8H), 7.60 (d, J = 8.4 Hz, 1H), 7.68-7.70 (m, 2H), 7.85 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.5, 110.7, 111.5, 120.7, 122.7,

123.5, 125.3, 125.6, 125.9, 126.3, 126.9, 128.9, 129.2, 129.9, 130.2, 134.6, 140.3, 141.7, 153.2, 153.9; HRMS Calcd for $C_{22}H_{13}IOS$: 451.97318. Found: 451.97428.

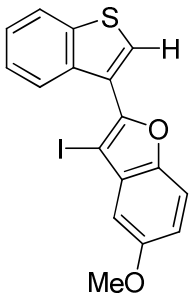


3-Iodo-1-methyl-2-(2-phenylbenzofuran-3-yl)-1*H*-indole (7c). Reaction time: 1 h. After purification, the product was obtained (yield = 96%) as a white solid: mp 201-204 ^{o}C (turns black); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3H), 7.23-7.39 (m, 9H), 7.57-7.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 61.4, 107.6, 110.2, 111.6, 120.9, 121.0, 121.6, 123.2, 123.6, 125.3, 126.2, 129.1, 129.3, 129.8, 130.2, 130.9, 134.0, 138.1, 153.9, 154.1; HRMS Calcd for $C_{23}H_{16}INO$: 449.02767. Found: 449.02867.



3-Iodo-2-(2-phenylbenzo[*b*]thiophen-3-yl)benzofuran (7d). Reaction time: 3 h. After purification, the product was obtained (yield = 67%) as a brown solid: mp 134-137 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.45 (m, 10H), 7.49-7.51 (m, 1H), 7.63-7.66 (m, 1H), 7.87-7.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.1, 111.7, 121.0, 121.8, 122.4, 123.7, 123.9,

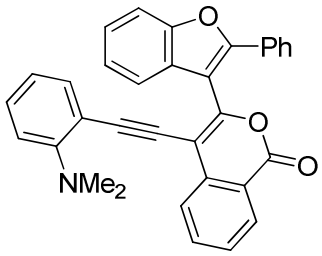
125.1, 125.2, 125.8, 126.86, 128.97, 129.1, 131.6, 134.0, 138.6, 140.1, 146.7, 151.9, 154.9; HRMS Calcd for $C_{22}H_{13}IOS$: 451.97319. Found: 451.97380.



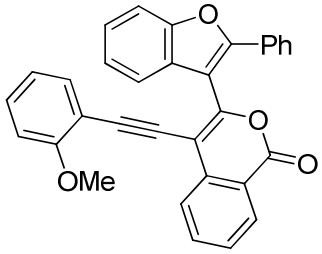
2-(Benzo[*b*]thiophen-3-yl)-3-iodo-5-methoxybenzofuran (7e). Reaction time: 3 h. After purification, the product was obtained (yield = 66%) as a yellow solid: mp 63-66 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.02 (dd, J = 2.0, 8.4 Hz, 1H), 7.12 (d, J = 2.0, 1H), 7.36 (d, J = 8.4, 1H), 7.46-7.53 (m, 2H), 7.95 (d, J = 8.0, 1H), 8.25 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 63.3, 95.7, 112.9, 121.9, 122.7, 124.6, 124.86, 124.96, 125.1, 125.8, 128.2, 137.3, 139.8, 150.4, 154.7, 159.1; HRMS Calcd for $C_{17}H_{11}IO_2S$: 405.95245. Found: 405.95354.

General Sonogashira Coupling Procedure for the Preparation of 8a-e. To a solution of the appropriate iodo starting material **7** (0.2 mmol) in DMF (3 mL) were added $PdCl_2(PPh_3)_2$ (3 mol %) and CuI (4 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (4.0 equiv) was added by a syringe. The reaction mixture was then heated to 80 °C. A solution of the corresponding terminal alkyne (1.2 equiv) in DMF (1 mL) was added dropwise over 5 min, and the mixture was allowed to stir at 80 ^{o}C for 2-4 h (the reaction progress was monitored by TLC). After cooling, the

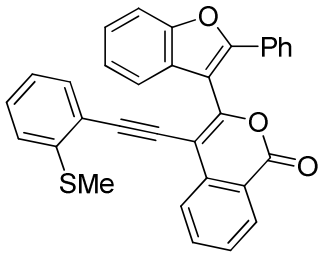
reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane-EtOAc as the eluent.



4-[(2-(Dimethylamino)phenyl)ethynyl]-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (8a). After purification, the product was obtained (yield = 79%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 6.72 (td, J = 0.8, 7.6 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.84-6.86 (m, 1H), 7.16 (td, J = 2.0, 7.6 Hz, 1H), 7.27-7.29 (m, 1H), 7.34-7.38 (m, 4H), 7.58 (d, J = 8.0 Hz, 1H), 7.64 (td, J = 1.2, 7.6 Hz, 1H), 7.75 (dd, J = 0.8, 7.6 Hz, 1H), 7.82-7.89 (m, 3H), 8.15 (d, J = 7.6 Hz, 1H), 8.41 (dd, J = 0.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.5, 86.4, 98.4, 104.7, 109.8, 111.4, 114.7, 117.1, 120.3, 120.5, 121.4, 123.7, 125.3, 125.7, 127.3, 128.4, 128.8, 129.2, 129.69, 129.72, 129.9, 130.2, 134.2, 135.4, 137.0, 151.3, 153.9, 154.8, 155.1, 161.6; HRMS Calcd for $C_{33}H_{23}NO_3$: 481.16779. Found: 481.16886.

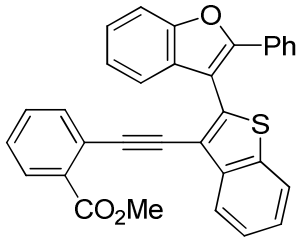


4-[(2-Methoxyphenyl)ethynyl]-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (8b). After purification, the product was obtained (yield = 75%) as a yellow solid: mp 159-161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.74-6.78 (m, 3H), 7.18-7.21 (m, 1H), 7.27-7.38 (m, 5H), 7.57-7.63 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.82-7.87 (m, 3H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.40 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 85.6, 95.9, 104.3, 109.7, 110.5, 111.3, 111.8, 120.2, 120.3, 121.6, 123.5, 125.2, 125.9, 127.4, 128.4, 128.8, 129.2, 129.6, 129.8, 130.2, 130.3, 132.9, 135.4, 137.0, 151.5, 153.9, 155.2, 160.0, 161.6; HRMS Calcd for $C_{32}H_{20}O_4$: 468.13616. Found: 468.13682.

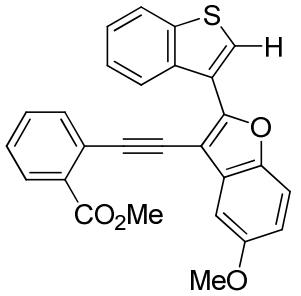


4-[(2-(Methylthio)phenyl)ethynyl]-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (8c). After purification, the product was obtained (yield = 55%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.30-7.39 (m, 5H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.83-7.85 (m, 2H), 7.91 (t, *J* = 7.6 Hz, 1H), 8.30 (d, *J*

= 8.0 Hz, 1H), 8.41 (d, *J* = 7.6 Hz, 1H); HRMS Calcd for $C_{32}H_{20}O_3S$: 484.11332. Found: 484.11396.



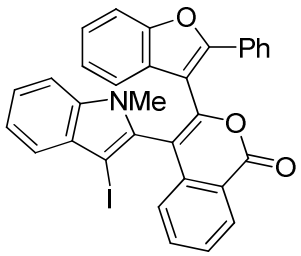
Methyl 2-[(2-(2-phenylbenzofuran-3-yl)benzo[*b*]thiophen-3-yl)ethynyl]benzoate (8d). After purification, the product was obtained (yield = 89%) as a yellow semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.89-6.91 (m, 1H), 7.24-7.38 (m, 7H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.53-7.60 (m, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 6.4 Hz, 2H), 7.85-7.87 (m, 2H), 8.28 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 88.3, 94.8, 109.8, 111.3, 118.2, 121.2, 122.5, 123.4, 123.6, 123.9, 125.2, 125.3, 125.6, 127.5, 127.9, 128.6, 129.2, 129.9, 130..37, 130.43, 131.4, 131.6, 134.3, 137.9, 139.2, 140.5, 153.2, 154.2, 166.7; HRMS Calcd for $C_{32}H_{20}O_3S$: 484.11331. Found: 484.11445.



Methyl 2-[(2-(benzo[*b*]thiophen-3-yl)-5-methoxybenzofuran-3-yl)ethynyl]benzoate (8e). After purification, the product was obtained (yield = 81%) as a yellow solid: mp 173-175 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.94 (s, 3H), 7.01 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.14

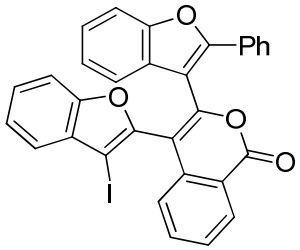
(d, *J* = 2.0, 1H), 7.39-7.43 (m, 2H), 7.51-7.53 (m, 2H), 7.69-7.74 (m, 2H), 7.92 (d, *J* = 8.0, 1H), 8.00-8.03 (m, 1H), 8.69 (d, *J* = 8.0, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 56.0, 86.9, 95.8, 96.1, 99.9, 112.9, 120.7, 122.7, 122.8, 124.1, 124.95, 124.98, 125.0, 126.2, 127.8, 128.1, 130.7, 131.4, 132.0, 134.4, 136.8, 140.2, 154.3, 154.5, 158.9, 166.6; HRMS Calcd for $C_{27}H_{18}O_4S$: 438.09257. Found: 438.09418.

General Iodocyclization Procedure for the Synthesis of 9a-e. The appropriate alkyne starting material **8** (0.10 mmol) in 1.5 mL of CH_2Cl_2 was placed in a 2-dram vial and flushed with Ar. I_2 (2 equiv) [ICl (1.2 equiv) in the case of **9d** and **9e**] in 0.5 mL of CH_2Cl_2 was added and the reaction was stirred at room temperature for the indicated time. After the reaction was over, the reaction mixture was diluted with 15 mL of EtOAc, washed with 10 mL of satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column and/or recrystallization.

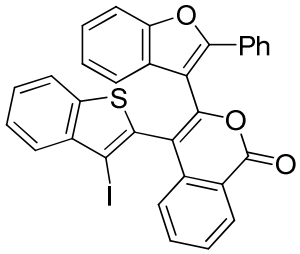


4-(3-Iodo-1-methyl-1*H*-indol-2-yl)-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (9a). Reaction time: 1 h. The product was obtained (yield = 91%) as a brown solid: mp 241-243 ^{o}C (turns black); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 3H), 6.87 (d, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.18-7.33 (m, 7H), 7.38-7.43 (m, 3H), 7.59-7.66 (m,

2H), 7.72 (d, *J* = 7.6 Hz, 1H), 8.49 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 63.0, 109.9, 111.1, 111.4, 120.6, 120.8, 121.4, 121.7, 123.2, 123.4, 125.3, 125.4, 128.2, 128.4, 128.8, 129.3, 129.7, 129.9, 130.2, 130.4, 133.4, 135.4, 137.4, 137.5, 150.6, 154.1, 155.2, 162.0 (one signal missing due to overlap); HRMS Calcd for $C_{32}H_{20}INO_3$: 593.04880. Found: 593.04960.

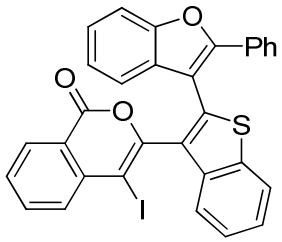


4-(3-Iodobenzofuran-2-yl)-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (9b). Reaction time: 24 h. This product could not be completely purified (yield: approx.70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.28 (m, 6H), 7.30-7.39 (m, 2H), 7.45-7.47 (m, 2H), 7.52-7.65 (m, 5H), 7.68-7.72 (m, 1H), 8.47 (d, *J* = 8.0 Hz, 1H); HRMS Calcd for $C_{31}H_{17}IO_4$: 580.01716. Found: 580.01799.

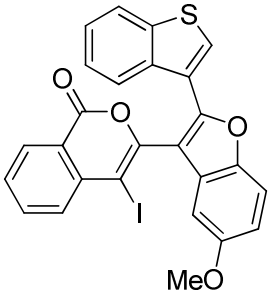


4-(3-Iodobenzo[*b*]thiophen-2-yl)-3-(2-phenylbenzofuran-3-yl)-1*H*-isocoumarin (9c). Reaction time: 1 h. The product was obtained (yield = 96%) as a yellow solid: mp 210-213 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.24-

7.29 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.35-7.38 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.60-7.72 (m, 6H), 8.50 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5, 109.3, 111.4, 114.9, 120.8, 121.0, 122.3, 123.4, 125.2, 125.4, 125.9, 126.0, 126.1, 127.5, 128.9, 129.1, 129.3, 129.8, 129.9, 130.2, 134.2, 135.3, 136.7, 139.9, 140.8, 149.2, 153.9, 154.9, 162.2; HRMS Calcd for $C_{31}H_{17}IO_3S$: 595.99432. Found: 595.99538.

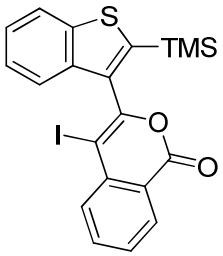


4-Iodo-3-(2-(2-phenylbenzofuran-3-yl)benzo[*b*]thiophen-3-yl)-1*H*-isocoumarin (9d). For this reaction, the ICl (1.2 equiv) in 0.5 mL of CH_2Cl_2 was added dropwise to the vial by syringe (reaction time: 30 min). The product was obtained (yield = 63%) as a white solid: mp 249 ^{o}C (became a brown gel that completely melted at 265 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.6 Hz, 2H), 7.27-7.29 (m, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.43-7.61 (m, 8H), 7.70 (t, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 6.8 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.9, 109.4, 111.4, 120.4, 120.9, 122.5, 123.6, 123.7, 125.2, 125.3, 125.4, 127.7, 128.6, 129.46, 129.54, 129.7, 131.4, 135.5, 137.1, 137.7, 138.7, 139.6, 150.4, 153.6, 154.3, 160.9 (three signals missing due to overlap); HRMS Calcd for $C_{31}H_{17}IO_3S$: 595.99431. Found: 595.99628.



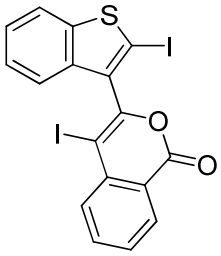
3-(2-(Benzo[*b*]thiophen-3-yl)-5-methoxybenzofuran-3-yl)-4-iodo-1*H*-isocoumarin (9e). For this reaction, the ICl (1.2 equiv) in 0.5 mL of CH_2Cl_2 was added dropwise to the vial by syringe (reaction time: 30 min). The product was obtained (yield = 71%) as a yellow solid: mp 148-151 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.98 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.38-7.47 (m, 3H), 7.61 (t, J = 7.2 Hz, 1H), 7.70 (s, 1H), 7.76-7.83 (m, 2H), 7.87 (d, J = 7.6 Hz, 1H), 8.31-8.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ56.0, 81.4, 96.2, 113.0, 113.6, 120.6, 120.7, 121.0, 122.9, 124.1, 125.1, 125.2, 126.3, 127.7, 129.9, 130.1, 131.5, 135.9, 136.9, 138.0, 140.2, 149.6, 150.8, 155.0, 158.9, 161.9; HRMS Calcd for $C_{26}H_{15}IO_4S$: 549.97359. Found: 549.97467.

Simultaneous and Stepwise Diiodination: Synthesis of 10 and 11.



4-Iodo-3-(2-(trimethylsilyl)benzo[*b*]thiophen-3-yl)-1*H*-isocoumarin (10). The alkyne starting material **6f** (0.25 mmol) in 4 mL of CH_2Cl_2 was placed in a 4-dram vial and flushed with Ar. ICl (2.2 equiv) in 1 mL of CH_2Cl_2 was added slowly and the reaction was stirred at

room temperature for 3 h. After the reaction was over, the reaction mixture was diluted with 25 mL of EtOAc, washed with 15 mL of satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column. The product was obtained (yield = 92%) as a white solid: mp 168-171 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 9H), 7.36-3.38 (m, 2H), 7.56-7.58 (m, 1H), 7.62-7.66 (m, 1H), 7.86 (d, J = 4.0 Hz, 2H), 7.90-7.92 (m, 1H), 8.36 (d, , J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ-0.07, 81.2, 120.6, 122.5, 122.9, 124.7, 124.9, 129.8, 130.2, 131.2, 136.0, 137.8, 137.9, 139.1, 142.6, 144.9, 151.7, 161.7; HRMS Calcd for $C_{20}H_{17}IO_2SSi$: 475.97633. Found: 475.97746.

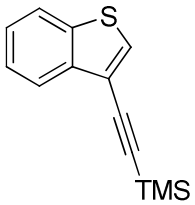


4-Iodo-3-(2-iodobenzo[*b*]thiophen-3-yl)-1*H*-isocoumarin (11). The trimethylsilyl-containing starting material **10** (0.10 mmol, 48 mg) in 0.7 mL of CH_2Cl_2 was placed in a 2-dram vial and flushed with Ar. The vial was cooled to -78 ^oC and ICl (0.11 mmol, 1.1 equiv, 18 mg) in 0.3 mL of CH_2Cl_2 was added slowly and the reaction was stirred at -78 ^oC for 1 h. After the reaction was over, the reaction mixture was diluted with 15 mL of EtOAc, washed with 5 mL of satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column. The product was obtained (yield = 95%) as a white solid: mp 236-238 ^oC (turns black); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.39 (m, 2H), 7.53-7.56 (m, 1H), 7.65-7.70 (m,

1H), 7.80-7.85 (m, 1H), 7.88-7.89 (m, 2H), 8.37 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ82.4, 87.2, 121.4, 122.3, 122.7, 125.8, 130.3, 130.6, 131.8, 136.4, 137.9, 138.0, 138.6, 144.2, 150.8, 161.8 (one signal missing due to overlap); HRMS Calcd for $C_{17}H_8I_2O_2S$: 529.83345. Found: 529.83470.

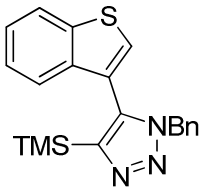
Alternatively, diiodo compound **11** can be prepared from alkyne **6f** using the following procedure. The alkyne starting material **6f** (0.1 mmol, 36 mg) in 0.7 mL of CH_2Cl_2 was placed in a 2-dram vial and flushed with Ar. ICl (2.2 equiv) in 0.3 mL of CH_2Cl_2 was added slowly and the reaction was stirred at room temperature for 3 h. Additional ICl (4 equiv) in 0.5 mL CH_2Cl_2 was added slowly and the reaction was stirred at room temperature for 1 h. After the reaction was over, the reaction mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated (yield = 91%) by chromatography on a silica gel column. The ^{1}H and ^{13}C NMR data matched that of **11** prepared from compound **10** above.

Click Chemistry, Followed by Iodo-desilylation: Synthesis of 12-14



(Benzo[*b*]thiophen-3-ylethynyl)trimethylsilane (12). This reaction was run using **4d** (1.0 g, 3.85 mmol) as the starting material and following the Sonogashira coupling procedure used for the synthesis of **6b**. The product was obtained (yield = 88%) as a yellow liquid: ^{1}H NMR

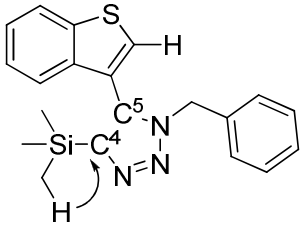
(400 MHz, $CDCl_3$) δ 0.50 (s, 9H), 7.47 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.77 (s, 1H), 7.91 (d, J = 8.0Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ0.3, 97.2, 98.7, 118.5, 122.6, 123.1, 124.8, 125.1, 130.8, 138.8, 139.3; HRMS Calcd for $C_{13}H_{14}SSi$: 230.05854. Found: 230.05905.

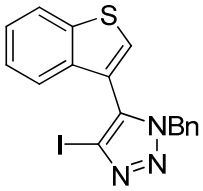


5-(Benzo[*b*]thiophen-3-yl)-1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (13). A modified literature procedure was used.[32b] In a round bottom flask, compound **12** (270 mg, 1.17 mmol) was dissolved in 9 mL of reagent grade toluene. Benzyl azide (282 mg, 2.12 mmol, 1.81 equiv) was added and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography. The product was obtained (yield = 73%) as a yellow solid: mp 59-61 ^{o}C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.05 (s, 9H), 5.20 (d, J = 14.8 Hz, 1H), 5.43 (d, J = 14.8 Hz, 1H), 6.90-6.92 (m, 2H), 7.13-7.17 (m, 4H), 7.28-7.31 (m, 2H), 7.40 (t, J = 7.6, 1H), 7.94 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ-1.1, 51.9, 122.3, 122.7, 123.6, 124.8, 125.0, 127.7, 127.9, 128.4, 128.5, 135.2, 136.9, 138.4, 139.3, 146.6; HRMS Calcd for $C_{20}H_{21}N_3SSi$: 363.12254. Found: 363.12326.

An HMBC NMR experiment was carried out to confirm the regiochemistry of the product **13** (Figure S1). **Observation:** An HMBC correlation was observed from the TMS group (δ 0.05) to C-4 [(δ 146.6); assignment based on literature data].

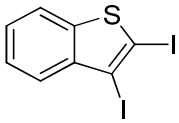
Figure S1. HMBC NMR Observation



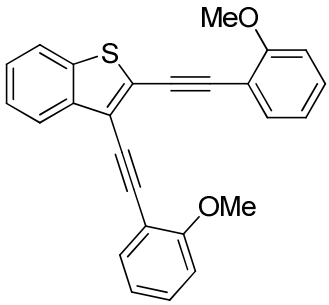


5-(Benzo[*b*]thiophen-3-yl)-1-benzyl-4-iodo-1*H*-1,2,3-triazole (14). The trimethylsilyl starting material **13** (60 mg, 0.17 mmol) in 1.0 mL of CH_2Cl_2 was placed in a 2-dram vial and the vial was cooled to -78 ^oC. ICl (110 mg, 0.68 mmol, 4 equiv) in 0.5 mL of CH_2Cl_2 was added slowly and the reaction was stirred at -78 ^oC for 0.5 h and then at room temperature for 21 h. The reaction was periodically monitored by TLC. After 21 h, the reaction mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a long silica gel column. The product was obtained (yield: 39%) as a white solid: mp 114-116 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (d, J = 14.8 Hz, 1H), 5.59 (d, J = 14.8 Hz, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.15-7.20 (m, 3H), 7.25-7.28 (m, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 92.2, 121.2, 122.7, 123.2, 125.2, 125.5, 127.8, 128.6, 128.9, 129.9, 134.7, 135.7, 137.1, 139.8; HRMS Calcd for $C_{17}H_{12}IN_3S$: 416.97967. Found: 416.98064.

Double Sonogashira Coupling, Followed by Double Iodocyclization: Synthesis of 15-17.

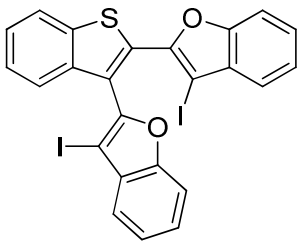


2,3-Diiodobenzo[*b*]thiophene (15). This diidobenzothiophene was prepared from **4c** using an iodination procedure from the literature.[44] To a solution of **4c** (0.315 g, 0.95 mmol) in CH_2Cl_2 (2 mL) was added ICl (0.170 g, 1.04 mmol) in CH_2Cl_2 (3 mL) at -78 ^oC. The reaction mixture was stirred at -78 ^oC for 1 h. Then the excess ICl was destroyed by adding satd aq $Na_2S_2O_3$ (15 mL) and diluted with 50 ml of EtOAc. The organic layer was dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The crude compound was purified by column chromatography using 20:1 hexanes/ethyl acetate to afford 0.318 g (88%) of the desired compound **15** as a white solid: mp 58-61 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.40 (m, 2H), 7.67-7.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.5, 95.3, 121.6, 125.5, 125.9, 126.8, 141.5, 143.9; HRMS Calcd for $C_8H_4I_2S$: 385.81232. Found: 385.81336.



2,3-Bis((2-methoxyphenyl)ethynyl)benzo[*b*]thiophene (16). To a solution of **15** (97 mg, 0.25 mmol) in DMF (3 mL) were added $PdCl_2(PPh_3)_2$ (11 mg, 6 mol %) and CuI (4 mg, 8 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (202 mg, 8.0 equiv) was added by syringe. The reaction mixture

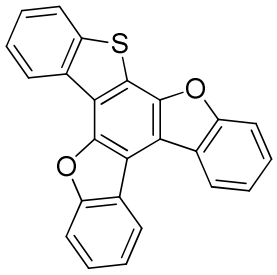
was then heated to 65 °C. A solution of 2-ethynylanisole (79 mg, 0.6 mmol, 2.4 equiv) in DMF (1 mL) was added dropwise over 10 min, and the mixture was allowed to stir at 65 ^{o}C for 1 h. After 1 h, another batch of 2-ethynylanisole (40 mg, 0.3 mmol, 1.2 equiv) in DMF (1 mL) was added dropwise over 5 min, and the mixture was allowed to stir at 65 ^{o}C for 1 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl, brine and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane-EtOAc as the eluent. After purification, the product was obtained (yield = 65%) as a yellow solid: mp 103-105 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.91 (s, 3H), 6.90-6.98 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.41-7.46 (m, 2H), 7.58-7.63 (m, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ56.0, 56.1, 86.9, 87.2, 93.0, 96.4, 111.01, 111.03, 112.2, 112.8, 120.67, 120.70, 122.2, 123.2, 123.8, 125.2, 126.2, 130.1, 130.6, 133.9, 134.0, 138.7, 139.1, 160.29, 160.32 (one signal missing due to overlap); HRMS Calcd for $C_{26}H_{18}O_2S$: 394.10274. Found: 394.10362.



2,2'-(Benzo[*b*]thiophene-2,3-diyl)bis(3-iodobenzofuran) (17). The alkyne starting material **16** (59 mg, 0.15 mmol) in 4 mL of CH_2Cl_2 was placed in a 4-dram vial. I_2 (152 mg, 0.60 mmol, 4 equiv) in 1 mL of CH_2Cl_2 was added and the reaction was stirred at room temperature for 2 h. After the reaction was over, the reaction mixture was diluted with

EtOAc, washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column. The product was obtained (yield = 62%) as a yellow solid: mp 211-213 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.50 (m, 9H), 7.52-7.58 (m, 1H), 7.92 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ68.0, 68.6, 111.5, 111.6, 122.0, 122.3, 122.4, 122.5, 123.7, 123.9, 124.7, 125.5, 125.9, 126.3, 126.6, 131.9, 132.2, 138.8, 139.6, 149.6, 151.2, 154.6, 154.9 (one signal missing due to overlap); HRMS Calcd for $C_{24}H_{12}I_2O_2S$: 617.86476. Found: 617.86583.

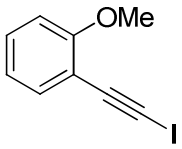
Palladium-catalyzed Ullmann Reaction: Synthesis of 18.



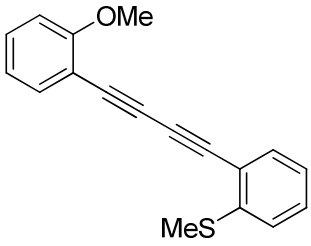
A modified literature procedure was used:[34] A mixture of diiodo compound **17** (0.09 mmol), $Pd(OAc)_2$ (2 mg, 10 mol %), dppf (10 mg, 20 mol %), and KOAc (44 mg, 0.45 mmol, 5 equiv) was stirred in DMF (0.7 mL) at 100 ^oC for 3 h. The reaction was monitored by TLC (the compound looks fluorescent blue under UV). The mixture was diluted with EtOAc, washed with aq NH_4Cl, satd aq NaCl and water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the product (yield = 64%) as a white solid: m.p. 258-261 ^oC (turns black); ^1H NMR (400 MHz, $CDCl_3$ + CD_2Cl_2) δ 7.57-7.63 (m, 5H),

7.67 (t, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.54 (d, *J* = 7.2 Hz, 2H), 8.94 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR data could not be obtained because of the poor solubility of the product in common NMR solvents; HRMS Calcd for $C_{24}H_{12}O_2S$: 364.05580. Found: 364.05669.

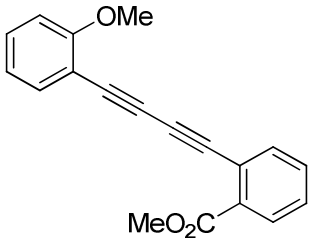
Preparation of 1,3-Diynes: Preparation of 25-27.



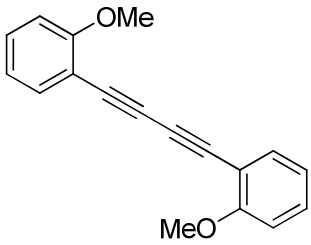
1-Iodoethynyl-2-methoxybenzene (25). A literature procedure was used.[45] In a 6-dram vial, 2-alkynylanisole (132 mg, 1.0 mmol) was dissolved in 2.5 mL of dry THF. The vial was then sealed, purged with Ar and cooled to -78 ^{o}C. BuLi (0.5 mL of 2.5 M solution in hexanes, 1.2 equiv) was added dropwise by syringe through the septum and the reaction mixture was stirred for 30 min at -78 ^{o}C. I_2 (356 mg, 1.4 mmol, 1.4 equiv) dissolved in 1.5 mL of THF was added and the reaction mixture was stirred for 30 min at -78 ^{o}C and warmed to room temperature. The reaction was quenched with satd aq $Na_2S_2O_3$ (20 mL), extracted with ether, washed with water, and dried (Na_2SO_4). The crude product was purified by column chromatography. The product was obtained (yield = 100%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.79-6.87 (m, 2H), 7.23 (td, *J* = 1.5, 8.4 Hz, 1H), 7.36 (dd, *J* = 1.5, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 55.7, 90.4, 110.5, 112.3, 120.3, 130.3, 134.2, 160.8; HRMS Calcd for C_9H_7IO: 257.95417. Found: 257.95450.



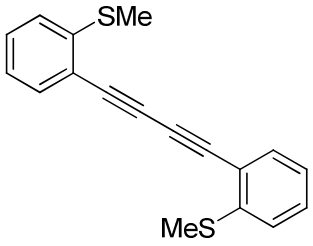
2-[(2-Methoxyphenyl)buta-1,3-diynyl]thioanisole (26). In a 6-dram vial, iodo alkyne **25** (65 mg, 0.25 mmol) was dissolved in DMF (2 mL) and 2-alkynylthioanisole (44 mg, 1.2 equiv) in 1 mL of DMF was added. $PdCl_2(PPh_3)_2$ (5 mg, 3 mol %) and CuI (2 mg, 4 mol %) were added, the reaction vial was flushed with Ar, and the reaction mixture was stirred for 5 min at room temperature. DIPA (101 mg, 4.0 equiv) was added through a syringe and the reaction mixture was then heated at 70 °C for 1 h. After cooling, the reaction mixture was diluted with EtOAc, washed with satd aq NH_4Cl, brine and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane-EtOAc as the eluent. The product was obtained (yield = 60%) as a yellow solid: mp 79-81 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.86 (s, 3H), 6.84-6.92 (m, 2H), 7.04-7.14 (m, 2H), 7.26-7.33 (m, 2H), 7.44-7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ15.2, 55.9, 77.5, 79.5, 80.2, 80.4, 110.8, 110.9, 120.1, 120.6, 124.4, 129.6, 130.9, 133.5, 133.6, 134.4, 143.2, 161.4; HRMS Calcd for $C_{18}H_{14}OS$: 278.07654. Found: 278.07715.



Methyl 2-[(2-methoxyphenyl)buta-1,3-diynyl]benzoate (27). The reaction was run by using the procedure used for the preparation of **26** above. The product was obtained (yield = 55%) as a white solid: mp 89-91 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.94 (s, 3H), 6.86-6.92 (m, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.45-7.49 (m, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ52.3, 55.8, 77.9, 79.2, 80.0, 80.4, 110.7, 110.9, 120.5, 122.7, 128.6, 130.5, 130.9, 131.8, 132.4, 134.4, 135.1, 161.4, 166.0; HRMS Calcd for $C_{19}H_{14}O_3$: 290.09429. Found: 290.09488.

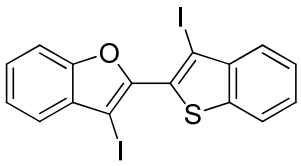


1,4-Bis(2-methoxyphenyl)buta-1,3-diyne (28). This compound was isolated as a side product (32% with respect to the 2-ethynylanisole starting material) during the preparation of **16**. The product was obtained as a colorless solid: mp 135-137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 6H), 6.86-6.92 (m, 4H), 7.31 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ56.0, 78.2, 78.9, 110.9, 111.5, 120.7, 130.7, 134.6, 161.5; HRMS Calcd for $C_{18}H_{14}O_2$: 262.09937. Found: 262.10004.



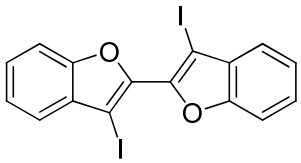
1,4-Bis(2-(methylthio)phenyl)buta-1,3-diyne (29). This compound was isolated as a side product (34% with respect to the 2-ethynylthioanisole starting material) during the preparation of **26**. The product was obtained as a yellow solid: mp 98-101 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 6H), 7.09 (t, J = 7.6 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 80.1, 80.9, 120.3, 124.6, 124.7, 129.8, 133.8, 143.4; HRMS Calcd for $C_{18}H_{14}S_2$: 294.05369. Found: 294.05431.

Iodocyclization of Homo- and Hetero-1,3-diynes: Synthesis of 30-34.

