New palladium-catalyzed approaches to heterocycles and carbocycles

by

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To my wife, Chunrong Pan

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LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
br m	broad multiplet
br s	broad singlet
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
cat.	Catalytic
concd	concentrated
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq	equation
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared

m	multiple
Me	methyl
mL	milliliter(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
q	quartet
s	singlet
<i>t</i>	triplet
TBAC	tetra- <i>n</i> -butylammonium chloride
<i>tert</i>	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	<i>p</i> -toluenesulfonyl

ABSTRACT

The *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes and analogous pyridinecarbaldehydes have been cyclized under very mild reaction conditions in the presence of I₂, ICl, PhSeCl, PhSCl and *p*-O₂NC₆H₄SCl to give the corresponding halogen-, selenium- and sulfur-containing disubstituted isoquinolines and naphthyridines, respectively. Monosubstituted isoquinolines and naphthyridines have been synthesized by the metal-catalyzed ring closure of these same iminoalkynes. This methodology accommodates a variety of iminoalkynes and affords the anticipated heterocycles in moderate to excellent yields.

The Pd(II)-catalyzed cyclization of 2-(1-alkynyl)arylaldimines in the presence of various alkenes provides an efficient way to synthesize a variety of 4-(1-alkenyl)-3-arylisoquinolines in moderate to excellent yields. The introduction of an *ortho*-methoxy group on the arylaldimine promotes the Pd-catalyzed cyclization and stabilizes the resulting Pd(II) intermediate, improving the yields of the isoquinoline products.

Highly substituted naphthalenes have been synthesized by the palladium-catalyzed annulation of a variety of internal alkynes, in which two new carbon-carbon bonds are formed in a single step under relatively mild reaction conditions. This method has also been used to synthesize carbazoles, although a higher reaction temperature is necessary. The process involves arylpalladation of the alkyne, followed by intramolecular Heck olefination and double bond isomerization. This method accommodates a variety of functional groups and affords the anticipated highly substituted naphthalenes and carbazoles in good to excellent yields.

Novel palladium migration/arylation methodology for the synthesis of complex fused polycycles has been developed, in which one or more sequential Pd-catalyzed intramolecular migration processes involving C-H activation are employed. The chemistry works best with electron-rich aromatics, which is in agreement with the idea that these palladium-catalyzed C-H activation reactions parallel electrophilic aromatic substitution.

A relatively efficient synthesis of cyclopropanes has been developed using palladium-catalyzed C-H activation chemistry, in which two new carbon-carbon bonds are formed in a single step. This method involves the palladium-catalyzed activation of relatively unreactive C-H bonds, and provides a very efficient way to synthesize cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics.

GENERAL INTRODUCTION

Transition metal-catalyzed processes have proven to be extremely effective in organic synthesis. More specifically, palladium-catalyzed methodology has been extensively utilized in recent years.¹ The ability to create multiple carbon-carbon bonds from simple starting materials, the regio- and stereospecificity of the reactions, the exceptional tolerance for functional groups, the insensitivity to air or moisture, and the procedural ease with which the reactions can be carried out have all contributed to the success of palladium in organic synthesis.

The Larock group has shown in a series of recent papers that palladium-catalyzed cyclization or annulation methodology² can be effectively employed for the synthesis of indoles, isoindolo[2,1-*a*]indoles, benzofurans, benzopyrans, isocoumarins, α -pyrones, isoquinolines, carbolines and polycyclic aromatic hydrocarbons with a wide variety of substituent patterns. In this dissertation, extension of this approach to the synthesis of isoquinolines, naphthyridines, naphthalenes, carbazoles, and their derivatives have been investigated.

The ability of palladium to activate C-H bonds has been used extensively in organic synthesis.³ In recent years, palladium-catalyzed C-H activation has received considerable attention due to the wide variety of reactions this metal will catalyze. Newly discovered palladium migration chemistry and the palladium-catalyzed activation of alkyl C-H bonds interests us as both an opportunity to study the behavior of palladium and an unusual pathway to construct complicated polycyclic compounds.

Dissertation Organization

This dissertation is divided into five chapters. Each of the chapters presented herein is written by following the guidelines for a full paper in the *Journal of Organic Chemistry* and is composed of the abstract, introduction, results and discussion, conclusion, experimental section, and references.

Chapter 1 discusses the synthesis of halogen-, selenium- and sulfur-containing disubstituted isoquinolines and naphthyridines by the electrophilic cyclization of the *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes and analogous pyridinecarbaldehydes under very mild reaction conditions using I₂, ICl, PhSeCl, PhSCl and *p*-O₂NC₆H₄SCl as electrophiles.

Chapter 2 investigates the Pd(II)-catalyzed cyclization of 2-(1-alkynyl)arylaldimines in the presence of various alkenes as an efficient way to synthesize a variety of 4-(1-alkenyl)-3-arylisoquinolines in moderate to excellent yields. Various imine substrates and alkenes have been studied. A mechanism for this transformation is proposed.

Chapter 3 presents a palladium-catalyzed annulation of a variety of internal alkynes to synthesize highly substituted naphthalenes. The process involves arylpalladation of the alkyne, followed by intramolecular Heck olefination and double bond isomerization. Highly substituted carbazoles have also been synthesized in good to excellent yields by this methodology.

Chapter 4 reports a novel palladium-catalyzed aryl-to-aryl migration. This reaction is both mechanistically and synthetically interesting, because it involves multiple C-H activation process and provides an unusual pathway for the synthesis of heterocyclic and carbocyclic compounds.

Chapter 5 describes a novel palladium-catalyzed activation of alkyl C-H bonds, which provides a novel way to synthesize cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics.

Finally, all of the ^1H and ^{13}C NMR spectra for the starting materials and reaction products have been compiled in appendices A-E following the general conclusions for this dissertation.

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CHAPTER 1. SYNTHESIS OF SUBSTITUTED ISOQUINOLINES BY ELECTROPHILIC CYCLIZATION OF IMINOALKYNES

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Abstract

The *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes and analogous pyridinecarbaldehydes have been cyclized under very mild reaction conditions in the presence of I₂, ICl, PhSeCl, PhSCl and *p*-O₂NC₆H₄SCl to give the corresponding halogen-, selenium- and sulfur-containing disubstituted isoquinolines and naphthyridines, respectively. This methodology accommodates a variety of iminoalkynes and affords the anticipated heterocycles in moderate to excellent yields. Monosubstituted isoquinolines and naphthyridines have been synthesized by the metal-catalyzed ring closure of these same iminoalkynes. The silver-catalyzed ring closure is highly effective in cyclizing aryl, alkenyl, and alkyl-substituted iminoalkynes at 50 °C.

Introduction

The isoquinoline backbone appears in numerous natural products. Thus, the synthesis of isoquinolines has received much recent attention.¹ Although classical methods have been frequently employed in the total synthesis of isoquinoline alkaloids, these approaches often have drawbacks. For example, the Bischler-Napieralski,² Pictet-Spengler,³ and Pomeranz-

Fritsh⁴ protocol require relatively strong acids to cyclize *E*-phenethylamines. Also, the Bischler-Napieralski² and the Pictet-Spengler³ reactions afford dihydro- and tetrahydroisoquinolines, respectively. An additional step involving dehydrogenation is thus required to complete the synthesis of the isoquinoline.

Recently, substituted isoquinolines have been synthesized by employing palladium chemistry. Widdowson has published a synthesis of isoquinolines by the reaction of a cyclopalladated *N*-*tert*-butylarylaldimine and acrylonitrile.⁵ His synthesis suffers from the use of stoichiometric amounts of palladium salts and high reaction temperatures (180-200 °C) for the final step. Heck has also reported the formation of 3,4-diphenylisoquinoline by the reaction of diphenylacetylene and a cyclopalladated *N*-*tert*-butylbenzalimine tetrafluoroborate complex (eq 1).⁶ This synthesis also utilizes a stoichiometric amount of palladium salts, which is not very practical in organic synthesis.

We have recently reported the formation of numerous 3,4-disubstituted isoquinolines by the palladium-catalyzed annulation of internal alkynes (eq 2)⁷ and carbopalladation of the *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes (eq 3).⁸ 3-Substituted isoquinoline derivatives can be prepared by the palladium and copper-catalyzed cross coupling of terminal alkynes and subsequent ring closure by catalytic CuI (eq 4)⁹ or by the reaction of *o*-(1-alkynyl)benzaldehydes with NH₃ (eq 5).¹⁰

$\text{R}^2 = \text{aryl, allylic, benzylic, 1-alkynyl}$

During the course of our isoquinoline annulation studies, we were encouraged to examine the electrophilic cyclization of our iminoalkynes by electrophiles other than organopalladium compounds in order to obtain 3,4-disubstituted isoquinolines (Scheme 1). The requisite iminoalkynes can be easily prepared by the Sonogashira reaction of a 2-halobenzaldehyde and a terminal alkyne, followed by reaction with *tert*-butylamine. We now wish to report that the electrophilic cyclization of the *tert*-butyl imines of *o*-(1-alkynyl)benzaldehydes and analogues provides a very efficient synthesis of a wide variety of substituted isoquinolines.

Scheme 1

Results and Discussion

First, we studied the reaction of iminoalkyne **1** with I_2 in CH_3CN at room temperature in the presence of a variety of bases (eq 6). The results are summarized in Table 1, entries 1-11.

Table 1. Ring Closure of Iminoalkyne **1** by I_2 (eq 6).^a

entry	base	time (h)	% yield of 2 ^b	% yield of 3 ^b
1	-	3	17	trace
2	NaHCO_3	3	36	24
3	Na_2CO_3	24	30	26
4	K_2CO_3	3	31	28
5	$\text{NaOCO}_2\text{CH}_3$	0.5	68	0
6	<i>t</i> -BuOK	3	17	0
7	<i>n</i> - $\text{C}_3\text{H}_7\text{CO}_2\text{Na}$	72	20	0
8	Et_3N	72	trace	0
9	pyridine ^c	72	20	0

10		72	32	trace
11		72	22	0
12 ^d		72	30	0
13 ^e		72	trace	0

^a All reactions were run under the following conditions, unless otherwise described: 0.25 mmol of 1 and 0.75 mmol of the base in 7 ml of CH₃CN were stirred at room temperature under Ar for the specific period of time. ^b Isolated yields. ^c Pyridine (7 ml) were used as both the solvent and the base. ^d No I₂ was employed and 7 ml of CH₂Cl₂ were used as the solvent. ^e No I₂ was employed.

When no base was employed, this cyclization reaction only gave 17 % of the desired isoquinoline product 2 (entry 1). The addition of carbonate bases, such as NaHCO₃, Na₂CO₃ and K₂CO₃ increased the yields of 2 to 36 %, 30 % and 31 %, respectively (entries 2-4), while side product 3 was observed in 24 % to 28 % yields. The side product 3 probably arises from reaction of the intermediate isoquinolinium salt with water, hydroxide or the carbonate base (see the later mechanistic discussion). Surprisingly, the use of NaOCO₂CH₃¹¹ as the base (entry 5) produced a 68 % yield of 2 and none of the side product 3 was produced. This reaction was complete in 0.5 h. The very different results from the reaction of NaOCO₂CH₃ and the other carbonate bases can be explained by the fact that NaOCO₂CH₃ reacts with a proton to produce CO₂ and MeOH, while the reactions of a proton with the bases NaHCO₃, Na₂CO₃ or K₂CO₃ generate CO₂ and H₂O. The H₂O generated probably leads to the formation of side product 3 and thus results in low yields of 2. When a stronger

base, KO-*t*-Bu was employed, only a 17 % yield of 2 was observed (entry 6). The low yield may be a direct result of the fact that the imine appears to be unstable in the presence of this strong base. The reactions employing the less basic salt *n*-C₃H₇CO₂Na and the organic base Et₃N were quite slow (entries 7 and 8). These reactions are not complete even in 3 days and give only a 20 % yield and a trace of 2, respectively. Pyridine and hindered pyridine derivatives, such as 2,4,6-trimethylpyridine and 2,6-di-*tert*-butyl-4-methylpyridine, have also been employed (entries 9-11). Although no side product 3 was produced, all of these reactions were slow and suffered low yields ranging from 20 % to 32 %. The use of *bis*-(2,4,6-trimethylpyridine)iodine(I) hexafluorophosphate, which is both a source of iodine cation and a potential base, failed to improve the yield of 2. A 30 % yield of 2 was observed when the reaction was carried out in CH₂Cl₂ (entry 12), while only trace amounts of 2 were produced in CH₃CN (entry 13). We have found that using less than 3 equivs of the base and 6 equivs of I₂ results in a lower yield. So we have chosen the following conditions as optimal for all subsequent experiments: 0.25 mmol of the iminoalkyne, 6 equivs of I₂, 3 equivs of NaOCO₂CH₃ in 7 ml of CH₃CN are stirred at room temperature for an appropriate amount of time. Most of the reactions are complete in 0.5 h and afford good to excellent yields of the corresponding iodoisoquinolines and idonaphthyridines. The results using I₂ are summarized in Table 2, entries 1, 3, 4, 6, 8, 10, 12 and 13.

The stronger electrophilic reagent ICl has also been employed in these cyclizations and the corresponding cyclization products have been observed in yields comparable to those obtained using I₂, except for iminoalkynes 10 (compare entries 8 and 9) and 16 (compare entries 13 and 14). The reasons for this are not obvious. The reaction times are also usually

pretty similar to those of I_2 . The results are summarized in Table 2, entries 2, 5, 7, 9, 11, and 14.

Of all of the electrophilic reagent examined, I_2 and ICl close the six-membered ring the fastest. Most of these reactions are complete in 0.5 h. The reactions of 1 with I_2 and ICl gave almost identical yields, 67 % and 68 % respectively (entries 1 and 2). When the iminoalkyne 4 bearing a cyclohexenyl group was allowed to react with I_2 (entry 3), the yield was similar to that of 1. This indicates that this electrophilic reaction can tolerate double bonds.