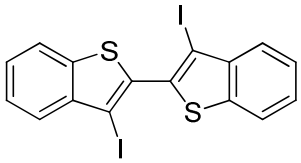


3-Iodo-2-(3-iodobenzo[*b*]thiophen-2-yl)benzofuran (30). The alkyne starting material **26** (70 mg, 0.25 mmol) in 3 mL of CH_2Cl_2 was placed in a 4-dram vial and stirred at room temperature to get a clear solution. I_2 (254 mg, 4 equiv) in 1 mL of CH_2Cl_2 was added and the reaction was stirred at room temperature for 40 min. After the reaction was over, the reaction mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by recrystallization from hexanes/EtOAc. The product was obtained (yield = 94%) as a yellow

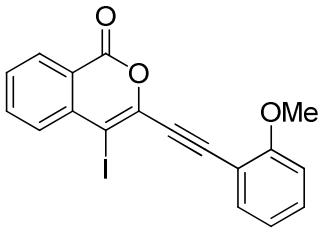
solid: mp 164-166 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, J = 7.6 Hz, 1H), 7.42-7.56 (m, 5H), 7.84 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ69.1, 84.7, 111.8, 122.3, 122.4, 124.1, 125.9, 126.76, 126.80, 126.9, 130.6, 131.7, 139.7, 141.3, 149.5, 154.7; HRMS Calcd for $C_{16}H_8I_2OS$: 501.83854. Found: 501.83912.



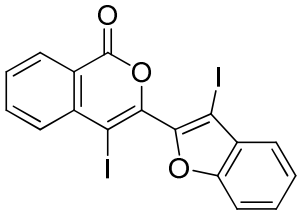
3,3'-Diiodo-2,2'-bibenzofuran (31). Using the starting diyne **28**, the reaction was run using the same procedure used for the preparation of **30** above (reaction time: 2 h). This compound was obtained (yield = 76%) as a white solid: mp 208-211 ^{o}C (turned dark brown). The spectral properties were identical to those previously reported.[3h]



3,3'-Diiodo-2,2'-bibenzo[*b*]thiophene (32). Using the starting diyne **29**, the reaction was run using the same procedure used for the preparation of **30** above (reaction time: 1 h). The product was obtained (yield = 98%) as a brown solid: mp 215-217 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.54 (m, 4H), 7.85 (t, J = 7.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ86.7, 122.5, 125.9, 126.6, 126.7, 135.5, 140.3, 141.2; HRMS Calcd for $C_{16}H_8I_2S_2$: 517.81569. Found: 517.81698.



4-Iodo-3-[(2-methoxyphenyl)ethynyl]-1*H*-isocoumarin (33). The hetero diyne starting material **27** (73 mg, 0.25 mmol) in 3 mL of CH_2Cl_2 was placed in a 4-dram vial. I_2 (191 mg, 0.75 mmol, 3 equiv) in 1 mL of CH_2Cl_2 was added and the reaction was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by column chromatography, followed by recrystallization using hexanes/EtOAc. The product was obtained (yield = 85%) as a yellow solid: mp 223-225 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 6.92-6.99 (m, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 8.0 Hz, 2H), 7.74-7.82 (m, 2H), 8.27 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 83.2, 88.7, 94.9, 110.5, 111.2, 120.8, 121.3, 129.8, 130.2, 131.6, 131.8, 134.1, 135.9, 137.9, 141.1, 161.1, 161.2; HRMS Calcd for $C_{18}H_{11}IO_3$: 401.97529. Found: 401.97606.



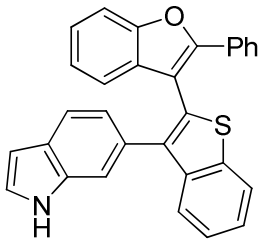
4-Iodo-3-(3-iodobenzofuran-2-yl)-1*H*-isocoumarin (34). The alkyne starting material **33** (40 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 was placed in a 4-dram vial. ICl (18 mg, 0.11 mmol,

1.1 equiv) in 0.5 mL of CH_2Cl_2 was slowly added and the reaction was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc, washed with satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated (yield = 35%) by column chromatography using hexanes/EtOAc.

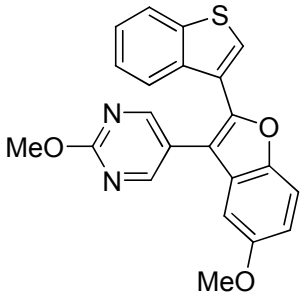
Alternatively, diiodo compound **34** can be prepared directly from the diyne **27** using the following procedure. The alkyne starting material **27** (0.25 mmol, 73 mg) in 2 mL of CH_2Cl_2 was placed in a 4-dram vial and the reaction mixture was stirred at room temperature to obtain a clear solution. ICl (89 mg, 0.55 mmol, 2.2 equiv) in 1 mL of CH_2Cl_2 was added dropwise and the reaction was stirred at room temperature for 5 h. Our standard iodocyclization work-up was followed and the product was isolated by chromatography on a silica gel column using hexanes/EtOAc. The product was obtained (yield = 54%) as a white solid: mp 173-175 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, J = 7.6 Hz, 1H), 7.46-7.57 (m, 3H), 7.67 (t, J = 7.6 Hz, 1H), 7.85-7.92 (m, 2H), 8.35 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.0, 82.2, 112.1, 121.5, 122.7, 124.3, 127.6, 130.2, 130.7, 132.2, 136.0, 137.4, 145.8, 149.2, 154.4, 160.7 (one signal missing due to overlap); HRMS Calcd for $C_{17}H_8I_2O_3$: 513.85630. Found: 513.85756.

General Procedure for Suzuki-Miyaura Cross-coupling. A literature procedure was used.[16c] To a 4-dram vial was added the appropriate iodoheterocycle (0.125 mmol), the boronic acid (1.4 equiv, 0.175 mmol), $KHCO_3$ (1.4 equiv, 0.175 mmol) and $PdCl_2$ (5 mol %) in 4:1 DMF:H_2O (2.5 mL). The solution was stirred for 5 min at room temperature and

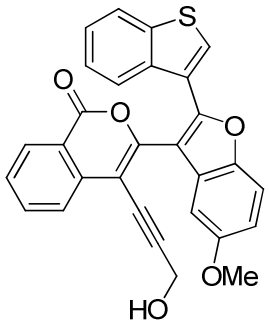
flushed with Ar and then heated to 80 ^{o}C for 2 h. After cooling, the reaction mixture was diluted with EtOAc, washed with satd aq NH_4Cl, brine and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane-EtOAc as the eluent.



6-[2-(2-Phenylbenzofuran-3-yl)benzo[*b*]thiophen-3-yl]-1*H*-indole (35). The product was obtained (yield = 71%) as a brown solid: mp 226-228 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 7.04-7.06 (m, 2H), 7.12 (t, J = 8.0 Hz, 2H), 7.19-7.25 (m, 4H), 7.34-7.45 (m, 4H), 7.50 (s, 1H), 7.67-7.68 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.07, 103.12, 110.5, 110.9, 111.1, 120.6, 121.9, 122.6, 123.2, 124.1, 124.4, 124.7, 124.8, 126.5, 127.0, 127.9, 128.6, 128.7, 129.1, 130.4, 130.8, 135.2, 138.2, 140.6, 140.8, 153.1, 153.9 (one signal missing due to overlap); HRMS Calcd for $C_{30}H_{19}NOS$: 441.11873. Found: 441.12003.

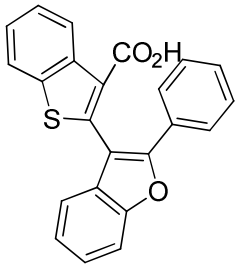


5-[2-(Benzo[*b*]thiophen-3-yl)-5-methoxybenzofuran-3-yl]-2-methoxypyrimidine (36). The product was obtained (yield = 86%) as a yellow semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 4.04, (s, 3H), 6.98 (dd, J = 2.4, 8.4 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.38-7.40 (m, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.88-7.90 (m, 1H), 7.97-8.00 (m, 1H), 8.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ55.3, 56.0, 96.3, 111.9, 112.9, 115.5, 119.7, 120.8, 121.7, 122.9, 124.0, 125.0, 125.2, 125.9, 127.5, 137.0, 140.3, 147.4, 155.7, 158.9, 159.3, 164.9; HRMS Calcd for $C_{22}H_{16}N_2O_3S$: 388.08816. Found: 388.08932.



3-[2-(Benzo[*b*]thiophen-3-yl)-5-methoxybenzofuran-3-yl]-4-(3-hydroxyprop-1-ynyl)-1*H*-isocoumarin (37). To a solution of the iodo starting material **9e** (55 mg, 0.1 mmol) in DMF (2 mL) were added $PdCl_2(PPh_3)_2$ (4 mg, 5 mol %) and CuI (1 mg, 5 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (40 mg, 0.4 mmol, 4.0 equiv) was added by syringe. The reaction mixture was then heated to 85 °C. A solution of the terminal alkyne (4 equiv) in DMF (1 mL) was added dropwise over 5 min, and the mixture was allowed to stir at 85 ^{o}C for 2 h. The reaction was worked up and the product was purified by column chromatography on silica gel using hexane-EtOAc as the eluent. The product was obtained (yield = 62%) as a yellow solid: mp

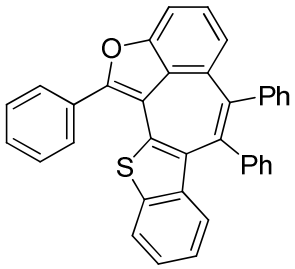
234-236 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (br s, 1H), 3.68 (s, 2H), 3.91 (s, 3H), 7.00 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 7.43-7.45 (m, 2H), 7.56-7.59 (m, 1H), 7.74-7.76 (m, 4H), 7.92-7.94 (m, 1H), 8.15-8.18 (m, 1H), 8.35 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.2, 56.0, 77.4, 96.0, 96.9, 101.9, 111.3, 113.1, 119.8, 120.7, 121.8, 123.1, 123.7, 125.2, 125.39, 125.44, 127.1, 128.1, 129.1, 129.8, 135.4, 136.9, 140.3, 150.7, 152.9, 155.3, 159.0, 161.3 (one signal missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3454, 3018, 2359, 1720; HRMS Calcd for $C_{29}H_{18}O_5S$: 478.08749. Found: 478.08846.



Palladium-catalyzed Cyclocarbonylation.

2-(2-Phenylbenzofuran-3-yl)benzo[*b*]thiophene-3-carboxylic acid (38). A literature procedure was used.[39b] DMF (4 mL), $Pd(PCy_3)_2$ (5 mg, 0.008 mmol, 5 mol %), anhydrous cesium pivalate (0.075 g, 0.32 mmol, 2 equiv), and the iodo starting material **7b** (0.070 g, 0.16 mmol) were stirred under an Ar atmosphere at room temperature for 5 min. The mixture was flushed with CO and fitted with a CO filled balloon. The reaction mixture was heated to 110 °C with vigorous stirring for 8 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (25 mL), and washed with aq NH_4Cl, brine and water. The aqueous layer was reextracted with EtOAc (15 mL). The organic layers were combined, dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The

residue was purified by column chromatography on a silica gel column. The product was obtained (yield = 61%) as a yellow solid: mp 258-261 ^{o}C (turned black); ^{1}H NMR (400 MHz, DMF-d_7) δ 7.34 (t, J = 7.2 Hz, 1H), 7.43-7.45 (m, 5H), 7.57 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.73-7.77 (m, 3H), 8.16 (d, J = 7.6 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, *d*-DMF) δ 111.7, 112.4, 121.1, 123.7, 124.8, 126.3, 126.5, 126.6, 126.7, 127.7, 128.4, 130.0, 130.4, 130.9, 131.4, 139.7, 140.5, 142.6, 152.8, 154.7, 165.2; IR ($CHCl_3$, cm^{-1}) 3463, 1642, 1110; HRMS Calcd for $C_{23}H_{14}O_3S$: 370.06636. Found: 370.06721.



Palladium-catalyzed Alkyne Annulation. (39). A literature procedure was used.[40] The iodo starting material **7b** (50 mg, 0.11 mmol), $Pd(OAc)_2$ (2.4 mg, 0.012 mmol), NaOAc (18 mg, 0.22 mmol, 2 equiv), *n*-Bu_4NCl (92 mg, 0.33 mmol, 3 equiv), diphenyl acetylene (39 mg, 0.22 mmol, 2 equiv), and 2.2 mL of DMF were placed in a 2-dram vial, which was heated at 100 °C for 24 h. The reaction mixture was allowed to cool, diluted with EtOAc, washed with satd aq NH_4Cl, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography. The product was obtained (yield = 52%) as a yellow solid: mp > 275 ^{o}C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.65 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 7.02-7.06 (m, 5H), 7.12-7.14 (m, 4H), 7.20-7.33 (m, 4H), 7.48 (d, J = 7.6 Hz, 1H), 7.58-7.61 (m, 3H), 8.03 (d, J = 4.0 Hz,

2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ110.5, 114.9, 121.9, 124.0, 124.6, 125.25, 125.31, 125.8, 126.6, 126.8, 127.5, 128.5, 129.1, 129.9, 130.5, 131.20, 131.24, 133.5, 133.7, 135.4, 136.9, 137.2, 138.9, 140.3, 142.5, 142.8, 144.1, 151.1, 154.3 (three signals missing due to overlap); HRMS Calcd for $C_{36}H_{22}OS$: 502.13913. Found: 502.14038.

X-ray Crystallographic Data for Compounds 38 and 39

Data Collection for 38

A very small crystal was selected under ambient conditions. The crystal was mounted and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed at 153K on a APEX2 CCD diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the detector to crystal distance of 5.03 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3º in a 10º range about ω with the exposure time of 40 seconds per frame. The obtained reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of strong reflections from the actual data collection. The data were collected using the full sphere routine by collecting four sets of frames with 0.3º scans in ω with an exposure time 40 sec per frame. This dataset was corrected for Lorentz and polarization effects. The absorption correction was based on a fit of a spherical harmonic function to the empirical transmission surface as sampled by multiple equivalent measurements using SADABS software.[46,47]

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space groups $P1$ and $P\bar{1}$.[47] The *E*-statistics strongly suggested the centrosymmetric space group $P\bar{1}$ yielded chemically reasonable and computationally stable results of refinement. The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined in full-matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The H-atom of CO(OH) was not located, but was included in calculations of the metric parameters. The ORTEP diagram was drawn at the 50% probability level. H-atoms were omitted for clarity. The resulting CIF file has been tested with PLATON software.[48] The results and comments have been included in the output package (Platon_Lar35.doc.).

Figure S2. Molecular structure of 38.

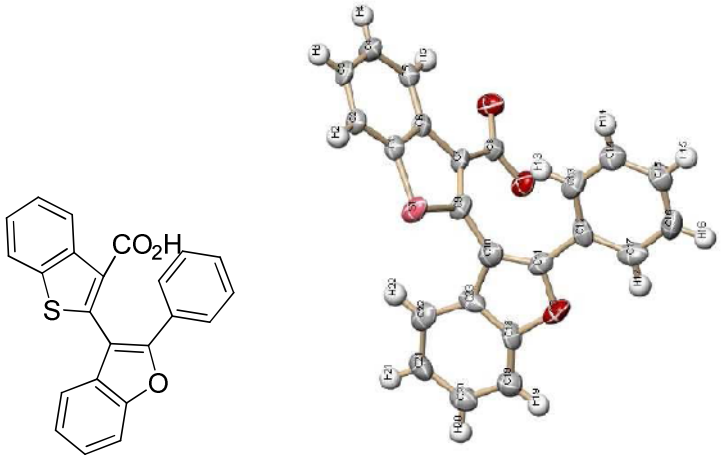


Table S1. Crystal data and structure refinement for 38.

Empirical formula	$C_{23}H_{14}O_3S$	
Formula weight	370.40	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.407(2) Å	α = 81.428(4)°
	b = 8.400(2) Å	β = 82.824(4)°
	c = 13.789(4) Å	γ = 86.874(4)°
Volume	841.1(4) $Å^3$	
Z	2	
Density (calculated)	1.463 Mg/m^3	
Absorption coefficient	0.215 mm^{-1}	
F(000)	384	
Crystal size	0.22 x 0.14 x 0.08 mm^3	
Theta range for data collection	1.50 to 22.61°.	
Index ranges	-8<=h<=7, -9<=k<=9, -14<=l<=14	
Reflections collected	5269	
Independent reflections	2200 [R(int) = 0.0384]	
Completeness to theta = 22.61°	99.3 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9830 and 0.9543
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2200 / 0 / 244
Goodness-of-fit on F^2	1.069
Final R indices [I>2sigma(I)]	R1 = 0.0695, wR2 = 0.1664
R indices (all data)	R1 = 0.0926, wR2 = 0.1830
Largest diff. peak and hole	1.306 and -0.646 e.Å^{-3}

$R1 = \Sigma \mid |F_O| - |F_c| \mid / \Sigma |F_o|$ and $wR2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$

Data Collection for 39

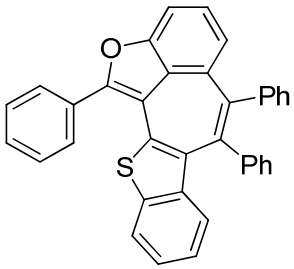
A well-shaped crystal was selected under ambient conditions. The crystal was mounted and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed at 173K on a Bruker APEX2 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the detector to crystal distance of 5.03 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3º in a 10º range about ω with the exposure time of 10 seconds per frame. The obtained reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of strong reflections from the actual data collection. The data were collected using the full sphere routine by collecting four sets of frames with 0.3º scans in ω with an exposure

time 10 sec per frame. This dataset was corrected for Lorentz and polarization effects. The absorption correction was based on a fit of a spherical harmonic function to the empirical transmission surface as sampled by multiple equivalent measurements using SADABS software.[46,47]

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space group $P2_1/c$ and yielded chemically reasonable and computationally stable results of refinement. The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined in a full-matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The ORTEP diagram was drawn at the 50% probability level. H-atoms were omitted for clarity. The resulting CIF file has been tested with PLATON software. The results and comments have been included in the output package (Platon_Jef08.doc.).[48]

Figure S3. Molecular Structure of 39.



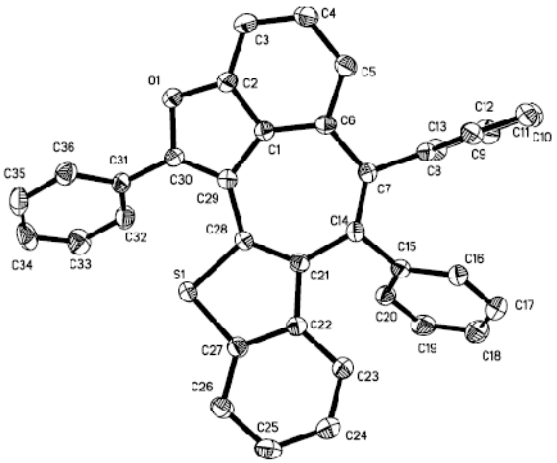


Table S2. Crystal data and structure refinement for 39.

Empirical formula	$C_{36}H_{22}OS$	
Formula weight	502.60	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 13.3780(15) Å	α = 90°
	b = 11.9434(14) Å	β = 91.457(2)°
	c = 15.3988(18) Å	γ = 90°
Volume	2459.6(5) $Å^3$	
Z	4	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	0.161 mm^{-1}	

F(000)	1048
Crystal size	0.27 x 0.22 x 0.18 mm^3
Theta range for data collection	1.99 to 28.27°.
Index ranges	-17<=h<=17, -15<=k<=15, -20<=l<=20
Reflections collected	24165
Independent reflections	6079 [R(int) = 0.0408]
Completeness to theta = 28.27°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9715 and 0.9577
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6079 / 0 / 343
Goodness-of-fit on F^2	0.980
Final R indices [I>2sigma(I)]	R1 = 0.0445, wR2 = 0.1138
R indices (all data)	R1 = 0.0619, wR2 = 0.1293
Largest diff. peak and hole	0.435 and -0.336 $e.Å^{-3}$

$R1 = \Sigma \, | \, |F_o| - |F_c| \, | \, / \, \Sigma \, |F_o|$ and $wR2 = \{ \, \Sigma \, [\, w(F_o^2 - F_c^2)^2 \,] \, / \, \Sigma \, [\, w(F_o^2)^2 \,] \, \}^{1/2}$

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CHAPTER 3. A Simple and Mild Synthesis of 1*H*-Isochromenes and (*Z*)-1-Alkylidene-1,3-dihydroisobenzofurans by the Iodocyclization of 2-(1-Alkynyl)benzylic Alcohols

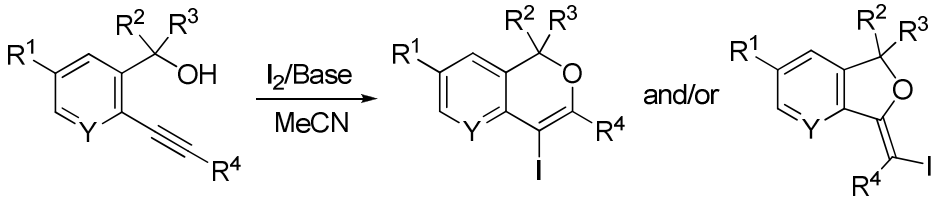
Based on a paper to be published in the *Journal of Organic Chemistry*[51]

Raffaella Mancuso,[a] *Saurabh Mehta,*[b] *Bartolo Gabriele,*[c] *Giuseppe Salerno,*[a] *William S. Jenks,*[b] *and Richard C. Larock*,*[b]

[a]Dipartimento di Chimica, Università della Calabria, 87036 Arcavacata di Rende (CS), Italy. [b]Department of Chemistry, Iowa State University, Ames, Iowa 50011 USA. [c]Dipartimento di Scienze Farmaceutiche, Università della Calabria, 87036 Arcavacata di Rende (CS), Italy.

larock@iastate.edu

Abstract



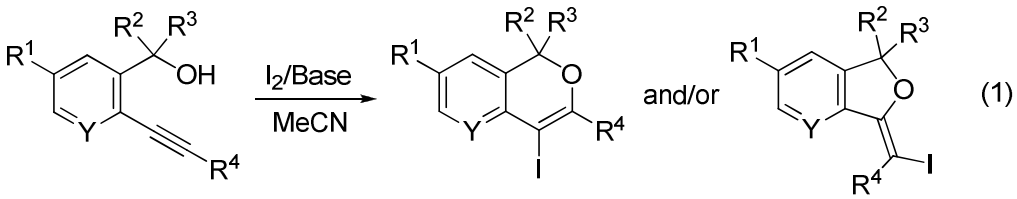
Y = CH, N; R^1 = H, OMe, NO_2; R^2, R^3 = H, alkyl; R^4 = alkyl, aryl, thienyl

A variety of iodo-substituted isochromenes, dihydroisobenzofurans, and pyranopyridines are readily prepared in good to excellent yields under mild conditions by the iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines. The regiochemical outcome of the reaction strongly depends on the substitution pattern of the starting material.

Introduction

The iodocyclization of alkynes has emerged as a powerful tool in organic synthesis.[1] Recently, we and others have utilized this methodology to accomplish efficient syntheses of a wide variety of interesting carbocyclic and heterocyclic compounds, including benzofurans,[2] furans,[3] benzothiophenes,[4] thiophenes,[5] benzopyrans,[6] benzoselenophenes,[7] selenophenes,[8] naphthols,[9] indoles,[10] quinolines,[11] isoquinolines,[12] α-pyrones,[13] isocoumarins,[13] naphthalenes[14] and polycyclic aromatics,[15] isoxazoles,[16] chromones,[17] bicyclic β-lactams,[18] cyclic carbonates,[19] pyrroles,[20] furopyridines,[21] spiro[4.5]trienones,[22] coumestrol and coumestans,[23] furanones,[24] benzothiazine-1,1-dioxides,[25] and others.[26] In general, these electrophilic cyclization reactions are very clean and efficient, and tolerate a wide variety of functional groups. Furthermore, the iodine-containing products can be further diversified using a number of subsequent palladium-catalyzed processes.

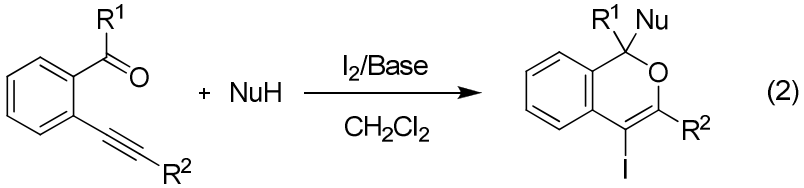
Herein we report a simple and efficient method for the synthesis of 1*H*-isochromene and/or (*Z*)-1-(1-iodoalkylidene)-1,3-dihydroisobenzofuran derivatives, based on the iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols (Eq 1). Isochromenes and 1,3-dihydroisobenzofurans are important heterocyclic compounds, and there are several examples of naturally occurring and biologically active compounds containing these ring systems.[27, 28]



(1)

(Y = CH, N; R^1 = H, OMe, NO_2; R^2, R^3 = H, alkyl; R^4 = alkyl, aryl, thienyl)

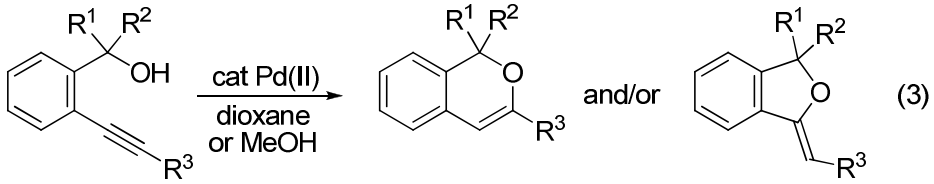
Over the years, several groups have reported a variety of synthetic approaches to isochromene and dihydroisobenzofuran derivatives by the heterocyclization of acyclic precursors.[29] In particular, we[30] and Barluenga and co-workers[31] have independently reported the formation of 4-iodo-1*H*-isochromenes by the iodocyclization of 2-(1-alkynyl)benzaldehydes in the presence of suitable nucleophiles (Eq 2).



(2)

R^1 = H, Me; NuH = MeOH, EtOH, $PhNMe_2$, PhOH; R^2 = alkyl, aryl, heteroaryl

We have also previously disclosed the Pd(II)-catalyzed cycloisomerization of 2-(1-alkynyl)benzylic alcohols to 1*H*-isochromenes and/or (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans, depending on the nature of the substrate and the reaction conditions (Eq 3).[29k]



(3)

R^1, R^2 = H, alkyl; R^3 = alkyl, aryl

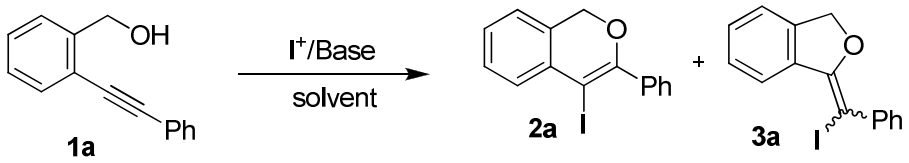
The new methodology reported in this work is complementary to those previously reported procedures, and allows the direct synthesis of 3-iodo-1*H*-isochromenes, (*Z*)-1-(1-

iodoalkylidene)-1,3-dihydroisobenzofurans, and iodopyranopyridines by the iodocyclization of variously substituted 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines under mild conditions (see Eq 1).

Results and Discussion

2-(2-Phenylethynyl)benzyl alcohol (**1a**, Y = CH, $R^1 = R^2 = R^3 = H$, R^4 = Ph) was chosen as a model substrate for determining the optimum conditions for the iodocyclization reaction. A range of iodine sources, solvents, bases and reaction times were screened and the results of these optimization studies are shown in Table 1.

Table 1. Iodocyclization of 2-(2-Phenylethynyl)benzyl Alcohol: Optimization Studies[a]



entry	I^+	base	temp. (°C)	time (h)	solvent	total yield (**2a** + **3a**)[b] (%)	**2a**/**3a** ratio[c]
1	1.5 I_2	-	25	72	CH_3CN	-	-
2	3.0 I_2	-	25	15	CH_3CN	-	-
3	1.5 I_2	1.5 $NaHCO_3$	25	72	CH_3CN	49	29/20
4	2.0 I_2	2.0 $NaHCO_3$	25	72	CH_3CN	56	42/14
5	2.0 I_2	3.0 $NaHCO_3$	25	72	CH_3CN	56	40/16
6	3.0 I_2	3.0 $NaHCO_3$	25	3	CH_3CN	31	23/4
7	3.0 I_2	3.0 $NaHCO_3$	25	8	CH_3CN	61	56/5

8	3.0 I_2	3.0 $NaHCO_3$	25	15	CH_3CN	71	65/6
9	3.0 I_2	3.0 $NaHCO_3$	25	24	CH_3CN	62	59/3
10	3.0 I_2	3.0 $NaHCO_3$	25	15	CH_2Cl_2	45	45/0
11	3.0 I_2	3.0 $NaHCO_3$	25	15	EtOH	45	45/0
12[d]	3.0 I_2	3.0 $NaHCO_3$	25	15	CH_3CN	33	21/12
13[e]	3.0 I_2	3.0 $NaHCO_3$	40	3	CH_3CN	-	-
14	3.0 I_2	3.0 K_2CO_3	25	24	CH_3CN	56	27/29
15	3.0 I_2	3.0 $KHCO_3$	25	24	CH_3CN	46	22/24
16	3.0 I_2	3.0 NaH	25	24	CH_3CN	10	10/0
17	3.0 I_2	3.0 Morpholine	25	24	CH_3CN	-	-
18	3.0 ICl	3 $NaHCO_3$	25	1.5	CH_3CN	38	38/0
19	3.0 ICl	3 $NaHCO_3$	25	1.5	CH_2Cl_2	25	25/0

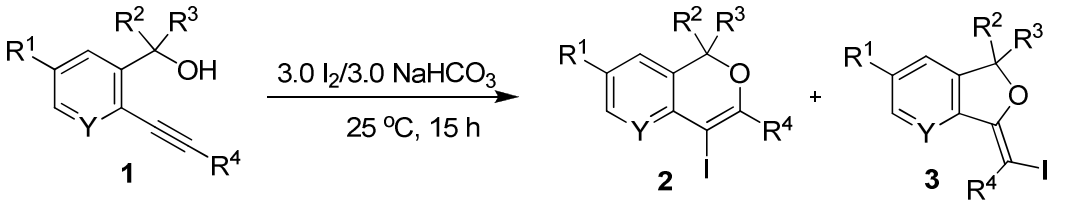
[a]Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale in 6 mL of acetonitrile. [b]Isolated yield of **2a** + **3a**, based on starting **1a**. In most cases, an inseparable mixture of the two regioisomers was obtained from column chromatography. [c]The **2**:**3** ratio is based on ^{1}H NMR spectroscopic data. [d]The reaction was carried out in 2.5 mL of acetonitrile. [e]The reaction led to a complex reaction mixture.

As can be seen from Table 1, the isochromene derivative **2a** derived from a 6-*endo-dig* cyclization was consistently obtained in higher yield than the dihydroisobenzofuran derivative **3a** derived from a 5-*exo-dig* cyclization.[32] The optimal reaction conditions in terms of total yield for the iodocyclization of **1a** are those reported in entry 8 (Substrate: I_2 : $NaHCO_3$ molar ratio = 1:3:3, T = 25 °C, substrate concentration = 0.05 M in CH_3CN, time = 15 h). Under these conditions, **1a** was converted into approximately an 11:1 mixture of **2a** and **3a** in a total yield of 71%. On the other hand, no formation of **3a** was observed using I_2 as the iodine source in CH_2Cl_2 or EtOH as the solvent (entries 10 and 11) or using ICl as the

iodine source either in MeCN or in CH_2Cl_2 (entries 18 and 19, respectively). However, the yields of **2a** obtained under these conditions ranged from only 25 to 45%.

A variety of 2-(1-alkynyl)benzylic alcohols **1b-t** were then subjected to iodocyclization under the conditions of Table 1, entry 8. The results obtained are summarized in Table 2.

Table 2. Synthesis of 3-Iodo-1*H*-isochromenes and 1-(1-Iodoalkylidene)-1,3-dihydroisobenzofurans by the Iodocyclization of 2-(1-Alkynyl)benzylic alcohols[a]



entry	**1**	Y	R^1	R^2	R^3	R^4	isolated yield (%) **2**	**3**
1	**1a**	CH	H	H	H	Ph	71[b] (11:1)[c]	
2	**1b**	CH	H	H	H	4-methylphenyl	92	-
3	**1c**	CH	H	H	H	4-methoxyphenyl	85	-
4	**1d**	CH	H	H	H	3,5-dimethoxyphenyl	41	35
5	**1e**	CH	H	H	H	4-chlorophenyl	85[b] (3:1)[c]	
6	**1f**	CH	H	H	H	4-nitrophenyl	88[b] (1:3)[c]	
7	**1g**	CH	H	H	H	3,5-*bis*(trifluoromethyl)phenyl	74[b] (1:4)[c]	
8	**1h**	CH	H	H	H	3-thienyl	82	-
9	**1i**	CH	H	H	H	1-cyclohexenyl	80	-
10	**1j**	CH	H	H	H	*n*-Bu	57	-

11[d]	**1k**	CH	H	H	H	*t*-Bu	-	-
12[d]	**1l**	CH	H	H	H	TMS	-	-
13[d]	**1m**	CH	H	H	H	H	-	-
14	**1n**	CH	OMe	H	H	Ph	51	
15	**1o**	CH	OMe	H	H	4-methylphenyl	61	
16	**1p**	CH	NO_2	H	H	4-methylphenyl	92	
17	**1q**	N	H	H	H	Ph	98	
18	**1r**	N	H	H	H	4-methylphenyl	92	
19	**1s**	CH	H	Bu	H	Ph	76[b] (3:1)[c]	
20	**1t**	CH	H	Bu	H	4-methylphenyl	72	
21	**1u**	CH	H	Et	Et	Ph	-	70
22	**1v**	CH	H	Et	Et	4-methylphenyl	-	70
23	**1w**	CH	H	Bu	Et	Ph	-	82

[a]Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale in 6 mL of acetonitrile. The reactions were allowed to stir at room temperature for 15 h. All yields are isolated yields after column chromatography. [b]An inseparable mixture of the two regioisomers was obtained from column chromatography. [c]The **2**:**3** ratio is based on ^{1}H NMR spectroscopic data. [d]This reaction resulted in a complex reaction mixture.

As can be seen from the results reported in Table 2, the regiochemistry of the process strongly depends on the substitution pattern of the substrate. Interestingly, the presence of a electron-donating group in the *para* position of a phenyl ring conjugated with the triple bond (R^4 = *p*-MeC_6H_4 or *p*-$MeOC_6H_4$, substrates **1b** and **1c**, respectively) led to preferential formation of the isochromene derivative (compare entries 2 and 3 with entry 1). In fact, the electron-donating effect of the *para* substituent should increase the electron density on C-1 of the arylethynyl group, thus favoring intramolecular nucleophilic attack of the hydroxyl group on C-2. As expected, this effect was not observed when the substituents are in the *meta* positions, as shown by the results obtained in the case of substrate **1d** (R^4 = 3,5-

dimethoxyphenyl), whose iodocyclization led to a mixure of the isochromene and isobenzofuran derivatives (entry 4). A mixture of **2e** and **3e** was also obtained in the case of a *p*-chloro substituent (R^4 = *p*-ClC_6H_4, substrate **1e**, entry 5). On the other hand, the presence of a nitro group in the *para* position (R^4 = *p*-$O_2NC_6H_4$, substrate **1f**, entry 6) significantly augments the electrophilicity of C-1 of the arylethynyl group, thus reversing the selectivity of the reaction in favor of the 5-membered ring product **3f**. A similar effect is observed when R^4 is a 3,5-*bis*(trifluoromethyl)phenyl substituent (substrate **1g**, entry 7). When the triple bond is substituted with a 3-thienyl, 1-cyclohexenyl, or butyl group, the reaction consistently follows a 6-*endo*-*dig* pathway, with selective formation of the corresponding isochromene derivatives **2h**-**2j** (entries 8-10). Substrates bearing a sterically demanding substituent [R^4 = *t*-butyl (**1k)** or TMS (**1l)**, entries 11 and 12)] led to complex reaction mixtures. The reaction did not proceed well with a terminal triple bond (R^4 = H, **1m**, entry 13), and partial decomposition of the substrate occurred. Interestingly, the presence of either an electron-donating or an electron-withdrawing group *meta* with respect to the hydroxymethyl group (R^1 = OMe or NO_2, substrates **1n**-**1p**) also tended to favor selective formation of the 6-membered ring products **2n**-**2p** (entries 14-16). Excellent yields of pyranopyridine derivatives **2q** and **2r** were obtained by 6-*endo*-*dig* iodocyclization of the corresponding 2-(1-alkynyl)-3-(hydroxymethyl)pyridines **1q** and **1r** (entries 17 and 18).

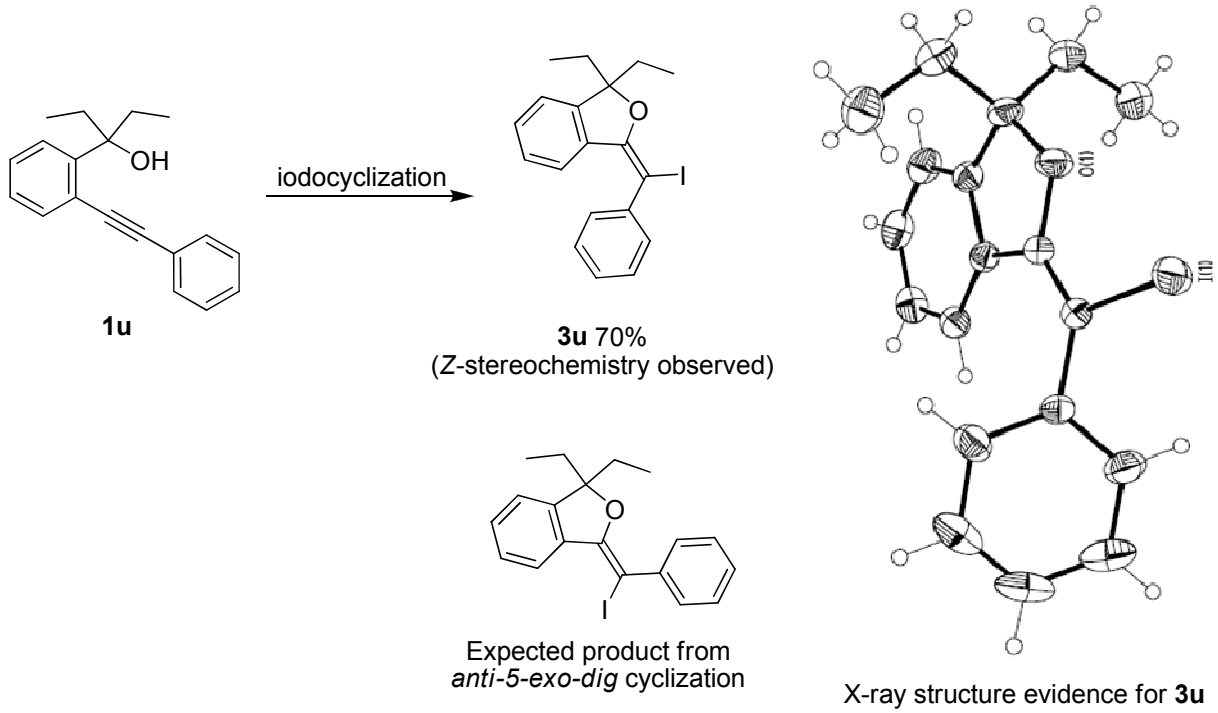
Substrates bearing a secondary alcoholic group (**1s** and **1t**) behaved similarly to substrates with a primary alcoholic group, as can be seen by comparing entries 19 and 20 (Table 2) with entries 1 and 2 (Table 2). On the other hand, as expected in view of the *gem*-dialkyl effect,[32] and in agreement with what has been previously observed in the Pd(II)-catalyzed cycloisomerization of 2-(1-alkynyl)benzylic alcohols,[29k] substrates **1u**-**1w**, bearing

a tertiary alcohol group, selectively proceed by a 5-*exo-dig* cyclization, with formation of the corresponding dihydroisobenzofurans **3u-3w** in good yields (70-82%, entries 21-23). In fact, in the presence of α,α-dialkyl substitution, the hydroxyl group is forced closer to the triple bond, thus favoring the 5-*exo-dig* pathway with respect to the 6-*endo-dig* pathway.

X-ray crystallographic experiments were performed in order to confirm the regiochemistry of the cyclized products.[33] Interestingly, the 1-alkylidene-1,3-dihydroisobenzofuran product **3u** was found to be the *Z*-isomer, instead of the *E*-isomer that would be expected from an *anti*-5-*exo-dig* cyclization (Figure 1). This *Z*-stereochemistry was also found in other 5-membered ring products (by ^{1}H NMR spectral data correlation with **3u**).

Given the unexpected stereochemistry, an immediately reasonable hypothesis was that the predicted stereoisomer is originally formed, and then equilibrates to the observed isomer. This would imply that the observed *Z*-isomer would need to be more stable than the expected *E*-isomer. In order to substantiate this idea, computations were carried out at MP2 and B3LYP levels of theory using a 6-31G(d) basis set on carbon and hydrogen atoms, and an approximately equivalent electron core potential and valence basis set on I. (Details are given in the Experimental Section) At both levels of theory, the *Z*-isomer was favored, by 3.6 and 3.9 kcal/mol using B3LYP and MP2, respectively.

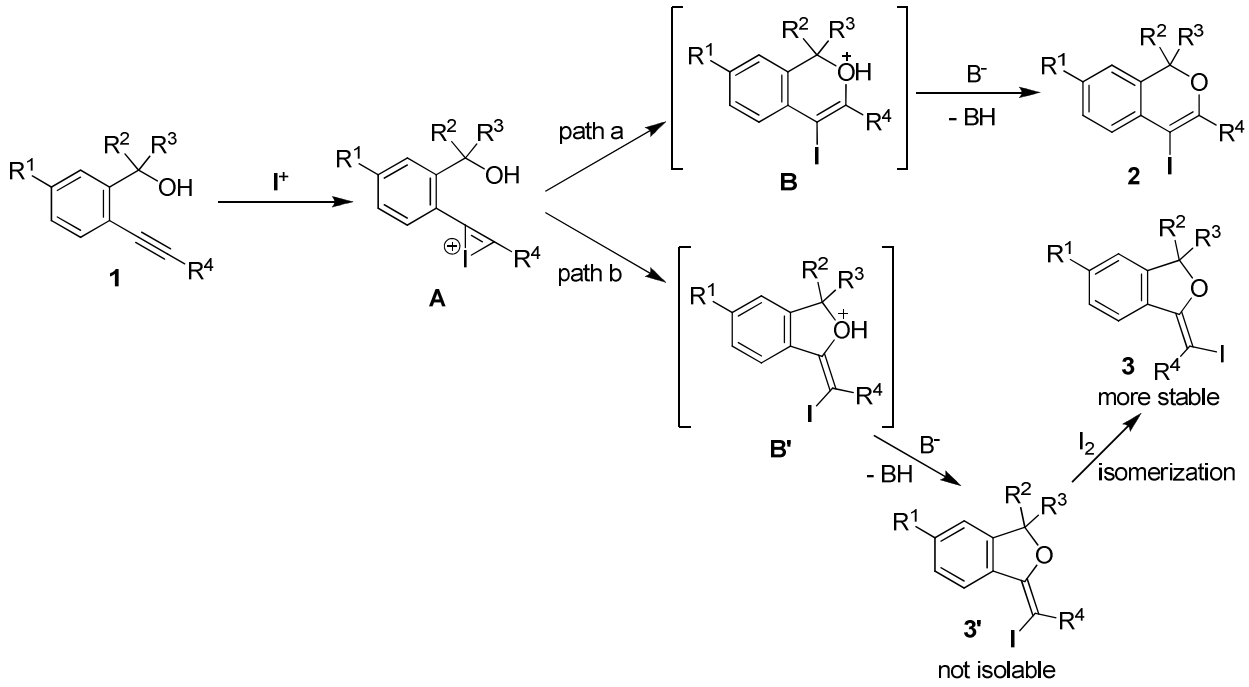
Figure 1. X-ray Evidence for the Structural Assignment of 1-Alkylidene-1,3-dihydroisobenzofurans



On the basis of these observations, the following reaction mechanism can be proposed for the iodocyclization of **1** (Scheme 1).[34] Coordination of an I^+ equivalent to the alkyne leads to electrophilic activation of the alkyne carbon-carbon triple bond generating iodonium intermediate **A**. Nucleophilic attack by the hydroxyl group may then take place by either of two intramolecular cyclization modes (*anti*-6-*endo-dig* or *anti*-5-*exo-dig*, paths *a* and *b*, respectively) to give intermediates **B** or **B'** respectively. Deprotonation of intermediate **B** leads to the isochromene product **2** that is isolated as the major product in most cases. However, dihydroisobenzofuran derivative **3'** with *E* stereochemistry derived from intermediate **B'** was not isolated. Presumably, isomerization of the initially formed *E*-isobenzofuran (**3'**) leads to the more stable *Z*-isomer (**3**). A few examples of the

isomerization of substituted *cis*-alkenes to the more stable corresponding *trans*-isomers in the presence of iodine are known.[35] In order to demonstrate the feasibility of the isomerization, *cis*-stilbene was subjected to our reaction conditions and partial isomerization was observed. The ratio of *cis*:*trans* stilbene was found to be 1:0.6 at 10 h and 1:0.9 at 19 h by ^{1}H NMR spectral data.

Scheme 1. Proposed Mechanistic Pathway for the Iodocyclization of 2-(1-Alkynyl)benzylic alcohols (1)



Conclusions

A simple and mild synthesis of 6- and 5-membered iodoheterocyclic ether derivatives (**2** and **3**, respectively) *via* iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols **1** is reported. The nature of the substituents in the starting material governs the regiochemistry of the reaction products. The 5-membered ring products obtained (1-

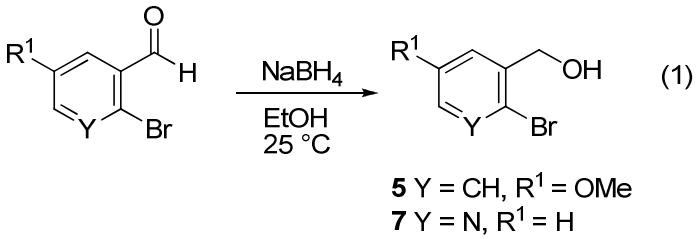
alkylidene-1,3-dihydroisobenzofurans **3**) exhibit unexpected *Z*-stereochemistry, and are presumably derived from the initially formed less stable *E*-isomers through iodine-mediated isomerization.

Experimental Section

General. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ at 300 MHz or 400 MHz and 75 MHz or 100 MHz, respectively, with Me_4Si as an internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. The IR spectra were taken with an FT-IR spectrometer. All reactions were analyzed by TLC on silica gel 60 [visualization was effected with short wavelength UV light (254 nm)], and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). All melting points are uncorrected. HRMS data: the electron impact ionization experiments were performed on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA) fitted with a Finnigan EI/CI ion source. The samples were introduced to the mass spectrometer using a solids probe. The probe was heated gradually from 100 to 400 ^{o}C. The instrument was used as a single quadrupole and scanned from 50 to 1000 daltons. Accurate mass measurements were conducted using manual peak matching technique with the KRATOS MS50 double focusing mass spectrometer.

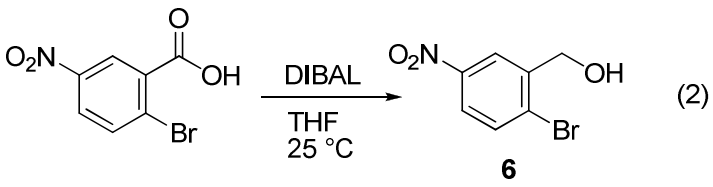
Preparation of the Non-commercial *o*-Haloarenes. 2-Iodobenzyl alcohol (**4)** was commercially available and used as received; all of the other precursors **5-7** were prepared as described below.

General Procedure for Preparation of the 2-Bromobenzylic Alcohols 5 and 7 (Eq 1)



To a stirred solution of commercially available 2-bromo-5-methoxybenzaldehyde or 2-bromopyridine-3-carboxaldehyde (4.06 mmol) in EtOH (10.7 mL) was added $NaBH_4$ (4.87 mmol). After being stirred at 25 °C for 1 h (2-bromopyridine-3-carboxaldehyde) or 3 h (2-bromo-5-methoxybenzaldehyde), the cooled mixture (0 °C) was acidified with 0.1 N HCl with stirring. After additional stirring at 0 °C for 15 min, Et_2O and satd aq $NaHCO_3$ were added. The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with satd aq $NaHCO_3$ and then with H_2O to neutral pH. After drying over Na_2SO_4, the solvent was removed by rotary evaporation, and the crude products **5**[37] and **7**[38] thus obtained were used as such for the next step (**5**: white solid, 3.96 mmol, 860 mg, 91%; **7**: white solid, 2.72 mmol, 511 mg, 67%).

Procedure for the Preparation of 2-Bromobenzylic Alcohol 6



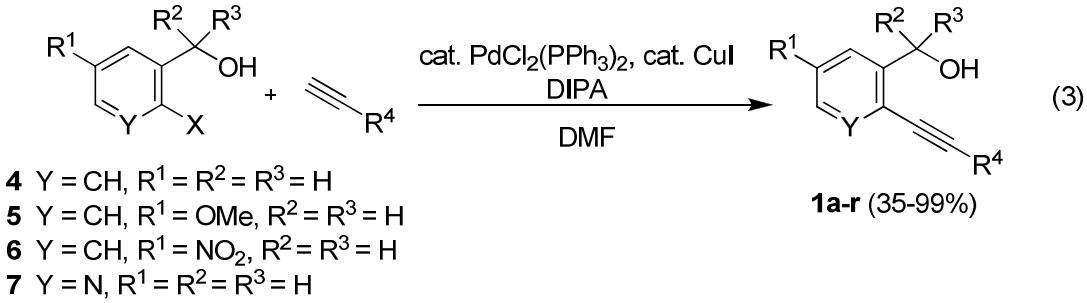
To a cooled (0 °C), stirred solution of commercially available 5-nitro-2-bromobenzoic acid (2.32 mmol) in THF (5 mL) was added DIBAL (5.09 mmol). After being stirred at 0 °C for 4 h, the mixture was acidified with 0.1 N HCl at 0 °C with stirring. After

additional stirring at 0 °C for 15 min, Et_2O and satd aq $NaHCO_3$ were added. The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with satd aq $NaHCO_3$ and then with H_2O to neutral pH. After drying over Na_2SO_4, the solvent was removed by rotary evaporation, and the crude product **6**[39] thus obtained was purified by column chromatography on silica gel using 9:1 to 4:1 hexane/EtOAc as the eluent (white solid, 188 mg, 35%).

Preparation of the 2-(1-Alkynyl)benzylic Alcohols

Preparation of Substrates Bearing a Primary Alcohol (1a-r)

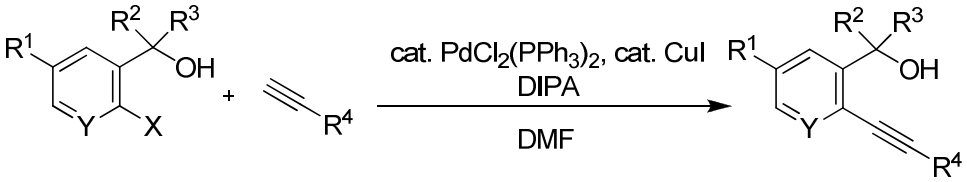
Substrates **1a-1o** were prepared by Sonogashira coupling[36] of the appropriate *o*-halobenzylic alcohols **4-6** or (hydroxymethyl)pyridine **7** and terminal alkynes (Eq 3 and Table S1).



General Procedure for the Sonogashira Coupling. To a mixture of the *o*-halobenzylic alcohol **4-6** or 2-bromo-3-(hydroxymethyl)pyridine (**7**, 2.0 mmol) in DMF (10 mL) were added $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol), and CuI (3.8 mg, 0.02 mmol) under argon. After the reaction mixture was stirred for 5 min at room temperature, DIPA (809 mg, 4.0 equiv) was added by a syringe. The reaction mixture was then heated at 70 °C. A solution of the

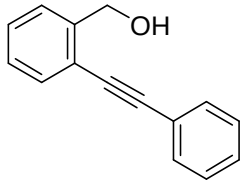
alkyne (1.2 equiv) in DMF (2 mL) was added dropwise over 10 min, and the mixture was allowed to stir at 70 ^{o}C for 2 h. After cooling, the reaction mixture was washed with satd aq NH_4Cl and water, and then extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to give the crude product **1**, which was purified by column chromatography on silica gel using 9:1 to 4:1 hexane-EtOAc as eluent.

TABLE S1

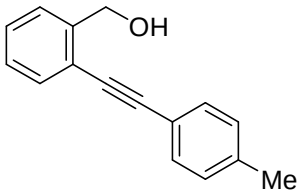


entry	*o*-halo-benzylic alcohol	**X**	**Y**	R^1	R^2	R^3	R^4	**1**	isolated yield (%) **1**
1	**4**	I	CH	H	H	H	Ph	**1a**	80
2	**4**	I	CH	H	H	H	4-methylphenyl	**1b**	98
3	**4**	I	CH	H	H	H	4-methoxyphenyl	**1c**	77
4	**4**	I	CH	H	H	H	3,5-dimethoxyphenyl	**1d**	93
5	**4**	I	CH	H	H	H	4-chlorophenyl	**1e**	99
6	**4**	I	CH	H	H	H	4-nitrophenyl	**1f**	99
7	**4**	I	CH	H	H	H	3,5-bis(trifluoromethyl)phenyl	**1g**	86
8	**4**	I	CH	H	H	H	3-thienyl	**1h**	94
9	**4**	I	CH	H	H	H	1-cyclohexenyl	**1i**	90
10	**4**	I	CH	H	H	H	*n*-Bu	**1j**	71
11	**4**	I	CH	H	H	H	*t*-Bu	**1k**	81

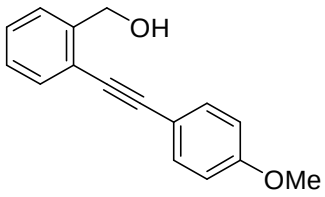
12	**4**	I	CH	H	H	H	TMS	**1l**	86
13	**5**	Br	CH	OMe	H	H	Ph	**1n**	35
14	**5**	Br	CH	OMe	H	H	4-methylphenyl	**10**	91
15	**6**	Br	CH	NO_2	H	H	4-methylphenyl	**1p**	80
16	**7**	Br	N	H	H	H	Ph	**1q**	80
17	**7**	Br	N	H	H	H	4-methylphenyl	**1r**	92



[2-(Phenylethynyl)phenyl]methanol (1a). This reaction was run using TEA (10 mL) as the solvent. Also, TEA (2 mL) was used for alkyne addition to the reaction mixture. After purification, the product was obtained as a yellow solid (yield: 334 mg, 80%); mp 65-66 °C, lit. mp 65-66 °C[40]; IR (KBr) 3210 (br s), 2065 (w), 1598 (w), 1571 (w), 1491 (m), 1453 (m), 1368 (w), 1191 (w), 1097 (w), 1039 (m), 987 (w), 919 (w), 757 (s), 692 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.40 (m, 4H, aromatic), 7.38-7.19 (m, 5H, aromatic), 4.87 (s, 2H, CH_2), 2.60 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 132.1, 131.5, 128.7, 128.5, 128.4, 127.3, 127.1, 122.9, 121.1, 94.2, 86.7, 63.8; GC-MS *m/z* = 208 (M^+, 11), 180 (24), 178 (29), 165 (18), 152 (20), 149 (22), 130 (38), 79 (19), 78 (78), 77 (100); HRMS calcd for $C_{15}H_{12}O$ 208.08881. Found 208.08909.

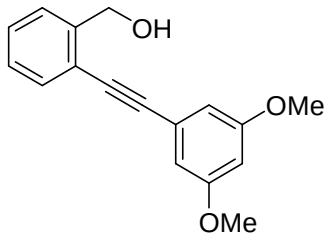


[2-(*p*-Tolylethynyl)phenyl]methanol (1b). Colorless solid (205 mg, 92%): mp 102-103 °C, lit. mp 102-103 °C[41]; IR (KBr) 3346 (s), 3256 (s), 1949 (w), 1511 (s), 1479 (w), 1451 (m), 1336 (w), 1250, (w), 1192 (w), 1097 (w), 1041 (s), 1034 (s), 1021 (m), 990 (w), 950 (w), 819 (w), 760 (s), 754 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 1H, aromatic), 7.47-7.40 (m, 3H, aromatic), 7.32 (td, J = 7.5, 0.9 Hz, 1H, aromatic), 7.28-7.24 (m, 1H, aromatic), 7.15 (d, J = 7.5 Hz, 2H, aromatic), 4.91 (d, J = 6.1 Hz, 2H, CH_2), 2.37 (s, 3H, Me), 2.23 (t, J = 6.1 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 139.0, 132.3, 131.7, 129.4, 128.8, 127.7, 127.5, 121.7, 120.0, 94.7, 86.3, 64.3, 21.8; GC-MS m/z = 222 (M^+, 9), 178 (19), 131 (22), 130 (89), 115 (79), 111 (20), 110 (35), 103 (22), 102 (100), 92 (66), 91 (70), 89 (32); HRMS calcd for $C_{16}H_{14}O$ 222.10446. Found 222.10486.

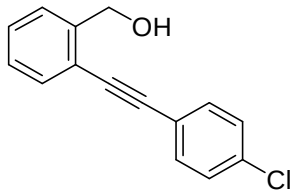


[2-(4-Methoxyphenylethynyl)phenyl]methanol (1c). Pale orange solid (377 mg, 77%); mp 99-100 °C, lit. mp 102-103 °C[42]; IR (KBr) 3348 (br s), 3382 (br s), 2956 (m), 1909 (w), 1605 (m), 1569 (w), 1512 (s), 1469 (m), 1366 (w), 1288 (m), 1248 (s), 1181 (m), 1108 (w), 1045 (m), 1031 (m), 948 (w), 840 (s), 760 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.2 Hz, 1H, aromatic), 7.47-7.41 (m, 3H, aromatic), 7.33 (t, J = 7.2 Hz, 1H, aromatic), 7.26 (t, J

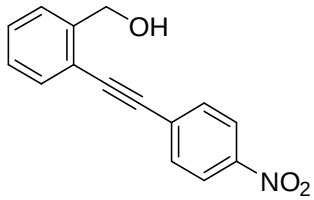
= 7.2 Hz, 1H, aromatic), 6.87 (d, *J* = 7.2 Hz, 1H, aromatic), 4.90 (s, 2H, CH_2), 3.83 (s, 3H, OMe), 2.24 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 142.3, 133.0, 131.9, 128.4, 127.4, 127.2, 121.6, 114.9, 114.0, 94.2, 85.4, 64.1, 55.3; GC-MS *m/z* = 238 (M^+, 18), 179 (36), 167 (36), 166 (100), 152 (63), 149 (27), 135 (25), 129 (39) ; HRMS calcd for $C_{16}H_{14}O_2$ 238.09937. Found 238.09980.



[2-(3,5-Dimethoxyphenylethynyl)phenyl]methanol (1d). Brown solid (499 mg, 93%); mp 71-72 °C; IR (KBr) 3324 (br s), 2965 (m), 1969 (w), 1590 (s), 1451 (m), 1416 (m), 1449 (w), 1357 (m), 1368 (w), 1235 (w), 1208 (s), 1158 (s), 1154 (m), 1066 (m), 928 (w), 846 (m), 825 (m), 759 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.5, 2.4 Hz, 1H, aromatic), 7.46 (dd , *J* = 7.5, 2.4 Hz, 1H, aromatic), 7.36 (td, *J* = 7.5, 1.2 Hz, 1H, aromatic), 7.29 (td, *J* = 7.5, 1.2 Hz, 1H, aromatic), 6.68 (d, *J* = 2.3 Hz, 2H, aromatic), 6.47 (t, *J* = 2.3 Hz, 1H, aromatic), 4.91 (d, *J* = 6.4 Hz, 2H, CH_2), 3.82 (s, 6H, OMe), 2.20-2.09 (m, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 142.5, 132.2, 128.8, 127.4, 127.2, 124.1, 121.1, 109.3, 101.9, 94.1, 86.2, 64.0, 55.5; GC-MS *m/z* = 268 (M^+, 100), 267 (36), 240 (16), 239 (45), 238 (18), 224 (17), 209 (16), 208 (21), 164 (27); HRMS calcd for $C_{17}H_{16}O_3$ 268.10994. Found 268.11032.

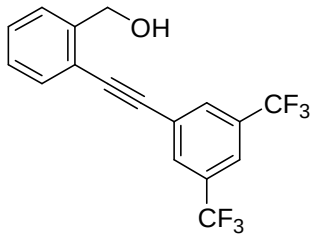


[2-(4-Chlorophenylethynyl)phenyl]methanol (1e). Yellow solid (480 mg, 99%); mp 90-92 °C; IR (KBr) 3314 (br s), 2921 (m), 2216 (w), 1492 (s), 1449 (w), 1398 (w), 1368 (w), 1239 (w), 1119 (w), 1093 (s), 1044 (s), 1015 (m), 942 (w), 830 (s), 757 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.43 (m, 4H, aromatic), 7.40-7.24 (m, 4H, aromatic), 4.90 (s, 2H, CH_2), 2.17 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 134.5, 132.7, 132.1, 128.9, 128.7, 127.5, 127.2, 121.3, 120.9, 92.3, 87.6, 63.9; GC-MS *m/z* 242 (M^+, 100), 241 (28), 239 (18), 208 (22), 207 (38), 179 (57), 178 (68), 177 (18), 176 (42); HRMS calcd for $C_{15}H_{11}ClO$ 242.04984. Found 242.05022.

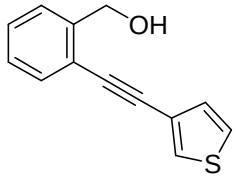


[2-(4-Nitrophenylethynyl)phenyl]methanol (1f). Reaction time: 3h. After purification, the compound was obtained as an orange solid (501 mg, 99%): mp 114-115 °C; IR (KBr) 3325 (br s), 2935 (m), 2217 (w), 1592 (m), 1514 (s), 1447 (w), 1342 (s), 1289 (w), 1192 (w), 1108 (w), 1031 (m), 983 (w), 852 (s), 758 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 2H, aromatic), 7.67 (distorted d, J = 8.5 Hz, 2H, aromatic), 7.60-7.52 (m, 2H, aromatic), 7.44 (t, J = 7.5 Hz, 1H, aromatic), 7.29 (distorted t, J = 7.5 Hz, 1H, aromatic), 4.94 (s, 2H, CH_2), 2.05 (m, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 142.3, 132.4, 132.2, 129.8,

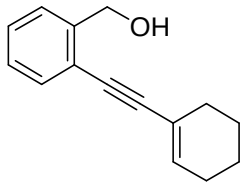
129.7, 127.6, 127.3, 123.7, 120.1, 92.03, 92.00, 63.7; GC-MS *m/z* = 253 (M^+, 43), 207 (12), 206 (13), 179 (32), 178 (100), 177 (43), 176 (26), 165 (18), 152 (21), 151 (16); HRMS calcd for $C_{15}H_{11}NO_3$ 253.07389 Found 253.07419.



[2-(3,5-Bis-trifluoromethylphenylethynyl)phenyl]methanol (1g). Pale yellow solid (104 mg, 74%): mp 105-106 °C; IR (KBr) 3341 (m), 3324 (m, br), 2957 (w), 2225 (w), 1467 (w), 1435 (w), 1386 (s), 1284 (s), 1192 (m), 1169 (m), 1129 (s), 1043 (w), 1006 (w), 923 (m), 902 (m), 847 (w), 763 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.92 (m, 2H, aromatic), 7.86-7.81 (m, 1H, aromatic), 7.56 (t, *J* = 7.8 Hz, 2H, aromatic), 7.44 (t, *J* = 7.8 Hz, 1H, aromatic), 7.32 (distorted t, *J* = 7.8 Hz, 1H, aromatic), 4.95 (d, *J* = 5.4 Hz, 2H, CH_2), 1.99 (distorted t, *J* = 5.4 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 132.5, 132.2, 131.8, 131.3, 129.7, 127.6, 127.3, 125.3, 121.8, 119.8, 90.8, 90.1, 63.7; GC-MS *m/z* 344 (M^+, 100), 343 (26), 325 (20), 323 (23), 296 (29), 295 (24), 275 (78), 247 (25), 246 (48), 227 (29), 225 (22), 178 (31), 131 (33), 103 (21); HRMS calcd for $C_{17}H_{10}F_6O$ 344.06358. Found 344.06398.

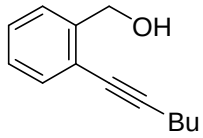


(2-Thiophen-3-ylethynylphenyl)methanol (1h). Orange solid (402 mg, 94%): mp 78-80 °C; IR (KBr) 3350 (m), 3323 (m), 2918 (w), 1961 (w), 1517 (w), 1479 (s), 1450 (m), 1365 (m), 1238 (w), 1205 (w), 1100 (w), 1045 (s), 990 (w), 941 (w), 868 (m), 785 (w), 760 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.49 (m, 2H, aromatic), 7.47-7.44 (m, 1H, aromatic), 7.37-7.24 (m, 3H, aromatic), 7.21-7.17 (m, 1H, aromatic), 4.89 (s, 2H, CH_2), 2.17 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 132.1 129.7, 128.8, 128.6, 127.4, 127.2, 125.5, 121.9, 121.2, 89.2, 86.2, 64.0; GC-MS *m/z* 214 (M^+, 36), 213 (22), 186 (25), 185 (100), 184 (84), 183 (29), 171 (20), 152 (40), 151 (23), 141 (37), 139 (32) ; HRMS calcd for $C_{13}H_{10}OS$ 214.04523. Found 214.04559.



(2-Cyclohex-1-enylethynylphenyl)methanol (1i). Yellow oil[12b] (394 mg, 90%): IR (KBr) 3391 (br s), 2931 (s), 2859 (m), 2200 (w), 1481 (w), 1449 (m), 1436 (w), 1373 (w), 1241 (m), 1091 (w), 1044 (s), 919 (w), 842 (w), 758 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.2 Hz, 2H, aromatic), 7.32-7.26 (m, 1H, aromatic), 7.26-7.20 (m, 1H, aromatic), 6.25-6.19 (m, 1H, C=CH), 4.80 (s, 2H, CH_2OH), 2.30-2.21 (m, 3H, CCH_2CH$_2$CH$_2$CH$_2$CH + OH), 2.19-2.10 (m, 2H, CCH$_2$CH$_2$CH$_2$CH_2CH), 1.73-1.60 (m, 4H, CCH$_2$CH_2CH_2CH$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 135.6, 131.9, 128.1, 127.4, 127.2, 121.8, 120.5, 96.2, 84.1, 64.1, 29.2, 25.8, 22.3, 21.4; GC-MS *m/z* 212 (M^+, 100), 178 (33), 165 (43), 164 (91), 156

(66), 155 (53), 154 (51), 152 (56), 140 (65), 130 (62), 129 (42), 127 (71); HRMS calcd for $C_{15}H_{16}O$ 212.12011. Found 212.12047.



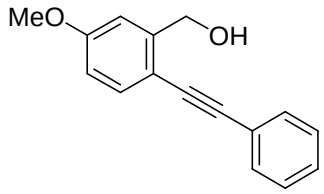
(2-Hex-1-ynylphenyl)methanol (1j). Yellow oil[29k] (267.3 mg, 71%): IR (KBr) 3398 (br s), 2957 (w), 2871 (w), 2227 (w), 1482 (m), 1453 (m), 1383 (m), 1041 (m), 757 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 2H, aromatic), 7.25 (td, J = 7.7, 1.6 Hz, 1H, aromatic), 7.18 (td, J = 7.7, 1.6 Hz, 1H, aromatic), 4.76 (s, 2H, CH_2OH), 2.57 (br s, 1H, OH), 2.46 (t, J = 7.1 Hz, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.67-1.53 (m, 2H, CH_2CH$_2$CH$_3$), 1.53-1.40 (m, 2H, CH$_2$CH_2CH$_3$), 0.95 (t, J = 7.3 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 132.1, 127.9, 127.2, 127.0, 122.0, 95.4, 78.1, 63.9, 30.8, 22.0, 19.2, 13.6; GC-MS m/z 188 (M^+, 80), 155 (64), 145 (100), 144 (27), 132 (29), 131 (24), 128 (32), 117 (33), 116 (28), 115 (58), 114 (23); HRMS calcd for $C_{13}H_{16}O$ 188.12011. Found 188.12046.