To further test the scope of this electrophilic ring closure, alkyl-substituted acetylenes, such as iminoalkynes o -(t -BuN=CH) $C_6H_4C\{CR [R = \text{cyclohexyl (38) or } CH_2CH_2OTHP (40)]$ have been allowed to react with I_2 and ICl . Cacchi has reported that alkyl-substituted o -(1-alkynyl)phenols react with I_2 to give substituted iodobenzofurans.¹¹ However, in our chemistry, I_2 and ICl do not react with either of the alkyl-substituted iminoalkynes to afford the desired products and neither do $PhSeCl$ or $PhSCl$ as will be discussed later. The coordination of iodine to the carbon-carbon triple bonds in these iminoalkynes should result in a partial positive charge on the carbon next to the aromatic ring, since an aryl group stabilizes a carbocation better than an alkyl group. Obviously, the formation of isoquinolines from such an intermediate is impossible.

Table 2. Synthesis of Isoquinolines and Naphthyridines by the Reaction of Iminoalkynes and Electrophiles.^a

entry	iminoalkyne	electrophile	time (h)	product	% isolated yield
1		(1) I ₂ ^b	0.5		68
2		ICl ^c	0.5		67
3		(4) I ₂ ^b	0.5		67
4		I ₂ ^b	0.5		30
5		ICl ^c	0.5		24
6		I ₂ ^b	0.1		37
7		ICl ^c	0.5		40
8		I ₂ ^b	0.5		0
9		ICl ^c	0.5		52

Table 2 continued

10		(12)	I ₂ ^b	0.5		(13)	90
11		(13)	ICl ^c	0.5		(13)	92
12		(14)	I ₂ ^b	0.5		(15)	76
13		(16)	I ₂ ^b	0.2		(17)	13
14			ICl ^c	24		(17)	72
15	1		PhSeCl	24		(18)	76
16	4		PhSeCl	24		(19)	96
17	6		PhSeCl	48		(20)	95

Table 2 continued

18		(21)	PhSeCl	72		(22)	18
19	10		PhSeCl	72		(23)	60
20	16		PhSeCl	72		(24)	80
21	12		PhSeCl	24		(25)	72
22	14		PhSeCl	72		(26)	61
23	1	$p\text{-O}_2\text{NC}_6\text{H}_4\text{SeCl}$	48	R = Ph		(27)	46

Table 2 continued

24	4	$p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$	48		R =	(28)	33
25	8	$p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$	72		R =	(29)	25
26	4	PhSCl	24		R =	(30)	45
27	6	PhSCl	24		R =	(31)	43
28	14	PhSCl	24		R =	(32)	40
29	1	AgNO_3^d	24		R =	(33)	82
30		CuI^e	3			(33)	100

Table 2 continued

31	4	AgNO ₃ ^d	24		(34)	78
32		CuI ^e	3		(34)	81
33	6	AgNO ₃ ^d	72		(35)	71
34		(36)	72		(37)	54
35		(38)	24		(39)	75
36		CuI ^e	6		(39)	93
37		(40)	24	$R = \text{CH}_2\text{CH}_2\text{OTHP}$	(41)	62
38		CuI ^e	5		(41)	83
39	9	AgNO ₃ ^d	24		(42)	56

Table 2 continued

40	11	AgNO ₃ ^d	24		(43)	92
41	13	AgNO ₃ ^d	72		(44)	45
42	15	AgNO ₃ ^d	72		(45)	80

^a All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the iminoalkyne, 2 equivs of electrophile in 7 ml of CH₂Cl₂ at room temperature. ^b 0.25 Mmol of the iminoalkyne, 6 equivs of I₂, 3 equivs of NaOCO₂CH₃ in 7 ml of CH₃CN at room temperature. ^c 4 Equiv of ICl have been used. ^d 0.25 Mmol of the iminoalkyne, 5 mol % of AgNO₃ in 7 ml of CHCl₃ at 50 °C. ^e 0.25 Mmol of the iminoalkyne, 10 mol % of CuI in 5 ml of DMF at 100 °C.

While iminoalkyne **21**, *o*-(*t*-BuN=CH)C₆H₄C{CC₆H₄-*p*-CF₃, bearing an electron-deficient arylethynyl group didn't react with I₂ or ICl at all, the introduction of an electron-rich arylethynyl group, as found in iminoalkynes **6** (entries 4 and 5) and **8** (entries 6 and 7) rather surprisingly resulted in low yields of the desired heterocyclic iodides. Similarly, none of the desired product has been obtained when iminoalkyne **10** with a methylenedioxy substituent is allowed to react with I₂ (entry 8), although all of the starting material is gone in 0.5 h. However, a 52 % yield of **11** was observed when ICl was employed as the electrophile (entry 9). This is possibly because ICl is a stronger electrophile than I₂.

From entries 10 and 11 in Table 2, one can see that the introduction of a pyridine ring into the starting material results in relatively high yields when either I₂ or ICl are employed as electrophiles. This might be explained by an intermediate such as **46**. The pyridine

nitrogen might first coordinate to the electrophile to form a pyridinium cation. Because of this coordination, electrophilic attack of the triple bond might then occur in an intramolecular fashion. The intramolecular assistance significantly increases the yields for the reactions of I₂ and ICl from 68 % and 67 % for iminoalkyne **1** (entries 1 and 2) to 90 % and 92 % for iminoalkyne **12** (entries 10 and 11), respectively.

Alternatively, the presence of the pyridine moiety in iminoalkyne **12** may simply be directing the cationic charge of the intermediate iodonium ion to the more remote carbon of the alkyne, which should favor formation of the 6-membered ring isoquinoline. Whatever

the reason, the result is very encouraging, since it broadens the potential applications of this cyclization and improves its efficiency.

As described above, iminoalkynes derived from *o*-iodobenzaldehyde and acetylenes bearing simple alkyl groups do not react with I_2 . However, iminoalkyne **14** can be cyclized by I_2 giving naphthyridine **15** in a 76 % yield (entry 12). Again, we believe that the key is the coordination of the electrophile to the pyridine nitrogen and formation of an intermediate like **4**.

In an attempt to try to confirm this intramolecular assistance, iminoalkyne **16** has been allowed to react with I_2 , and only a 13 % yield of **17** was obtained (entry 13). Compared to the reaction of **12** and I_2 (entry 10), the yield dropped from 90 % to 13 %. This may arise because **16** geometrically disfavors intramolecular assistance or it may simply be that we have now further removed the more electron-withdrawing nitrogen from the vicinity of the carbon-carbon triple bond. However, iminoalkyne **16** reacts with ICl to give naphthyridine **17** in 72 % yield, although this reaction requires 1 day to reach completion (entry 14). It is logical that ICl , a stronger electrophile than I_2 , should work better in this reaction.

The next electrophilic reagent studied was $PhSeCl$. A variety of reaction conditions have been examined and the results are summarized in Table 3. Very similar yields, 74 % and 78 % respectively, of isoquinoline **18** have been obtained from iminoalkyne **1** using one or two equivs of $PhSeCl$ (Table 3, entries 1 and 2). The concentration of the reactants seems

to play a minor role in this reaction. From entry 3, one can see that a more concentrated reaction actually gave a slightly lower yield. The reagent PhSeSePh failed to yield any of the corresponding isoquinoline (entry 4). Thus, we chose 0.25 mmol of the iminoalkyne, 2 equivs of PhSeCl in 7 ml of CH₂Cl₂ at room temperature as our standard reaction conditions for the reaction of PhSeCl and our iminoalkynes. In general, the reaction of iminoalkynes and PhSeCl requires 1-3 days and good to excellent yields of selenium-containing isoquinolines and naphthyridines are obtained (Table 2, entries 15-22). The major exception was iminoalkyne **21**, which gave only an 18 % yield after 3 days reaction time (entry 18).

Table 3. Optimization of the Cyclization Reaction Employing Se and S Electrophiles.^a

entry	electrophile	equiv of electrophile	temp (°C)	time (d)	% yield
1	PhSeCl	1	25 °C	1	74
2		2		1	78
3				1	70 ^b
4	PhSeSePh			1	0
5	<i>p</i> -NO ₂ C ₆ H ₄ SCl			3	47
6				3	45 ^c
7			60 °C	3	47

^a All reactions were run using 0.25 mmol of **1** in 7 ml of CH₂Cl₂, unless otherwise specified. ^b Two ml of CH₂Cl₂ were used. ^c Two equivs of ZnCl₂ were added.

Cyclizations employing PhSeCl have generally proven quite successful. A 76 % yield of the isoquinoline product **18** has been obtained, when iminoalkyne **1** is allowed to react with PhSeCl (entry 15). When employing an iminoalkyne bearing a vinylic group on the

triple bond, a 96 % yield of selenium-containing isoquinoline **19** has been observed (entry 16). In contrast to the reactions of I_2 and ICl , the introduction of an electron-rich arylethynyl group into the iminoalkyne increases the yield from 76 % (entry 15) to 95 % (entry 17). However, the reaction of $PhSeCl$ and iminoalkyne **21** bearing an electron-deficient arylethynyl group results in only an 18 % yield of isoquinoline (entry 18). Thus, electron-rich arylethynyl groups benefit the ring closure by $PhSeCl$, while an electron-deficient arylethynyl group disfavors cyclization. Obviously, the presence of an electron-rich arylethynyl group may be favoring the formation of the positive charge on the carbon necessary for formation of the six-membered ring. This supposition is confirmed by the reaction of **10** and $PhSeCl$, where the electron rich methylenedioxy group presumably favors cation formation on the "wrong" carbon of the alkyne, which results in a lower yield of selenium-substituted naphthalene (entry 19). Only a 60 % yield of **23** was obtained when **10** was allowed to react with $PhSeCl$. Although both iminoalkynes **6** (entry 17) and **10** (entry 19) have relatively electron-rich triple bonds, they afford quite different results. The lower yield of **23** can be explained as shown in Scheme 2. The positive charge on the alkyne carbon bearing the trimethoxyphenyl ring in intermediate **48** is better stabilized and therefore closure to a six-membered ring and formation of the isoquinoline product **20** are favored (entry 17). In intermediate **49**, more of the partial positive charge is located on the alkyne carbon bearing the methylenedioxyphenyl ring, which disfavors the formation of a six-membered ring and results in a decrease in the yield from 95 % (entry 17) to 60 % (entry 19).

Scheme 2

Although the electron density on both the triple bond and the imine nitrogen is decreased by the presence of a pyridine ring in compound **16**, we still obtain an 80 % yield from the reaction of iminoalkyne **16** and PhSeCl (entry 20). This may be explained by the fact that the partial positive charge in intermediate **50** (Scheme 2) is delocalized better by the phenyl group. Subsequent endo-6-trig attack apparently proceeds smoothly to form a stable isoquinoline product.

Iminoalkynes **12** and **14** also react with PhSeCl to give decent yields (entries 21 and 22). The success of these reactions may be the result of intramolecular assistance as described above. Alternatively, the presence of an electron-deficient pyridine ring may simply be favoring formation of an intermediate with a positive charge located on the carbon necessary to close the six-membered ring and disfavoring formation of the "wrong cation" on the carbon-carbon triple bond.

Unfortunately, when PhSeCl has been allowed to react with alkyl-substituted iminoalkynes, such as iminoalkynes *o*-(*t*-BuN=CH)C₆H₄C{CR [R = cyclohexyl (**38**) or CH₂CH₂OTHP (**40**)], none of the desired product was observed. The results are similar to those from the reactions of I₂ and iminoalkynes **38** and **40**.

The electrophile $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$ has been examined under the optimal reaction conditions developed for PhSeCl . The isoquinoline product **27** expected from iminoalkyne **1** was obtained in a rather low yield of 47 % (Table 3, entry 5). The addition of the Lewis acid ZnCl_2 (entry 6) or an increase in the reaction temperature (entry 7) in an attempt to induce cyclization had little effect on the product yield, so the optimal reaction conditions for PhSeCl have been used in the reactions of $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$ and PhSCl ¹² (Table 2, entries 23-28). In general, the yields of sulfur-containing isoquinolines from $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$ and PhSCl fall in the range of 25-46 %. The reactions producing nitro-containing products generally proceed in a slightly lower yield and require much longer reaction times.

The electrophile $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$ reacts with iminoalkynes **1**, **4** and **8** to produce the corresponding 4-(p -nitrophenylsulfenyl)isoquinoline derivatives in modest yields (entries 23-25). These yields are lower than those of reactions with I_2 , ICl or PhSeCl . This is probably because this reagent is a weaker electrophile. Much better yields of the sulfur-containing isoquinolines were obtained when PhSCl was employed as the electrophile. As shown in entries 26-28, iminoalkynes **4**, **6** and **14** were allowed to react with PhSCl and the corresponding sulfide products **30-32** were obtained in yields ranging from 40 % to 45 %. All of these reactions were complete in 24 h. However, the reactions of PhSCl and the alkyl-substituted iminoalkynes **38** and **40** afforded none of the desired product. Thus, rather surprisingly, the pyridine-containing iminoalkyne **32** actually gives better results than the corresponding alkyl-substituted phenyl analogues. This may be due to intramolecular assistance by the pyridine as described earlier.

In order to synthesize monosubstituted isoquinolines, 10 mol % of CuI has been employed to close these same iminoalkynes to heterocycles with a hydrogen in the 4

position.⁷ The results from these cyclizations are summarized in Table 2, entries 30, 32, 36 and 38. We now wish to report that catalytic amounts of AgNO₃ will effect the same transformation and the reaction occurs under milder reaction conditions, although the yields are often a bit lower. Thus, 0.25 mmol of iminoalkyne **1** have been allowed to react with 2 equivs of AgNO₃ in 7 ml of CHCl₃ at 50 °C (Table 4, entry 1). After 1 day, the monosubstituted isoquinoline **33** was obtained in a 90 % isolated yield. Further study indicated that 5 mol % of AgNO₃ is enough to close the six-membered ring in good yield (entries 2-4). The reaction failed when only 1 % of AgNO₃ was employed as the catalyst. Both AgNO₃ and AgOAc gave approximately the same yields for this ring closure (compare entries 3 and 5). Thus, the following standard conditions have been employed in all subsequent experiments: 0.25 mmol of the iminoalkyne and 5 mol % of AgNO₃ were stirred at 50 °C in 7 ml of CHCl₃ for the appropriate reaction time. The reaction takes 1-3 days at 50 °C and gives decent yields of the corresponding cyclization products (Table 2, entries 29, 31, 33-35, 37, and 39-42).