Alcohol **1k** was isolated as a yellow oil[29k] (305 mg, 81%); **1l** was isolated as a yellow oil[29k] (351 mg, 86%). The spectral data for these compounds matched those reported in the literature.

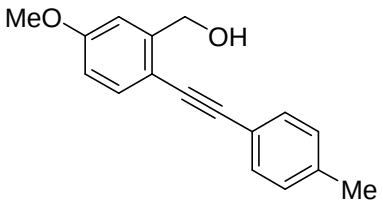
Preparation of (2-Ethynylphenyl)methanol (1m)

To a stirred solution of **1l** (300 mg, 1.59 mmol) in MeOH (8.3 mL) was added KF (5.68 mmol). The mixture was allowed to stir at rt for 3 h, and then diluted with CH_2Cl_2 and quenched with water. The phases were separated, the aqueous layer extracted with CH_2Cl_2,

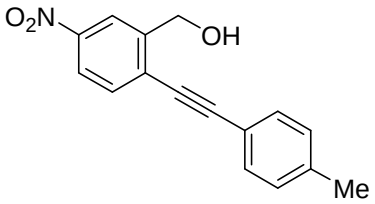
and the combined organic layers were dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel using 6:4 hexane-EtOAc as the eluent to give a yellow solid, which was then further purified by repeated crystallization (hexane) to give pure (2-ethynylphenyl)methanol (**1m**) as a colorless solid [29k] (147 mg, 70%).



[5-Methoxy-2-(phenylethynyl)phenyl]methanol (1n). This reaction was run by following the general Sonogashira procedure above, except for a few differences: 4 mol % $PdCl_2(PPh_3)_2$ (28.1 mg) and 3 mol % CuI (5.7 mg) were used and the reaction mixture was heated at 100 ^oC for 2 h. After purification, the product was obtained as a brown solid (152 mg, 35%): mp 79-80 °C; IR (KBr) 3266 (br s), 2208 (w), 1605 (m), 1566 (w), 1454 (s), 1384 (w), 1294 (m), 1266 (s), 1226 (m), 1160 (m), 1105 (m), 1050 (s), 895 (w), 817 (s), 807 (m), 737 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.43 (m, 3H, aromatic), 7.39-7.30 (m, 3H, aromatic), 7.05 (br s, 1H, aromatic), 6.81 (d, J = 8.0 Hz, 1H, aromatic), 4.89 (s, 2H, CH_2), 3.84 (s, 3H, OMe), 2.21 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 144.4, 133.5, 131.3, 128.4, 128.2, 123.2, 113.1, 112.5, 92.8, 86.7, 81.8, 64.0, 53.4; GC-MS m/z 238 (M^+, 100), 237 (38), 223 (35), 217 (27), 215 (24), 195 (22), 194 (27), 165 (22); HRMS calcd for $C_{16}H_{14}O_2$ 238.09937. Found 238.09979.

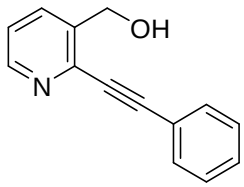


[5-Methoxy-2-(*p*-tolylethynyl)phenyl]methanol (1o). Reaction time: 14 h. After purification, the compound was obtained as an orange solid (459 mg, 91%): mp 99-100 °C; IR (KBr) 3341 (s), 2213 (w), 1607 (m), 1565 (w), 1497 (s), 1364 (m), 1294 (s), 1224 (s), 1162 (m), 1107 (m), 1046 (s), 874 (m), 807 (m), 759 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H, aromatic), 7.43-7.36 (m, 2H, aromatic), 7.17-7.12 (m, 2H, aromatic), 7.05-7.03 (m, 1H, aromatic), 6.84-6.77 (m, 1H, aromatic), 4.88 (s, 2H, CH_2), 3.83 (s, 3H, OMe), 2.37 (s, 3H, Me), 2.28 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 144.3, 138.3, 133.4, 131.2, 129.1, 120.1, 118.9, 113.3, 113.1, 112.5, 93.0, 86.0, 64.0, 55.3, 21.5; GC-MS m/z 252 (M^+, 100), 249 (19), 237 (18), 236 (19), 209 (19), 179 (15), 178 (20), 166 (16), 165 (19); HRMS calcd for $C_{17}H_{16}O_2$ 252.11502. Found 252.11541.

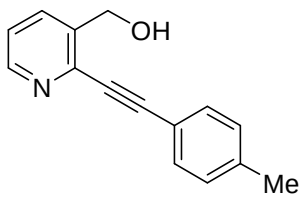


[5-Nitro-2-(*p*-tolylethynyl)phenyl]methanol (1p). Yellow solid (428 mg, 80%)**:** mp 136-138 °C; IR (KBr) 3532 (br m), 2210 (m), 1603 (w), 1584 (w), 1520 (m), 1348 (s), 1183 (w), 1089 (w), 1051 (w), 932 (w), 897 (w), 822 (m), 746 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H, aromatic), 8.12 (d, J = 8.0 Hz, 1H, aromatic), 7.64 (d, J = 8.0 Hz, 1H, aromatic), 7.50-7.40 (m, 2H, aromatic), 7.27-7.18 (m, 2H, aromatic), 5.00 (s, 2H, CH_2), 2.40 (s, 3H,

Me), 2.22 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 144.2, 139.9, 132.5, 131.7, 129.4, 127.7, 122.2, 121.6, 118.7, 99.8, 84.5, 62.9, 21.6; GC-MS m/z 267 (M^+, 100), 251 (17), 221 (14), 208 (16), 181 (16), 179 (18); HRMS calcd for $C_{16}H_{13}NO_3$ 267.08954. Found 267.09005.



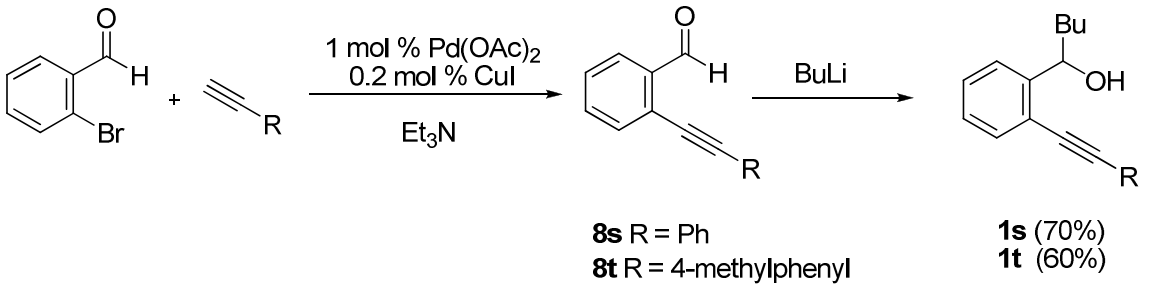
[2-(Phenylethynyl)pyridin-3-yl]methanol (1q). Brown oil[12b] (335 mg, 80%): IR (KBr) 3254 (br s), 2922 (m), 2218 (m), 1582 (m), 1577 (m), 1491 (m), 1428 (s), 1361 (m), 1251 (m), 1189 (w), 1106 (w), 1047 (s), 917 (w), 792 (m), 757 (s), 690 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 4.8 Hz, 1H, aromatic), 7.91 (d, J = 7.8 Hz, 1H, aromatic), 7.53-7.46 (m, 2H, aromatic), 7.37-7.26 (m, 3H, aromatic), 7.20 (dd, J = 7.8, 4.8 Hz, 1H, aromatic), 4.97 (s, 2H, CH_2), 4.21 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 140.5, 139.3, 134.4, 131.8, 129.1, 128.3, 123.0, 121.8, 94.2, 85.3, 61.5; GC-MS m/z 209 (M^+, 92), 208 (82), 180 (100), 77 (25), 52 (24), 51 (34), 50 (21); HRMS calcd for $C_{14}H_{11}NO$ 209.08406. Found 209.08432.



[2-(*p*-Tolylethynyl)pyridin-3-yl]methanol (1r). Brown solid (411 mg, 92%): mp 79-81 °C; IR (KBr) 3231 (br s), 2218 (m), 1581 (m), 1565 (m), 1509 (m), 1429 (s), 1364 (w), 1256 (w), 1178 (w), 1106 (w), 1046 (s), 973 (w), 816 (s), 796 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.6 Hz, 1H, aromatic), 7.87 (d, J = 7.9 Hz, 1H, aromatic), 7.45 (d, J = 7.9 Hz, 2H, aromatic), 7.29-7.20 (m, 1H, aromatic), 7.15 (d, J = 7.9 Hz, 2H, aromatic), 4.96 (s, 2H, CH_2), 3.11 (br s, 1H, OH), 2.37 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 141.0, 139.5, 138.8, 134.5, 131.8, 129.2, 122.9, 118.8, 94.5, 85.5, 62.0, 21.6; GC-MS m/z 223 (M^+, 33), 195 (25), 194 (33), 70 (37), 69 (21), 44 (100), 43 (66); HRMS calcd for $C_{15}H_{13}NO$ 223.09971. Found 223.10003.

Preparation of Substrates Bearing a Secondary Alcohol (1s and 1t)

According to a literature procedure, substrates **1s** and **1t** were prepared by Sonogashira coupling of 2-bromobenzaldehyde and the appropriate terminal alkyne, followed by addition of BuLi (Scheme S1).[29k]



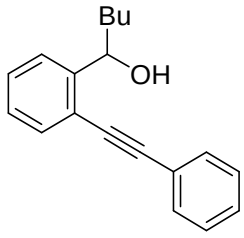
Scheme S1

General Procedure for the Preparation of Alcohols 1s and 1t

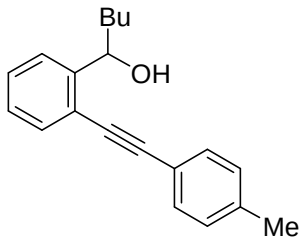
First step: Sonogashira coupling. To a stirred solution of 2-bromobenzaldehyde (10.0 g, 54.0 mmol) in anhydrous Et_3N (164 mL) were added $Pd(OAc)_2$ (108.0 mg, 0.48 mmol),

PPh_3 (218.0 mg, 0.83 mmol), CuI (16.0 mg, 0.084 mmol) and the alkyne (80.0 mmol). After being stirred at 80 °C for 5 h, the mixture was cooled, filtered and concentrated. Water was added to the residue, followed by Et_2O. The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed several times with H_2O and eventually dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel using as eluent 9:1 hexane/EtOAc (**8s**: yellow oil,[29k] 9.4 g, 84% isolated yield; **8t**: yellow solid, 10.0 g, 80% isolated yield).

Second step: BuLi addition. To a cooled (0 °C), stirred solution of aldehyde **8s** or **8t** (45.0 mmol) in anhydrous THF (450 mL) was added dropwise a 2 M solution of BuLi in pentane (18 mL, 36.0 mmol). After being stirred at 0 °C for 2 h, the mixture was quenched with ice water, followed by HCl (10% by volume) to neutral pH. The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, and then dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel using 8:2 hexane-EtOAc as eluent (**1s** was a yellow oil,[29k] 7.1 g, 60% with respect to starting aldehyde; **1t** was a yellow solid, mp 55-56 °C, 6.6 g, 70% with respect to starting aldehyde).



1-[2-(Phenylethynyl)phenyl]pentan-1-ol (1s). Yellow oil:[29k] IR (KBr) 3350 (br s), 2956 (m), 2931 (m), 2859 (m), 2216 (w), 1600 (w), 1493 (m), 1444 (m), 1309 (w), 1251 (w), 1048 (m), 890 (w), 756 (s), 690 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.44 (m, 4H, aromatic), 7.40-7.28 (m, 4H, aromatic), 7.22 (td, J = 7.5, 1.5 Hz, 1H, aromatic), 5.23 (dd, J = 7.7, 5.3 Hz, 1H, C*H*OH), 2.34 (br s, 1H, OH), 1.94-1.70 (m, 2H, CHOHCH_2), 1.53-1.24 (m, 4H, CH_2CH_2CH_3), 0.86 (t, J = 7.1 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 132.3, 131.5, 128.8, 128.4, 127.0, 125.5, 123.4, 120.8, 94.3, 87.4, 72.5, 38.1, 28.2, 22.7, 14.0; GC-MS m/z 264 (M^+, 37), 221 (62), 208 (60), 207 (100), 179 (70), 178 (82), 176 (43), 152 (33), 151 (20), 143 (22), 89 (25), 77 (21); anal. calcd for $C_{19}H_{20}O$ (264.36) C, 86.32; H, 7.63. Found C, 86.42; H, 7.68.

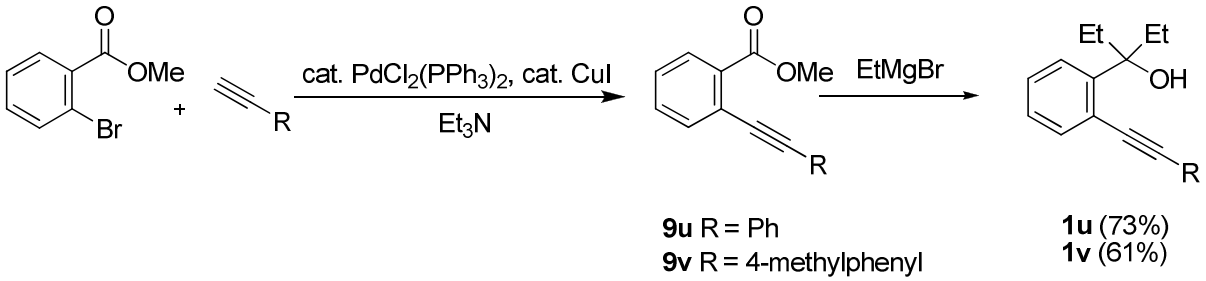


1-[2-(*p*-Tolylethynyl)phenyl]pentan-1-ol (1t). Yellow solid: mp 55-56 °C; IR (KBr) 3350 (br s), 3063 (m), 2956 (s), 2920 (s), 1911 (w), 1598 (w), 1511 (s), 1449 (m), 1272 (w), 1201 (w), 1123 (m), 1055 (m), 1019 (w), 994 (w), 946 (w), 816 (s), 753 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.45 (m, 2H, aromatic), 7.44-7.36 (m, 2H, aromatic), 7.31 (td, J = 7.5, 1.2 Hz, 1H, aromatic), 7.10-7.25 (m, 3H, aromatic), 5.22 (dd, J = 7.3, 5.3 Hz, 1H, C*H*OH), 2.36 (s, 4H, Me + OH), 1.98-1.68 (m, 2H, CHOHCH_2), 1.57-1.25 (m, 4H, CH_2CH_2CH_3), 0.86 (t, J = 6.9 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 138.6, 132.1, 131.3, 129.2, 128.6, 126.9, 125.4, 120.8, 120.1, 94.4, 86.6, 72.4, 38.1, 28.2, 22.6, 21.5, 14.1; GC-

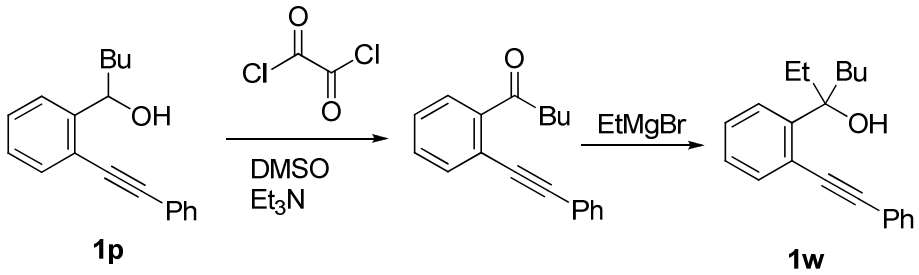
MS m/z 278 (M^+, 25), 235 (28), 222 (23), 221 (100), 193 (15), 191 (14), 190 (13), 179 (13), 178 (61), 165 (11), 143 (10), 115 (17); anal. calcd for $C_{20}H_{22}O$ (278.39) C, 86.29; H, 7.97. Found C, 86.49; H, 8.01.

Preparation of Substrates Bearing a Tertiary Alcohol (1u-w)

According to the literature,[29k] substrates **1u** and **1v** were prepared by Sonogashira coupling of methyl 2-iodobenzoate and the appropriate terminal alkyne, followed by the addition of EtMgBr (Scheme S2). Substrate **1w** was prepared by Swern oxidation of substrate **1s**, followed by the addition of EtMgBr (Scheme S3).



Scheme S2

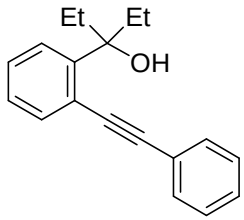


Scheme S3

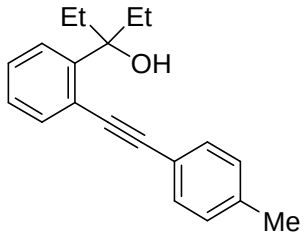
General Procedure for the Preparation of 1u and 1v

First step: Sonogashira coupling. To a stirred solution of methyl 2-bromobenzoate (obtained by esterification of commercially available 2-bromobenzoic acid) (10.2 g, 38.9 mmol) in anhydrous DMF (195 mL) were added $PdCl_2(PPh_3)_2$ (2.7 g, 3.9 mmol), CuI (742 mg, 3.9 mmol), (*i*-Pr)$_2$NEt (21 mL) and phenylacetylene or 1-ethynyl-4-methylbenzene (78.0 mmol). The mixture was allowed to stir at rt for 18 h, and then satd aq NH_4Cl (200 mL) and hexane (200 mL) were added. The phases were separated, and the aqueous layer was extracted with hexane. The combined organic layers were washed with H_2O and brine, and then dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel using 9:1 hexane–EtOAc as eluent (**9u** was a yellow oil,[29k] 8.8 g, 96%; **9v** was a yellow oil, 8.7 g, 89%).

Second step: EtMgBr addition. To a stirred solution of EtMgBr [78.0 mmol, prepared in anhydrous Et_2O (33 mL) from 1.9 g of Mg (78.0 mmol) and 8.8 g of EtBr (81.0 mmol)] was added dropwise a solution of the alkynyl ester **9u** or **9v** (37.0 mmol) in anhydrous benzene (17 mL) with cooling. The mixture was then refluxed with stirring for 1 h (**9u)** or 3 h (**9v**). After cooling, a mixture of ice (85.0 g) and conc. HCl (1.9 mL) was slowly added with external cooling, followed by the addition of NH_4Cl (2.86 g) and Et_2O. The phases were separated, and the organic layer was washed with water, 5% $NaHCO_3$, and water again. After drying over Na_2SO_4, the solvent was removed by rotary evaporation and the crude product was purified by column chromatography on silica gel using as eluent 95:5 hexane–EtOAc (**1u** was a yellow oil,[29k] 7.1 g, 73%; **1v** was a yellow oil, 6.3 g, 61%).



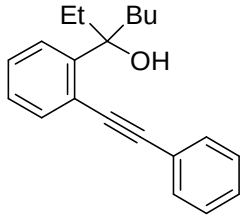
3-[2-(Phenylethynyl)phenyl]pentan-3-ol (1u). Yellow oil:[29k] IR (KBr) 3503 (br s), 2212 (w), 1599 (w), 1492 (s), 1461 (m), 1442 (m), 1376 (w), 1160 (m), 1027 (w), 959 (m), 894 (m), 846 (w), 756 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.45 (m, 4H, aromatic), 7.41-7.28 (m, 4H, aromatic), 7.31 (td, J = 7.4, 1.3 Hz, 1H, aromatic), 2.56-2.40 [m, 2H, $(CH_3CHH)_2COH$)], 1.96 [sext, J = 7.3 Hz, 3H, $(CH_3CHH)_2COH$) + OH], 0.86 (t, J = 7.2 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 134.5, 131.2, 128.5, 128.2, 127.2, 126.3, 123.4, 119.6, 94.5, 89.8, 78.5, 33.3, 8.0; GC-MS m/z 264 (M^+, 10), 236 (56), 235 (100), 220 (35), 215 (16), 202 (26), 191 (28), 176 (19), 129 (23), 105 (31), 89 (15); anal. calcd for $C_{19}H_{20}O$ (264.36) C, 86.32; H, 7.63. Found C, 86.12; H, 7.81.



3-[2-(*p*-Tolylethynyl)phenyl]pentan-3-ol (1v). Yellow oil: IR (KBr) 3509 (br m), 3028 (w), 2969 (s), 2935 (m), 2878 (w), 2212 (w), 1511 (s), 1462 (m), 1376 (w), 1253 (w), 1160 (m), 959 (m), 895 (w), 816 (s), 759 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61-7.42 (m, 2H, aromatic), 7.43-7.36 (m, 2H, aromatic), 7.30 (td, J = 7.7, 1.6 Hz, 1H, aromatic), 7.24-7.12 (m, 3H, aromatic), 2.60 (br s, 1H, OH), 2.47 [sext, J = 7.3 Hz, 2H, $(CH_3CHH)_2COH$)], 2.36

(s, 3H, Me), 1.95 [q, *J* = 7.3 Hz, 2H, $(CH_3CH\mathit{H})_2COH$)], 0.78 [t, *J* = 7.3 Hz, 6H, $(CH_2C\mathit{H}_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 138.6, 134.4, 131.0, 129.2, 128.0, 127.0, 126.3, 120.1, 119.6, 94.7, 89.0, 78.5, 33.3, 21.5, 8.1; GC-MS m/z 288 (M^+, 6), 250 (21), 233 (10), 215 (5), 189 (7), 129 (6); anal. calcd for $C_{20}H_{22}O$ (278.39) C, 86.29; H, 7.97. Found C, 86.49; H, 7.81.

Procedure for the Preparation of 3-[2-(Phenylethynyl)phenyl]heptan-3-ol (1w).



Swern oxidation. To a cooled (-78 °C), stirred solution of ClCOCOCl (4.4 g, 35.2 mmol) in anhydrous CH_2Cl_2 (95 mL) under an inert atmosphere, was added dimethyl sulfoxide (3.7 g, 46.9 mmol). After being stirred at -78 °C for 15 min, a solution of the alcohol (6.2 g, 23.5 mmol) in anhydrous CH_2Cl_2 (31 mL) was added with stirring. After being stirred at -78 °C for an additional 15 min, anhydrous Et_3N (9.4 mL, 93.9 mmol) was added with stirring. The reaction was allowed to warm up to rt and then allowed to stir at rt for 15 min. Et_2O was added to the mixture, followed by water. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed several times with brine, 10% HCl, and eventually dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel using 9:1 hexane-EtOAc as eluent (yellow oil, 4.3 g, 70%).

EtMgBr addition: To a stirred solution of EtMgBr [19.8 mmol, prepared in anhydrous Et_2O (8.3 mL) from 481 mg of Mg (19.8 mmol) and 2.2 g of EtBr (20.4 mmol)] was added dropwise a solution of the alkynyl ester (16.5 mmol) in anhydrous benzene (7.7 mL) with cooling. The mixture was then refluxed with stirring for 1 h. After cooling, a mixture of ice (85 g) and conc. HCl (0.25 mL) was slowly added with external cooling, followed by the addition of NH_4Cl (0.75 g) and Et_2O. The phases were separated, and the organic layer was washed with water, 5% $NaHCO_3$, and water again. After drying over Na_2SO_4, the solvent was removed by rotary evaporation, and the crude product was purified by column chromatography on silica gel using 9:1 hexane–EtOAc as eluent to give pure **1w** as a yellow oil (3.5 g, 73%):[29k] IR (KBr) 3492 (br s), 2212 (w), 1599 (m), 1492 (s), 1460 (s), 1441 (s), 1378 (m), 1250 (w), 1158 (m), 1070 (m), 1026 (w), 960 (m), 846 (w), 756 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.6, 1.2 Hz, 1H, aromatic), 7.56 (dd, J = 7.6, 1.2 Hz, 1H, aromatic), 7.53-7.47 (m, 2H, aromatic), 7.40-7.28 (m, 4H, aromatic), 7.20 (distorted td, J = 7.6, 1.2 Hz, 1H, aromatic), 2.95-2.80 (m, 2H, C*H*HCH_3), 2.60-2.40 (m, 3H, C*H*$_2CH_2CH_2CH_3$ + OH), 2.10-2.80 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.39-1.20 (m, 3H, C*H*HCH_3 + $CH_2CH_2CH_2CH_3$), 0.83 (t, J = 7.1 Hz, 3H, CH_2CH_3 or $CH_2CH_2CH_2CH_3$), 0.78 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$ or CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 134.4, 131.1, 128.5, 128.2, 126.9, 126.3, 123.3, 119.3, 94.4, 89.7, 78.2, 45.2, 40.3, 33.6, 25.9, 23.4, 14.1, 8.0; GC-MS m/z 292 (M^+, 6), 264 (44), 263 (98), 236 (51), 235 (100), 221 (17), 220 (49), 215 (13), 202 (24), 191 (34), 189 (14), 178 (21), 176 (21), 165 (12), 129 (15), 115 (21), 105 (33), 91 (26), 77 (21); anal. calcd for $C_{21}H_{24}O$ (292.41) C, 86.26; H, 8.27. Found C, 86.45; H, 8.32.

General Procedure for the Iodocylization of 1a-w. To a solution of **1** (0.30 mmol) in CH_3CN (6.0 mL) was added $NaHCO_3$ (75.6 mg, 0.90 mmol), followed by I_2 (228.4 mg, 0.90 mmol) at room temperature with stirring. The resulting mixture was allowed to stir at room temperature for 15 h. The excess I_2 was removed by adding a satd aq soln of $Na_2S_2O_3$, followed by stirring for 5-10 min. The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude products were purified by column chromatography on silica gel using hexane-EtOAc (from 95:5 to 9:1) as the eluent.

Characterization Data for the Products

The products 4-iodo-3-aryl-1*H*-isochromene **2** and 3-(iodoarylmethylene)-1,3-dihydro-isobenzofuran **3** were fully characterized by IR, MS, ^{1}H NMR, and ^{13}C NMR spectroscopic analyses. The structures of 4-iodo-3-*p*-methoxyphenyl-1*H*-isochromene (**2c**) and (*Z*)-1,1-diethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (**3u**) were confirmed by X-ray diffraction analysis (Figures S1 and S2). In the case of **2e** and **3e**, **2f** and **3f**, **2g** and **3g**, **2s** and **3s,** it was not possible to separate the two regioisomers, so we characterized them as a mixture. The ratio between the two regioisomers was determined by ^{1}H NMR spectroscopy.

X-ray Crystallographic Data for Compounds 2c and 3u[43]

Data Collection for 2c

A colorless crystal of **2c** was selected under ambient conditions. The crystal was mounted and centered in the X-ray beam by using a video camera. The crystal evaluation and data collection were performed at 173K on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the detector to crystal distance of 5.03 cm (Table S2). The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3º in a 10º range about ω with the exposure time of 10 seconds per frame. The obtained reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of strong reflections from the actual data collection. The data were collected using the full sphere routine by collecting four sets of frames with 0.3º scans in ω with an exposure time 10 sec per frame. This data set was corrected for Lorentz and polarization effects. The absorption correction was based on a fit of a spherical harmonic function to the empirical transmission surface as sampled by multiple equivalent measurements using SADABS software.[44,45]

Figure S1. Molecular Structure of 4-Iodo-3-(4-methoxyphenyl)-1*H*-isochromene (2c)

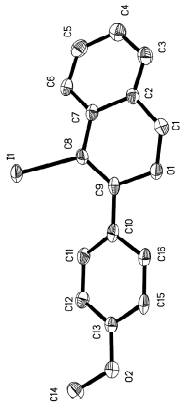


TABLE S2. Crystallographic Data for 2c

Empirical formula	$C_{16}H_{13}IO_2$	
Formula weight	364.16	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pca2(1)	
Unit cell dimensions	a = 11.537(7) Å	α = 90°
	b = 14.916(7) Å	β = 90°
	c = 7.794(4) Å	γ = 90°
Volume	1341.2(13) $Å^3$	
Z	4	
Density (calculated)	1.803 Mg/m^3	
Absorption coefficient	2.382 mm^{-1}	
F(000)	712	

Crystal size	0.35 x 0.35 x 0.24 mm^3
Theta range for data collection	1.37 to 28.87°
Index ranges	-15<=h<=15, -19<=k<=19, -10<=l<=10
Reflections collected	11635
Independent reflections	3282 [R(int) = 0.0631]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5987 and 0.4894
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3282 / 1 / 173
Goodness-of-fit on F^2	0.910
Final R indices [I>2sigma(I)]	R1 = 0.0408, wR2 = 0.0974
R indices (all data)	R1 = 0.0583, wR2 = 0.1137
Absolute structure parameter	0.01(4)
Largest diff. peak and hole	0.741 and -1.366 e.$Å^{-3}$

$R1 = \Sigma \, | \, |F_o| - |F_c| \, | \, / \, \Sigma \, |F_o|$ and $wR2 = \{ \, \Sigma \, [\, w(F_o^2 - F_c^2)^2 \,] \, / \, \Sigma \, [\, w(F_o^2)^2 \,] \, \}^{1/2}$

X-ray Crystallographic Data for Compound 3u[43]

X-ray data for **3u** were collected at room temperature on a Bruker-Nonius X8 Apex CCD area detector equipped with a graphite monochromator and Mo Kα radiation (λ = 0.71073), and data reduction were performed using the SAINT programs; absorption

corrections based on multi-scan were obtained by SADABS.[46] The structures were solved by direct methods (SHELXS/L program in the SHELXTL-NT software package)[47] and refined by full-matrix least-squares based on F^2. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as idealized atoms riding on the respective carbon atoms with C-H bond lengths appropriate to the carbon atoms hybridization. Details of the crystal data, data collection and structure refinement are listed in Table S3.

Figure S2. Molecular Structure of (*Z*)-1,1-Diethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran 3u

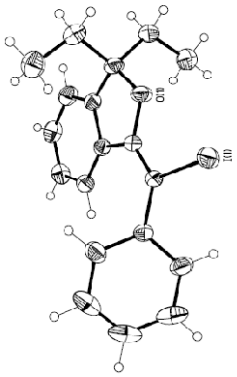
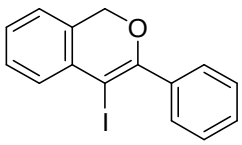


TABLE S3. Crystallographic data for (*Z*)-1,1-Diethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (**3u**)

	3u
Empirical formula	$C_9H_{19}IO$
Formula weight	390.24
Space group	$P2_1/n$
a (Å)	11.264(2)

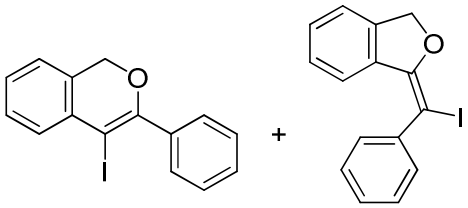
b (Å)	10.372(2)
c (Å)	15.229(3)
α (°)	90
β (°)	108.350(3)
γ (°)	90
V (Å^3)	1688.7(5)
Z	4
Density (g/cm^3)	1.535
Absorption coefficient (mm^{-1})	1.893
F(000)	776
Reflection collected	26961
Unique reflections	3481 [R(int) = 0.0322]
Refined parameters	192
goodness-of-fit	1.048
R indices [a, b]	$R1$ = 0.0246, $wR2$ = 0.0610
R indices (all data)	$R1$ = 0.0271, $wR2$ = 0.0626

[a] $R1 = \Sigma(|F_O| - |F_C|)/\Sigma|F_O|$. [b] $wR2 = [\Sigma w(F_O^2 - F_C^2)^2 / \Sigma w(F_O^2)^2]^{1/2}$.



4-Iodo-3-phenyl-1*H*-isochromene (2a). Yellow oil: IR (KBr) 3059 (m), 2978 (m), 2918 (m), 2843 (m), 1602 (m), 1587 (m), 1564 (m), 1478 (m), 1443 (m), 1374 (w), 1247 (m), 1085

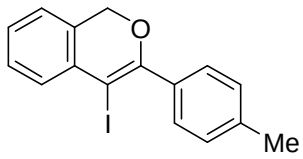
(s), 979 (m), 919 (m), 845 (w), 754 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 2H, aromatic), 7.47 (d, J = 7.5 Hz, 1H, aromatic), 7.44-7.38 (m, 3H, aromatic), 7.44-7.38 (m, 3H, aromatic), 7.35 (distorted td, J = 7.5, 1.1 Hz, 1H, aromatic), 7.23 (distorted td, J = 7.5, 1.1 Hz, 1H, aromatic), 7.01 (d, J = 7.5 Hz, 1H, aromatic), 5.23 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 136.5, 133.5, 130.4, 129.5, 128.7, 128.6, 128.5, 127.8, 127.6, 123.3, 73.3, 69.6; GC-MS *m/z* 334 (M^+, 100), 179 (37), 178 (38), 176 (13); HRMS calcd for $C_{15}H_{11}IO$ 333.98546. Found 333.98588.



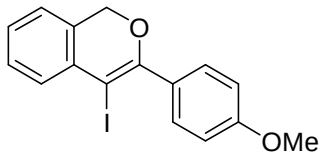
2a **3a**

4-Iodo-3-phenyl-1*H*-isochromene and (*Z*)-1-(Iodophenylmethylene]-1,3-dihydroisobenzofuran (mixture 2a + 3a). Yellow oil (yield = 71%; 11:1 mixture **2a**:**3a** determined by ^1H NMR spectroscopy): IR (KBr) 3059 (m), 2978 (m), 2918 (m), 2843 (m), 1602 (m), 1587 (m), 1564 (m), 1478 (m), 1443 (m), 1374 (w), 1247 (m), 1085 (s), 979 (m), 919 (m), 845 (w), 754 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.59 (m, 2H, aromatic, **2a**), 7.50-7.28 (m, 5H, aromatic, **2a** + 7H, aromatic, **3a),** 7.22-7.15 (m, 1H, aromatic, **2a** + 1H, aromatic, **3a**), 6.96 (d, J = 7.1 Hz, 1H, aromatic, **2a**), 6.43 (d, J = 8.1 Hz, 1H, aromatic, **3a**), 5.39 (s, 2H, CH_2 , **3a**), 5.18 (s, 2H, CH_2 , **2a**); GC-MS (**2a**) *m/z* 334 (M^+, 99), 207 (21), 180 (27), 179 (100), 176 (32), 152 (30), 151 (15), 105 (17), 102 (46), 89 (31), 88 (12); GC-MS (**3a**) GC-MS m/z 334 (M^+, 69), 207 (934), 179 (164), 178 (100), 177 (18), 176 (23), 152

(22), 151 (13), 90 (13), 89 (64); anal. calcd for $C_{15}H_{11}IO$ (334.15): C, 53.92; H, 3.32; I, 37,98. Found C, 53.99; H, 3.28; I, 37.86.

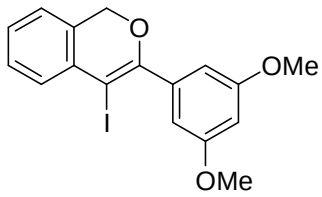


4-Iodo-3-*p*-tolyl-1*H*-isochromene (2b). Yellow solid (yield = 92%): mp 42-44 °C; IR (KBr) 3051 (m), 2924 (m), 2851 (m), 1590 (m), 1509 (m), 1477 (m), 1452 (m), 1265 (s), 1183 (w), 1084 (s), 919 (m), 819 (m), 737 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.52 (m, 2H, aromatic), 7.45 (d, J = 7.6 Hz, 1H, aromatic), 7.33 (t, J = 7.6 Hz, 1H, aromatic), 7.25-7.16 (m, 3H, aromatic), 6.97 (d, J = 7.6, 1H, aromatic), 5.20 (s, 2H, CH_2), 2.39 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 140.0, 133.7, 133.5, 130.3, 128.6, 128.5, 128.4, 127.4, 123.3, 121.2, 72.8, 69.5, 21.5; GC-MS m/z 348 (M^+, 100), 347 (7), 222 (4), 221 (4), 220 (3), 194 (5), 193 (8), 192 (6); HRMS calcd for $C_{16}H_{13}IO$ 348.00111. Found 348.00173.

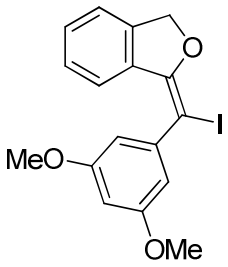


4-Iodo-3-(4-methoxyphenyl)-1*H*-isochromene (2c). Colorless solid (yield = 85%): mp 99-101 °C; IR (KBr) 3053 (m), 2965 (m), 2928 (m), 2850 (m), 1607(m), 1507 (m), 1448 (m), 1263 (s), 1175, 1079 (m), 1024 (m), 919 (w), 834 (m), 738 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.58 (m, 2H, aromatic), 7.44 (distorted dd, J = 7.7, 1.2 Hz, 1H aromatic), 7.33 (td, J = 7.7, 1.2 Hz, 1H, aromatic), 7.20 (td, J = 7.7, 1.2 Hz, 1H, aromatic), 6.98 (d, J = 7.7

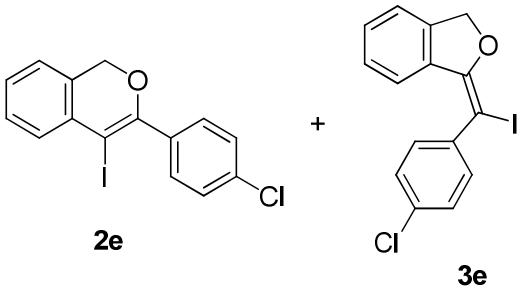
Hz, 1H, aromatic), 6.95-6.88 (m, 2H, aromatic), 5.18 (s, 2H, CH_2), 3.82 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 156.1, 133.9, 132.2, 128.6, 128.5, 127.4, 123.3, 113.1, 72.1, 69.5, 55.3, 30.0; GC-MS m/z 364 (M^+, 28), 195 (44), 194 (41), 176 (20), 167 (48), 165 (100), 162 (56), 151 (34); HRMS calcd for $C_{16}H_{13}IO_2$ 363.99603, Found 363.99664.



3-(3,5-Dimethoxyphenyl)-4-iodo-1*H*-isochromene (2d). White solid (yield = 41%): mp 101-102 °C; IR (KBr) 3053 (m), 2986 (w), 2840 (w), 1594 (s), 1456 (m), 1424 (m), 1330 (w), 1265 (s), 1205 (m), 1157 (m), 1063 (m), 1007 (w), 920 (w), 896 (w), 738 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.5, 1.0 Hz, 1H, aromatic), 7.34 (td, J = 7.5, 1.0 Hz, 1H, aromatic), 7.23 (td, J = 7.5, 1.0 Hz, 1H, aromatic), 6.99 (dd, J = 7.5, 1.0 Hz, 1H, aromatic), 6.78 (d, J = 2.4 Hz, 2H, aromatic), 6.50 (t, J = 2.4 Hz, 1H, aromatic), 5.21 (s, 2H, CH_2), 3.81 [(s, 6H, $(OMe)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 156.2, 138.1, 133.4, 128.7, 128.6, 128.5, 127.7, 123.4, 108.4, 102.1, 73.4, 70.0, 55.5; GC-MS m/z 394 (M^+, 100), 267 (39), 240 (15), 239 (80), 235 (18), 224 (25), 209 (30), 208 (72), 181 (26), 178 (15),165 (64), 153 (24), 152 (38), 102 (22). HRMS calcd for $C_{17}H_{15}IO_3$ 394.00659. Found 394.00741.



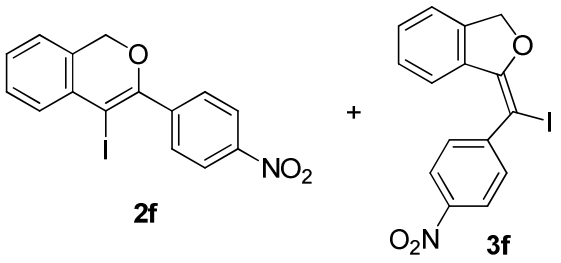
(*Z*)-1-[(3,5-Dimethoxyphenyl)iodomethylene]-1,3-dihydroisobenzofuran (3d). Yellow solid (yield = 35%): mp 82-83 °C; IR (KBr) 3053 (w), 2965 (s), 2832 (s), 1633 (m), 1461 (s), 1439 (w), 1350 (w), 1283 (w), 1215 (m), 1009 (m), 1059 (m), 940 (m), 855 (m), 776 (m), 746 (m), 709 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.21 (m, 2H, aromatic), 7.10-7.00 (m, 1 H, aromatic), 6.67-6.60 (m, 1H, aromatic), 6.57 (d, J = 2.4 Hz, 2H, aromatic), 6.46 (t, J = 2.4 Hz, 1H, aromatic), 5.40 (s, 2H, CH_2), 3.78 [(s, 6H, $(OMe)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 156.9, 142.5, 142.1, 130.8, 129.0, 127.8, 123.5, 121.3, 108.1, 101.0, 73.3, 62.8, 55.4; GC-MS m/z 394 (M^+, 100), 268 (17), 237 (10), 236 (10), 224 (13), 209 (20), 181 (22), 165 (32), 153 (18), 152 (30), 89 (13); anal. calcd for $C_{17}H_{15}IO_3$ (394.20) C, 51.80; H, 3.84; I, 12.18. Found C, 51.75; H, 3.81; I, 12.18.



2e **3e**

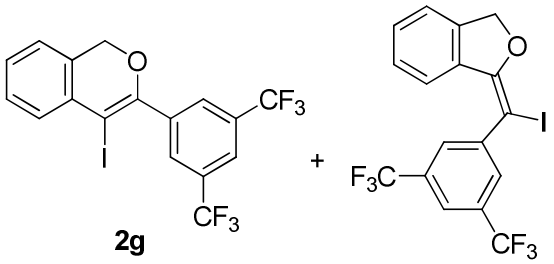
3-(4-Chlorophenyl)-4-iodo-1*H*-isochromene and (*Z*)-1-[(4-Chlorophenyl)iodomethylene]-1,3-dihydroisobenzofuran (2e + 3e). Yellow solid (yield = 85%; 3:1 mixture **2e**:**3e**, determined by ^{1}H NMR spectroscopy): IR (KBr) 3064 (m), 2971

(m), 2920 (m), 2855 (m), 1645 (w), 1594 (m), 1488 (s), 1453 (m), 1399 (m), 1242 (m), 1206 (w), 1091 (s), 1017 (m), 978 (w), 919 (m), 826 (m), 750 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.55 (m, 2H, aromatic, **2e**), 7.50-7.41 (m, 1H, aromatic, **2e**), 7.40-7.17 (m, 4H, aromatic, **2a** + 6H, aromatic, **3e**), 7.06-6.95 (m, 1H, aromatic, **2e** + 1H, aromatic, **3e**), 6.56-6.48 (m, 1H, aromatic, **3e**), 5.43 (s, 2H, CH_2 , **3e**), 5.20 (s, 2H, CH_2 , **2e**); GC-MS (**2e**) *m/z* 368 (M^+, 31), 213 (12), 179 (18), 178 (100), 176 (22), 111 (13), 102 (17), 89 (12), 88 (12); GC-MS (**3e**) *m/z* 368 (M^+, 52), 242 (14), 241 (24), 213 (24), 206 (21), 179 (22), 178 (100), 176 (39), 152 (15), 103 (11), 89 (37), 88 (26); HRMS calcd for $C_{15}H_{10}ClIO$ 367.94649. Found 367.94726.

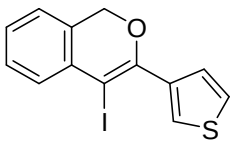


4-Iodo-3-(4-nitrophenyl)-1*H*-isochromene and (*Z*)-1-[Iodo-(4-nitrophenyl)methylene]-1,3-dihydroisobenzofuran (2f + 3f). Yellow solid (yield = 88%; 1:3 mixture **2f**:**3f** determined by ^1H NMR spectroscopy): IR (KBr) 3100 (w), 3065 (w), 2927 (w) 2875 (w), 1637 (w), 15891 (m), 1516 (s), 1346 (s), 1290 (w), 1195 (w), 1106 (m), 1071 (s), 999 (m), 845 (m), 769 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32-8.22 (m, 2H, aromatic, **3f**), 8.20-8.15 (m, 2H, aromatic, **2f**), 7.82-7.75 (m, 2H, aromatic, **2f**), 7.68-7.59 (m, 2H, aromatic, **3f**), 7.53-7.25 (m, 2H, aromatic, **3f** + 4H, aromatic, **2f**), 7.10-7.01 (m, 2H, aromatic, **3f**), 6.56 (d, *J* = 7.7 Hz, 1H, aromatic, **3f**), 5.48 (s, 2H, CH_2, **3f**), 5.34 (s, 2H, CH_2, **2f**); GC-MS (**3f**) m/z 379 (M+, 96), 252 (16), 224 (15), 206 (38), 205 (24), 178 (100), 177 (39), 176 (65). 165 (45),

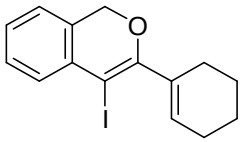
152 (33), 151 (23), 89 (36), 88 (23); HRMS calcd for $C_{15}H_{10}INO_3$ 378.97054. Found 378.97098.



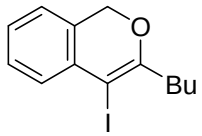
3-(3,5-Bis-trifluoromethylphenyl)-4-iodo-1*H*-isochromene and (*Z*)-1-[(3,5-Bis-trifluoromethylphenyl)iodomethylene]-1,3-dihydroisobenzofuran (2g + 3g). Yellow oil (yield = 74%; 4:1 mixture **2g**:**3g** determined by ^{1}H NMR spectroscopy): IR (KBr) 1656 (w), 1614 (m), 1467 (m), 1373 (m), 1279 (s), 1265 (s), 1178 (s), 1136 (s), 1072 (w), 1014 (w), 1079 (w), 898 (w), 737 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.0 (m, 1H, aromatic, **3g**), 7.87-7.82 (m, 2H, aromatic, **3g** + 2H, aromatic, **2g**), 7.57-7.23 (m, 2H, aromatic, **3g** + 4H, aromatic, **2g**), 7.07-7.01 (m, 2H, aromatic, **3g** + 2H, aromatic, **2g**), 6.45 (d, *J* = 8.1 Hz, 1H, aromatic, **3g**), 5.48 (s, 2H, CH_2, **3g**), 5.34 (s, 2H, CH_2, **2g**); GC-MS (**2g**) *m/z* 470 (M^+, 100), 468 (28), 177 (14), 176 (14), 129 (10), 127 (32), 89 (14); GC-MS (**3g**) *m/z* 470 (M^+, 100), 469 (58), 468 (15), 467 (11), 344 (16), 343 (21), 316 (14), 315 (16), 295 (14), 275 (13), 246 (21); HRMS calcd for $C_{17}H_9F_6IO$ 469.96023. Found 469.96130.



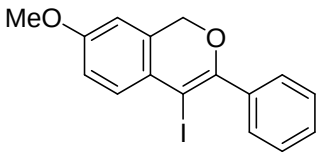
4-Iodo-3-(thiophen-3-yl)-1*H*-isochromene (2h). Yellow solid (yield = 82%): mp 26-27 °C. IR (KBr) 3052 (m), 2952 (m), 2851 (m), 1590 (m), 1477 (m), 1453 (w), 1362 (w), 1230 (w), 1183 (w), 1089 (m), 1079 (m), 1004 (m), 922 (m), 838 (m), 735 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 2.8, 1.2 Hz, 1H, aromatic), 7.57 (dd, J = 5.3, 1.2 Hz, 1H, aromatic), 7.45 (dd, J = 8.1, 0.8 Hz, 1H, aromatic), 7.36 -7.25 (m, 2H, aromatic), 7.57 (td, J = 7.3, 1.2 Hz, 1H, aromatic), 6.97 (d, J = 6.9 Hz, 1H, aromatic), 5.13 (s, 2H, CH_2), 2.17 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 136.7, 133.7, 129.0, 128.92, 128.88, 128.51, 128.53, 127.5, 124.4, 123.3, 72.8, 69.2, 17.9; GC-MS m/z 340 (M^+, 82), 185 (65), 184 (100), 183 (90), 153 (34), 151 (37), 141 (18), 138 (22); HRMS calcd for $C_{13}H_9IOS$ 339.94189. Found 339.94249.



3-(Cyclohex-1-enyl)-4-iodo-1*H*-isochromene (2i). Yellow solid (yield = 80%): mp 46-48 °C; IR (KBr) 3055 (m), 2950 (m), 2847 (m), 1607 (m), 1507 (m), 1448 (m), 1263 (s), 1175 (3), 1079 (m), 1024 (m), 919 (w), 834 (m), 738 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.4 Hz, 1H, aromatic), 7.30 (t, J = 7.4 Hz, 1H, aromatic), 7.17 (t, J = 7.4 Hz, 1H, aromatic), 6.94 (d, J = 7.4 Hz, 1H, aromatic), 6.07 (s, 1H, C=C*H*), 5.05 (s, 2H, CH_2O), 2.30-2.11 (m, 4H, CCH_2CH_2CH_2CH_2CH), 1.77-1.60 (m, 4H, CCH$_2$CH_2CH_2CH$_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 134.8, 133.3, 128.4, 128.3, 127.1, 123.2, 72.0, 69.1, 30.3, 29.7, 26.9, 25.1, 22.4, 21.7; GC-MS m/z 338 (M^+, 100), 336 (87), 213 (35), 212 (32), 209 (25); HRMS calcd for $C_{15}H_{15}IO$ 338.01676. Found 338.01743.

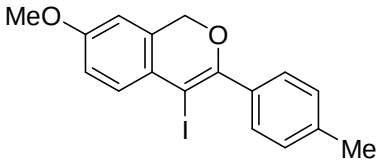


3-Butyl-4-iodo-1*H*-isochromene (2j). Yellow oil (yield = 57%): IR (KBr) 2959 (m), 2870 (m), 1603 (m), 1574 (m), 1516 (m), 1454 (s), 1379 (w), 1256 (w), 1103 (w), 752 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 2H, aromatic), 7.20-7.10 (m, 2H, aromatic), 6.93 (d, J = 7.1 Hz, 1H, aromatic), 5.02 (s, 2H, CH_2O), 2.60 (t, J = 7.6 Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.62-1.45 (m, 2H, $CH_2CH_2CH_3$), 1.41 (sext, J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.3, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.85, 132.8, 128.4, 128.0, 127.4, 126.9, 123.2, 73.7, 68.7, 36.6, 29.5, 22.4, 14.0; GC-MS m/z 314 (M^+, 60), 271 (11), 146 (15), 145 (97), 144 (11), 131 (10), 129 (16), 128 (16), 117 (78), 116 (54), 115 (100), 103 (34), 102 (48), 91 (20), 89 (16); anal. calcd for $C_{13}H_{15}IO$ (314.16) C, 49.70; H, 4.81; I, 40.39. Found C, 49.81; H, 4.81; I, 40.48.

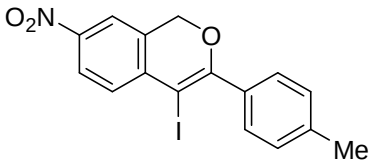


4-Iodo-7-methoxy-3-phenyl-1*H*-isochromene (2n). Yellow solid (yield = 51%): mp 106-108 °C; IR (KBr) 3051 (w), 2960 (m), 2930 (m), 2856 (w), 1612 (w), 1490 (m), 1448 (m), 1265 (s), 1075 (m), 1042 (m), 982 (w), 809 (m), 739 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.60 (m, 2H, aromatic), 7.45-7.35 (m, 4H, aromatic), 6.87 (dd, J = 8.5, 2.0 Hz, 1H, aromatic), 6.65-6.57 (m, 1H, aromatic), 5.19 (s, 2H, CH_2), 3.83 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.4, 136.6, 130.3, 130.2, 130.0, 129.3, 127.7, 126.4, 113.1, 109.4,

73.1, 69.5, 55.5; GC-MS m/z 364 (M^+, 100), 237 (41), 209 (68), 208 (23), 194 (41), 165 (41); HRMS calcd for $C_{16}H_{13}IO_2$ 363.99603. Found 363.99664.

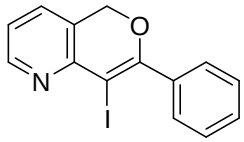


4-Iodo-7-methoxy-3-*p*-tolyl-1*H*-isochromene (2o). Yellow solid (yield = 61%): mp 76-78 °C; IR (KBr) 3053 (w), 2925 (w), 2840 (w), 1611 (m), 1491 (m), 1312 (w), 1264 (s), 1084 (m), 1043 (m), 1024 (w), 943 (w), 819 (m), 720 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.8 Hz, 2H, aromatic), 7.38 (d, J = 8.5 Hz, 1H, aromatic), 7.20 (d, J = 7.8 Hz, 2H, aromatic), 6.85 (dd, J = 8.5, 1.6 Hz, 1H, aromatic), 6.59 (s, 1H, aromatic), 5.17 (s, 2H, CH_2), 3.82 (s, 3H, OMe), 2.39 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 154.4, 139.4, 133.6, 130.3, 130.1, 128.4, 126.7, 113.1, 109.4, 109.3, 72.6, 69.4, 55.5, 21.5; GC-MS m/z 378 (M^+, 31), 251 (25), 224 (41), 223 (64), 222 (36), 220 (34), 208 (52) 206 (38), 205 (100), 178 (21); HRMS calcd for $C_{17}H_{15}IO_2$ 378.01168. Found 378.01227.

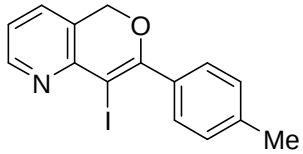


4-Iodo-7-nitro-3-*p*-tolyl-1*H*-isochromene (2p). Yellow solid (yield = 92%): mp 164-165 °C; IR (KBr) 3054 (m), 2986 (w), 2927 (w), 1602 (w), 1505 (br m), 1344 (m), 1265 (s), 1079 (w), 893 (w), 739 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.8 Hz, 1H, aromatic), 7.94 (s, 1H, aromatic), 7.65-7.51 (m, 3H, aromatic), 7.32-7.15 (m, 2H, aromatic), 5.30 (s, 2H,

CH_2), 2.42 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 146.5, 140.8, 140.2, 132.6, 130.4, 129.2, 128.7, 128.6, 124.1, 118.7, 70.0, 69.0, 21.5; GC-MS m/z 393 (M^+, 100), 267 (25), 265 (45), 237 (36), 193 (40), 192 (82), 191 (93), 189 (33), 176 (21), 165 (37), 91 (23); HRMS calcd for $C_{16}H_{12}INO_3$ 392.98619. Found 392.98689.

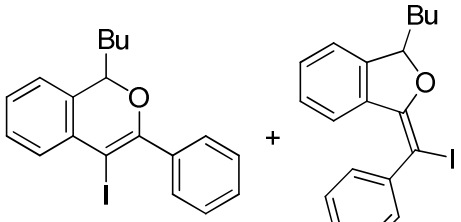


8-Iodo-7-phenyl-5*H*-pyrano[4,3-*b*]pyridine (2q). Yellow solid (yield = 98%): mp 95-97 °C; IR (KBr) 3049 (m), 2982 (w), 2923 (w), 2854 (w),1613 (w), 1588 (m), 1420 (m), 1261 (s), 1071 (m), 913 (w), 712 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, aromatic), 7.72 (s, 2H, aromatic), 7.54-7.26 (m, 4H, aromatic), 7.15 (m, 1H, aromatic), 5.31 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 150.2, 149.3, 135.8, 131.1, 130.3, 130.1, 127.8, 123.2, 122.3, 118.9, 69.1; GC-MS m/z 335 (M^+, 100), 334 (30), 180 (37), 179 (32), 77 (40); HRMS calcd for $C_{14}H_{10}INO$ 334.98071. Found 334.98125.



8-Iodo-7-*p*-tolyl-5*H*-pyrano[4,3-*b*]pyridine (2r). Yellow solid (yield = 92%): mp 90-91 °C; IR (KBr) 3052 (m), 2985 (w), 2924 (w), 2853 (w), 1611 (w), 1582 (m), 1425 (m), 1265 (s), 1088 (m), 922 (w), 729 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 5.0 Hz, 1H, aromatic), 7.62 (d, J = 8.0 Hz, 2H, aromatic), 7.30 (d, J = 7.3 Hz, 2H, aromatic), 7.23 (d, J =

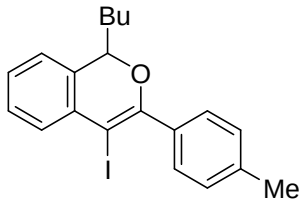
8.0 Hz, 2H, aromatic), 7.13 (dd, *J* = 7.3, 5.0 Hz, 1H, aromatic), 5.27 (s, 2H, CH_2), 2.40 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 150.4, 149.2, 140.3, 132.8, 131.1, 130.3, 128.5, 123.2, 122.1, 75.2, 69.0, 21.5; GC-MS m/z 349 (M^+, 50), 255 (38), 194 (100), 193 (39), 86 (43), 84 (60); HRMS calcd for $C_{15}H_{12}INO$ 348.99636. Found 348.99689.



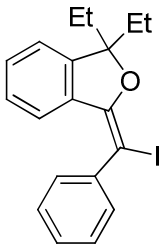
2s **3s**

1-Butyl-4-iodo-3-phenyl-1*H*-isochromene and (*Z*)-1-Butyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (2s + 3s). Yellow oil (yield = 76%; 3:1 mixture **2s:3s** determined by ^1H NMR spectroscopy): IR (KBr) 3027 (m), 2953 (s), 2856 (m), 1671 (m), 1593 (s), 1503 (m), 1458 (m), 1253 (m), 1080 (s), 1025 (w), 932 (m), 816 (m), 750 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.55 (m, 2H, aromatic, **2s**), 7.50-7.45 (m, 1H, aromatic, **2s**), 7.44-7.10 (m, 5H, aromatic, **2s** + 7H, aromatic, **3s**), 7.00-6.99 (m, 1H, aromatic, **2s** + 1H, aromatic, **3s**), 6.43 (d, *J* = 7.7 Hz, 1H, aromatic, **3s**), 5.55 (distorted dd, *J* = 7.3, 4.0 Hz, 1H, OC*H*, **3s**), 5.55 (distorted dd, *J* = 8.2, 5.5 Hz, 1H, OC*H*, **2s**); 2.18-1.85 (m, 2H, $CH_2CH_2CH_2CH_3$, **2s** + 2H, $CH_2CH_2CH_2CH_3$, **3s**), 1.65-1.20 (m, 1H, 4H, $CH_2CH_2CH_2CH_3$, **2s** + 4H, $CH_2CH_2CH_2CH_3$, **3s**), 1.01-0.79 (m, 3H, $CH_2CH_2CH_3$, **2s** + 3H, $CH_2CH_2CH_3$, **3s**); GC-MS (**2s**) *m/z* 390 (M^+, 22), 334 (16), 333 (100), 207 (16), 206 (56), 178 (16), 105 (29); GC-MS (**3s**) *m/z* 390 (M^+, 92), 333 (72), 207 (50), 206 (65), 191 (18), 178 (56), 176 (32), 152 (25), 149 (25), 131 (20),

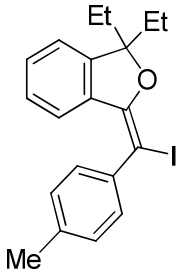
115 (31), 105 (28), 91 (100), 89 (33); anal. calcd for $C_{19}H_{19}IO$ (390.26) C, 58.47; H, 4.91; I, 32.52 . Found C, 58.31; H, 4.99; I, 32.55.



1-Butyl-4-iodo-3-*p*-tolyl-1*H*-isochromene (2t). Yellow oil (yield = 72%): IR (KBr) 3028 (m), 2955 (s), 2859 (m), 1675 (m), 1595 (s), 1567 (w), 1507 (m), 1451 (m), 1378 (w), 1253 (m), 1182 (w), 1082 (s), 1021 (w), 934 (m), 818 (m), 757 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2H, aromatic), 7.47 (distorted dd, J = 7.5, 1.2 Hz, 1H, aromatic), 7.30 (td, J = 7.5, 1.2 Hz, 1H, aromatic), 7.24-7.17 (m, 3H, aromatic), 6.95 (d distorted, J = 7.5 Hz, 1H, aromatic), 5.15 (dd, J = 8.1, 5.3 Hz, 1H, OCH), 2.38 (s, 3H, Me), 2.18-2.03 (m, 1H, C*H*HCH$_2$CH$_2$CH$_3$), 1.97-1.85 (m, 1H, CH*H*CH$_2$CH$_2$CH$_3$), 1.68-1.23 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, J = 7.1 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 139.5, 134.1, 132.7, 132.0, 130.2, 129.0, 128.5, 128.1, 127.4, 123.3, 78.5, 72.03, 32.9, 27.5, 22.5, 21.5, 14.0; GC-MS m/z 404 (M^+, 51), 348 (25), 347 (100), 221 (24), 220 (92), 205(11), 191 (23), 189 (18), 178 (10), 165 (12), 119 (39), 91 (35); anal. calcd for $C_{20}H_{21}IO$ (404.28) C, 59.42; H, 5.24; I, 31.39. Found C, 59.54; H, 5.28; I, 31.42.

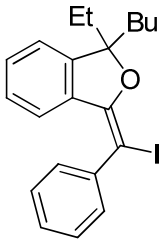


(*Z*)-1,1-Diethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (3u). Yellow solid (yield = 70%): mp 93-95 °C; IR (KBr) 3071 (w), 2966 (s), 2934 (m), 2876 (w), 1635 (s), 1461 (s), 1353 (w), 1290 (w), 1100 (m), 1076 (m), 1023 (w), 953 (s), 875 (m), 810 (w), 765 (m), 750 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.27 (m, 5H, aromatic), 7.22 (t, *J* = 7.4 Hz, 1H, aromatic), 7.04 (d, *J* = 7.4 Hz, 1H, aromatic), 6.95-6.90 (m, 1H, aromatic), 6.42 (d, *J* = 7.4 Hz, 1H, aromatic), 2.05 [sext, *J* = 7.3 Hz, 2H, ($CHHCH_3$)$_2$], 1.85 [(sext, *J* = 7.3 Hz, 2H, ($CHHCH_3$)$_2$], 0.76 [(t, *J* = 7.3 Hz, 6H, CH_2CH_3)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 147.4, 141.2, 130.8, 128.83, 128.76, 128.1, 127.5, 122.8, 121.0, 92.7, 62.1, 32.6, 7.7; GC-MS m/z 390 (M^+, 39), 362 (19), 361 (100), 235 (15), 234 (11), 205 (47), 177 (10), 176 (24), 151 (12), 105 (16), 91 (20), 89 (10); anal. calcd for $C_{19}H_{19}IO$ (390.26) C, 58.47; H, 4.91; I, 32.52. Found C, 58.59; H, 4.88; I, 32.51.



(*Z*)-1,1-Diethyl-3-(iodo-*p*-tolylmethylene)-1,3-dihydroisobenzofuran (3v). Yellow solid (yield = 70%): mp 60-63 °C; IR (KBr) 3019 (w), 2965 (m), 2936 (w), 2878 (w), 1634 (m), 1507 (w), 1462 (s), 1355 (w), 1291 (w), 1209 (w), 1099 (m), 1073 (m), 952 (s), 877 (m), 766 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H, aromatic), 7.26-7.15 (m, 3H, aromatic), 7.06-7.02 (m, 1H, aromatic), 7.00-6.92 (m, 1H, aromatic), 6.49 (d , *J* = 7.7 Hz, 1H, aromatic), 2.40 (s, 3H, Me), 2.06 (sext, *J* = 7.3 Hz, 2H, ($CHHCH_3$)$_2$), 1.84 [(sext, *J* = 7.3

Hz, 2H, ($CH\mathit{H}CH_3)_2$], 0.77 [(t, J = 7.3 Hz, 6H, $CH_2C\mathit{H}_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 147.4, 138.3, 137.9, 132.0, 130.6, 129.6, 128.7, 127.4, 122.9, 121.0, 92.5, 62.5, 32.6, 21.4, 7.7; GC-MS m/z 404 (M^+,75), 376 (23), 375 (100), 248 (17), 220 (10), 219 (39), 189 (20), 119 (11), 105 (13); anal. calcd for $C_{20}H_{21}IO$ (404.28) C, 59.42; H, 5.24; I, 31.39. Found C, 59.35; H, 5.10; I, 31.31.



(*Z*)-1-Butyl-1-ethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (3w). Yellow solid (yield = 82%): mp 84-86 °C; IR (KBr) 3058 (w), 2968 (s), 2936 (s), 2873 (m), 1641 (m), 1465 (s), 1441 (w), 1378 (w), 1291 (w), 1209 (m), 1005 (m), 1068 (m), 961 (m), 864 (m), 771 (m), 753 (m), 700 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.27 (m, 5H, aromatic), 7.26-7.18 (m, 1H, aromatic), 7.05 (d, J = 7.9 Hz, 1H, aromatic), 6.99 (td, J = 7.9, 0.8 Hz, 1H, aromatic), 6.42 (d , J = 7.9 Hz, 1H, aromatic), 2.14-1.93 (m, 2H, $C\mathit{H}_2CH_3$), 1.91-1.70 (m, 2H, $C\mathit{H}_2CH_2CH_2CH_3$), 1.44-1.15 (m, 4H, $CH_2C\mathit{H}_2C\mathit{H}_2CH_3$), 0.85 (t, J = 7.3 Hz, 3H, $CH_2C\mathit{H}_3$ or $CH_2CH_2CH_2C\mathit{H}_3$), 0.76 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_2C\mathit{H}_3$ or $CH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 147.8, 141.2, 131.7, 130.8, 128.8, 128.7, 128.1, 127.4, 122.8, 121.0, 92.4, 62.1, 39.4, 32.9, 25.4, 22.8, 14.0, 7.7; GC-MS m/z 418 (M^+, 80), 390 (22), 389 (100), 362 (20), 361 (95), 235 (13), 220 (14), 206 (14), 205 (68), 191 (11), 189 (11), 177 (18), 176 (30), 151 (12), 91 (21); anal. calcd for $C_{21}H_{23}IO$ (418.31) C, 60.30; H, 5.54; I, 30.34. Found C, 60.23; H, 5.61; I, 30.31.

Computational Details. All computations were carried out using the GAMESS suite of programs.[48] The 6-31G(d) basis set was used for all C and H atoms, and the SBKJC effective core potential and corresponding basis set (with polarization) was used for I.[49,50] Optimizations were carried out at RHF, MP2, and B3LYP levels of theory, all using Cs symmetry. Hessians were calculated at the RHF level of theory and showed zero imaginary frequencies. Zero point energies and corrections to 298 K were taken from this calculation. Table S4 gives the absolute energies obtained at each level of theory. The coordinates for each molecule are given below.