Table 4. Silver-catalyzed Ring Closure of Iminoalkyne 1.^a

entry	silver salt (equivs)	solvent	product	% isolated yield
1	AgNO ₃ (2.00)	CHCl ₃	33	90
2	(0.10)			80
3	(0.05)			82
4	(0.01)			0 ^b
5	AgOAc (0.05)			80
6	AgNO ₃ (2.00)	CDCl ₃		69

^a All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of iminoalkyne 1 and the indicated amount of silver salt in 7 ml of the solvent were stirred at 50 °C for 24 h. ^b After 24 h, there was only a minimal amount of the desired product present by TLC.

The source of the hydrogen atom ending up in the 4 position of the isoquinoline is not obvious. If the hydrogen atom comes from the solvent, the use of DCCl₃ would have resulted in a deuterated product (Table 4, entry 6). This was not the case as indicated by ¹H NMR spectroscopic analysis. Thus, we believe that the hydrogen is coming from the *tert*-butyl group of the imine or from small amounts of water present in the reaction.

As described above, alkyl-substituted *N*-(*o*-(1-alkynyl)benzylidene)-*tert*-butylamines failed to afford any of the desired isoquinolines when allowed to react with I₂, ICl, PhSeCl or *p*-O₂NC₆H₄SCl. However, iminoalkyne **38** and **40** do react with AgNO₃ or CuI to afford decent yields of the corresponding isoquinolines (Table 2, entries 35-38).

In general, the reactions of I₂ and ICl form the six-membered ring isoquinolines the fastest. In most cases, these reactions are complete in 0.5 h. However, the yields are less than those obtained from the reactions of PhSeCl, AgNO₃ or CuI. The reagents PhSeCl and *p*-O₂NC₆H₄SCl are the least efficient electrophilic reagents for this process, and their reactions require longer reaction times and result in lower yields.

For the reactions of I₂ or ICl and iminoalkyne **1**, we propose the mechanism shown in Scheme 3. First, the carbon-carbon triple bond of iminoalkyne **1** coordinates to the iodine cation generated from I₂ to generate an iodonium intermediate. This is followed by attack of the imine nitrogen on the activated triple bond to form intermediate **52**. Alternatively, the coordination of the iodine cation to the carbon-carbon triple bond may form a cationic intermediate like **51**, which cyclizes to intermediate **52**. The isoquinolinium salt **52** then presumably ionizes to produce the iodoisoquinoline **2** and a *tert*-butyl cation, which generates isobutylene.

Scheme 3

Conclusions

In conclusion, a procedure for the efficient synthesis of a wide variety of substituted isoquinolines has been developed which employs very mild reaction conditions. This methodology accommodates a variety of iminoalkynes and affords the anticipated substituted isoquinolines in moderate to excellent yields.

Experimental Section

General. The 1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F) and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 +

5 ml of NaOH (5 %) + 300 ml of H₂O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Elemental analyses were performed at Iowa State University on a Perkin Elmer 2400 CHNS/O Series II Analyzer. All reagents were used directly as obtained commercially unless otherwise noted. 2-Bromopyridine-3-carboxaldehyde,¹³ 3-bromopyridine-4-carboxaldehyde¹³ and PhSCl¹⁴ were prepared according to literature procedures. The following starting materials were prepared as indicated.

2-(2-Propenylethynyl)benzyl alcohol. To a solution of 2-iodobenzyl alcohol (1.40 g, 6.0 mmol) and 2-methyl-1-buten-3-yne (0.47 g, 7.2 mmol) in Et₃N (24 ml) were added PdCl₂(PPh₃)₂ (84 mg, 2 mol %) and CuI (12 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 50 °C for 24 h. The mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using 5:1 hexane/EtOAc to afford 0.97 g (94 %) of the desired compound as a yellow oil: ¹H NMR (CDCl₃) δ 1.99 (dd, *J* = 0.9, 1.5 Hz, 3H), 2.72 (t, *J* = 6.0 Hz, 1H), 4.79 (d, *J* = 6.0 Hz, 2H), 5.31-5.33 (m, 1H), 5.40-5.42 (m, 1H), 7.22-7.33 (m, 2H), 7.40-7.44 (m, 2H); ¹³C NMR (CDCl₃) δ 23.7, 63.9, 86.0, 95.6, 121.3, 122.5, 126.8, 127.2, 127.5, 128.8, 132.2, 142.7.

Aldehydes Prepared

2-(2-Propenylethynyl)benzaldehyde. To a solution of 2-(2-propenylethynyl)benzyl alcohol (0.86 g, 5 mmol) in 75 ml of CH₂Cl₂ was added MnO₂ (6.52 g, 75 mmol). The

resulting mixture was stirred at 25 °C for 12 h. The extra MnO₂ was removed by filtration. The solvent was removed under reduced pressure and the oily residue was purified by flash column chromatography using 11:1 hexane/EtOAc to afford 0.73 g (86 %) of the desired compound as yellow oil: ¹H NMR (CDCl₃) δ 2.02 (dd, *J* = 0.9, 1.2 Hz, 3H), 5.38-5.40 (m, 1H), 5.48-5.49 (m, 1H), 7.41-7.44 (m, 1H), 7.54-7.56 (m, 2H), 7.90-7.93 (m, 1H), 10.54 (d, *J* = 0.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 23.4, 84.0, 97.7, 123.6, 126.4, 127.1, 127.3, 128.7, 133.4, 133.9, 136.0, 191.9.

General procedure for the preparation of other aldehydes. To a solution of the aryl halide (10.0 mmol) and the terminal alkyne (12.0 mmol, 1.2 equivs) in Et₃N (40 ml) were added PdCl₂(PPh₃)₂ (140 mg, 2 mol %) and CuI (20 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 50 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding arylalkyne.

2-(2-Phenylethynyl)benzaldehyde. 2-Bromobenzaldehyde (1.86 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol) were employed. Column chromatography using 20:1 hexane/EtOAc afforded 1.94 g (94 %) of the desired compound as a yellow oil with spectral properties identical to those previously reported.¹⁵

2-(2-Cyclohex-1-enylethynyl)benzaldehyde. 2-Bromobenzaldehyde (1.86 g, 10.0 mmol) and 1-ethynylcyclohexene (1.27 g, 12.0 mmol) were employed. Column chromatography using 25:1 hexane/EtOAc afforded 2.00 g (95 %) of the desired compound

as a yellow oil: ^1H NMR (CDCl_3) δ 1.57-1.72 (m, 4H), 2.11-2.18 (m, 2H), 2.20-2.25 (m, 2H), 6.27 (m, 1H), 7.33-7.39 (m, 1H), 7.49-7.51 (m, 2H), 7.87 (dt, $J = 1.2, 7.8$ Hz, 1H), 10.52 (d, $J = 0.9$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.5, 22.3, 25.9, 29.0, 82.5, 98.6, 120.4, 127.1, 127.7, 128.1, 133.1, 133.8, 135.7, 136.9, 192.0.

2-(3,4,5-Trimethoxyphenylethynyl)benzaldehyde. 3,4,5-Trimethoxyiodobenzene (2.94 g, 10.0 mmol) and 2-ethynylbenzaldehyde (1.56 g, 12.0 mmol) were employed. Column chromatography using 9:1 hexane/EtOAc afforded 2.67 g (90 %) of the desired compound as a yellow oil: ^1H NMR (CDCl_3) δ 3.89 (s, 3H), 3.90 (s, 6H), 6.80 (s, 2H), 7.46 (t, $J = 7.2$ Hz, 1H), 7.56-7.66 (m, 2H), 7.95 (d, $J = 7.8$ Hz, 1H), 10.66 (d, $J = 0.9$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 56.5, 61.2, 84.2, 96.6, 109.1, 117.5, 127.0, 127.5, 128.8, 133.4, 134.0, 136.0, 139.7, 153.4, 191.9.

2-(4-Methoxyphenylethynyl)benzaldehyde. 2-Bromobenzaldehyde (1.86 g, 10.0 mmol) and 4-methoxyphenylacetylene (1.58 g, 12.0 mmol) were employed. Column chromatography using 11:1 hexane/EtOAc afforded 2.20 g (93 %) of the desired compound as a yellow solid: mp 50-51 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 3.85 (s, 3H), 6.92 (d, $J = 8.7$ Hz, 2H), 7.44 (t, $J = 7.2$ Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 2H), 7.58-7.66 (m, 2H), 7.95 (d, $J = 8.1$ Hz, 1H), 10.66 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.5, 83.9, 96.7, 114.3, 114.5, 127.3, 127.5, 128.4, 133.2, 133.4, 133.9, 135.8, 160.4, 192.1.

4,5-Methylenedioxy-2-(phenylethynyl)benzaldehyde. 2-Bromo-4,5-(methylenedioxy)benzaldehyde (2.30 g, 10.0 mmol) and phenylacetylene (1.22 g, 12.0 mmol) were employed. Column chromatography using 20:1 hexane/EtOAc afforded 2.40 g (96 %) of the desired compound as a yellow solid: mp 98-101 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 6.10

(s, 1H), 7.04 (s, 1H), 7.26 (s, 1H), 7.38-7.40 (m, 3H), 7.54-7.56 (m, 2H), 10.50 (s, 1H); ^{13}C NMR (CDCl_3) δ 85.0, 95.4, 102.6, 106.3, 112.2, 122.5, 123.9, 128.8, 129.2, 131.8, 132.4, 148.9, 152.6, 190.3.

2-(Phenylethynyl)pyridine-3-carboxaldehyde. 2-Bromopyridine-3-carboxaldehyde¹³ (1.88 g, 10.0 mmol) and phenylacetylene (1.22 g, 12.0 mmol) were employed. Column chromatography using 7:1 hexane/EtOAc afforded 1.85 g (96 %) of the desired compound as a yellow oil with spectral properties identical to those previously reported.^{13a}

2-(1-Octyn-1-yl)pyridine-3-carboxaldehyde. 2-Bromopyridine-3-carboxaldehyde¹³ (1.88 g, 10.0 mmol) and 1-octyne (0.98 g, 12.0 mmol) were employed. Column chromatography using 7:1 hexane/EtOAc afforded 2.04 g (95 %) of the desired compound as a yellow oil: ^1H NMR (CDCl_3) δ 0.89-0.92 (m, 3H), 1.33-1.40 (m, 4H), 1.40-1.57 (m, 2H), 1.66-1.71 (m, 2H), 7.36-7.37 (m, 1H), 8.14-8.17 (m, 1H), 8.75-8.77 (m, 1H), 10.54-10.56 (m, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 19.7, 22.7, 28.3, 28.9, 31.5, 76.8, 98.8, 122.9, 131.9, 134.7, 146.8, 154.5, 191.5.

3-(Phenylethynyl)pyridine-4-carboxaldehyde. 3-Bromopyridine-4-carboxaldehyde¹³ (1.88 g, 10.0 mmol) and phenylacetylene (1.22 g, 12.0 mmol) were employed. Column chromatography using 7:1 hexane/EtOAc afforded 1.89 g (95 %) of the desired compound as a yellow oil with spectral properties identical to those previously reported.^{13a}

2-(4-Trifluoromethylphenylethynyl)benzaldehyde. 4-Iodobenzotrifluoride (2.72 g, 10.0 mmol) and 2-ethynylbenzaldehyde (1.56 g, 12.0 mmol) were employed. Column chromatography using 9:1 hexane/EtOAc afforded 2.33 g (85 %) of the desired compound as a yellow oil: ^1H NMR (CDCl_3) 7.49 (t, $J = 7.5$ Hz, 1H), 7.57-7.67 (m, 6H), 7.96 (d, $J = 7.2$

Hz, 1H), 10.62 (s, 1H); ^{13}C NMR (CDCl_3) δ 87.4, 94.7, 125.7 (q, $J = 15$ Hz), 126.1, 126.3, 126.3, 127.8, 129.4, 132.1, 133.6, 134.0, 136.2, 191.4.

2-(Cyclohexylethynyl)benzaldehyde. 2-Bromobenzaldehyde (1.86 g, 10.0 mmol) and cyclohexylacetylene (1.30 g, 12.0 mmol) were employed. Column chromatography using 25:1 hexane/EtOAc afforded 2.00 g (94 %) of the desired compound as a yellow oil with spectral properties identical to those previously reported.¹⁶

2-(4-(Tetrahydropyran-2-yloxy)but-1-ynyl)benzaldehyde. 2-Bromobenzaldehyde (1.86 g, 10.0 mmol) and 2-(3-butynyloxy)tetrahydro-2H-pyran (1.85 g, 12.0 mmol) were employed. Column chromatography using 10:1 hexane/EtOAc afforded 2.30 g (90 %) of the desired compound as a yellow oil with spectral properties identical to those previously reported.¹⁶

Imines Prepared

N-(2-Phenylethynylbenzylidene)-tert-butylamine (1). To 2-(2-phenylethynyl)benzaldehyde (1.04 g, 5.0 mmol) in a 4 dram vial was added *t*-BuNH₂ (6 equiv). The mixture was then stirred under an Ar atmosphere at room temperature for 24 h. The resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.27 g (98 %) of imine 1 as a yellow solid: mp 53-54 °C; ^1H NMR (CDCl_3) δ 1.36 (s, 9H), 7.35-7.41 (m, 5H), 7.54-7.58 (m, 3H), 8.07-8.10 (m, 1H), 8.95 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.0, 58.0, 86.9, 95.1, 123.3, 124.1, 126.6, 128.7, 128.8, 129.9, 131.7, 132.4, 138.0, 154.4; IR (CHCl_3 , cm^{-1}) 3060, 2214, 1637; HRMS Calcd for $\text{C}_{19}\text{H}_{19}\text{N}$: 261.1518. Found: 261.1518.

***N*-[2-(Cyclohex-1-enylethynyl)benzylidene]-*tert*-butylamine (4).** This imine was prepared from 2-(2-cyclohex-1-enylethynyl)benzaldehyde (1.06 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.22 g (92 %) of the imine 4 as a reddish oil: ^1H NMR (CDCl_3) δ 1.32 (s, 9H), 1.59-1.74 (m, 4H), 2.13-2.20 (m, 2H), 2.22-2.27 (m, 2H), 6.23 (dddd, $J = 1.8, 1.8, 6.0, 6.0$ Hz, 1H), 7.29-7.33 (m, 2H), 7.39-7.45 (m, 1H), 7.98-8.05 (m, 1H), 8.82 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.6, 22.5, 25.9, 29.4, 29.9, 57.9, 84.3, 97.0, 120.8, 124.5, 125.9, 128.2, 129.7, 132.1, 135.6, 137.6, 154.6; IR (neat, cm^{-1}) 3062, 2200, 1637; HRMS Calcd for $\text{C}_{19}\text{H}_{23}\text{N}$: 265.1830. Found: 265.1831.