Table S4. Absolute and relative energies of *E* and *Z*- 1,1-diethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (**3u**)

	Z-isomer energy (Hartree)	*E*-isomer energy (Hartree)	*E-Z* (kcal/mol)	ΔH, *E-Z* (kcal/mol)
RHF	-816.6343792	-816.6282395	3.85	3.79
B3LYP	-821.5739791	-821.5681677	3.65	3.59
MP2	-819.3257530	-819.3194268	3.97	3.91
ZPE + H, kcal/mol	233.401	233.341	-0.06	

E-isomer

B3LYP:

COORDINATES OF SYMMETRY UNIQUE ATOMS (ANGS)

ATOM CHARGE X Y Z

C	6.0	-0.8055600665	0.0161259902	0.0000000000
C	6.0	-1.7671509728	1.1470834420	0.0000000000
C	6.0	-3.5825656905	3.2930583197	0.0000000000
C	6.0	4.2716544721	-1.8127070308	0.0000000000
C	6.0	4.1322900796	-0.4219757675	0.0000000000
C	6.0	2.8517944980	0.1229940982	0.0000000000
C	6.0	1.7106268746	-0.6946801037	0.0000000000
C	6.0	1.8541272392	-2.0882063610	0.0000000000
C	6.0	3.1390788020	-2.6341712549	0.0000000000
C	6.0	0.5344342842	0.1933022997	0.0000000000
C	6.0	2.4392828984	1.5751478133	0.0000000000
C	6.0	2.8765014465	2.3421515730	1.2679493169
C	6.0	-3.1295241762	2.7578019775	1.2082045126
C	6.0	2.4143254607	1.7272486097	2.5923502475
C	6.0	-2.2304040954	1.6911295238	1.2083160527
O	8.0	0.9850441970	1.4980858629	0.0000000000
I	53.0	-1.7205456159	-1.9121181713	0.0000000000
H	1.0	2.4899192073	3.3657466871	1.1834105793
H	1.0	3.9725433761	2.4181053556	1.2504414796
H	1.0	1.3218681410	1.6711379578	2.6352542946
H	1.0	2.7531962467	2.3412260742	3.4343236128
H	1.0	2.8136449078	0.7166929741	2.7304500089
H	1.0	-1.8811758803	1.2709227532	2.1478707327

H	1.0	-3.4778573902	3.1703043989	2.1518602958
H	1.0	3.2570105093	-3.7144316220	0.0000000000
H	1.0	5.2633759613	-2.2574908659	0.0000000000
H	1.0	0.9912244740	-2.7409174739	0.0000000000
H	1.0	5.0110226615	0.2184889007	0.0000000000
H	1.0	-4.2862583035	4.1217586345	0.0000000000

MP2:

COORDINATES OF SYMMETRY UNIQUE ATOMS (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	-0.8097088859	-0.0046101440	0.0000000000
C	6.0	-1.7425779271	1.1386897353	0.0000000000
C	6.0	-3.4892279278	3.3310361071	0.0000000000
C	6.0	4.2894331681	-1.7585811196	0.0000000000
C	6.0	4.1300798648	-0.3695357688	0.0000000000
C	6.0	2.8389482355	0.1520929369	0.0000000000
C	6.0	1.7114556599	-0.6832380371	0.0000000000
C	6.0	1.8700345611	-2.0765349247	0.0000000000
C	6.0	3.1662800907	-2.5970928143	0.0000000000
C	6.0	0.5327610024	0.1869562726	0.0000000000
C	6.0	2.4124052029	1.5888924513	0.0000000000
C	6.0	2.8295935166	2.3381469558	1.2670886282
C	6.0	-3.0529336692	2.7832664866	1.2103150895

C	6.0	2.3569814297	1.6711905171	2.5547613254
C	6.0	-2.1857789692	1.6893043573	1.2121138261
O	8.0	0.9555901642	1.5074225455	0.0000000000
I	53.0	-1.7163534598	-1.9179727253	0.0000000000
H	1.0	2.4232967575	3.3549358802	1.1979590253
H	1.0	3.9242134886	2.4291675319	1.2596656636
H	1.0	1.2682722626	1.5750140174	2.5539521895
H	1.0	2.6465076565	2.2702101843	3.4235037784
H	1.0	2.7934491795	0.6751529102	2.6696153399
H	1.0	-1.8445032493	1.2555567555	2.1502307502
H	1.0	-3.3908944690	3.2074699502	2.1532608851
H	1.0	3.3035640864	-3.6759951676	0.0000000000
H	1.0	5.2874523307	-2.1910613050	0.0000000000
H	1.0	1.0163540995	-2.7433357134	0.0000000000
H	1.0	4.9991516366	0.2867728359	0.0000000000
H	1.0	-4.1670889805	4.1815462223	0.0000000000

RHF:

COORDINATES OF SYMMETRY UNIQUE ATOMS (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	-0.7865181320	0.0140741022	0.0000000000
C	6.0	-1.7446864770	1.1559376585	0.0000000000
C	6.0	-3.5365488286	3.2908285895	0.0000000000

C	6.0	4.2594899136	-1.7928685738	0.0000000000
C	6.0	4.1141086496	-0.4160273522	0.0000000000
C	6.0	2.8367564861	0.1141006459	0.0000000000
C	6.0	1.7165209637	-0.7011900388	0.0000000000
C	6.0	1.8641343015	-2.0841382941	0.0000000000
C	6.0	3.1411116791	-2.6176056288	0.0000000000
C	6.0	0.5322635297	0.1887049340	0.0000000000
C	6.0	2.4152912199	1.5615068123	0.0000000000
C	6.0	2.8489120615	2.3292607913	1.2583933957
C	6.0	-3.0900410422	2.7568666311	1.1981098225
C	6.0	2.3926328207	1.7238497436	2.5843016044
C	6.0	-2.2013389094	1.6947290038	1.1974724644
O	8.0	0.9910222251	1.4654662430	0.0000000000
I	53.0	-1.7228368573	-1.8847080640	0.0000000000
H	1.0	2.4575079636	3.3383076688	1.1735544027
H	1.0	3.9327221915	2.4122188257	1.2447449373
H	1.0	1.3122755925	1.6533720225	2.6281032009
H	1.0	2.7175220808	2.3515001889	3.4080641407
H	1.0	2.8054620856	0.7334420146	2.7413471615
H	1.0	-1.8597836640	1.2786391365	2.1280943379
H	1.0	-3.4332656052	3.1652242326	2.1318997414
H	1.0	3.2663844820	-3.6850484492	0.0000000000
H	1.0	5.2428396642	-2.2275756449	0.0000000000

H	1.0	1.0191240964	-2.7386249414	0.0000000000
H	1.0	4.9794838317	0.2223582016	0.0000000000
H	1.0	-4.2281911085	4.1142717614	0.0000000000

Z-Isomer

B3LYP:

COORDINATES OF SYMMETRY UNIQUE ATOMS (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	2.6225569016	1.2298550856	2.5913569680
C	6.0	-1.9812901040	-1.9202877883	1.2090192274
C	6.0	-2.7031189729	-3.1145741603	1.2088271316
C	6.0	3.1888814923	1.7518077990	1.2678437752
C	6.0	2.6327650025	1.0678332442	0.0000000000
C	6.0	0.5327698737	0.0236995488	0.0000000000
C	6.0	-0.8134656237	-0.0598051656	0.0000000000
C	6.0	-1.6018135197	-1.3130000046	0.0000000000
C	6.0	3.8690192427	-2.5845263051	0.0000000000
C	6.0	2.6120884913	-3.2024122862	0.0000000000
C	6.0	1.4391206468	-2.4455629172	0.0000000000
C	6.0	1.5446521580	-1.0493554327	0.0000000000
C	6.0	2.8037461989	-0.4340374003	0.0000000000
C	6.0	-3.0636658201	-3.7155486695	0.0000000000

C	6.0	3.9722777063	-1.1903074720	0.0000000000
O	8.0	1.1805740697	1.2291157439	0.0000000000
I	53.0	-1.9482952687	1.7487220983	0.0000000000
H	1.0	-1.7009254338	-1.4500058118	2.1476683532
H	1.0	-2.9840065928	-3.5754531729	2.1524784112
H	1.0	2.9860390014	2.8266280055	1.1793155180
H	1.0	4.2817449882	1.6371446925	1.2541616313
H	1.0	1.5359978112	1.3575369913	2.6267905943
H	1.0	3.0542297427	1.7840727903	3.4324089332
H	1.0	2.8476276476	0.1678407187	2.7393019057
H	1.0	4.9484914669	-0.7112756215	0.0000000000
H	1.0	4.7695979231	-3.1930031357	0.0000000000
H	1.0	2.5466907486	-4.2872004590	0.0000000000
H	1.0	0.4724074028	-2.9342141980	0.0000000000
H	1.0	-3.6259687923	-4.6458427776	0.0000000000

MP2:

COORDINATES OF SYMMETRY UNIQUE ATOMS (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	2.6013914851	1.1583551357	2.5554773998
C	6.0	-1.9302290925	-1.8692420718	1.2125097555
C	6.0	-2.5863703122	-3.1014909532	1.2107834929
C	6.0	3.1799805643	1.7348446202	1.2673673328

C	6.0	2.6269922324	1.0812525798	0.0000000000
C	6.0	0.5143562411	0.0858139318	0.0000000000
C	6.0	-0.8368341650	0.0173613240	0.0000000000
C	6.0	-1.5814226195	-1.2522327671	0.0000000000
C	6.0	3.7915592366	-2.5803370296	0.0000000000
C	6.0	2.5201186216	-3.1734894366	0.0000000000
C	6.0	1.3563670147	-2.4010871060	0.0000000000
C	6.0	1.4946031410	-1.0055505223	0.0000000000
C	6.0	2.7643930369	-0.4132423060	0.0000000000
C	6.0	-2.9144024320	-3.7203219845	0.0000000000
C	6.0	3.9223526103	-1.1881419262	0.0000000000
O	8.0	1.1781256586	1.2879851521	0.0000000000
I	53.0	-1.9587919778	1.8090453534	0.0000000000
H	1.0	-1.6675518259	-1.3825219803	2.1497736270
H	1.0	-2.8463382864	-3.5777463522	2.1536127719
H	1.0	2.9659332854	2.8089858536	1.2043218294
H	1.0	4.2725992038	1.6240837052	1.2530141724
H	1.0	1.5126142170	1.2530822474	2.5595789956
H	1.0	2.9930577229	1.6969282333	3.4236747663
H	1.0	2.8592319837	0.1015737528	2.6674213804
H	1.0	4.9083298954	-0.7254655520	0.0000000000
H	1.0	4.6798301562	-3.2081115713	0.0000000000
H	1.0	2.4373615078	-4.2581058874	0.0000000000

H	1.0	0.3809643539	-2.8766974462	0.0000000000
H	1.0	-3.4260755327	-4.6799700979	0.0000000000

RHF:

COORDINATES OF SYMMETRY UNIQUE ATOMS (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	2.6172718645	1.2142650623	2.5842454040
C	6.0	-1.9668986097	-1.9142344324	1.1983029815
C	6.0	-2.7026175666	-3.0878139462	1.1988230371
C	6.0	3.1640723976	1.7406848282	1.2587593470
C	6.0	2.6151355151	1.0523405708	0.0000000000
C	6.0	0.5398805195	0.0091865315	0.0000000000
C	6.0	-0.7857400463	-0.0655215845	0.0000000000
C	6.0	-1.5831581124	-1.3193728584	0.0000000000
C	6.0	3.8732298197	-2.5683308222	0.0000000000
C	6.0	2.6302913716	-3.1928210630	0.0000000000
C	6.0	1.4625534989	-2.4506742643	0.0000000000
C	6.0	1.5606908878	-1.0638702797	0.0000000000
C	6.0	2.7982894826	-0.4461206283	0.0000000000
C	6.0	-3.0705523102	-3.6783092399	0.0000000000
C	6.0	3.9671166039	-1.1868149629	0.0000000000
O	8.0	1.1903042847	1.1885992669	0.0000000000
I	53.0	-1.9131924489	1.7289801813	0.0000000000

H	1.0	-1.6847956574	-1.4545366553	2.1281065380
H	1.0	-2.9886515192	-3.5384836406	2.1322652342
H	1.0	2.9382259034	2.7990887031	1.1745364480
H	1.0	4.2472932391	1.6497998273	1.2447975950
H	1.0	1.5392501798	1.3147975502	2.6281362587
H	1.0	3.0365225669	1.7832200191	3.4079889896
H	1.0	2.8701335590	0.1713920797	2.7412609396
H	1.0	4.9297009862	-0.7072508713	0.0000000000
H	1.0	4.7680103531	-3.1644446886	0.0000000000
H	1.0	2.5749833401	-4.2662658852	0.0000000000
H	1.0	0.5125247211	-2.9448931354	0.0000000000
H	1.0	-3.6432163113	-4.5883659681	0.0000000000

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(33) The structures of iodocyclization products **2c** and **3u** were unequivocally confirmed by X-ray diffraction analysis. The structures of all other regioisomeric products **2** and **3** were determined by spectroscopic techniques, and confirmed by comparison with compounds **2c** and **3u**, respectively. See the Experimental Section for details.

(34) The possibility of base-promoted cyclization, followed by iodination of the resulting vinylic ethers, was examined. The 2-(1-alkynyl)benzylic alcohol substrates **1a**, **1s** and

1w were subjected to our usual cyclization conditions omitting iodine. In all of these cases, no cyclization was observed and the starting materials were recovered.

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CHAPTER 4. Solution Phase Parallel Synthesis of a Multi-substituted Cyclic Imidate Library

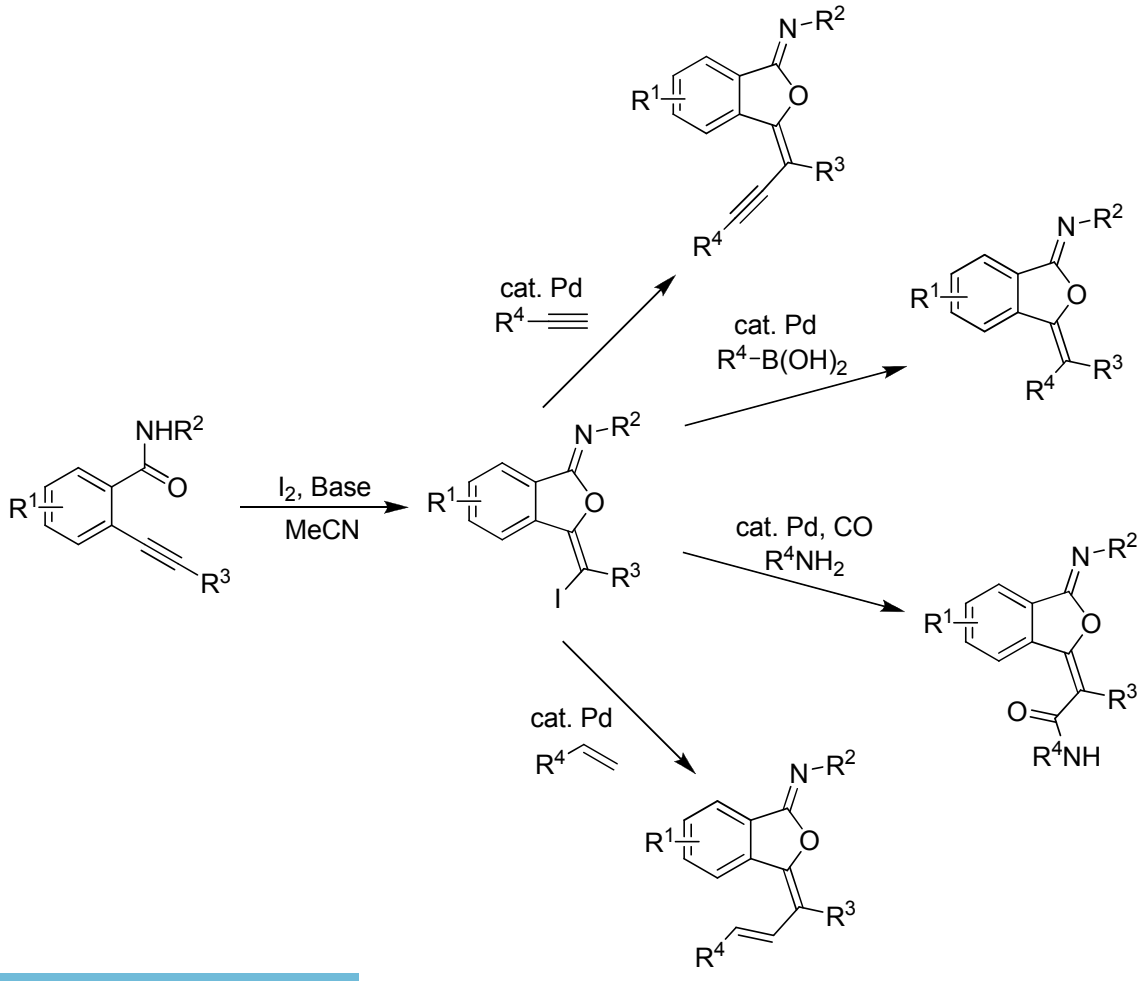
Based on a paper to be published in the *Journal of Combinatorial Chemistry*[22]

Saurabh Mehta,[a] *Jesse P. Waldo,*[a] *Benjamin Neuenswander,*[b] *Gerald H. Lushington,*[b] *and Richard C. Larock*,*[a]

[a]Department of Chemistry, Iowa State University, Ames, Iowa 50011. [b]The University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development, Lawrence, Kansas 66047

larock@iastate.edu

Abstract

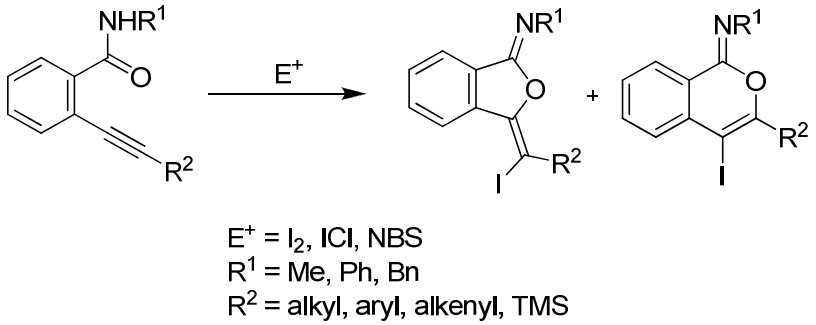


The solution-phase parallel synthesis of a 71 member diverse library of multi-substituted cyclic imidates is described. The key intermediates, 3-iodomethylene-containing cyclic imidates, are readily prepared in good to excellent yields by the palladium/copper-catalyzed cross-coupling of various *o*-iodobenzamides and terminal alkynes, followed by electrophilic cyclization with I_2. These cyclic imidates were further functionalized by palladium-catalyzed Suzuki-Miyaura, Sonogashira, carbonylative amidation and Heck chemistry using sublibraries of commercially available building blocks.

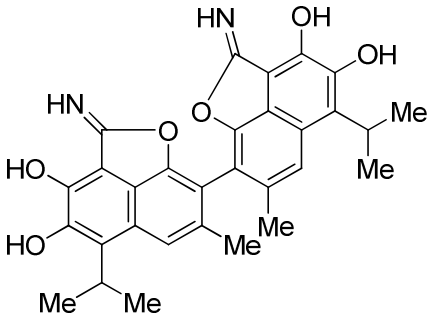
Introduction

Heterocyclic compounds are of great importance in a variety of areas, including medicinal chemistry, materials chemistry *etc*. There has been an increasing demand for new and efficient strategies for the synthesis of important heterocyclic ring systems for the purpose of exploring their potential applications in pharmaceuticals and other relevant areas. We have previously reported the generation of various important heterocycles and carbocycles through very efficient electrophilic cyclization chemistry using halogen, sulfur and selenium electrophiles.[1] In particular, we have recently found that the iodocyclization of 2-alkynyl benzamides leads to formation of the corresponding cyclic imidates, also known in the literature as iminolactones (Scheme 1),[2] where electrophilic attack occurs on oxygen rather than nitrogen.[3,4]

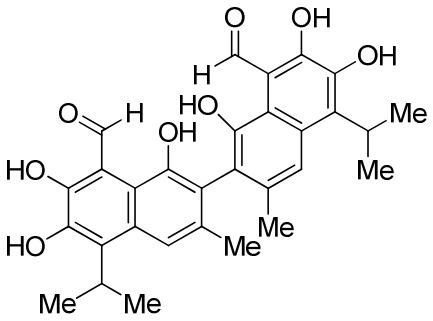
Scheme 1. Synthesis of Cyclic Imidates by Electrophilic Cyclization



Over the years, several groups have reported various synthetic routes to cyclic imidates/iminolactones.[5] In a few cases, the biological potential of this heterocyclic scaffold has also been investigated. For example, gossylic iminolactone (GIL, **I**) derived from the natural product Gossypol (**II**) has been found to exhibit anti-HIV activity.[6] As a part of our ongoing library generation program,[7] we continued to further incorporate diversity into the cyclic imidate/iminolactone heterocyclic ring system to study the biological profile of the resulting imidates. Here we report our studies on the solution phase synthesis of a 71 member diverse library of these cyclic imidates.



GIL (**I**)

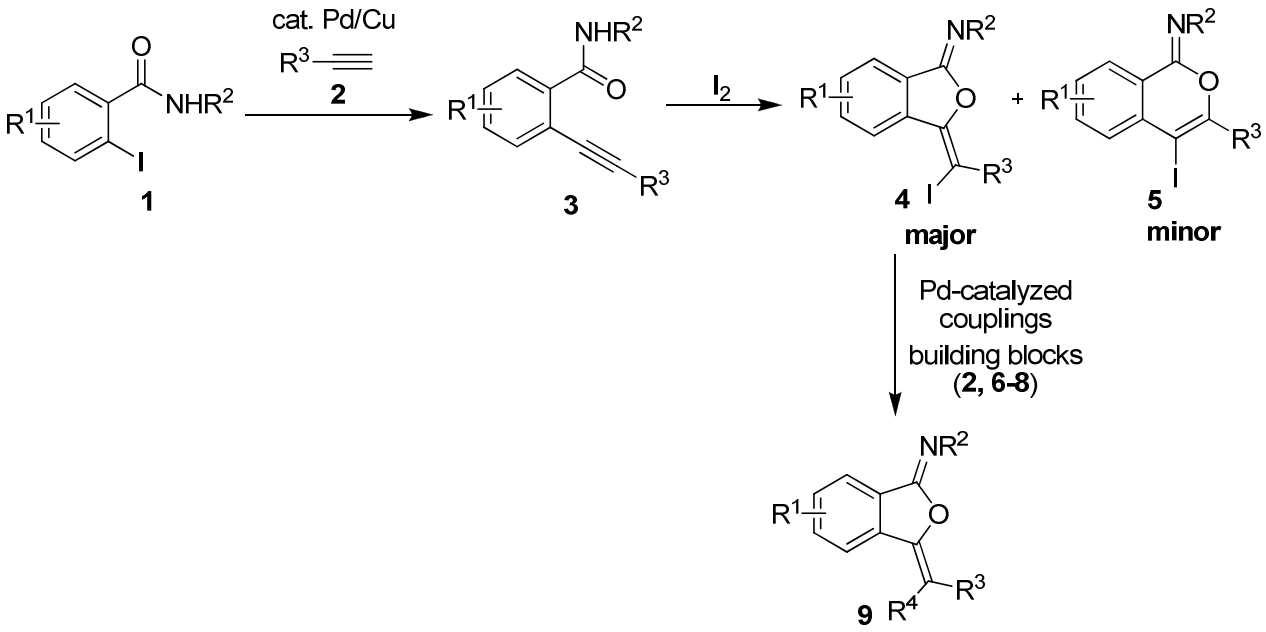


Gossypol (**II**)

Results and Discussion

Our strategy for library production is shown in Scheme 2. We anticipated that our previously described iodocyclization process should readily afford trisubstituted 3-iodomethylene-containing cyclic imidates (**4**) as key intermediates. Further functionalization can be achieved by taking advantage of the iodine handle present on the exocyclic double bond at the 3-position, through various coupling reactions to generate a library with four points of diversity.

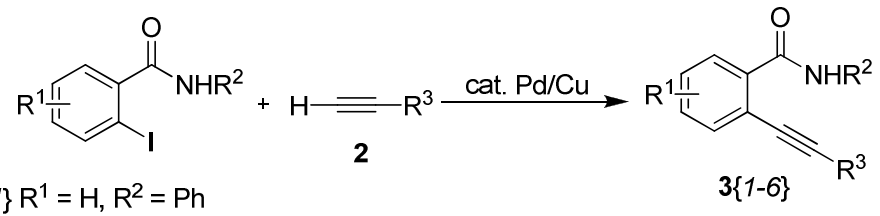
Scheme 2. Library Design for Tetrasubstituted Cyclic Imidates



The starting *o*-iodobenzamides (**1**) were conveniently prepared from the corresponding commercially available carboxylic acids by first refluxing the acid with thionyl chloride, followed by reaction with the corresponding amine in the same pot.[2,8] The alkynes **3** required for cyclization are readily prepared by the palladium/copper-catalyzed

Sonogashira cross-coupling[9] of the *o*-iodobenzamides **1** with terminal alkynes **2** and the results are summarized in Table 1. As shown in the Table, the requisite alkynes **3**{*1-6*} are readily obtained in good to excellent yields by this straightforward approach.

Table 1. Library Data for the 2-(1-Alkynyl)benzamides **3**{*1-6*}



1{*1*} R^1 = H, R^2 = Ph
1{*2*} R^1 = H, R^2 = PMB
1{*3*} R^1 = 4,5-$(OMe)_2$, R^2 = Me

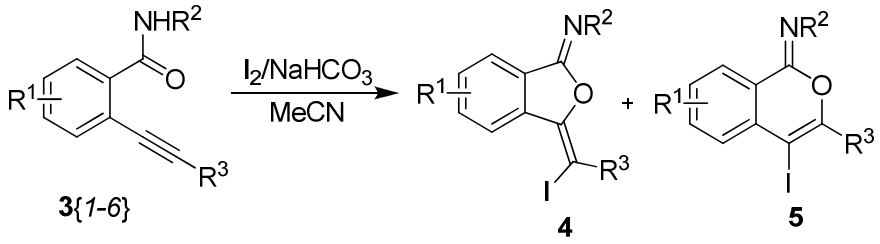
compd[a]	R^1	R^2	R^3	yield[b] (%)
3{*1*}	H	Ph	*n*-Pr	91
3{*2*}	H	Ph	TMS	76
3{*3*}	4,5-$(MeO)_2$	PMB	TMS	96
3{*4*}	4,5-$(MeO)_2$	Me	Ph	87
3{*5*}	4,5-$(MeO)_2$	Me	2-pyr	76
3{*6*}	4,5-$(MeO)_2$	Me	2-thienyl	83

[a]All reactions were carried out on a 5.0 mmol scale using 1.2 equiv of the alkyne, 2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI and DIPA (4 equiv) in DMF (25 mL) at 65 °C (see the Supporting Information for the detailed procedures). [b]Isolated yields after column chromatography.

As the key step in our library synthesis, variously substituted iodo cyclic imidates **4** have been efficiently prepared within 1-2 h by electrophilic cyclization of the corresponding *o*-(1-alkynyl)benzamides **3**{*1-6*} using $I_2/NaHCO_3$ in MeCN at ambient temperature (Table

2). All of the cyclized products **4** have been purified by column chromatography. The reaction works well for all substrates containing alkyl, aryl, TMS or heteroaryl groups at the distal end of the carbon-carbon triple bond. It is noteworthy that in the presence of electron-donating methoxy groups on the amide phenyl ring **3**{*3-6*}, only one regioisomer was isolated exclusively. In fact, the electron-donating effect of the *para* methoxy group (with respect to the alkyne) should increase the electron density on C-2 of the arylethynyl group, thus favoring intramolecular nucleophilic attack of the amide oxygen on C-1. The structure of the cyclized iodo imidates **4**{*2*} and **4**{*4*} has been confirmed by single crystal X-ray crystallography (see the Supporting Information).

Table 2. Library Data for Compounds **4**{*1-6*}

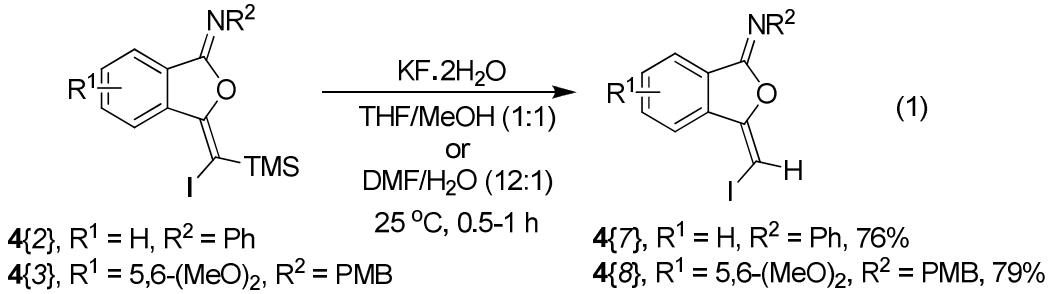


3{*1-6*} **4** **5**

compd[a]	R^1	R^2	R^3	yield[b] (%) **4** + **5**
4{*1*}	H	Ph	*n*-Pr	92 + 6
4{*2*}	H	Ph	TMS	77 + 7
4{*3*}	5,6-$(MeO)_2$	PMB	TMS	80 + 0
4{*4*}	5,6-$(MeO)_2$	Me	Ph	79 + 0
4{*5*}	5,6-$(MeO)_2$	Me	2-py	91 + 0
4{*6*}	5,6-$(MeO)_2$	Me	2-thienyl	93 + 0

[a]All reactions were carried out on a 4.0 mmol scale using I_2 (3 equiv) and $NaHCO_3$ (3 equiv) in MeCN (20 mL) at 25 °C for 1-2 h. [b]Isolated yields after column chromatography.

Furthermore, the trimethylsilyl-containing cyclic imidates **4**{*2*} and **4**{*3*} were treated with fluoride to afford the corresponding deprotected cyclic imidates **4**{*7*} and **4**{*8*} respectively, in good yields (eq 1).



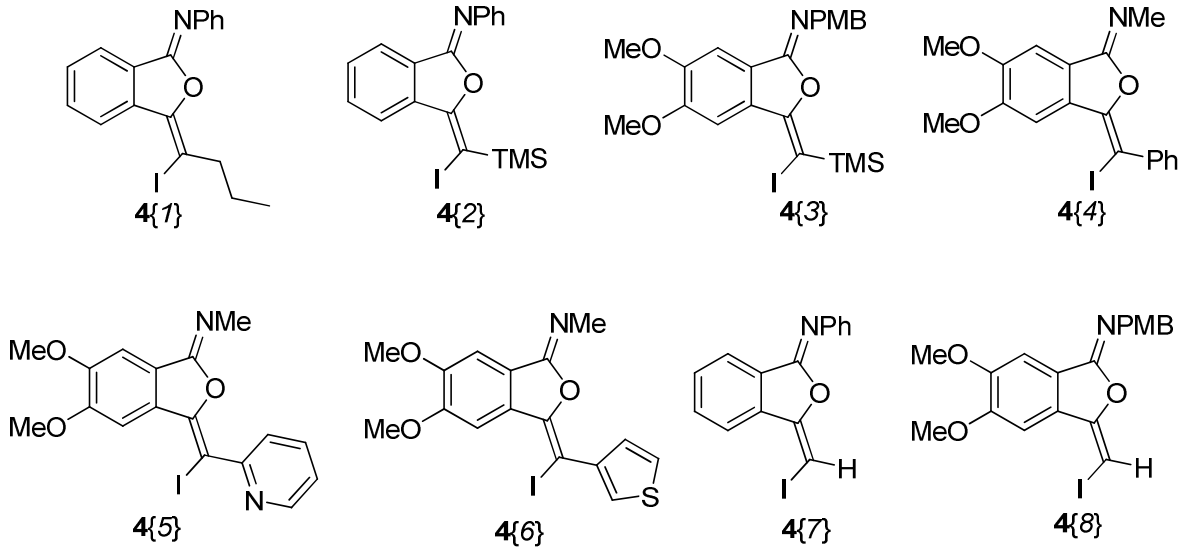
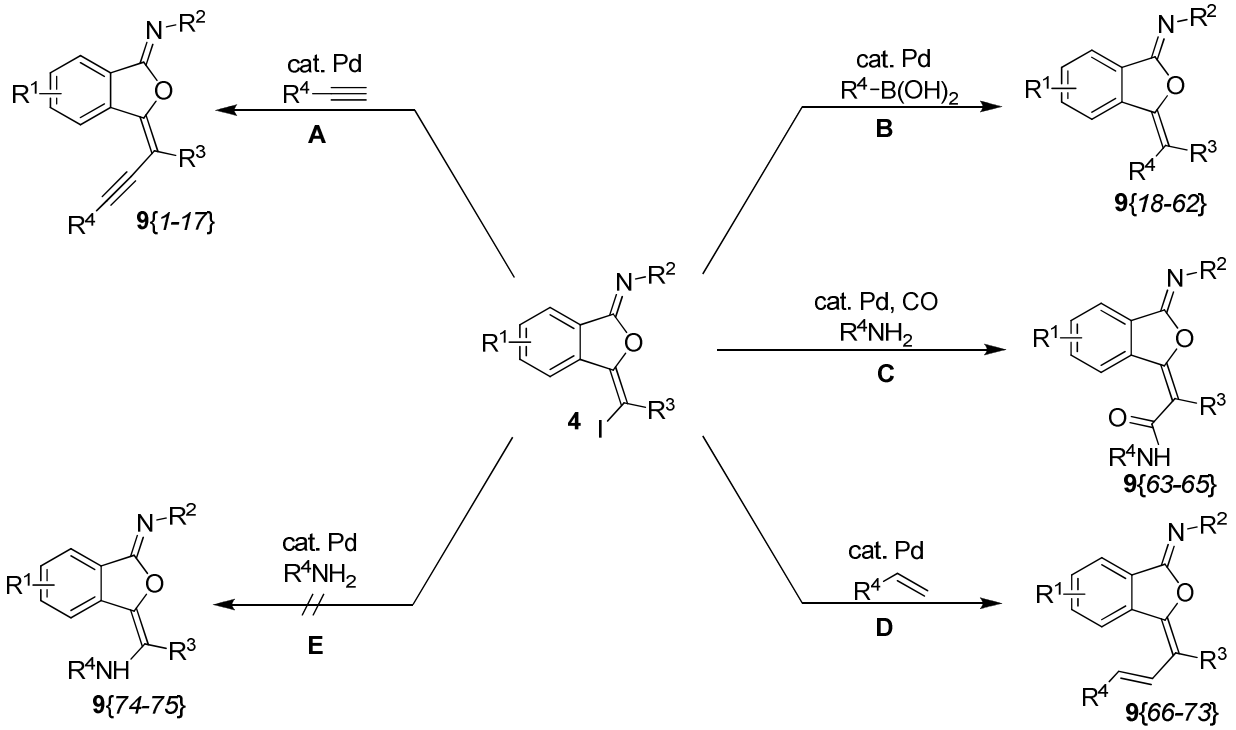


Figure 2. Sublibrary of 3-Iodomethylene-containing Cyclic Imidates **4**{*1-8*}.