***N*-[2-(3,4,5-Trimethoxyphenylethynyl)benzylidene]-*tert*-butylamine (6).** This imine was prepared from 2-(3,4,5-trimethoxyphenylethynyl)benzaldehyde (1.48 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.47 g (84 %) of the imine 6 a yellow oil: ^1H NMR (CDCl_3) δ 1.36 (s, 9H), 3.89 (s, 9H), 6.77 (s, 2H), 7.35-7.38 (m, 2H), 7.53 (dd, $J = 3.0, 6.0$ Hz, 1H), 8.05 (dd, $J = 3.6, 6.0$ Hz, 1H), 8.92 (s, 1H); ^{13}C NMR (CDCl_3) δ 29.9, 56.3, 58.0, 61.2, 86.1, 95.1, 108.9, 118.3, 124.0, 126.2, 128.8, 129.9, 132.2, 138.0, 139.3, 153.4, 154.3; IR (neat, cm^{-1}) 2958, 2206, 1698; HRMS Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_3$: 351.1834. Found: 351.1839.

***N*-[2-(4-Methoxyphenylethynyl)benzylidene]-*tert*-butylamine (8).** This imine was prepared from 2-(4-methoxyphenylethynyl)benzaldehyde (1.18 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.41 g (97 %) of the imine 8 as a yellow oil: ^1H NMR (CDCl_3) δ 1.34 (s, 9H), 3.84 (s, 3H), 6.90 (td, $J = 2.1, 9.0$ Hz, 2H), 7.32-7.36 (m, 2H), 7.47 (td, $J = 2.1, 9.0$ Hz, 2H), 7.50-7.54 (m, 1H), 8.04-8.07 (m, 1H), 8.92 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.0, 55.6, 58.1, 85.7, 95.2, 114.4, 115.4, 124.5, 126.1, 128.5, 129.9,

132.3, 133.2, 137.7, 154.7, 160.0; IR (neat, cm^{-1}) 2963, 2836, 1699; HRMS Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$: 291.1623. Found: 291.1626.

***N*-[(6-Phenylethynyl)benzo[1,3]dioxol-5-ylmethylene]-*tert*-butylamine (10).** This imine was prepared from 4,5-methylenedioxy-2-(phenylethynyl)benzaldehyde (1.25 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.53 g (100 %) of the imine **10** as a yellow solid: mp 88-90 °C; ^1H NMR (CDCl_3) δ 1.32 (s, 9H), 6.02 (s, 2H), 6.97 (s, 1H), 7.36-7.39 (m, 3H), 7.50-7.53 (m, 2H), 7.57 (s, 1H), 8.85 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.1, 57.8, 86.9, 93.9, 101.9, 105.9, 111.3, 118.6, 123.4, 128.6, 131.6, 134.1, 148.8, 149.2, 153.7; IR (CHCl_3 , cm^{-1}) 3018, 2969, 2904, 1612; HRMS Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_2$: 305.1416. Found: 305.1420.

***N*-[(2-Phenylethynyl)pyridin-3-ylmethylene]-*tert*-butylamine (12).** This imine was prepared from 2-(phenylethynyl)pyridine-3-carboxaldehyde (1.04 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.31 g (100 %) of the imine **12** as a yellow oil: ^1H NMR (CDCl_3) δ 1.35 (s, 9H), 7.29 (ddd, $J = 0.3, 3.6, 6.0$ Hz, 1H), 7.38-7.41 (m, 3H), 7.59-7.62 (m, 2H), 8.36 (dd, $J = 1.5, 6.0$ Hz, 1H), 8.63 (dd, $J = 1.5, 3.6$ Hz, 1H), 8.88 (s, 1H); ^{13}C NMR (CDCl_3) δ 29.8, 58.4, 86.3, 94.5, 122.2, 123.3, 128.7, 129.4, 132.1, 133.9, 134.2, 143.5, 151.3, 152.5; IR (neat, cm^{-1}) 3057, 2967, 2928, 2218, 1699; HRMS Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2$: 262.1470. Found: 262.1475.

***N*-[2-(1-Octyn-1-yl)pyridin-3-ylmethylene]-*tert*-butylamine (14).** This imine was prepared from 2-(1-octyn-1-yl)pyridine-3-carboxaldehyde (1.08 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.35 g (100 %) of the imine **14** as a yellow oil: ^1H NMR (CDCl_3) δ 0.87-0.92 (m, 3H), 1.29-1.34 (m, 13H), 1.46-1.52 (m, 2H),

1.60-1.71 (m, 2H), 2.52 (t, $J = 6.9$ Hz, 2H), 7.23 (dd, $J = 4.8, 7.8$ Hz, 1H), 8.30 (dd, $J = 1.8, 7.8$ Hz, 1H), 8.55 (dd, $J = 1.8, 4.8$ Hz, 1H), 8.74 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 19.7, 22.7, 28.6, 28.9, 29.8, 31.5, 58.2, 78.1, 96.6, 122.8, 133.7, 133.8, 144.1, 151.1, 152.9; IR (neat, cm^{-1}) 3056, 2961, 2928, 2858, 2227, 1636, 1578; HRMS Calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2$: 270.2096. Found: 270.2099.

***N*-[3-(Phenylethynyl)pyridin-4-ylmethylene]-*tert*-butylamine (16).** This imine was prepared from 3-(phenylethynyl)pyridine-4-carboxaldehyde (1.04 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.27 g (97 %) of the imine 16 as a yellow solid: mp 91-92 °C; ^1H NMR (CDCl_3) δ 1.35 (s, 9H), 7.38-7.40 (m, 3H), 7.54-7.56 (m, 2H), 7.91 (d, $J = 3.9$ Hz, 1H), 8.56 (d, $J = 3.9$ Hz, 1H), 8.81 (s, 2H); ^{13}C NMR (CDCl_3) δ 29.7, 58.9, 83.8, 97.7, 119.5, 120.3, 122.6, 128.8, 129.3, 131.8, 144.2, 149.0, 152.5, 153.5; IR (CHCl_3 , cm^{-1}) 3016, 2970, 2870, 2217, 1492; HRMS Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2$: 262.1470. Found: 262.1476.

***N*-[2-(4-Trifluoromethylphenylethynyl)benzylidene]-*tert*-butylamine (21).** This imine was prepared from 2-(4-trifluoromethylphenylethynyl)benzaldehyde (1.37 g, 5.0 mmol) by the method used to prepare 1. Removal of the solvent afforded 1.56 g (95 %) of the imine 21 as a yellow solid: mp 104-105 °C; ^1H NMR (CDCl_3) δ 1.34 (s, 9H), 7.38-7.42 (m, 2H), 7.55-7.58 (m, 1H), 7.63 (s, 4H), 8.07-8.10 (m, 1H), 8.89 (s, 1H); ^{13}C NMR (CDCl_3) δ 29.9, 58.2, 89.3, 93.4, 123.2, 125.5, 125.6 (q, $J = 15.2$ Hz), 126.4, 127.1, 129.4, 130.0, 130.2, 131.8, 132.6, 138.2, 153.9; IR (CHCl_3 , cm^{-1}) 3019, 2970, 1755, 1323; HRMS Calcd for $\text{C}_{20}\text{F}_3\text{H}_{18}\text{N}$: 329.1391. Found: 329.1397.

***N*-[2-(2-Propenylethynyl)benzylidene]-*tert*-butylamine (36).** This imine was prepared from 2-(2-propenylethynyl)benzaldehyde (0.85 g, 5.0 mmol) by the method used to prepare **1**. Removal of the solvent afforded 1.07 g (95 %) of the imine **36** as a yellow oil: ^1H NMR (CDCl_3) δ 1.30 (s, 9H), 2.03 (d, $J = 0.6$ Hz, 3H), 5.34 (d, $J = 0.6$ Hz, 1H), 5.43 (s, 1H), 7.27-7.35 (m, 2H), 7.45-7.47 (m, 1H), 8.03-8.05 (m, 1H), 8.82 (s, 1H); ^{13}C NMR (CDCl_3) δ 23.7, 29.9, 58.0, 85.9, 96.3, 122.4, 124.1, 126.1, 126.8, 128.8, 129.9, 132.3, 137.9, 154.5; IR (neat, cm^{-1}) 2967, 2926, 2867, 1637; HRMS Calcd for $\text{C}_{16}\text{H}_{19}\text{N}$: 225.1517. Found: 225.1522.

***N*-[2-(Cyclohexylethynyl)benzylidene]-*tert*-butylamine (38).** This imine was prepared from 2-(cyclohexylethynyl)benzaldehyde (1.07 g, 5.0 mmol) by the method used to prepare **1**. Removal of the solvent afforded 1.31 g (98 %) of the imine **38** as a yellow oil: ^1H NMR (CDCl_3) δ 1.31 (s, 9H), 1.35-1.45 (m, 3H), 1.50-1.63 (m, 3H), 1.73-1.81 (m, 2H), 1.85-1.92 (m, 2H), 2.68 (dddd, $J = 3.6, 3.6, 12.3, 12.3$ Hz, 1H), 7.26-7.31 (m, 2H), 7.37-7.43 (m, 1H), 7.98-8.03 (m, 1H), 8.83 (s, 1H); ^{13}C NMR (CDCl_3) δ 24.8, 26.0, 29.8, 29.9, 32.7, 57.8, 78.0, 100.2, 124.9, 125.8, 127.9, 129.7, 132.2, 137.8, 154.8; IR (neat, cm^{-1}) 3062, 2224, 1683; HRMS Calcd for $\text{C}_{19}\text{H}_{25}\text{N}$: 267.1987. Found: 267.1987.

***N*-[2-(4-(Tetrahydropyran-2-yloxy)but-1-ynyl)benzylidene]-*tert*-butylamine (40).** This imine was prepared from 2-(4-(tetrahydropyran-2-yloxy)but-1-ynyl)benzaldehyde (1.29 g, 5.0 mmol) by the method used to prepare **1**. Removal of the solvent afforded 1.45 g (93 %) of the imine **40** as a yellow oil: ^1H NMR (CDCl_3) δ 1.30 (s, 9H), 1.48-1.65 (m, 4H), 1.68-1.89 (m, 2H), 2.78 (t, $J = 7.2$ Hz, 2H), 3.48-3.56 (m, 1H), 3.67 (ddd, $J = 7.2, 7.2, 9.6$ Hz, 1H), 3.86-3.97 (m, 2H), 4.68 (t, $J = 3.0$ Hz, 1H), 7.26-7.31 (m, 2H), 7.37-7.42 (m, 1H),

7.97-8.03 (m, 1H), 8.78 (s, 1H); ^{13}C NMR (CDCl_3) δ 19.5, 21.2, 25.5, 29.8, 30.7, 57.7, 62.3, 65.9, 78.8, 92.7, 98.9, 124.4, 125.9, 128.1, 129.7, 132.4, 137.8, 154.5; IR (neat, cm^{-1}) 3063, 2229, 1637; HRMS Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_2$: 313.2040. Found: 313.2042.

General procedure for the electrophilic cyclization of iminoalkynes by I_2 , ICl , PhSeCl , PhSCl and $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$. The electrophile (6 or 2 equivs), the solvent (5 ml), and the base, where required (3 equivs), were placed in a 2 dram vial. The iminoalkyne (0.25 mmol) in 2 ml of the solvent was added dropwise to the vial. The vial was flushed with Ar and the reaction was stirred at room temperature for the indicated period of time. The reactions were monitored by TLC to establish completion. The reaction mixture was then diluted with 25 ml of ether, washed with either 25 ml of saturated $\text{Na}_2\text{S}_2\text{O}_3$ (for the reactions of I_2 and ICl) or saturated NaCl , dried (Na_2SO_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-phenylisoquinoline (2). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 56 mg (68 %) (Table 2, entry 1) or 55 mg (67 %) (Table 2, entry 2) of the product from I_2 or ICl , respectively, as a yellow solid: mp 84-85 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 7.26-7.52 (m, 3H), 7.61-7.70 (m, 3H), 7.70-7.85 (m, 2H), 7.95 (d, $J = 8.1$ Hz, 1H), 8.22 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 98.3, 128.1, 128.2, 128.3, 128.5, 130.3, 132.4, 132.6, 138.8, 143.9, 152.2, 157.4 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3055, 1630, 1549; HRMS Calcd for $\text{C}_{15}\text{H}_{10}\text{IN}$: 330.9858. Found: 330.9862.

3-(Cyclohex-1-enyl)-4-iodoisoquinoline (5). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 56 mg (67 %) of the product as a yellow oil: ^1H NMR (CDCl_3)

δ 1.73-1.79 (m, 2H), 1.84-1.92 (m, 2H), 2.25-2.29 (m, 2H), 2.40-2.43 (m, 2H), 5.85 (s, 1H), 7.57-7.60 (m, 1H), 7.73-7.78 (m, 1H), 7.87 (d, $J = 8.1$ Hz, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (CDCl_3) δ 22.1, 22.9, 25.3, 28.5, 97.7, 127.6, 128.0, 128.2, 129.5, 132.0, 132.2, 138.7, 141.8, 152.1, 159.7; IR (neat, cm^{-1}) 3019, 2936, 1618; HRMS Calcd for $\text{C}_{15}\text{H}_{14}\text{IN}$: 335.0165. Found: 335.0168.

4-Iodo-3-(3,4,5-trimethoxyphenyl)isoquinoline (7). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 32 mg (30 %) (Table 2, entry 4) or 25 mg (24 %) (Table 2, entry 5) of the product from I_2 or ICl , respectively, as a yellow solid: mp 132-134 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 3.92 (s, 6H), 3.93 (s, 3H), 6.86 (s, 2H), 7.69 (dt, $J = 1.2, 7.5$ Hz, 1H), 7.84 (dt, $J = 1.5, 8.4$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H), 8.24 (dd, $J = 0.6, 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 56.4, 61.2, 98.3, 107.5, 128.2, 128.3, 128.3, 132.6, 132.7, 138.3, 138.9, 139.1, 152.0, 152.9, 156.9; IR (CHCl_3 , cm^{-1}) 3017, 2939, 2836, 1586; HRMS Calcd for $\text{C}_{18}\text{H}_{16}\text{IO}_3\text{N}$: 421.0175. Found: 421.0182.

4-Iodo-3-(3-methoxyphenyl)isoquinoline (9). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 34 mg (37 %) (Table 2, entry 6) or 36 mg (40 %) (Table 2, entry 7) of the product from I_2 or ICl , respectively, as a yellow solid: mp 113-115 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 3.88 (s, 3H), 7.01 (d, $J = 9.0$ Hz, 2H), 7.61 (d, $J = 9.0$ Hz, 2H), 7.65 (dt, $J = 0.9, 7.5$ Hz, 1H), 7.81 (dt, $J = 1.8, 8.4$ Hz, 1H), 7.93 (d, $J = 8.1$ Hz, 1H), 8.21 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 55.6, 98.2, 113.5, 128.0, 128.1, 128.1, 131.5, 132.4, 132.6, 136.4, 138.9, 152.2, 156.9, 159.8; IR (CHCl_3 , cm^{-1}) 3017, 2958, 2835, 2283, 1608, 1514; HRMS Calcd for $\text{C}_{16}\text{H}_{12}\text{INO}$: 360.9964. Found: 360.9970.

6-Iodo-7-phenyl-1,3-dioxolo[4,5-g]isoquinoline (11). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 48 mg (52 %) of the product as a dark sticky oil: ^1H NMR (CDCl_3) δ 6.17 (s, 2H), 7.17 (s, 1H), 7.42-7.49 (m, 3H), 7.56-7.60 (m, 2H), 7.62 (s, 1H), 8.89 (s, 1H); ^{13}C NMR (CDCl_3) δ 97.1, 102.4, 103.2, 109.6, 125.4, 128.1, 128.3, 129.9, 137.6, 144.1, 149.1, 149.8, 152.9, 156.6; IR (CHCl_3 , cm^{-1}) 3018, 2926, 2855, 1473; HRMS Calcd for $\text{C}_{16}\text{H}_{10}\text{INO}_2$: 374.9756. Found: 374.9760.

8-Iodo-7-phenyl-1,6-naphthyridine (13). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 75 mg (90 %) (Table 2, entry 10) or 76 mg (92 %) (Table 2, entry 11) of the product from I_2 or ICl , respectively, as a yellow solid: mp 163-164 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 7.45-7.52 (m, 3H), 7.59-7.62 (dd, $J = 3.3, 6.3$ Hz, 1H), 7.69 (dd, $J = 1.2, 6.0$ Hz, 2H), 8.29 (dd, $J = 1.5, 6.0$ Hz, 1H), 9.16 (s, 1H), 9.21 (dd, $J = 1.2, 3.3$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 101.8, 123.1, 123.4, 128.2, 128.9, 130.0, 136.4, 143.0, 151.1, 152.3, 156.0, 161.1; IR (CHCl_3 , cm^{-1}) 3048, 1618; HRMS Calcd for $\text{C}_{14}\text{H}_9\text{IN}_2$: 331.9810. Found: 331.9816.

7-*n*-Hexyl-8-iodo-1,6-naphthyridine (15). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 65 mg (76 %) of the product as a yellow oil: ^1H NMR (CDCl_3) δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.31-1.51 (m, 6H), 1.77-1.88 (m, 2H), 3.31-3.36 (m, 2H), 7.53 (dd, $J = 4.2, 8.1$ Hz, 1H), 8.22 (dd, $J = 1.5, 8.1$ Hz, 1H), 9.06 (s, 1H), 9.15 (dd, $J = 1.5, 4.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 22.7, 29.3, 29.5, 31.8, 42.7, 102.3, 122.6, 122.6, 136.2, 150.6, 152.1, 155.5, 163.1; IR (neat, cm^{-1}) 3018, 2955, 2925, 2854, 1603, 1579; HRMS Calcd for $\text{C}_{14}\text{H}_{17}\text{IN}_2$: 340.0436. Found: 340.0441.

4-Iodo-3-phenyl-2,6-naphthyridine (17). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 11 mg (13 %) (Table 2, entry 13) or 60 mg (72 %) (Table 2, entry

14) of the product from I₂ or ICl, respectively, as a yellow solid: mp 150-151 °C; ¹H NMR (CDCl₃) δ 7.47-7.54 (m, 3H), 7.62-7.66 (m, 2H), 7.70 (dd, *J* = 0.9, 5.7 Hz, 1H), 8.82 (d, *J* = 5.7 Hz, 1H), 9.23 (d, *J* = 0.6 Hz, 1H), 9.63 (s, 1H); ¹³C NMR (CDCl₃) δ 95.5, 118.6, 128.3, 128.9, 130.0, 130.4, 132.4, 142.6, 145.7, 151.5, 157.6, 158.8; IR (CHCl₃, cm⁻¹) 3018, 2927, 2854, 1568, 1533; HRMS Calcd for C₁₄H₉N₂: 331.9810. Found: 331.9816.

3-Phenyl-4-(phenylselenyl)isoquinoline (18). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 69 mg (76 %) of the product as a yellow solid: mp 112-114 °C; ¹H NMR (CDCl₃) δ 7.04-7.08 (m, 5H), 7.39-7.42 (m, 3H), 7.55-7.56 (m, 3H), 7.71 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 9.35 (s, 1H); ¹³C NMR (CDCl₃) δ 121.8, 126.4, 127.8, 127.9, 128.3, 128.4, 128.4, 128.9, 129.4, 129.9, 130.1, 132.1, 133.3, 138.9, 142.0, 153.3, 158.4; IR (CHCl₃, cm⁻¹) 3056, 2924, 1575; HRMS Calcd for C₂₁H₁₅N⁸⁰Se: 361.0370. Found: 361.0378.

3-(Cyclohex-1-enyl)-4-(phenylselenyl)isoquinoline (19). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 88 mg (96 %) of the product as a yellow solid: mp 103-105 °C; ¹H NMR (CDCl₃) δ 1.69-1.82 (m, 4H), 2.15-2.21 (m, 2H), 2.44-2.48 (m, 2H), 5.67-5.70 (m, 1H), 7.09-7.14 (m, 5H), 7.52-7.65 (m, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 9.23 (s, 1H); ¹³C NMR (CDCl₃) δ 22.0, 22.9, 25.5, 29.1, 120.8, 126.1, 127.0, 128.1, 128.2, 128.4, 129.2, 129.3, 129.9, 131.4, 133.8, 138.4, 140.0, 153.1, 161.2; IR (CHCl₃, cm⁻¹) 3019, 2936, 1571; HRMS Calcd for C₂₁H₁₉N⁸⁰Se: 365.0684. Found: 365.0690.

4-Phenylselenyl-3-(3,4,5-trimethoxyphenyl)isoquinoline (20). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 107 mg (95 %) of the product as a yellow oil:

^1H NMR (CDCl_3) δ 3.70 (s, 6H), 3.88 (s, 3H), 6.76 (s, 2H), 7.04-7.11 (m, 5H), 7.65 (dt, $J = 0.6, 5.5$ Hz, 1H), 7.75 (dt, $J = 0.9, 5.8$ Hz, 1H), 8.03 (d, $J = 5.8$ Hz, 1H), 8.49 (d, $J = 6.3$ Hz, 1H), 9.34 (s, 1H); ^{13}C NMR (CDCl_3) δ 56.0, 61.0, 107.0, 121.0, 126.1, 127.7, 128.2, 128.3, 128.7, 129.4, 129.5, 132.0, 133.8, 137.7, 138.0, 139.1, 152.6, 153.3, 158.4; IR (neat, cm^{-1}) 3057, 2936, 2833, 1607; HRMS Calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_3^{80}\text{Se}$: 451.0687. Found: 451.0695.

4-Phenylselenenyl-3-(3-trifluoromethylphenyl)isoquinoline (22). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 19 mg (18 %) of the product as a yellow solid: mp 116-117 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 6.97-7.02 (m, 2H), 7.04-7.11 (m, 3H), 7.64 (d, $J = 1.8$ Hz, 4H), 7.68 (dt, $J = 1.2, 8.4$ Hz, 2H), 7.74 (dt, $J = 1.5, 9.0$ Hz, 1H), 8.05 (d, $J = 0.84$ Hz, 1H), 8.50 (d, $J = 8.4$ Hz, 1H), 9.35 (s, 1H); ^{13}C NMR (CDCl_3) δ 122.3, 124.8 (q, $J = 15.6$ Hz), 126.6, 128.2, 128.4, 128.5, 128.7, 129.5, 129.9, 130.0, 130.3, 130.4, 132.2, 132.8, 138.8, 145.7, 153.6, 157.1; IR (neat, cm^{-1}) 2952, 2918, 2850, 1476; HRMS Calcd for $\text{C}_{22}\text{F}_3\text{H}_{14}\text{N}^{80}\text{Se}$: 429.0244. Found: 429.0250.

6-Phenylselenenyl-7-phenyl-1,3-dioxolo[4,5-g]isoquinoline (23). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 53 mg (60 %) of the product as a yellow solid: mp 140-143 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 6.08 (s, 2H), 6.92-7.02 (m, 2H), 7.07-7.11 (m, 3H), 7.22 (s, 1H), 7.36-7.38 (m, 3H), 7.49-7.54 (m, 2H), 7.78 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (CDCl_3) δ 102.1, 103.6, 105.5, 125.6, 126.3, 127.8, 128.1, 129.4, 129.6, 129.9, 133.2, 135.4, 138.1, 142.5, 148.7, 151.1, 152.6, 158.2; IR (CHCl_3 , cm^{-1}) 2958, 2962, 2855, 1516; HRMS Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2^{80}\text{Se}$: 405.0268. Found: 405.0273.

3-Phenyl-4-phenylselenenyl-2,6-naphthyridine (24). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 72 mg (80 %) of the product as a yellow solid:

mp 104-106 °C; ^1H NMR (CDCl_3) δ 7.07-7.10 (m, 5H), 7.44-7.47 (m, 3H), 7.59-7.62 (m, 2H), 7.78 (d, $J = 5.6$ Hz, 1H), 8.74 (d, $J = 5.6$ Hz, 1H), 9.39 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (CDCl_3) δ 119.1, 121.6, 127.1, 128.1, 128.8, 129.6, 130.2, 130.4, 130.8, 132.3, 132.5, 141.1, 145.0, 152.5, 154.2, 159.7; IR (CHCl_3 , cm^{-1}) 3061, 3017, 2930, 2360, 1570; HRMS Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2^{82}\text{Se}$: 364.0324. Found: 364.0330.

7-Phenyl-8-phenylselenyl-1,6-naphthyridine (25). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 66 mg (72 %) of the product as a yellow solid: mp 122-124 °C; ^1H NMR (CDCl_3) δ 6.95-7.10 (m, 5H), 7.31-7.37 (m, 3H), 7.53-7.57 (m, 3H), 8.32 (dd, $J = 1.8, 8.4$ Hz, 1H), 9.17 (dd, $J = 1.8, 4.2$ Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (CDCl_3) δ 122.9, 123.0, 125.9, 126.5, 127.9, 128.4, 128.9, 129.9, 131.8, 132.7, 136.4, 141.6, 151.8, 152.7, 155.3, 160.8; IR (CHCl_3 , cm^{-1}) 3017, 2976, 2283 (broad), 1601; HRMS Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2^{82}\text{Se}$: 364.0324. Found: 364.0331.

7-*n*-Hexyl-8-phenylselenyl-1,6-naphthyridine (26). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 56 mg (61%) of the product as a yellow oil: ^1H NMR (CDCl_3) δ 0.83-0.87 (m, 3H), 1.24-1.36 (m, 6H), 1.67-1.76 (m, 2H), 3.31-3.36 (m, 2H), 7.09-7.13 (m, 3H), 7.20-7.24 (m, 2H), 7.50 (dd, $J = 4.2, 8.4$ Hz, 1H), 8.28 (dd, $J = 1.8, 8.4$ Hz, 1H), 9.14 (dd, $J = 1.8, 4.2$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 22.7, 29.5, 30.4, 31.8, 39.5, 122.2, 122.6, 124.4, 126.3, 129.1, 130.4, 133.0, 136.3, 151.8, 153.4, 155.4, 165.1; IR (neat, cm^{-1}) 3056, 2954, 2855, 1602; HRMS Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2^{80}\text{Se}$: 370.0948. Found: 370.0952.

3-Phenyl-4-(4-nitrophenylsulfenyl)isoquinoline (27). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 42 mg (47 %) of the product as a yellow solid:

mp 193-195 °C; ^1H NMR (CDCl_3) δ 6.97-6.99 (m, 2H), 7.40-7.42 (m, 3H), 7.57-7.60 (m, 2H), 7.68-7.80 (m, 2H), 7.97-8.00 (m, 2H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.27 (d, $J = 8.4$ Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (CDCl_3) δ 119.5, 124.4, 125.6, 126.1, 128.2, 128.3, 128.5, 128.8, 128.9, 129.7, 132.7, 138.1, 140.2, 145.4, 147.8, 154.6, 159.0; IR (CHCl_3 , cm^{-1}) 3019, 2926, 1518; HRMS Calcd for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: 358.007. Found: 358.0781.

3-(Cyclohex-1-enyl)-4-(4-nitrophenylsulfenyl)isoquinoline (28). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 30 mg (33 %) of the product as a yellow oil: ^1H NMR (CDCl_3) δ 1.67-1.77 (m, 4H), 2.13 (d, $J = 0.5$ Hz, 2H), 2.41 (d, $J = 0.5$ Hz, 2H), 5.78 (s, 1H), 6.98-7.01 (m, 2H), 7.59-7.74 (m, 2H), 7.98-8.16 (m, 3H), 8.18-8.20 (m, 1H), 9.35 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.9, 22.8, 25.5, 28.9, 118.8, 124.3, 125.4, 126.1, 126.6, 127.8, 128.3, 128.8, 129.8, 132.5, 138.1, 138.4, 148.7, 154.4, 161.9; IR (CHCl_3 , cm^{-1}) 3019, 2932, 1517; HRMS Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: 362.1089. Found: 362.1094.