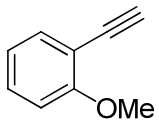
The 3-iodomethylene-containing cyclic imidates **4** can be further elaborated by using a variety of palladium-catalyzed processes, such as Sonogashira coupling,[9] Suzuki-Miyaura coupling,[10] carbonylative amidation,[11] Heck coupling,[12] and amination[13] (Scheme 4). The reagents used (*e.g.* boronic acids **6**, terminal alkynes **2**, styrenes **7**, and amines **8**) for substitution of the iodine-containing products **4** were chosen on the basis of their commercial availability, functional group diversity and potential drug-like properties (Figure 3). This could result in a library of ~1300 theoretically possible products. This number was arrived at by determining all possible combinations of the R group and available starting materials. However, only a small subset of 71 compounds out of these 1300 virtual structures was actually prepared in the laboratory. The crude products **9** were analyzed by LC/MS, followed by purification by either column chromatography or preparative HPLC. The results of this parallel library synthesis are summarized in Table 3, which indicates that the products **9** can be obtained in modest to good yields with high purities.

Scheme 4. Synthesis of Cyclic Imidates **9** Using Various Palladium-catalyzed Reactions[a]

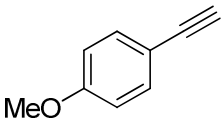


[a]Method A (Sonogashira coupling): 3 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, DIPA (4 equiv), $R^4C{\equiv}CH$ (**2**, 1.2 equiv), DMF, 70 °C, 2 h. Method B (Suzuki-Miyaura coupling): 5 mol % $PdCl_2$, $KHCO_3$ (1.4 equiv), $R^4B(OH)_2$ (**6**, 1.2 equiv), 4:1 DMF/H_2O, 80 °C, 2 h. Method C (carbonylative amidation): CO (1 atm), 5 mol % $PdCl_2(PPh_3)_2$, R^4NH_2 (**7**, 0.25 mL), DMF, 65 °C, 3-6 h. Method D (Heck coupling): 5 mol % $Pd(OAc)_2$, *n*-Bu_4NCl (1.0 equiv), Na_2CO_3 (2.5 equiv), $R^4CH{=}CH_2$ (**8**, 4 equiv), DMF, 85 °C, 5-24 h. Method E (amination): 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 5 mol % BINAP, *t*-BuONa (1.4 equiv), R^4NH_2 (**7**, 1.2 equiv), DMF, 80 °C, 2.5 h.

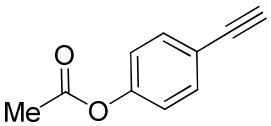
Alkyne Sublibrary



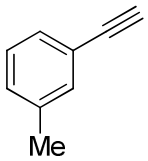
2{*1*}



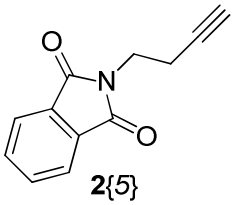
2{*2*}



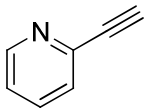
2{*3*}



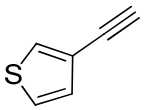
2{*4*}



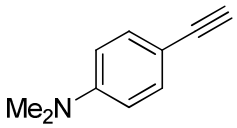
2{*5*}



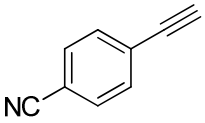
2{*6*}



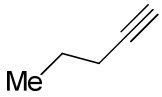
2{*7*}



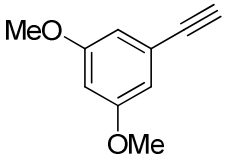
2{*8*}



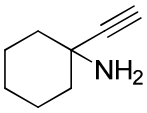
2{*9*}



2{*10*}

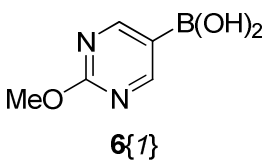


2{*11*}

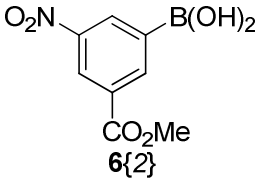


2{*12*}

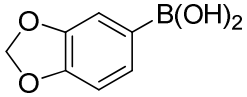
Boronic Acid and Boronate Ester Sublibrary



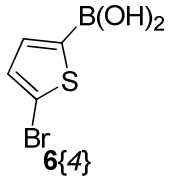
6{*1*}



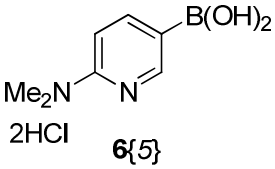
6{*2*}



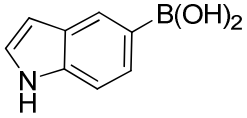
6{*3*}



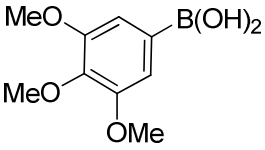
6{*4*}



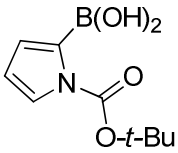
6{*5*}



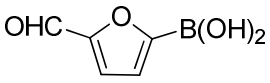
6{*6*}



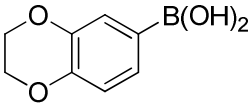
6{*7*}



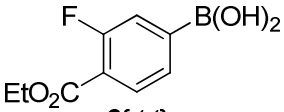
6{*8*}



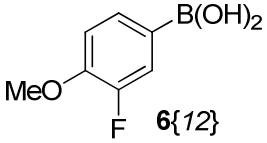
6{*9*}



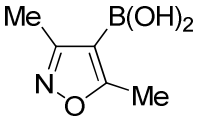
6{*10*}



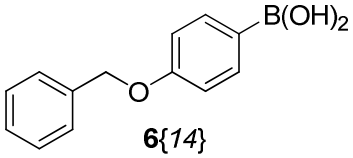
6{*11*}



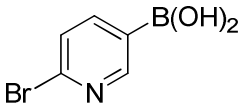
6{*12*}



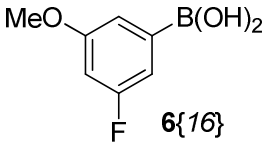
6{*13*}



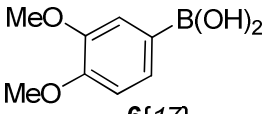
6{*14*}



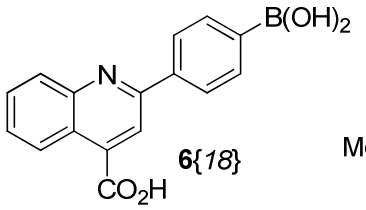
6{*15*}



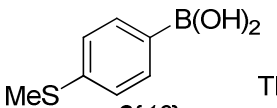
6{*16*}



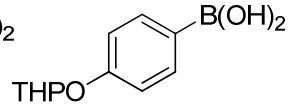
6{*17*}



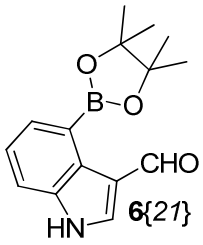
6{*18*}



6{*19*}

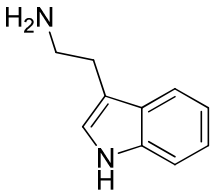


6{*20*}

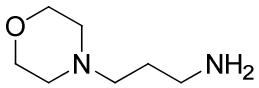


6{*21*}

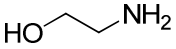
Amine Sublibrary



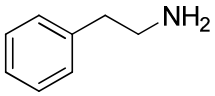
7{*1*}



7{*2*}

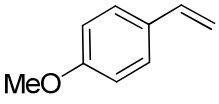


7{*3*}

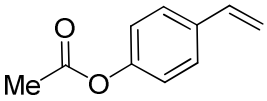


7{*4*}

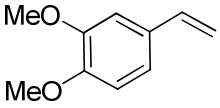
Styrene Sublibrary



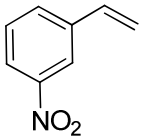
8{*1*}



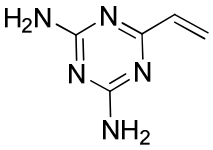
8{*2*}



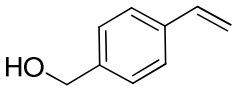
8{*3*}



8{*4*}



8{*5*}



8{*6*}

Figure 3. Diverse terminal alkynes **2**{*1-12*}, boronic acids **6**{*1-2*}, boronate ester **6**{*21*}, amines **7**{*1-4*}, and styrenes **8**{*1-6*} used for library synthesis.

Table 3. Library Data for Compounds **9**{*1-75*}

compd	**4**	R^4	method[a]	yield[b] (%)	purity[c] (%)
9{*1*}	**4**{*1*}	**2**{*1*}	A	34	89
9{*2*}	**4**{*1*}	**2**{*5*}	A	26	98
9{*3*}	**4**{*1*}	**2**{*7*}	A	30	98
9{*4*}	**4**{*1*}	**2**{*8*}	A	34	100
9{*5*}	**4**{*1*}	**2**{*9*}	A	27	97

9{*6*}	**4**{*1*}	**2**{*10*}	A	21	99
9{*7*}	**4**{*1*}	**2**{*11*}	A	14	100
9{*8*}	**4**{*1*}	**2**{*12*}	A	8	91
9{*9*}	**4**{*6*}	**2**{*4*}	A	51	87
9{*10*}	**4**{*6*}	**2**{*6*}	A	19	89
9{*11*}	**4**{7}	**2**{*1*}	A	55	97
9{*12*}	**4**{7}	**2**{*2*}	A	59	100
9{*13*}	**4**{7}	**2**{*3*}	A	38	91
9{*14*}	**4**{7}	**2**{*4*}	A	63	80
9{*15*}	**4**{7}	**2** {*5*}	A	16	97
9{*16*}	**4**{7}	**2** {*6*}	A	69	100
9{*17*}	**4**{7}	**2** {*7*}	A	8	98
9{*18*}	**4**{*1*}	**6**{*1*}	B	43	100
9{*19*}	**4**{*1*}	**6**{*2*}	B	28	100
9{*20*}	**4**{*1*}	**6**{*3*}	B	62	99
9{*21*}	**4**{*1*}	**6**{*4*}	B	7	94
9{*22*}	**4**{*1*}	**6**{*5*}	B	52	100
9{*23*}	**4**{*1*}	**6**{*6*}	B	73	100
9{*24*}	**4**{*1*}	**6**{*7*}	B	67	100
9{*25*}	**4**{*1*}	**6**{*9*}	B	25	98
9{*26*}	**4**{*1*}	**6**{*10*}	B	59	99
9{*27*}	**4**{*1*}	**6**{*11*}	B	62	100

9{*28*}	**4**{*1*}	**6**{*12*}	B	78	100
9{*29*}	**4**{*1*}	**6**{*13*}	B	16	100
9{*30*}	**4**{*1*}	**6**{*14*}	B	64	61
9{*31*}	**4**{*1*}	**6**{*15*}	B	13	98
9{*32*}	**4**{*1*}	**6**{*17*}	B	52	95
9{*33*}	**4**{*1*}	**6**{*18*}	B	7	100
9{*34*}	**4**{*1*}	**6**{*20*}	B	49	99
9{*35*}	**4**{*4*}	**6**{*1*}	B	30	100
9{*36*}	**4**{*4*}	**6**{*10*}	B	28	97
9{*37*}	**4**{*4*}	**6**{*16*}	B	92	58
9{*38*}	**4**{*5*}	**6**{*6*}	B	15	84
9{*39*}	**4**{*5*}	**6**{*10*}	B	32	64
9{*40*}	**4**{*5*}	**6**{*14*}	B	26	54
9{*41*}	**4**{*5*}	**6**{*16*}	B	36	60
9{*42*}	**4**{*6*}	**6**{*1*}	B	22	94
9{*43*}	**4**{*6*}	**6**{*6*}	B	30	84
9{*44*}	**4**{*6*}	**6**{10}	B	39	93
9{*45*}	**4**{*6*}	**6**{*19*}	B	32	81
9{*46*}	**4**{7}	**6**{*1*}	B	27	100
9{*47*}	**4**{7}	**6**{*2*}	B	33	96
9{*48*}	**4**{7}	**6**{*3*}	B	57	88
9{*49*}	**4**{7}	**6**{*4*}	B	18	95

9{*50*}	**4**{7}	**6** {*5*}	B	43	98
9{*51*}	**4**{7}	**6**{*6*}	B	29	93
9{52}	**4**{7}	**6**{*7*}	B	14	71
9{*53*}	**4**{7}	**6**{*8*}	B	25	98
9{*54*}	**4**{7}	**6**{*9*}	B	52	98
9{*55*}	**4**{7}	**6**{*10*}	B	32	87
9{*56*}	**4**{7}	**6**{*11*}	B	48	100
9{*57*}	**4**{7}	**6**{*12*}	B	38	82
9{*58*}	**4**{7}	**6**{*13*}	B	7	75
9{*59*}	**4**{7}	**6**{*14*}	B	34	85
9{*60*}	**4**{7}	**6**{*15*}	B	43	91
9{*61*}	**4**{7}	**6**{*20*}	B	36	99
9{*62*}	**4**{7}	**6**{*21*}	B	4	81
9{*63*}	**4**{*1*}	**7**{*2*}	C	0	
9{*64*}	**4**{*1*}	**7**{*3*}	C	14	90
9{*65*}	**4**{*1*}	**7**{*4*}	C	0	
9{*66*}	**4**{*1*}	**8**{*1*}	D	41	85
9{*67*}	**4**{*1*}	**8**{*2*}	D	50	95
9{*68*}	**4**{*1*}	**8**{*3*}	D	46	86
9{*69*}	**4**{*1*}	**8**{*4*}	D	20	92
9{*70*}	**4**{*1*}	**8**{*5*}	D	10	96
9{*71*}	**4**{7}	**8**{*2*}	D	50	80

9{*72*}	**4**{7}	**8**{*5*}	D	14	100
9{*73*}	**4**{7}	**8**{*6*}	D	31	78
9{*74*}	**4**{7}	**7**{*1*}	E	0	
9{*75*}	**4**{7}	**7**{*2*}	E	0	

[a]Method A, Sonogashira coupling; B, Suzuki-Miyaura coupling; C, carbonylative amidation; D Heck coupling; E, amination. [b]Isolated yield after preparative HPLC. [c]UV purity determined at 214 nm after preparative HPLC.

Sonogashira coupling of the 3-iodomethylene-containing cyclic imidates **4** with various terminal acetylenes **2** affords the corresponding alkynyl products **9**{*1-17*} (method A). Suzuki-Miyaura coupling of the 3-iodomethylene-containing cyclic imidates **4** with various arylboronic acids **6** proceeded smoothly to give the desired products **9**{*18-62*} in modest yields. Most reactions were complete within 2 h at 80 ^{o}C in DMF (method B). The reaction was also examined using a boronate ester **6**{*21*}. However, the yield of the isolated compound **9**{*62*} was very low in this case. The structure of one of the products from the Suzuki-Miyaura coupling **9**{*24*} was confirmed using single crystal X-ray crystallography (see the Supporting Information for details). The stereochemistry around the C-C and C-N double bonds was found to be preserved during the Suzuki-Miyaura cross-coupling. Next, in an effort to synthesize amide-containing cyclic imidates, carbonylative amidation of the 3-iodomethylene-containing cyclic imidates **4** using one atmosphere of carbon monoxide and various amines **7** in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ was investigated (method C). However, the reaction product was isolated in only one case **9**{*64*} and only in low yield. Furthermore, by allowing the compounds **4** to react under Heck reaction conditions in the presence of the styrenes **8**, we obtained the substituted olefin-containing

cyclic imidate products **9**{*66-73*} (method D). Palladium-catalyzed amination reactions have also been attempted to introduce amino substituents into the library (method E). However, the reaction did not proceed well and the process resulted in complex reaction mixtures.

Because of our interest in the synthesis of potentially biologically active heterocycles for their use in high-throughput screening, an *in silico* evaluation of the library members was carried out to check their conformity with Lipinski's "rule of five" and Veber's rules.[14,15] The molecular weight, clog P, number of hydrogen bond donors and acceptors, and the number of rotatable bonds were calculated for each of the library members using the SYBYL program.[16] Most of the 71 cyclic imidate library members were found to be either Lipinski compliant or had only one violation. In addition, the cell monolayer absorption model Caco-2, a parameter indicating the ability of a compound to passively permeate epithelial cells, *i.e* skin and muscle sheaths, was also calculated.[17] The mean values, as well as the range of these parameters for this cyclic imidate library, is provided in Table 4.

Table 4. *In silico* Data for Lipinski and Cell Permeability Parameters

parameter	mean	range	optimum value
mol. weight	391.3	315.3-510.6	≤ 500
H-bond acceptors	3.9	2 -7	≤ 10
H-bond donors	1.5	1-3	≤ 5
C log *P*	5.7	2.9-9.2	≤ 5.0
rotatable bonds	4.8	2-7	≤ 10
Caco-2	1.2	0.2-2.1	≥ 0.4

Conclusions

A highly substituted 71 member library of cyclic imidates **9** with four points of diversity has been synthesized. 3-Iodomethylene-containing cyclic imidates **4** are readily prepared by iodocyclization chemistry. We have demonstrated the diversification of these 3-iodomethylene-containing cyclic imidates **4** with various building blocks, for example, terminal alkynes **2,** boronic acids **6**, carbon monoxide plus amines **7**, and styrenes **8**, to construct a diverse library through a variety of C-C bond forming reactions. The cyclic imidate library members **9** will be evaluated against various biological screens by the National Institutes of Health Molecular Library Screening Center Network.

Experimental Section

General Information

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm).

HRMS Data for Compounds 3{*1-6*} and 4{*1-8*}: The electron impact ionization experiments were performed on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA) fitted with a Finnigan EI/CI ion source. The samples were introduced to the mass spectrometer using a solids probe. The probe was heated gradually from 100 to 400 ^{o}C. The instrument was used as a single quadrupole and scanned from 50 to

1000 daltons. Accurate mass measurements were conducted using a manual peak matching technique on a KRATOS MS50 double focusing mass spectrometer.

General Methods Used for Analysis and Purification of the Library Members 9{*1-75*}. HPLC analysis was carried out using an XBridge MS C-18 column (5 μM, 4.6 × 150 mm) with gradient elution (5% CH_3CN to 100% CH_3CN) on a Waters Alliance 2795 Separation Module with a Waters 2996 Photodiode Array UV detector and a Waters/Micromass LCT Premier (TOF) detector. Purification was performed using an XBridge MS C-18 column (5 μM, 19 × 150 mm) with gradient elution (a narrow CH_3CN gradient was chosen based on the targets retention time from LCMS analysis of the crude sample) on a Mass Directed Fractionation instrument with a Waters 2767 sample manager, a Waters 2525 HPLC pump, a Waters 2487 dual λ absorbance detector, and a Waters/Micromass ZQ (quadrupole) detector. Fractions were triggered using an MS and/or UV threshold determined by an LCMS analysis of the crude sample. One of three aqueous mobile phases were chosen for both analysis and purification to promote the targets neutral state (water, 0.05% formic acid or pH 9.8 1mM HCO_2NH_4). High resolution mass spectra (HRMS) were obtained using a Waters/Micromass LCT Premier (TOF instrument).

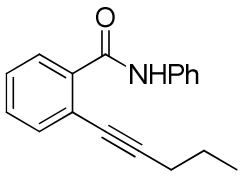
Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

Solvents. All solvents were used directly as obtained commercially, except for DCM which was distilled over CaH_2.

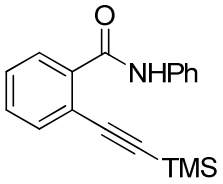
General Sonogashira Coupling Procedure Used for Preparation of the 2-(1-Alkynyl)benzamides 3{*1-6*}.

To a solution of the appropriate *o*-iodobenzamide **1** (5.0 mmol) in DMF (20 mL) were added $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (1 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (4.0 equiv) was added by syringe. The reaction mixture was then heated to 65 °C. A solution of alkyne **2** (1.2 equiv) in DMF (5 mL) was added dropwise over 10 min, and the mixture was allowed to stir at 65 ^oC for 2 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane-EtOAc as eluent.

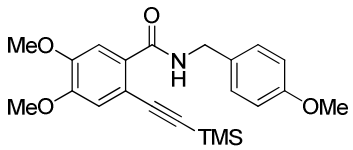
Characterization Data for the 2-(1-Alkynyl)benzamides 3{*1*-*6*}.



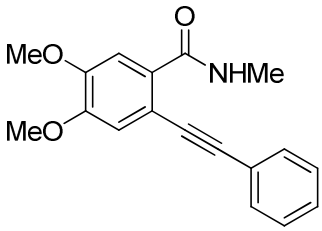
Benzamide 3{*1*}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3H), 1.53-1.59 (m, 2H), 2.40 (t, J = 7.2 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.27-7.33 (m, 4H), 7.41-7.43 (m, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.95-7.97 (m, 1H), 9.43 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 21.5, 21.9, 79.2, 97.9, 119.8, 120.2, 124.1, 128.0, 128.8, 129.7, 130.5, 133.5, 135.5, 138.0, 164.4; HRMS Calcd for $C_{18}H_{17}NO$: 263.13101. Found: 263.13162.



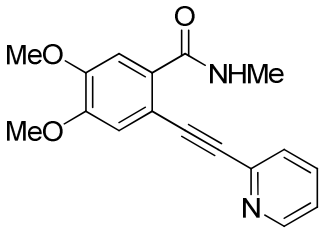
Benzamide 3{*2*}. The spectral properties were identical to those previously reported.[2]



Benzamide 3{*3*}. The spectral properties were identical to those previously reported.[2]

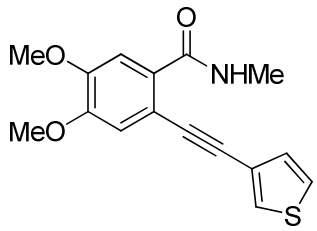


Benzamide 3{*4*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (d, J = 4.8 Hz, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.01 (s, 1H), 7.39-7.41 (m, 3H), 7.51-7.53 (m, 2H), 7.65 (br s, 1H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 56.2, 56.3, 88.1, 94.5, 112.1, 112.7, 115.1, 122.4, 128.8, 129.05, 129.13, 131.5, 149.6, 150.5, 166.6; HRMS Calcd for $C_{18}H_{17}NO_3$: 295.12084. Found: 295.12139.



Benzamide 3{*5*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (d, J = 4.8 Hz, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 7.09 (s, 1H), 7.28-7.32 (m, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.63 (br s, 1H), 7.67 (s, 1H), 7.73 (t, J = 7.6 Hz, 1H), 8.66 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2,

56.3, 56.4, 87.8, 93.6, 111.1, 112.9, 115.4, 123.4, 126.9, 130.1, 136.5, 142.9, 150.2, 150.5, 150.6, 166.4; HRMS Calcd for $C_{17}H_{16}N_2O_3$: 296.11609. Found: 296.11664.

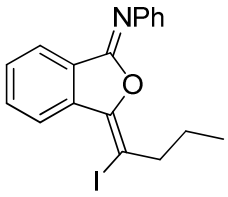


Benzamide 3{*6*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (d, J = 4.8 Hz, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.99 (s, 1H), 7.19 (dd, J = 1.2, 4.8 Hz, 1H), 7.36-7.38 (m, 1H), 7.56 (dd, J = 1.2, 3.2 Hz, 1H), 7.60 (br s, 1H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 56.26, 56.30, 87.7, 89.7, 112.1, 112.7, 115.0, 121.4, 126.2, 128.9, 129.4, 129.6, 149.6, 150.5, 166.6; HRMS Calcd for $C_{16}H_{15}NO_3S$: 301.07726. Found: 301.07786.

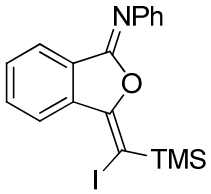
General Iodocyclization Procedure Used for Preparation of the Cyclic Imidates 4{*1*-*6*}.[2]

To a solution of the starting alkyne **3** (4.0 mmol) in MeCN (20 mL) were added I_2 (3.0 equiv) and $NaHCO_3$ (3.0 equiv). The reaction mixture was allowed to stir at 25 °C and the reaction was monitored by TLC for completion. The excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexane-EtOAc as the eluent.

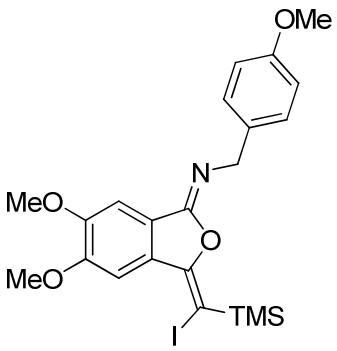
Characterization Data for the 3-Iodomethylene-containing Cyclic Imidates 4{*1-8*}



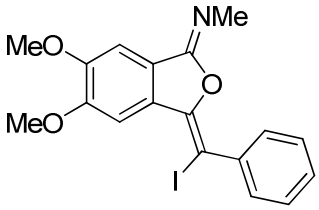
Imidate 4{*1*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 3H), 1.56-1.62 (m, 2H), 2.81 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.42-7.51 (m, 4H), 7.94 (d, J = 7.2 Hz, 1H), 8.56 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 22.5, 41.6, 82.2, 123.7, 123.9, 124.2, 124.8, 128.7, 129.9, 131.6, 132.2, 135.3, 145.5, 147.3, 152.1; HRMS Calcd for $C_{18}H_{16}INO$: 389.02766. Found: 389.02853.



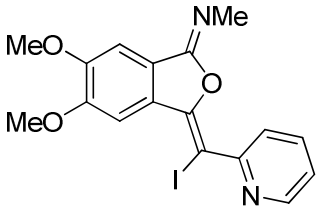
Imidate 4{*2*}. The spectral properties were identical to those previously reported.[2]



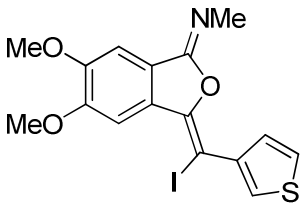
Imidate 4{*3*}. The spectral properties were identical to those previously reported.[2]



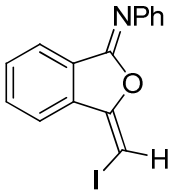
Imidate 4{*4*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 7.25-7.29 (m, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 56.46, 56.53, 71.6, 103.9, 106.9, 125.3, 128.0, 128.2, 129.5, 130.4, 140.7, 147.3, 151.8, 154.8 (one signal missing due to overlap); HRMS Calcd for $C_{18}H_{16}INO_3$: 421.01749. Found: 421.01870.



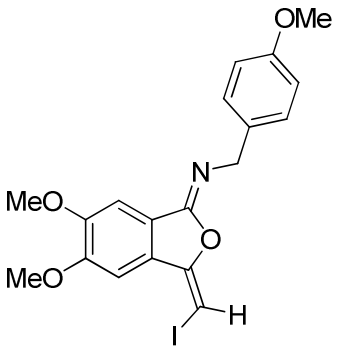
Imidate 4{*5*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 7.18 (t, J = 6.4 Hz, 1H), 7.27 (s, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 8.42 (s, 1H), 8.74 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2, 56.5, 56.6, 74.9, 104.0, 107.5, 122.6, 124.5, 125.2, 129.7, 135.9, 149.3, 149.5, 152.0, 152.3, 154.7, 156.1; HRMS Calcd for $C_{17}H_{15}IN_2O_3$: 422.01274. Found: 422.01393.



Imidate 4{*6*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (s, 3H), 3.96 (s, 3H), 4.01 (s, 3H), 7.25 (s, 1H), 7.37-7.39 (m, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.73 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 56.4, 56.5, 67.0, 103.9, 106.9, 124.6, 125.0, 127.4, 129.8, 129.9, 140.3, 146.9, 151.6, 151.7, 154.8; HRMS Calcd for $C_{16}H_{14}INO_3S$: 426.97391. Found: 426.97489.



Imidate 4{*7*}. A modified literature procedure was used for TMS-deprotection.[18] To a solution of compound **4**{*2*} (4.0 g, 9.5 mmol) in 1:1 THF:MeOH (20 mL), $KF{\cdot}2H_2O$ (5.37 g, 57 mmol, 6 equiv) was added and the reaction mixture was stirred for 0.5 h at 25 ^{o}C. After the reaction was over, the methanol was removed under vacuum and the residue was extracted with EtOAc (3 x 20 mL), washed with 0.1M HCl and brine, dried ($MgSO_4$), filtered, and the solvent removed under vacuum. Purification by flash chromatography afforded the deprotected product in a 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (s, 1H), 7.18-7.20 (m, 1H), 7.37-7.43 (m, 4H), 7.53-7.56 (m, 2H), 7.98 (d, J = 7.2 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8, 123.8, 123.93, 123.97, 124.9, 128.7, 130.8, 131.9, 132.4, 134.9, 145.3, 151.6, 152.2; HRMS Calcd for $C_{15}H_{10}INO$: 346.98071. Found: 346.98168.



Imidate 4{*8*}. A modified literature procedure was used.[2] Compound **4{*3*}** (440 mg, 0.84 mmol) and $KF{\cdot}2H_2O$ (132 mg, 1.4 mmol, 1.67 equiv) were dissolved in DMF (6 mL) and H_2O (0.5 ml) and the resulting reaction mixture was stirred at 25 ^oC for 1 h. The mixture was then diluted with EtOAc, washed with brine and H_2O (3 × 25 ml), dried ($MgSO_4$) and filtered. The filtrate was characterized as the deprotected product **4{*8*}**. ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.95 (s, 3H), 4.01 (s, 3H), 4.72 (s, 2H), 6.03 (s, 1H), 6.88 (d, J = 8.0 Hz, 2H), 7.29 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.9, 51.4, 55.5, 56.5, 56.6, 104.4, 105.7, 114.1, 125.8, 129.1, 129.3, 132.3, 151.8, 152.0, 152.3, 154.3, 158.7; HRMS Calcd for $C_{19}H_{18}INO_4$: 451.02805. Found: 451.02921.

Diversification of the 3-Iodomethylene-containing Cyclic Imidates 4 Using Various Palladium-catalyzed Reactions[7a]

General Sonogashira Coupling Procedure Used for the Preparation of Alkynes 9{*1-17*}.

To a solution of the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol) in DMF (4 mL) were added $PdCl_2(PPh_3)_2$ (3 mol %) and CuI (2 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (4.0 equiv) was added by syringe. The reaction mixture was heated to 70 °C. A solution of alkyne **2** (1.2 equiv) in DMF (1 mL) was added dropwise over 10 min, and the

mixture was allowed to stir at 70 ^{o}C for 2 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was either purified by column chromatography on silica gel using hexane-EtOAc as the eluent, or was flushed through a short silica gel plug and purified by preparative HPLC.

General Suzuki-Miyaura Coupling Procedure Used for the Preparation of Imidates 9{*18-62*}.

To a 4-dram vial were added the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol), the boronic acid **6** (0.30 mmol), $KHCO_3$ (0.35 mmol) and $PdCl_2$ (0.0125 mmol) in 4:1 DMF:H_2O (2.5 mL). The reaction mixture was stirred for 5 min at room temperature and flushed with Ar and then heated to 80 ^{o}C for 2 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was either purified by column chromatography on silica gel using hexane-EtOAc as the eluent, or was flushed through a short silica gel plug and purified by preparative HPLC.

Carbonylative Amidation Procedure Used for the Preparation of Amide 9{*64*}.

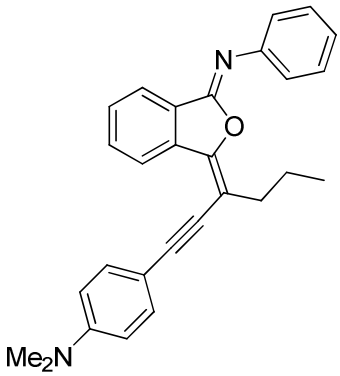
To a 4-dram vial were added the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), DMF (1 mL) and the amine **7** (0.25 mL if liquid or 0.5 mmol if solid). The reaction mixture was stirred for 2 min at room temperature and flushed with carbon monoxide. A balloon of carbon monoxide was placed on the vial,

which was heated to 65 ^{o}C for 3-6 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was flushed through a short silica gel plug and purified by preparative HPLC.

General Heck Coupling Procedure Used for the Preparation of Alkenes 9{*66-73*}.

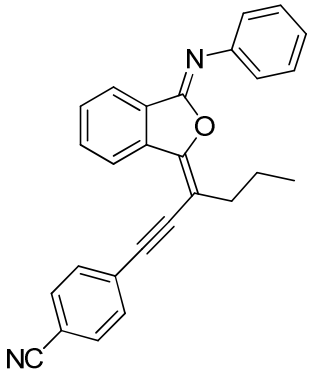
To a 4-dram vial were added the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol), the styrene **8** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), *n*-Bu_4NCl (0.25 mmol), Na_2CO_3 (0.625 mmol) and DMF (2 mL). The reaction mixture was then heated to 85 ^{o}C for 5-24 h. After cooling, the reaction mixture was diluted with EtOAc (20 mL), and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was flushed through a short silica gel plug and purified by preparative HPLC.

Characterization Data for Representative Library Members:

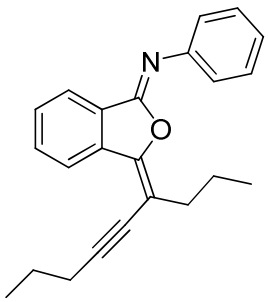


Imidate 9{*4*}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.73-1.80 (m, 2H), 2.55 (t, J = 7.5 Hz, 2H), 3.03 (s, 6H), 6.71 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 7.40-

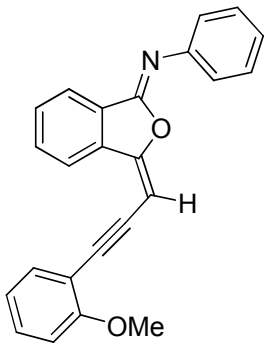
7.54 (m, 7H), 7.63 (t, J = 7.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.8, 33.4, 40.4, 85.9, 98.7, 104.0, 110.2, 112.1, 123.2, 123.6, 124.5, 124.9, 128.9, 129.5, 130.9, 132.4, 132.7, 135.8, 145.8, 150.4, 151.6, 153.4; HRMS Calcd for $C_{28}H_{27}N_2O$: 407.2118 $[M+H]^+$, Found: 407.2129.