3-(4-Methoxyphenyl)-4-(4-nitrophenylsulfenyl)isoquinoline (29). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 21 mg (25 %) of the product as a yellow solid: mp 161-163 °C; ^1H NMR (CDCl_3) δ 3.86 (s, 3H), 6.96 (d, $J = 9.0$ Hz, 2H), 7.01 (d, $J = 9.0$ Hz, 2H), 7.61 (d, $J = 9.0$ Hz, 2H), 7.69 (dt, $J = 1.2, 7.8$ Hz, 1H), 7.74 (dt, $J = 1.2, 9.3$ Hz, 1H), 8.01 (d, $J = 8.7$ Hz, 2H), 8.12 (dd, $J = 0.9, 7.8$ Hz, 1H), 8.26 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 55.5, 113.5, 118.6, 124.3, 125.5, 125.9, 128.0, 128.2, 128.7, 131.3, 132.6, 132.7, 138.2, 145.3, 148.0, 154.5, 158.7, 160.1; IR (CHCl_3 , cm^{-1}) 3019, 2971, 2838, 1608, 1578, 1515; HRMS Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$: 338.0082. Found: 338.0085.

3-(Cyclohex-1-enyl)-4-(phenylsulfenyl)isoquinoline (30). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 36 mg (45 %) of the product as a yellow solid:

mp 130-131 °C; ^1H NMR (CDCl_3) δ 1.68-1.79 (m, 4H), 2.15-2.17 (m, 2H), 2.41-2.43 (m, 2H), 5.77-5.79 (m, 1H), 6.96-6.98 (m, 2H), 7.03-7.07 (m, 1H), 7.11-7.15 (m, 2H), 7.56 (t, J = 5.4 Hz, 1H), 7.65 (t, J = 5.4 Hz, 1H), 7.97 (d, J = 6.0 Hz, 1H), 8.31 (d, J = 6.6 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (CDCl_3) δ 22.0, 23.0, 25.5, 28.9, 121.4, 125.3, 126.0, 127.1, 127.2, 128.2, 128.2, 129.0, 129.2, 131.6, 138.3, 138.7, 138.7, 153.2, 161.2; IR (CHCl_3 , cm^{-1}) 3019, 2936, 1630; HRMS Calcd for $\text{C}_{21}\text{H}_{19}\text{NS}$: 317.1238. Found: 317.1241.

4-Phenylsulfenyl-3-(3,4,5-trimethoxyphenyl)isoquinoline (31). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 43 mg (43 %) of the product as a yellow oil:

^1H NMR (CDCl_3) δ 3.67 (s, 6H), 3.87 (s, 3H), 6.82 (s, 2H), 6.95 (d, J = 7.2 Hz, 2H), 7.06 (t, J = 7.2 Hz, 1H), 7.16 (t, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.77 (t, J = 7.2 Hz, 1H), 8.07 (d, J = 4.0 Hz, 1H), 8.46 (d, J = 7.6 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.9, 61.0, 106.9, 121.1, 125.3, 126.3, 126.4, 127.8, 128.3, 128.4, 129.2, 132.2, 136.3, 138.1, 138.8, 139.0, 152.7, 153.5, 158.4; IR (CHCl_3 , cm^{-1}) 3015, 2939, 2860, 1585; HRMS Calcd for $\text{C}_{24}\text{H}_{21}\text{NO}_3\text{S}$: 403.1242. Found: 403.1246.

7-*n*-Hexyl-8-phenylsulfenyl-1,6-naphthyridine (32). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 32 mg (40 %) of the product as a yellow oil:

^1H NMR (CDCl_3) δ 0.85 (t, J = 6.9 Hz, 3H), 1.24-1.37 (m, 6H), 1.67-1.76 (m, 2H), 3.30 (t, J = 8.4 Hz, 2H), 7.00-7.13 (m, 5H), 7.51 (dd, J = 4.2, 8.1 Hz, 1H), 8.30 (dd, J = 1.8, 8.1 Hz, 1H), 9.15 (dd, J = 1.8, 4.2 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.2, 22.7, 29.5, 30.2, 31.8, 37.6, 122.3, 122.8, 124.4, 125.4, 127.2, 128.9, 136.4, 137.9, 151.8, 153.5, 155.6, 165.7; IR (neat, cm^{-1}) 3056, 2925, 2854, 2221, 1602; HRMS Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{S}$: 322.1504. Found: 322.1508.

General procedure for the silver-catalyzed cyclization of iminoalkynes. 5 Mol % of AgNO_3 and 5 ml of CHCl_3 were placed into a 2 dram vial. The iminoalkyne (0.25 mmol) in 2 ml of CHCl_3 was added dropwise to the vial. The vial was then flushed with Ar and heated at 50 °C for the indicated period of time. The reaction mixture was cooled, diluted with 25 ml of ether, washed with 25 ml of saturated NaCl, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

General procedure for the copper-catalyzed cyclization of iminoalkynes. DMF (5 ml), the iminoalkyne (0.25 mmol), and CuI (5 mg, 0.025 mmol) were placed in a 2 dram vial. The vial was then flushed with Ar and heated in an oil bath at 100 °C for the indicated period of time. The reaction were monitored by TLC to establish completion. The reaction mixture was cooled, diluted with 25 ml of ether, washed with 25 ml of saturated NaCl, dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

3-Phenylisoquinoline (33). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 42 mg (82 %) (Table 2, entry 29) or 51 mg (100 %) (Table 2, entry 30) of the product from AgNO_3 or CuI, respectively, as a yellow solid with spectral properties identical to those previously reported¹⁷: mp 102-103 °C (lit.¹⁷ mp 101-102 °C).

3-(Cyclohexen-1-yl)isoquinoline (34). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 40 mg (78 %) (Table 2, entry 31) or 43 mg (81 %) (Table 2, entry 32) of the product from AgNO_3 or CuI, respectively, as a white solid: mp 114-115 °C; ^1H NMR (CDCl_3) δ 1.69-1.77 (m, 2H), 1.83-1.91 (m, 2H), 2.30-2.38 (m, 2H), 2.56-2.62 (m,

2H), 7.04 (tt, $J = 2.4, 3.6$ Hz, 1H), 7.50 (dt, $J = 0.6, 14.4$ Hz, 1H), 7.59 (s, 1H), 7.65 (dd, $J = 1.2, 6.9$ Hz, 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 9.20 (s, 1H); ^{13}C NMR (CDCl_3) δ 22.4, 23.2, 26.2, 26.3, 114.3, 126.5, 126.9, 127.7, 127.7, 128.6, 130.4, 135.8, 136.8, 151.7, 152.6; IR (CHCl_3 , cm^{-1}) 3060, 2919, 1621, 1574; MS m/z (rel intensity) 209 (100, M^+), 208 (89), 194 (42), 180 (51). Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}$: C, 86.09; H, 7.23; N, 6.69. Found: C, 86.03; H, 7.30; N, 6.73.

3-(3,4,5-Trimethoxyphenyl)isoquinoline (35). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 52 mg (71 %) of the product as a yellow solid: mp 122-124 °C; ^1H NMR (CDCl_3) δ 3.93 (s, 3H), 4.00 (s, 6H), 7.38 (s, 2H), 7.58 (dt, $J = 0.9, 7.5$ Hz, 1H), 7.70 (dt, $J = 0.9, 7.6$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 8.01 (s, 1H), 9.31 (s, 1H); ^{13}C NMR (CDCl_3) δ 56.4, 61.2, 104.3, 116.3, 126.9, 127.2, 127.7, 127.8, 130.7, 135.4, 136.7, 138.8, 151.0, 152.4, 153.7; IR (CHCl_3 , cm^{-1}) 3018, 2968, 2939, 1578; HRMS Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3$: 295.1208. Found: 295.1211.

3-(2-Propenyl)isoquinoline (37). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 23 mg (54 %) of the product as a yellow solid: mp 66-68 °C; ^1H NMR (CDCl_3) δ 2.32 (d, $J = 0.4$ Hz, 3H), 5.36 (d, $J = 1.6$ Hz, 1H), 6.20 (dd, $J = 0.4, 1.6$ Hz, 1H), 7.56 (dt, $J = 1.2, 6.8$ Hz, 1H), 7.70 (dt, $J = 0.8, 7.2$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 20.9, 115.8, 115.9, 127.1, 127.2, 127.7, 127.9, 130.5, 136.6, 142.4, 151.8, 151.9; IR (CHCl_3 , cm^{-1}) 3057, 3014, 2976, 1625, 1580; HRMS Calcd for $\text{C}_{12}\text{H}_{11}\text{N}$: 169.0892. Found: 169.0894.

3-Cyclohexylisoquinoline (39). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 40 mg (75 %) (Table 2, entry 35) or 49 mg (93 %) (Table 2, entry

36) of the product from AgNO₃ or CuI, respectively, as a white solid: mp 40-41 °C; ¹H NMR (CDCl₃) δ 1.25-1.67 (m, 6H), 1.89 (dt, J = 2.7, 12.6 Hz, 2H), 2.06 (dd, J = 1.5, 12.9 Hz, 2H), 2.86 (tt, J = 3.3, 11.7 Hz, 1H), 7.47 (s, 1H), 7.52 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.64 (td, J = 1.2, 6.9 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 9.21 (s, 1H); ¹³C NMR (CDCl₃) δ 26.4, 26.9, 33.3, 46.3, 116.2, 126.4, 126.5, 127.4, 127.6, 130.2, 136.8, 152.0, 160.3; IR (CHCl₃, cm⁻¹) 3055, 2926, 1628, 1585; HRMS Calcd for C₁₅H₁₇N: 211.1356. Found: 211.1361.

3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (41). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 39 mg (62 %) (Table 2, entry 37) or 52 mg (83 %) (Table 2, entry 38) of the product from AgNO₃ or CuI, respectively, as a yellow oil: ¹H NMR (CDCl₃) δ 1.40-1.46 (m, 4H), 1.61-1.82 (m, 2H), 3.23 (t, J = 7.2 Hz, 2H), 3.42-3.48 (m, 1H), 3.76 (ddd, J = 3.3, 8.1, 11.7 Hz, 1H), 3.87 (ddd, J = 6.9, 9.6, 16.5 Hz, 1H), 4.18 (ddd, J = 6.9, 9.6, 16.8 Hz, 1H), 4.64 (ddd, J = 2.7, 2.7, 2.7 Hz, 1H), 7.54 (ddd, J = 1.2, 6.9, 9.3 Hz, 1H), 7.57 (s, 1H), 7.65 (ddd, J = 1.2, 6.6, 9.3 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 9.21 (s, 1H); ¹³C NMR (CDCl₃) δ 19.7, 25.6, 30.8, 38.5, 62.4, 67.1, 99.0, 119.3, 126.3, 126.7, 127.4, 127.6, 130.5, 136.6, 152.2, 152.6; IR (CHCl₃, cm⁻¹) 3054, 2942, 1628, 1588; HRMS Calcd for C₁₆H₁₉NO₂: 257.1416. Found: 257.1415.

3-Phenyl-6,7-(methylenedioxy)isoquinoline (42) Purification by flash chromatography (3:1 hexane/EtOAc) afforded 35 mg (56 %) of the product as a yellow oil: ¹H NMR (CDCl₃) δ 6.10 (s, 1H), 7.16 (d, J = 7.1 Hz), 7.37-7.51 (m, 3H), 7.89 (s, 1H), 8.06 (d, J = 1.8 Hz, 1H), 9.06 (s, 1H); ¹³C NMR (CDCl₃) δ 101.9, 103.0, 103.4, 116.6, 125.3,

127.0, 128.5, 129.0, 135.3, 139.9, 148.6, 150.4, 150.8, 151.4; IR (CHCl₃, cm⁻¹) 3019, 2925, 1600, 1458; HRMS Calcd for C₁₆H₁₁NO₂: 249.0789. Found: 249.0793.

7-Phenyl-1,6-naphthyridine (43). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 47 mg (92 %) of the product as a pale yellow solid: mp 135-137 °C; ¹H NMR (CDCl₃) δ 7.42-7.55 (m, 4H), 8.15-8.21 (m, 2H), 8.29 (ddd, J = 0.6, 1.8, 8.4 Hz, 1H), 8.35 (s, 1H), 9.09 (dd, J = 1.8, 4.2 Hz, 1H), 9.34 (d, J = 0.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 118.0, 122.4, 122.9, 127.4, 129.1, 129.4, 135.8, 139.1, 151.6, 152.9, 155.3, 155.4; IR (CHCl₃, cm⁻¹) 3018, 2980, 1613; HRMS Calcd for C₁₄H₁₀N₂: 206.0844. Found: 206.0848.

7-*n*-Hexyl-1,6-naphthyridine (44). Purification by flash chromatography (3:1 hexane/EtOAc) afforded 24 mg (45 %) of the product as a yellow oil: ¹H NMR (CDCl₃) δ 0.88 (t, J = 4.2 Hz, 3H), 1.31-1.39 (m, 6H), 1.80-1.87 (m, 2H), 7.47 (dd, J = 4.5, 8.1 Hz, 1H), 7.75 (s, 1H), 8.26 (d, J = 8.1 Hz, 1H), 9.06 (dd, J = 1.5, 4.5 Hz, 1H), 9.23 (s, 1H); ¹³C NMR (CDCl₃) δ 14.3, 22.8, 29.2, 29.9, 31.9, 38.5, 119.8, 121.9, 122.1, 135.8, 151.3, 152.5, 155.0, 160.6; IR (CHCl₃, cm⁻¹) 2956, 2929, 2857, 1619; HRMS Calcd for C₁₄H₁₈N₂: 214.1470. Found: 214.1472.

3-Phenyl-2,6-naphthyridine (45). Purification by flash chromatography (2:1 hexane/EtOAc) afforded 41 mg (80 %) of the product as a yellow solid: mp 138-140 °C; ¹H NMR (CDCl₃) δ 7.45 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.78 (d, J = 5.6, 1H), 8.13 (d, J = 7.6 Hz, 2H), 8.16 (s, 1H), 8.69 (d, J = 5.6 Hz, 1H), 9.37 (s, 1H), 9.41 (s, 1H); ¹³C NMR (CDCl₃) δ 115.1, 119.4, 127.2, 129.2, 129.3, 129.4, 131.4, 138.9, 144.6, 151.8, 152.4, 153.3; IR (CHCl₃, cm⁻¹) 3018, 2984, 1572; HRMS Calcd for C₁₄H₁₀N₂: 206.0844. Found: 206.0848.

Characterization of compound 3. A yellow oil ($R_f = 0.25$, 3:1 hexane/EtOAc): ^1H NMR (CDCl_3) δ 1.42 (s, 9H), 5.73 (s, 1H), 7.17 (dd, $J = 0.6, 4.8$ Hz, 1H), 7.31 (dt, $J = 0.6, 6.0$ Hz, 2H), 7.49-7.54 (m, 3H), 7.65 (dd, $J = 0.9, 6.3$ Hz, 2H), 7.90 (td, $J = 0.6, 4.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 28.4, 57.2, 93.0, 121.5, 124.2, 129.0, 130.1, 130.6, 132.0, 132.5, 133.2, 134.5, 145.1, 169.9, 198.2; IR (CHCl_3 , cm^{-1}) 3429, 3018, 2978, 1693; HRMS Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$: 292.1337. Found: 292.1343.

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CHAPTER 2. SYNTHESIS OF 4-(1-ALKENYL)ISOQUINOLINES BY PALLADIUM(II)-CATALYZED CYCLIZATION/OLEFINATION

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Abstract

A variety of 4-(1-alkenyl)-3-arylisoquinolines have been prepared in moderate to excellent yields by the Pd(II)-catalyzed cyclization of 2-(1-alkynyl)arylaldimines in the presence of various alkenes. The introduction of an *ortho*-methoxy group on the arylaldimine promotes the Pd-catalyzed cyclization and stabilizes the resulting Pd(II) intermediate, improving the yields of the isoquinoline products. Ketone-containing isoquinolines 36 and 49-51 have also been prepared by this process when unsaturated alcohols are employed as the alkenes.

Introduction

The synthesis of isoquinolines has received considerable attention due to the fact that the isoquinoline ring system is present in numerous naturally-occurring alkaloids.¹ Although classical methods have frequently been employed in the total synthesis of isoquinoline alkaloids, these approaches often have drawbacks. For example, the Bischler-Napieralski,² Pictet-Spengler,³ and Pomeranz-Fritsch⁴ protocols require relatively strong acids to cyclize *E*-phenethylamines. Also, the Bischler-Napieralski² and Pictet-Spengler³ reactions afford

dihydro- and tetrahydroisoquinolines, respectively. An additional step involving dehydrogenation is thus required to complete the synthesis of the isoquinoline.

Substituted isoquinoline heterocycles have also been synthesized by employing palladium methodology. For instance, 3,4-disubstituted isoquinolines have been achieved by the annulation of internal alkynes by cyclopalladated *N,N*-dimethylbenzylamine complexes,⁵ cyclopalladated *N-tert*-butylbenzaldimine tetrafluoroborates,⁶ cyclopalladated *N-tert*-butylarylaldimines,⁷ and *N-tert*-butyl-*o*-iodobenzaldimines plus a palladium catalyst.⁸

The transition metal-catalyzed cyclization of alkynes,⁹ which possess nucleophilic centers in close proximity to the carbon-carbon triple bond, by *in situ* coupling/cyclization reactions,¹⁰ and reactions promoted by vinylic, aryl, and alkynylpalladium complexes,¹¹ have also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles.

The palladium(II)-catalyzed cyclization/olefination reaction of 2-(1-alkynyl)aniline derivatives to indoles has been reported by Sakamoto et al.¹² They report that the reaction of *N*-protected 2-(1-alkynyl)anilines with electron-deficient alkenes in the presence of PdCl₂ and CuCl₂ gives 2-substituted 3-(1-alkenyl)indoles (eq 1). Our interest in 4-(1-alkenyl)isoquinolines has prompted us to develop a convenient new synthesis of these isoquinolines by the Pd(II)-promoted cross coupling of a variety of alkenes and 2-(1-alkynyl)arylaldimines, which can be easily prepared from corresponding 2-halobenzaldehydes in two steps (eq 2).

Results and Discussion

Our initial studies on the synthesis of 4-(1-alkenyl)isoquinolines focused on the development of an optimum set of reaction conditions for their formation. A variety of Pd(II) catalysts, oxidants, bases, solvents and temperatures have been examined on the reaction of arylaldimine **1** and methyl acrylate (eq 3) and only some representative optimization reactions are summarized in Tables 1 and 2.

The optimization reactions shown in Table 1 employed 2 equiv of the oxidant (eq 3). In entry 1 (Table 1), benzaldimine **1** has been allowed to react with 5 equiv of methyl acrylate in the presence of 10 mol % of PdBr₂ under an O₂ balloon, and a 33 % yield of isoquinoline **2** was isolated in the absence of a base. However, the use of 2 equiv of CuCl₂ as the oxidant afforded none of the desired product, although all starting materials disappeared

within 20 h (entry 2). The use of CuCl_2 and the bases Et_3N , K_2CO_3 and NaOAc resulted in 10-20 % yields of the desired product **2** (entries 3-5). In entries 4 and 5, 4-chloro-3-phenylisoquinoline (**4**) was obtained in 15 % and 20 % yields, respectively.

Table 1. Optimization of the Reaction of Benzaldimine **1** and Methyl Acrylate by Examination of Different Oxidizing Reagents, Bases and Solvents (eq 3)^a

entry	oxidant	base	solvent	time (h)	2 (%) ^b	3 (%) ^b	4 (%) ^b
1	O_2	--	DMF	24	33 (37 ^c)	20	0
2	CuCl_2	--	DMF	20	0	0	0
3	CuCl_2	Et_3N	DMF	36	10	15	trace
4	CuCl_2	K_2CO_3	DMF	36	17	trace	15
5	CuCl_2	NaOAc	DMF	36	20	trace	20
6	$\text{Cu}(\text{OAc})_2$	NaOAc	DMF	24	35	0	0
7	$\text{Cu}(\text{OAc})_2$	NaOAc	CH_3CN	12	18	25	0
8	$\text{Cu}(\text{OAc})_2$	NaOAc	DMSO	12	61	5	0
9	$\text{Cu}(\text{CO}_3)_2$	NaOAc	DMSO	24	23	34	0
10	$\text{Cu}(\text{NO}_3)_2$	NaOAc	DMSO	24	37	19	0
11	benzoquinone	NaOAc	DMSO	24	40	30	0

^a All reactions were run under the following reaction conditions: 0.25 mmol of benzaldimine **1**, 5 equiv of methyl acrylate, 10 mol % PdBr_2 , 2 equiv of the oxidant, and 3 equiv of the base were stirred in 3 ml of the indicated solvent at 70 °C for the specified period of time. ^b Isolated yields. ^c Yield based on ^1H NMR spectroscopic analysis.

Possible mechanisms for the formation of isoquinolines **2** and **4** are shown in Scheme 1. The cyclization of benzaldimine **1** by PdBr_2 presumably forms intermediate **A**, which is an electron-deficient arylpalladium bromide. The *cis* addition of intermediate **A** to the carbon-carbon double bond of the olefin affords an alkylpalladium(II) intermediate, which

undergoes subsequent E-hydride elimination to afford intermediate **C** and Pd(0). Further fragmentation of the *tert*-butyl group from intermediate **C** generates the desired 4-(1-alkenyl)isoquinolines. The Pd(0) generated can be reoxidized back to PdBr₂ by the oxidant present in the reaction mixture.

Scheme 1

With the presence of excess chloride in the reaction mixture, the intermediate **A** is converted into intermediate **B** by halide exchange, because the Pd-Cl bond is much stronger than the Pd-Br bond.¹³ Isoquinoline **4** is then generated by the reductive elimination of intermediate **B**, followed by fragmentation of the *tert*-butyl group. This reductive

elimination is apparently promoted by the presence of the copper salt, since arylpalladium halides do not normally undergo this process spontaneously. The use of $\text{Cu}(\text{OAc})_2$ as the oxidant increased the yield of the desired isoquinoline **2** from 20 % (entry 5) to 35 % (entry 6). Obviously, the use of $\text{Cu}(\text{OAc})_2$ eliminates the formation of intermediate **B** and eventual formation of the chloroisoquinoline **4**.

When CH_3CN was chosen as the solvent, an 18 % yield of isoquinoline **2** was isolated, alongside a 25 % yield of isoquinoline **3** (entry 7). However, the use of DMSO resulted in a 61 % yield of isoquinoline **2** and only a 5 % yield of **3** in 12 h (entry 8). Obviously, DMSO is a better solvent than DMF or CH_3CN for this isoquinoline olefination process, presumably due to improved oxidation of $\text{Pd}(0)$ to $\text{Pd}(\text{II})$. Thus, DMSO has been chosen as the solvent for all subsequent optimization reactions. From entries 9-11, other oxidants $\text{Cu}(\text{CO}_3)_2$, $\text{Cu}(\text{NO}_3)_2$, and 1,4-benzoquinone have been employed and only 23-40 % yields of product **2** have been isolated. Based on the above results, the following reaction conditions have been chosen as the standard reaction conditions for procedure A: 0.25 mmol of benzaldimine, 5 equiv of the olefin, 10 mol % of PdBr_2 , 2 equiv of $\text{Cu}(\text{OAc})_2$, and 3 equiv of NaOAc are stirred in 3 mL of DMSO at 70 °C.

The drawback of procedure **A** is the use of 2 equiv of $\text{Cu}(\text{OAc})_2$. We have therefore tried to develop an alternative procedure using only catalytic amounts of the copper reagent (eq 4). In this optimization study, it has been found that only catalytic amounts of $\text{PdCl}_2(\text{PPh}_3)_2$ in the presence of 10 mol % CuCl_2 , 3 equiv of NaOAc and an O_2 atmosphere can cyclize benzaldimine **1**, affording a 38 % yield of isoquinoline **5** (entry 1, Table 2). Based on this reaction, various bases and additives have been examined and the results are summarized in entries 2-11.

Table 2. Optimization of the Reaction of Benzaldimine **1** and *n*-Butyl Acrylate Using Catalytic Amounts of the Copper Reagent(eq 4)^a

entry	catalyst	oxidant	base	additive	time (h)	% isolated yield of 5	% isolated yield of 3
1	$\text{PdCl}_2(\text{PPh}_3)_2$	CuCl_2	NaOAc	--	24	38	21
2			pyridine	--	24	48	9
3			Et_3N	--	28	46	12
4			Cs_2CO_3	--	24	trace ^b	20
5			K_2CO_3	--	28	29	18
6			KHCO_3	--	20	39	16
7			Na_2CO_3	--	20	47	12
8			NaHCO_3	--	14	51	11
9			NaHCO_3	TBAC	20	45	25
10			NaHCO_3	TBAB	20	46	15
11			NaHCO_3	TEAI	20	44	20

Table 2 continued

12	PdCl ₂	CuCl ₂	NaHCO ₃	--	16	49	12
13	PdI ₂			--	24	46	20
14	Pd(O ₂ CCF ₃) ₂			--	24	48	15
15	Pd(OAc) ₂			--	20	45	11
16	PdBr ₂			--	8	56	17
17	PdBr ₂			PPh ₃	20	48	17
18	PdBr ₂			dppp	20	53	15
19	PdBr ₂			dppe	18	51	11
20	PdBr ₂	CuF ₂		--	18	54	14
21		Cu(OAc) ₂		--	19	45	27
22		Cu(NO ₃) ₂		--	24	45	21
23		CuCO ₃		--	24	39	14
24		CuO		--	24	41	24
25		CuI		--	16	23	46

^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of benzaldimine **1**, 5 equiv of *n*-butyl acrylate, 10 mol % of the indicated Pd(II) salt, 10 mol % of the indicated oxidant and 3 equiv of the indicated base in 3 mL of DMSO were stirred at 70 °C for the specified period of time under a balloon of O₂. ^b Benzaldimine **1** was recovered in 40 % yield.

Table 3. Synthesis of Isoquinolines by Palladium(II)-Catalyzed Cyclization/Olefination^a

entry	aryaldimine	H ₂ C=CHR	procedure, time (h)	product	% isolated yield
1	(1)	R = CO ₂ Me	A, 12	(2)	61
2		R = CO ₂ - <i>n</i> -Bu	A, 10	(5)	61
3		R = CO ₂ - <i>n</i> -Bu	B, 8	(5)	56
4		R = CO ₂ - <i>t</i> -Bu	B, 24	(6)	50
5		R = Ph	B, 18	(7)	53
6		R = CMe ₂ OH	B, 17	(8)	34
7		R = O- <i>n</i> -Bu	B, 24	(9)	31
8	(10)	R = CO ₂ - <i>n</i> -Bu	B, 24	(11)	41
9	(12)	R = CO ₂ - <i>n</i> -Bu	B, 18	(13)	51

Table 3 continued

10		R = CO ₂ - <i>n</i> -Bu	A, 18		43
11		R = CO ₂ - <i>n</i> -Bu	B, 24		48
12		R = CO ₂ - <i>t</i> -Bu	B, 48		51
13		R = CONMe ₂	B, 18		51
14		R = SO ₂ CH ₃	B, 17		27
15		R = CO ₂ - <i>n</i> -Bu	B, 24		35
16		R = CO ₂ - <i>n</i> -Bu	A, 18		65
17		R = CO ₂ - <i>n</i> -Bu	B, 36		64
18		R = CO ₂ - <i>t</i> -Bu	B, 24		68
19		R = Ph	B, 72		64
20		R = SO ₂ Ph	B, 72		20
21		R = CONMe ₂	B, 18		65
22		R = CMMe ₂ OH	B, 48		25

Table 3 continued

23	(29)	R = CO ₂ - <i>t</i> -Bu	B, 14	(30)	R = CO ₂ - <i>t</i> -Bu (30)	92 ^b
24	(29)	R = CONMe ₂	B, 10	(31)	R = CONMe ₂ (31)	97 ^b
25	(29)	R = SO ₂ CH ₃	B, 12	(32)	R = SO ₂ CH ₃ (32)	52 ^b
26	(33)	R = CO ₂ - <i>t</i> -Bu	A, 12	(34)	R = CO ₂ - <i>t</i> -Bu (34)	61
27	(33)	R = CO ₂ - <i>t</i> -Bu	B, 10	(34)	R = CO ₂ - <i>t</i> -Bu (34)	82 ^b
28	(33)	R = CONMe ₂	B, 5	(35)	R = CONMe ₂ (35)	89 ^{b,c}
29		R = CH(OH)CH ₃	B, 24	(36)		48
30	(37)	R = CO ₂ - <i>t</i> -Bu	B, 16	(38)	R = CO ₂ - <i>t</i> -Bu (38)	69
31	(37)	R = CO ₂ - <i>t</i> -Bu	B, 2	(38)	R = CO ₂ - <i>t</i> -Bu (38)	67 ^b
32	(37)	R = CONMe ₂	B, 1.5	(39)	R = CONMe ₂ (39)	70 ^{b,d}

Table 3 continued

33	(40)	R = CO ₂ - <i>t</i> -Bu R = CONMe ₂	B, 12 B, 16	OMe	R = CO ₂ - <i>t</i> -Bu (41) R = CONMe ₂ (42)	71 ^b 70 ^b
35	(43)	R = CO ₂ - <i>n</i> -Bu R = CO ₂ - <i>t</i> -Bu R = CONMe ₂ R = Ph	A, 48 B, 36 B, 48 B, 16	MeO	R = CO ₂ - <i>n</i> -Bu (44) R = CO ₂ - <i>t</i> -Bu (45) R = CONMe ₂ (46) R = Ph (47)	51 ^b 62 ^b 50 ^b 78 ^b
39	(48)	R = CH(OH)CH ₃ R = CH(OH)Ph	B, 72 B, 4	MeO	R = CH ₃ (49) R = Ph (50)	50 36 ^b
41		R = (CH ₂) ₂ CH(OH)CH ₃	B, 8	OMe	(51)	27 ^b

^a See the text for the detailed reaction conditions for procedures A and B. ^b The reaction was run at 90 °C. ^c The product was isolated as a 73:27

mixture of *E/Z* isomers. ^d The product was isolated as a 91:9 mixture of *E/Z* isomers.