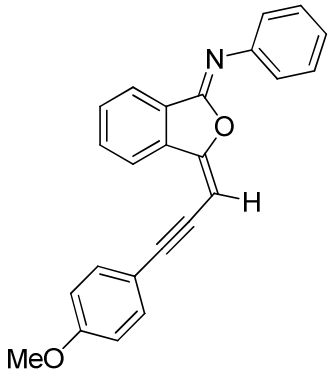
Imidate 9{5}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, J = 7.5 Hz, 3H), 1.70-1.78 (m, 2H), 2.55 (t, J = 7.5 Hz, 2H), 7.20 (tt, J = 1.0, 7.5 Hz, 1H), 7.40-7.43 (m, 2H), 7.45-7.48 (m, 2H), 7.58 (td, J = 1.0, 7.5 Hz, 1H), 7.62-7.65 (m, 2H), 7.66-7.70 (m, 3H), 8.05 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 21.8, 33.1, 92.6, 95.3, 101.7, 111.7, 118.7, 123.1, 123.9, 124.5, 125.3, 128.4, 128.9, 130.4, 131.5, 131.9, 132.4, 132.5, 135.2, 145.3, 152.5, 153.8; HRMS Calcd for $C_{27}H_{21}N_2O$: 389.1648 $[M+H]^+$, Found: 389.1668.



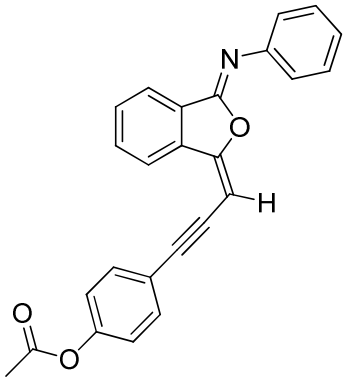
Imidate 9{*6*}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3H), 1.10 (t, J = 7.5 Hz, 3H), 1.63-1.75 (m, 4H), 2.44 (t, J = 7.5 Hz, 2H), 2.53 (t, J = 7.0 Hz, 2H), 7.17 (tt, J = 1.5, 7.5 Hz, 1H), 7.37-7.41 (m, 2H), 7.44-7.46 (m, 2H), 7.52 (td, J = 1.0, 7.5 Hz, 1H), 7.61 (td, J = 1.0, 7.5 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.90, 13.93, 21.6, 22.2, 22.5, 33.6, 78.8, 98.7, 103.8, 122.9, 123.6, 124.4, 124.9, 128.9, 129.6, 131.0, 132.3, 135.7, 145.8, 151.9, 153.4; HRMS Calcd for $C_{23}H_{24}NO$: 330.1852 $[M+H]^+$, Found: 330.1864.



Imidate 9{*11*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 5.92 (s, 1H), 6.93-6.99 (m, 2H), 7.17-7.22 (m, 1H), 7.32-7.42 (m, 5H), 7.49 (d, J = 7.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.81 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 87.6, 89.3, 94.3, 110.8, 112.9, 120.9, 123.6, 124.0, 124.1, 125.1, 128.9, 130.1, 130.8, 131.3, 132.5, 133.3, 135.3, 145.6, 153.0, 157.4, 160.1; HRMS Calcd for $C_{24}H_{18}NO_2$: 352.1332 $[M+H]^+$, Found: 352.1325.

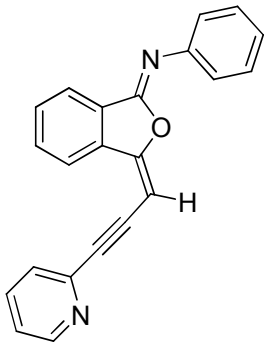


Imidate 9{*12*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.87 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.16-7.19 (m, 1H), 7.38-7.42 (m, 4H), 7.48 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 7.2 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 83.9, 87.6, 97.6, 114.5, 115.6, 123.6, 123.8, 124.0, 125.1, 128.9, 130.8, 131.5, 132.6, 133.0, 135.3, 145.6, 152.9, 157.1, 160.1; HRMS Calcd for $C_{24}H_{18}NO_2$: 352.1332 $[M+H]^+$, Found: 352.1330.

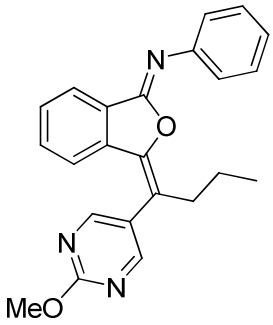


Imidate 9{*13*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.86 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 6.8 Hz, 1H), 7.36-7.42 (m, 4H), 7.55 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 8.39 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 85.2, 87.0, 96.5, 121.1, 122.1, 123.6, 123.8, 123.9, 125.2, 128.9,

131.0, 131.4, 132.66, 132.69, 135.1, 145.4, 150.8, 152.9, 157.6, 169.4; HRMS Calcd for $C_{25}H_{18}NO_3$: 380.1281 $[M+H]^+$, Found: 380.1300.

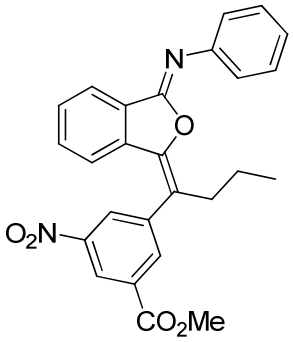


Imidate 9{*16*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (s, 1H), 7.19 (t, J = 6.8 Hz, 1H), 7.24-7.27 (m, 1H), 7.36-7.42 (m, 4H), 7.51 (d, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.67-7.72 (m, 2H), 8.02 (d, J = 7.6 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.9, 86.1, 96.5, 122.9, 123.7, 123.9, 124.0, 125.2, 126.9, 128.9, 131.2, 131.5, 132.8, 134.9, 136.3, 143.4, 145.3, 150.4, 152.5, 158.8; HRMS Calcd for $C_{22}H_{15}N_2O$: 323.1179 $[M+H]^+$, Found: 323.1202.

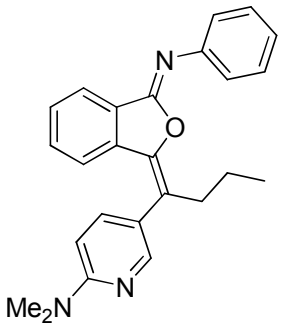


Imidate 9{*18*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.6 Hz, 3H), 1.43-1.52 (m, 2H), 2.62 (t, J = 7.6 Hz, 2H), 4.11 (s, 3H), 6.68 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.39-7.47 (m, 5H), 8.01 (d, J = 8.0 Hz, 1H), 8.50 (s, 2H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 13.9, 20.9, 35.6, 55.4, 115.0, 122.0, 124.0, 124.3, 124.9, 125.8, 128.9, 129.7, 131.7, 132.1, 135.2, 145.7, 147.3, 153.4, 159.8, 165.4; HRMS Calcd for $C_{23}H_{22}N_3O_2$: 372.1707 $[M+H]^+$, Found: 372.1690.

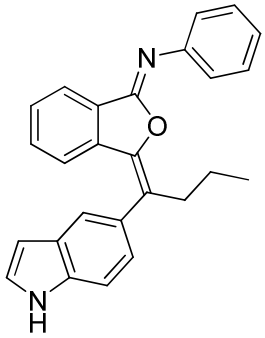


Imidate 9{*19*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 1.42-1.52 (m, 2H), 2.70 (t, J = 7.6 Hz, 2H), 4.00 (s, 3H), 6.42 (d, J = 8.0 Hz, 1H), 7.18-7.26 (m, 2H), 7.40-7.49 (m, 5H), 8.00 (d, J = 7.6 Hz, 1H), 8.36 (s, 1H), 8.40 (s, 1H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.2, 35.7, 53.2, 118.9, 121.8, 124.1, 124.2, 124.3, 125.1, 128.5, 128.9, 129.9, 131.9, 132.1, 132.9, 134.9, 136.6, 141.2, 145.7, 147.1, 149.1, 153.2, 164.9; HRMS Calcd for $C_{26}H_{23}N_2O_5$: 443.1601 $[M+H]^+$, Found: 443.1596.

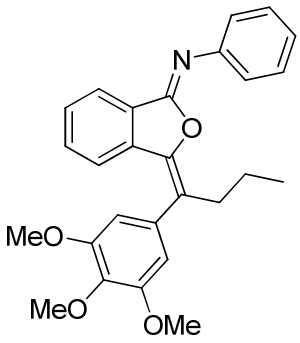


Imidate 9{*22*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.41-1.51 (m, 2H), 2.60 (t, J = 7.6 Hz, 2H), 3.17 (s, 6H), 6.61 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 7.16

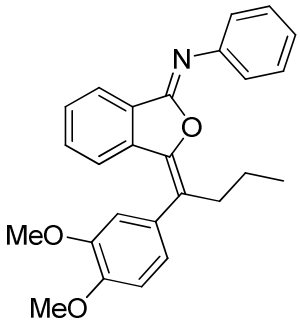
(t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.37-7.41 (m, 4H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.1, 35.8, 38.3, 105.8, 120.4, 121.2, 122.4, 123.6, 124.4, 124.6, 128.8, 128.9, 131.4, 131.9, 136.1, 138.3, 146.1, 146.2, 148.3, 154.4, 158.9; HRMS Calcd for $C_{25}H_{26}N_3O$: 384.2070 $[M+H]^+$, Found: 384.2075.



Imidate 9{*23*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.6 Hz, 3H), 1.45-1.54 (m, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 7.11-7.19 (m, 3H), 7.29-7.36 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.59 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.2, 36.5, 103.2, 111.7, 121.5, 122.8, 123.4, 123.5, 124.47, 124.52, 124.6, 125.0, 128.5, 128.6, 128.8, 129.8, 131.3, 131.7, 135.7, 136.4, 145.8, 146.4, 154.8; HRMS Calcd for $C_{26}H_{23}N_2O$: 379.1805 $[M+H]^+$, Found: 379.1799.

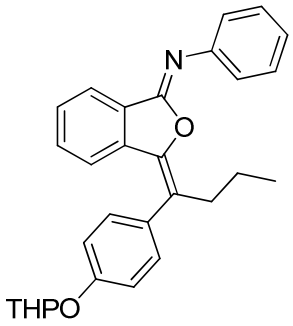


Imidate 9{*24*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.6 Hz, 3H), 1.47-1.56 (m, 2H), 2.64 (t, J = 7.6 Hz, 2H), 6.53 (s, 2H), 6.64 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.37-7.42 (m, 3H), 7.49 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.2, 35.8, 56.4, 61.3, 106.2, 122.7, 122.9, 123.5, 124.4, 124.6, 128.8, 129.0, 131.4, 131.8, 133.9, 135.9, 137.9, 145.9, 146.1, 153.8, 154.2; HRMS Calcd for $C_{27}H_{28}NO_4$: 430.2013 $[M+H]^+$, Found: 430.2010.

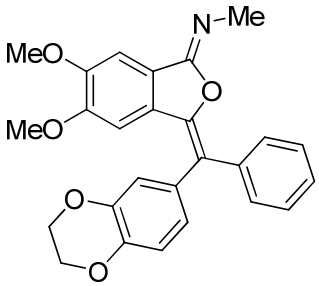


Imidate 9{*32*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.44-1.53 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.96 (s, 3H), 6.60 (d, J = 8.0 Hz, 1H), 6.83 (s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.35-7.42 (m, 3H), 7.49 (d, J = 7.6 Hz, 2H), 7.96 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.1, 35.9, 56.1, 56.2, 111.7, 112.4, 121.7, 122.6, 122.8, 123.5, 124.4,

124.6, 128.8, 128.9, 130.9, 131.4, 131.7, 136.0, 145.9, 146.2, 148.9, 149.5, 154.3; HRMS Calcd for $C_{26}H_{26}NO_3$: 400.1907 $[M+H]^+$, Found: 400.1902.

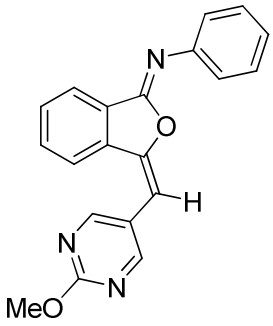


Imidate 9{*34*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.6 Hz, 3H), 142-1.51 (m, 2H), 1.67-1.76 (m, 3H), 191-1.92 (m, 2H), 2.00-2.07 (m, 1H), 2.61-2.64 (m, 2H), 3.65-3.68 (m, 1H), 3.99 (t, J = 9.2 Hz, 1H), 5.48 (s, 1H), 6.61 (d, J = 7.6 Hz, 1H), 7.12-7.18 (m, 3H), 7.22-7.26 (m, 3H), 7.35-7.41 (m, 3H), 7.48-7.50 (m, 2H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.2, 21.1, 25.4, 30.7, 35.9, 62.6, 96.9, 117.0, 122.6, 122.9, 123.5, 124.4, 124.6, 128.8, 130.2, 130.4, 131.4, 131.5, 131.7, 136.1, 145.8, 146.2, 154.4, 157.1; HRMS Calcd for $C_{29}H_{30}NO_3$: 440.2220 $[M+H]^+$, Found: 440.2229.

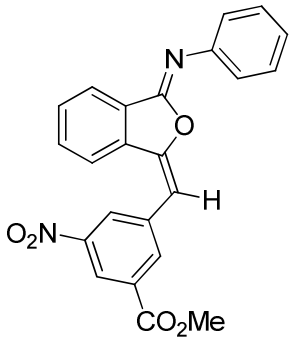


Imidate 9{*36*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H), 3.56 (s, 3H), 3.91 (s, 3H), 4.30 (s, 4H), 5.75 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 7.20 (s, 1H), 7.23-7.25 (m, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 35.4, 55.7, 56.5, 64.6, 64.8, 103.5, 105.4, 117.0, 118.1, 120.4, 123.7, 124.7, 127.2, 128.2, 129.7, 130.9, 131.6, 138.5, 143.7, 144.3, 146.1, 150.9, 151.8, 156.8; HRMS Calcd for $C_{26}H_{24}NO_5$: 430.1649 $[M+H]^+$, Found: 430.1643.

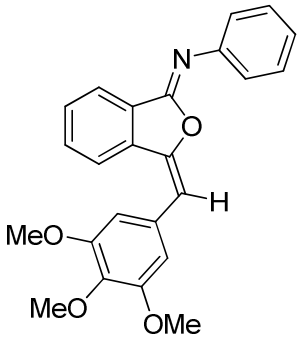


Imidate 9{*46*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 3H), 6.45 (s, 1H), 7.17-7.20 (m, 1H), 7.39-7.42 (m, 5H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 100.7, 121.8, 122.1, 123.9, 124.3, 125.0, 128.9, 130.9, 132.36, 132.41, 134.5, 145.7, 151.5, 153.1, 159.5, 165.1; HRMS Calcd for $C_{20}H_{16}N_3O_2$: 330.1237 $[M+H]^+$, Found: 330.1234.

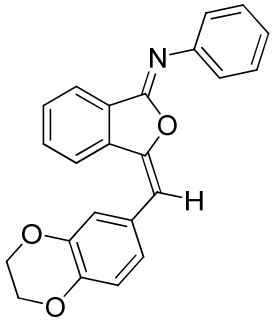


Imidate 9{*47*}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 3H), 6.68 (s, 1H), 7.19-7.22 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.41-7.47 (m, 5H), 7.58 (t, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 8.47 (s, 1H), 8.51 (d, *J* = 1.0 Hz, 1H), 8.83 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 53.2, 105.2, 122.1, 123.6, 123.9, 124.4, 125.2, 127.9, 129.0, 131.4, 132.4, 132.5, 132.6, 134.1, 136.1, 136.5, 145.5, 148.8, 152.1, 152.9, 164.9; HRMS Calcd for $C_{23}H_{17}N_2O_5$: 401.1132 $[M+H]^+$, Found: 401.1145.

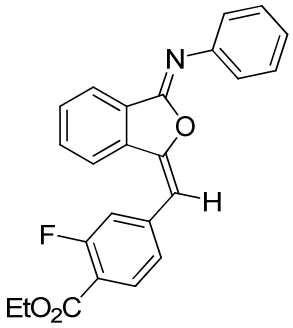


Imidate 9{*52*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 3.92 (s, 3H), 6.67 (s, 3H), 7.15-7.19 (m, 1H), 7.39-7.45 (m, 5H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 61.3, 106.6, 109.1, 115.6, 122.9, 123.9, 124.7, 128.9, 129.3, 130.4, 131.9, 132.2, 135.1, 138.1, 146.0, 150.2, 153.6, 153.8; HRMS Calcd for $C_{24}H_{22}NO_4$: 388.1543 $[M+H]^+$, Found: 388.1541.

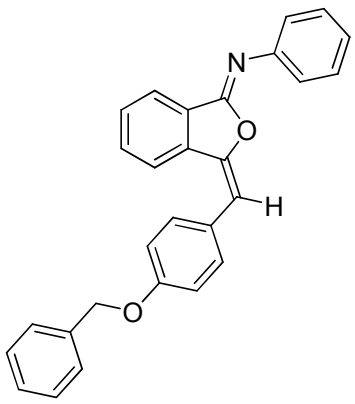


Imidate 9{*55*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (s, 4H), 6.61 (s, 1H), 6.90-6.95 (m, 3H), 7.15-7.18 (m, 1H), 7.38-7.39 (m, 4H), 7.43-7.45 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.6, 64.7, 108.9,

117.7, 118.2, 122.7, 123.8, 123.9, 124.7, 127.0, 128.9, 129.5, 130.2, 131.9, 132.1, 135.1, 143.6, 143,8, 146.1, 149.8, 154.0; HRMS Calcd for $C_{23}H_{18}NO_3$: 356.1281 $[M+H]^+$, Found: 356.1277.



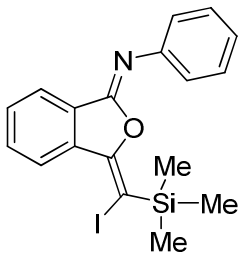
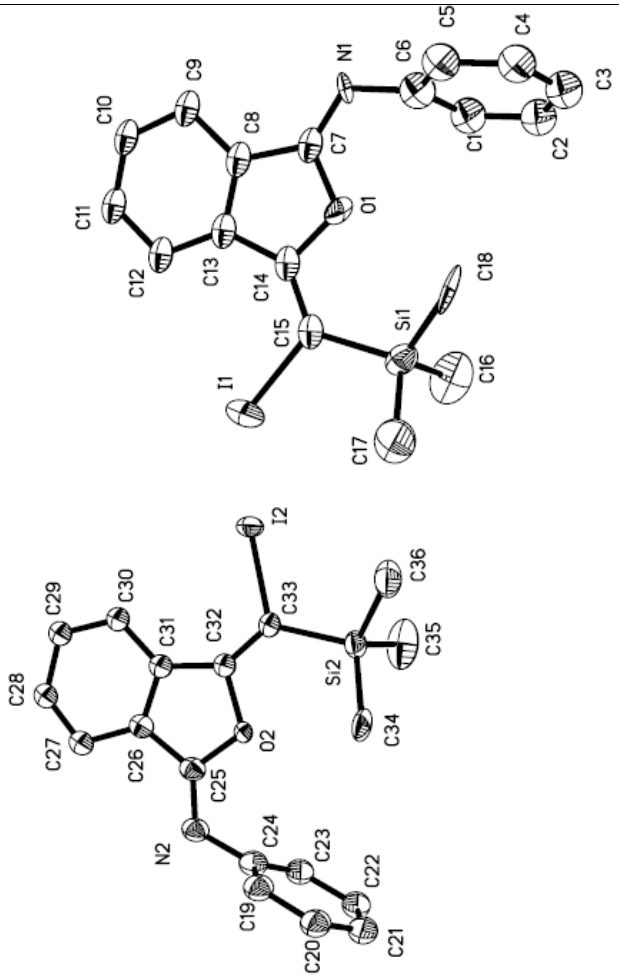
Imidate 9{*56*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 4.43 (q, J = 7.2 Hz, 2H), 6.62 (s, 1H), 7.17-7.20 (m, 1H), 7.22-7.25 (m, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.39-7.43 (m, 4H), 7.46 (d, J = 7.2 Hz, 1H), 7.54-7.57 (m, 2H), 7.97-8.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 61.6, 106.7, 117.6, 117.8, 118.2, 118.3, 122.7, 123.9, 124.1, 125.0, 125.06, 125.08, 128.9, 131.0, 132.2, 132.4, 132.6, 134.4, 140.8, 140.9, 145.6, 151.4, 153.2, 161.1, 163.2, 164.22, 164.25 (extra peaks due to C-F splitting); HRMS Calcd for $C_{24}H_{19}FNO_3$: 388.1343 $[M+H]^+$, Found: 388.1349.



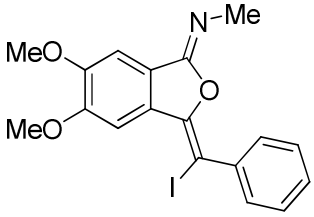
Imidate 9{*59*}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 2H), 6.66 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.14-7.18 (m, 1H), 7.35-7.43 (m, 10H), 7.46-7.49 (m, 3H), 7.52 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.4, 109.0, 115.3, 122.6, 123.86, 123.95, 124.7, 126.4, 127.7, 128.3, 128.8, 128.9, 130.1, 130.7, 131.9, 132.1, 135.2, 136.9, 146.2, 149.7, 154.1, 158.7; HRMS Calcd for $C_{28}H_{22}NO_2$: 404.1645 $[M+H]^+$, Found: 404.1643.

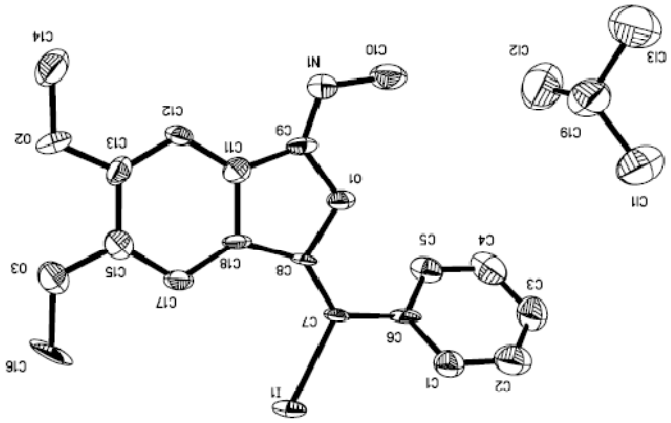
Crystallographic Experimental Section

Table 1. X-ray Crystallographic Data for Compounds 4{*2*}, 4{*4*}, and 9{*24*}.

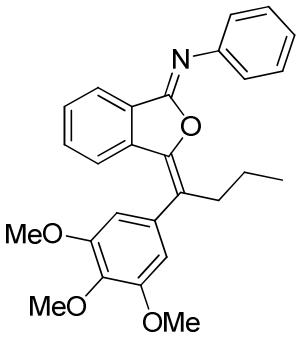
compd	Structure	ORTEP diagram
4{*2*}		

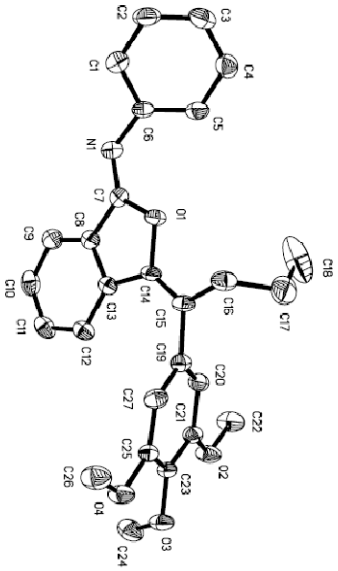
4{*4*}





9{*24*}





Data Collection for Imidate 4{*2*}.

A good crystal could not be obtained for this compound, so the X-ray studies were performed using a relatively poor quality crystal. The crystal was covered with Paratone oil under ambient conditions and was mounted and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed at 173 K on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and a detector to crystal distance of 5.03 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3º in a 10º range about ω with the exposure time of 20 seconds per frame. The reflections obtained were successfully indexed by an automated indexing routine built into the SMART program. The final cell constants were calculated from a set of strong reflections from the actual data collection.

The data were collected using a full sphere routine by collecting four sets of frames with 0.3º scans in ω with an exposure time of 20 sec per frame. This data set was corrected for Lorentz and polarization effects. The absorption correction was based on the fit of a spherical harmonic function to the empirical transmission surface as sampled by multiple equivalent measurements using SADABS software.[19,20]

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space group $P2_1/c$ and yielded chemically reasonable and computationally stable results of refinement.[20] The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles and difference Fourier maps. The observed resolution of the data set was above 1 Å. Therefore, the refinement lead to R-factors significantly exceeding the values required for publication of X-ray structure analysis. The poor quality of X-ray data also leads to some NPD (non-positive definite)

atoms. Therefore, rigid body restraints were applied to the final stages of refinement. All non-hydrogen atoms were refined in full-matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

Two structurally non-equivalent molecules were found in an asymmetric unit of primitive monoclinic cell. The ORTEP diagram was drawn at a 50% probability level. H-atoms were omitted for clarity. The resulting CIF file has been tested with PLATON software.[21] The results and comments have been included in the output package (Platon_Lar32.doc).

Table 2. Crystal data and structure refinement for Imidate 4{*2*}.

Empirical formula	$C_{18}H_{18}INOSi$	
Formula weight	419.32	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.793(3) Å	α = 90°
	b = 18.773(8) Å	β = 93.443(7)°
	c = 28.433(12) Å	γ = 90°
Volume	3619(3) $Å^3$	
Z	8	
Density (calculated)	1.539 Mg/m^3	

Absorption coefficient	1.837 mm^{-1}
F(000)	1664
Crystal size	0.46 x 0.38 x 0.24 mm^3
Theta range for data collection	1.43 to 20.82°.
Index ranges	-6<=h<=6, -18<=k<=18, -28<=l<=28
Reflections collected	17216
Independent reflections	3784 [R(int) = 0.0752]
Completeness to theta = 20.82°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6669 and 0.4854
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3784 / 262 / 404
Goodness-of-fit on F^2	1.247
Final R indices [I>2sigma(I)]	R1 = 0.1221, wR2 = 0.3340
R indices (all data)	R1 = 0.1387, wR2 = 0.3488
Extinction coefficient	0.0065(8)
Largest diff. peak and hole	3.726 and -1.441 e.$Å^{-3}$

$R1 = \Sigma \, | \, |F_O| - |F_c| \, | \, / \, \Sigma \, |F_o|$ and $wR2 = \{ \, \Sigma \, [\, w(F_o^2 - F_c^2)^2 \,] \, / \, \Sigma \, [\, w(F_o^2)^2 \,] \, \}^{1/2}$

Data Collection for Imidate 4{*4*}.

A colorless weakly diffracted crystal was selected under ambient conditions. The crystal was mounted and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed at room temperature on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and a detector to crystal distance of 5.03 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3º in a 10º range about ω with an exposure time of 20 seconds per frame. The sample was twinned. Therefore, the obtained reflections were indexed by visually separating two crystallites using the RLATT program.[20] The final cell constants were calculated from a set of strong reflections from the actual data collection.

The data were collected using a full sphere routine by collecting four sets of frames with 0.3º scans in ω with an exposure time of 20 sec per frame. This data set was corrected for Lorentz and polarization effects. The absorption correction was based on a fit of a spherical harmonic function to the empirical transmission surface as sampled by multiple equivalent measurements using SADABS software.[19,20]

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space group $P2_1/c$ and yielded chemically reasonable and computationally stable results of refinement.[20] The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined in full-matrix anisotropic approximation. The resolution of statistically relevant data was above 1Å. Therefore, rigid body restraints were applied to refine some C atoms anisotropically. All hydrogen atoms were placed in the

structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

One proposed molecule and one $CHCl_3$ solvent molecule were found in the asymmetric unit of the primitive monoclinic cell. The ORTEP diagram was drawn at 50% probability level. H-atoms were omitted for clarity. The resulting CIF file has been tested with PLATON software.[21] The results and comments have been included in the output package (Platon_Lar31.doc).

Table 3. Crystal data and structure refinement for imidate **4{*4*}**.

Empirical formula	$C_{19}H_{17}Cl_3INO_3$	
Formula weight	540.59	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.655(9) Å	α = 90°
	b = 18.309(11) Å	β = 95.567(10)°
	c = 7.846(5) Å	γ = 90°
Volume	2095(2) $Å^3$	
Z	4	
Density (calculated)	1.714 Mg/m^3	
Absorption coefficient	1.930 mm^{-1}	
F(000)	1064	

Crystal size	0.32 x 0.26 x 0.15 mm^3
Theta range for data collection	1.79 to 20.82°.
Index ranges	-14<=h<=14, -18<=k<=18, -7<=l<=7
Reflections collected	9731
Independent reflections	2183 [R(int) = 0.0987]
Completeness to theta = 20.82°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.74 and 0.69
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2183 / 14 / 247
Goodness-of-fit on F^2	1.111
Final R indices [I>2sigma(I)]	R1 = 0.0655, wR2 = 0.1678
R indices (all data)	R1 = 0.0911, wR2 = 0.1859
Largest diff. peak and hole	2.270 and -0.970 e.$Å^{-3}$

$R1 = \Sigma \, | \, |F_O| - |F_c| \, | \, / \, \Sigma \, |F_o|$ and $wR2 = \{ \, \Sigma \, [\, w(F_o^2 - F_c^2)^2 \,] \, / \, \Sigma \, [\, w(F_o^2)^2 \,] \, \}^{1/2}$

Data Collection for Imidate 9{*24*}.

A yellow crystal was selected under ambient conditions and covered with Paratone oil. The crystal was mounted and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed at 173 K on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and a detector to crystal distance of 5.03 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 30 frames collected at intervals of 0.3º in a 10º range about ω with an exposure time of 20 seconds per frame. The reflections obtained were successfully indexed by an automated indexing routine built into the SMART program. The final cell constants were calculated from a set of strong reflections from the actual data collection.

The data were collected using a full sphere routine by collecting four sets of frames with 0.3º scans in ω with an exposure time of 10 sec per frame. This data set was corrected for Lorentz and polarization effects. The absorption correction was based on a fit of a spherical harmonic function to the empirical transmission surface as sampled by multiple equivalent measurements using SADABS software.[19,20]

Structure Solution and Refinement

The systematic absences in the diffraction data were consistent for the space group $P2_1/c$ and yielded chemically reasonable and computationally stable results of refinement.[20] The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined in full-matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The ORTEP diagram was drawn at 50% probability level. H-atoms were omitted for clarity. The resulting CIF file has been tested with PLATON software.[21] The results and comments have been included in the output package (Platon_Lar30.doc.).

Table 4. Crystal data and structure refinement for imidate **9{*24*}**.

Empirical formula	$C_{27}H_{27}NO_4$	
Formula weight	429.50	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.037(3) Å	α = 90°
	b = 19.075(5) Å	β = 98.377(5)°
	c = 13.320(4) Å	γ = 90°
Volume	2271.6(11) $Å^3$	
Z	4	
Density (calculated)	1.256 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	912	
Crystal size	0.60 x 0.34 x 0.32 mm^3	
Theta range for data collection	2.14 to 23.26°.	
Index ranges	-10<=h<=10, -21<=k<=21, -14<=l<=14	
Reflections collected	14509	

Independent reflections	3254 [R(int) = 0.0520]
Completeness to theta = 23.26°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9736 and 0.9513
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3254 / 0 / 293
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0488, wR2 = 0.1141
R indices (all data)	R1 = 0.0741, wR2 = 0.1278
Largest diff. peak and hole	0.191 and -0.232 e.Å^{-3}

$R1 = \Sigma \, | \, |F_O| - |F_c| \, | \, / \, \Sigma \, |F_o|$ and $wR2 = \{ \, \Sigma \, [\, w(F_o^2 - F_c^2)^2 \,] \, / \, \Sigma \, [\, w(F_o^2)^2 \,] \, \}^{1/2}$

Acknowledgments

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GENERAL CONCLUSIONS

In this dissertation, new and synthetically useful approaches involving palladium catalysis and electrophilic cyclization have been described for the synthesis of potentially medicinally and industrially important heterocycles and carbocycles. The methods used are quite general and can be utilized to synthesize a wide variety of isochromenes, and cyclic imidates, as well as linear and fused polyheterocyclic compounds (PHCs) containing benzofurans, benzothiophenes, indoles, and isocoumarin subunits.

In Chapter 1, competition studies in alkyne electrophilic cyclization reactions have been performed. This has been accomplished by applying this electrophilic cyclization methodology to a variety of unsymmetrical functionally-substituted diarylalkynes using halogen and selenium electrophiles and the resulting products characterized in order to determine the relative reactivities of various functional groups towards electrophilic cyclization. The results suggest that a number of factors affect the cyclization. These include electronic (the relative nucleophilicity of the functional groups, and the cationic nature of the intermediate) and steric factors (hindrance and geometrical alignment of the functional groups), and the nature of the electrophile.

In Chapter 2, several iodocyclization/palladium-catalyzed approaches have been described for the generation of linked and fused polyheterocyclic compounds. The general method to prepare linked polyheterocyclic compounds involves iterative cycles of palladium-catalyzed Sonogashira coupling, followed by iodocyclization using I_2 or ICl. Important heterocyclic units, like indole, benzofuran, benzothiophene *etc.*, can be easily inserted at the desired location by just changing the order of the building blocks, easily accessible terminal alkynes. The reactions are very efficient, afford clean reactions, and tolerate almost all

important functional groups. Finally, this methodoogy is very flexible and can be quickly combined with other efficient transformations, like the palladium-catalyzed Ullmann reaction and alkyne annulation, to construct more complex fused heterocycles. These features enhance the synthetic utility and scope of the methodology, making this a very practical approach for PHC synthesis.

In Chapter 3, a variety of iodo-substituted isochromenes, dihydroisobenzofurans, and pyranopyridines are prepared in good to excellent yields under mild conditions by the iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines. The nature of the substituents in the starting material governs the regiochemistry of the reaction products. The 5-membered ring products obtained, namely 1-alkylidene-1,3-dihydroisobenzofurans, exhibit unexpected *Z*-stereochemistry, and are presumably derived from the initially formed less stable *E*-isomers through iodine-mediated isomerization.

In Chapter 4, the solution-phase parallel synthesis of a 71-member library of multi-substituted (with four diversity points) cyclic imidates is described. 3-Iodomethylene cyclic imidates are readily prepared by iodocyclization chemistry. Diversification of these 3-iodomethylene cyclic imidates has been accomplished by using various commercially available building blocks, for example, boronic acids, terminal alkynes, styrenes, and carbon monoxide plus amines, through a variety of C-C and C-N bond forming reactions. The cyclic imidate library members are being evaluated for their biological potential by the National Institutes of Health Molecular Library Screening Center Network.

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