The use of 3 equiv of the organic bases pyridine or Et₃N afforded a 48 % (entry 2) or a 46 % (entry 3) yield of isoquinoline **5**, respectively. In entries 4-8, the carbonate salts Cs₂CO₃, K₂CO₃, KHCO₃, Na₂CO₃ and NaHCO₃ have been examined. The results show that the more soluble carbonate bases, such as Cs₂CO₃ (entry 4), disfavor the reaction and the less soluble carbonates, such as NaHCO₃ (entry 8), favor the formation of isoquinoline **5**. The addition of *n*-Bu₄NCl (TBAC), *n*-Bu₄NBr (TBAB) or Et₄NI (TEAI) resulted in a slight decrease in the yield of isoquinoline **5** (entries 9-11). Thus, the reaction conditions employed in entry 8, which are the best reaction conditions shown in entries 2-11, have been chosen for further optimization reactions employing a variety of Pd(II) catalysts and ligands. The results for this latter study are summarized in entries 12-19 in Table 2.

When catalytic amounts of PdCl₂, PdI₂, Pd(O₂CCF₃)₂, Pd(OAc)₂ or PdBr₂ have been employed, the desired product, isoquinoline **5**, was isolated in 45-56 % yields with PdBr₂ giving the best yield (entries 12-16). In entries 17-19, addition of the ligands, PPh₃, dppp or dppe resulted in a slight decrease in the yield of isoquinoline **5**. Again, the reaction conditions in entry 16, which have afforded the best result so far, have been chosen for further optimization.

Based on the reaction conditions in entry 16, a variety of oxidants have been examined and the results are summarized in entries 20-25. As mentioned above, a 56 % isolated yield of isoquinoline **5** was obtained in the presence of 10 mol % of CuCl₂ (entry 16). The use of 10 mol % CuF₂ gave a 54 % yield of isoquinoline **5** (entry 20). Other copper(II) reagents, such as Cu(OAc)₂, Cu(NO₃)₂, CuCO₃ and CuO have also been examined and isoquinoline **5** was isolated in 39-45 % yields (entries 21-24). The use of CuI, a copper(I) reagent as the

oxidant, resulted in a decrease in the yield of isoquinoline **5** from 56 % (entry 16) to 23 %, while the side product **3** was isolated in a 46 % yield (entry 25).¹⁴

After the above optimization work, we have adopted the following standard reaction conditions using only a catalytic amount of Cu(II) reagent as procedure B: 0.25 mmol of arylaldimine, 5 equiv of the olefin, 10 mol % of PdBr₂, 10 mol % of CuCl₂, 3 equiv of NaHCO₃ in 3 mL of DMSO at 70 °C under an O₂ atmosphere.

By employing procedures A and B, a variety of 4-(1-alkenyl)- and 4-alkyl-3-arylisoquinolines have been prepared (Table 3). As mentioned above, using procedure A, isoquinoline **2** was isolated in a 61 % yield from the reaction of benzaldimine **1** and methyl acrylate (entry 1, Table 3). An identical yield of isoquinoline **5** was isolated from the reaction of benzaldimine **1** and *n*-butyl acrylate using procedure A (entry 2).

Several olefins, including electron-deficient and electron-rich alkenes, have been allowed to react with benzaldimine **1** using procedure B (entries 3-7). The use of *n*-butyl acrylate and *t*-butyl acrylate afforded a 56 % yield of isoquinoline **5** (entry 3) and a 50 % yield of isoquinoline **6** (entry 4), respectively. However, none of the desired isoquinoline product was observed when phenyl vinyl sulfone, an electron-deficient alkene, was allowed to react with benzaldimine **1**. The relatively electron-rich olefins, styrene and 2-methyl-3-buten-2-ol have been allowed to react with benzaldimine **1**. A 53 % yield of isoquinoline **7** (entry 5) and a 34 % yield of **8** (entry 6) were obtained, respectively. Instead of forming an internal alkene, the reaction of *n*-butyl vinyl ether afforded isoquinoline **9** bearing a terminal double bond, albeit in low overall yield (entry 7).¹⁵

Sakamoto et al. have reported that *N*-protected *alkyl*-substituted *o*-(1-alkynyl)anilines react with electron-deficient alkenes in the presence of PdCl₂ and CuCl₂ producing 2-

substituted 3-(1-alkenyl)indoles.¹² However, in our chemistry, the *N-tert*-butyl *alkyl*-substituted *o*-(1-alkynyl)benzaldimines **52** and **53** did not react with either electron-deficient or electron-rich terminal alkenes under either procedures A or B to afford isoquinoline products. Although *N-tert*-butyl *alkyl*-substituted *o*-(1-alkynyl)benzaldimines do not react with olefins, benzaldimine **10**, which is a *N-tert*-butyl *alkenyl*-substituted *o*-(1-alkynyl)benzalimine, did react with *n*-butyl acrylate affording a 41 % isolated yield of isoquinoline **11** (entry 8).

The reaction of arylaldimine **54**, bearing a pyridine moiety, and olefins gave none of the desired product. However, when arylaldimine **12** with the alkynyl group attached to C-3 of the pyridine nucleus was allowed to react with *n*-butyl acrylate, naphthyridine **13** was isolated in a 51 % yield (entry 9).

It is known that electron-deficient aryl halides or vinylic halides disfavor the Heck reaction.¹³ Thus, electron-donating groups have been introduced into the arylaldimine in order to increase the electron density in intermediate A (Scheme 1) and hopefully favor formation of the desired isoquinoline products. However, the experimental results indicate that the introduction of electron-donating groups into the arylaldimine does not really favor the isoquinoline olefination process, and instead results in a decrease in the yields of the desired isoquinoline products in most cases. For example, when benzaldimine **14** bearing a

methylenedioxy group on the benzylidene moiety was allowed to react with *n*-butyl acrylate using procedures A and B, the yield dropped from 61 % (entry 2) to 43 % (entry 10) or from 56 % (entry 3) to 48 % (entry 11), respectively. The reaction of **16**, another electron-rich arylaldimine, and *t*-butyl acrylate afforded isoquinoline **17** in a 51 % yield (entry 12), comparable to the 50 % yield from the reaction of benzaldimine **1** and *t*-butyl acrylate (entry 4). When *N,N*-dimethylacrylamide or methyl vinyl sulfone were allowed to react with arylaldimine **16**, a 51 % yield of isoquinoline **18** (entry 13) and a 27 % yield of isoquinoline **19** (entry 14) were obtained, respectively. The sulfone result is a bit surprising in view of our earlier failure to obtain any isoquinoline product from benzaldimine **1** and phenyl vinyl sulfone. The introduction of a *para*-methoxy group on the phenyl moiety resulted in the yield of the desired isoquinoline **21** dropping from 56 % (entry 3) to only 35 % (entry 15).

The presence of electron-donating groups increases the electron density of the carbon-carbon triple bond, which apparently disfavors cyclization by attack of the imine nitrogen on the activated triple bond and consequently results in low conversion of the arylaldimine to intermediate **A** and eventual formation of the isoquinoline (Scheme 1). Although the reactivity of intermediate **A** towards olefins is presumably improved by introducing electron-donating groups, the low conversion of arylaldimine to intermediate **A** results in a decrease in the overall yield of isoquinoline products.

The position of the electron-donating methoxy group in the arylaldimine is critical to the success of this process. Thus, the introduction of an *ortho*-methoxy group on the phenyl moiety facilitates isoquinoline formation. When benzaldimine **22** was allowed to react with *n*-butyl acrylate using procedures A and B, the yields increased to 65 % (entry 16) and 64 % (entry 17) from 61 % (entry 2) and 56 % (entry 3), respectively. Employing procedure B, a

variety of olefins have been allowed to react with arylaldimine **22** (entries 18-22). The reactions of **22** with *t*-butyl acrylate and styrene afforded a 68 % yield of isoquinoline **24** (entry 18) and a 64 % yield of isoquinoline **25** (entry 19), respectively. These yields are much better than the yields of 50 % and 53 % from the corresponding reactions of benzaldimine **1** (entries 4 and 5). As mentioned above, the reaction of benzaldimine **1** and phenyl vinyl sulfone gave none of the desired product. However, a 20 % yield of isoquinoline **26** was observed when benzaldimine **22** was allowed to react with phenyl vinyl sulfone (entry 20). When *N,N*-dimethylacrylamide was allowed to react with arylaldimine **22**, isoquinoline **27** was isolated in a 65 % yield (entry 21), much better than the yield of 51 % from the reaction of benzaldimine **16** and *N,N*-dimethylacrylamide (entry 13). The reaction of arylaldimine **22** and 2-methyl-3-buten-2-ol afforded isoquinoline **28** in a 25 % yield (entry 22). For some reason, this yield is lower than the 35 % yield obtained using benzaldimine **1** (entry 6).

The beneficial effects of an *ortho*-methoxy group can be explained by Scheme 2. Basically, the introduction of an *ortho*-methoxy group helps direct the PdBr₂ to the vicinity of the triple bond where attack by the imine nitrogen on the activated triple bond takes place generating an arylpalladium intermediate, which is stabilized by chelation with the *ortho*-methoxy group. Subsequent Heck olefination and fragmentation of the *t*-butyl group affords the desired isoquinoline olefin.

Scheme 2

The reactions of benzaldimine **29** and *t*-butyl acrylate or *N,N*-dimethylacrylamide are very slow at 70 °C. These reactions were thus run at 90 °C and the corresponding isoquinolines **30** and **31** have been obtained in 92 % and 97 % yields, respectively (entries 23 and 24). Comparing the results from entries 12, 13, 18, 21, 23 and 24, one can see that both electronic effects and facilitation by the *ortho*-methoxy group play a role in forming isoquinolines **30** and **31** in such high yields. The *ortho*-methoxy group improves the conversion of the arylaldimine to intermediate **A** and the introduction of electron-donating groups on the arylaldimine moiety presumably increases the reactivity of intermediate **A** towards olefins,¹⁴ affording mostly improved yields. When methyl vinyl sulfone was allowed to react with arylaldimine **29**, the yield of isoquinoline **32** increased to 52 % (entry 25) from the 27 % obtained without the *ortho*-methoxy group (entry 14).

Arylaldimine **33**, bearing a methylenedioxy group on the benzyldiene moiety and an *ortho*-methoxy group on the phenyl moiety, has been allowed to react with several olefins (entries 26-29). The reactions of arylaldimine **33** with *t*-butyl acrylate afforded a 61 % (entry 26) or an 82 % (entry 27) yield of isoquinoline **34** using procedures A and B, respectively. For this specific arylaldimine, procedure A is not as efficient as procedure B. When *N,N*-dimethylacrylamide was allowed to react with arylaldimine **33**, an 89 % yield of isoquinoline

35 was isolated as a 73:27 *E/Z* mixture (entry 28). Comparing entries 23, 24, 27 and 28, one can see that the introduction of two methoxy groups onto the benzylidene moiety is much more efficient in promoting the Heck reaction than the introduction of a methylenedioxy group onto the benzaldimine moiety.

Unsaturated alcohols undergo reaction to afford ketone-containing products. Thus, 3-buten-2-ol has been allowed to react with arylaldimine **33** (entry 29). The corresponding ketone **36** was isolated in a 48 % yield. The formation of ketone **36** can be explained by the mechanism shown in Scheme 3. The cyclization of arylaldimine **33** by PdBr_2 affords an arylpalladium(II) intermediate **D**, which is stabilized by the *ortho*-methoxy group. The *cis* addition of intermediate **D** to 3-buten-2-ol results in an alkylpalladium bromide intermediate, which undergoes β hydride elimination to form enol **E**.¹⁶ Subsequent tautomerization and fragmentation of intermediate **E** affords the desired ketone **36**.

Scheme 3

To further test the electronic effects of substituents on the isoquinoline olefination process, arylaldimines **37** and **40** have been prepared and allowed to react with *t*-butyl acrylate and *N,N*-dimethylacrylamide. The reaction of arylaldimine **37**, bearing a dimethylamino group *meta* to the alkynyl group, and *t*-butyl acrylate at 70 °C was complete in 16 h and afforded isoquinoline **38** in a 69 % yield (entry 30). When the reaction was run at 90 °C, it was complete in 2 h and gave isoquinoline **38** in a 67 % yield (entry 31). By employing *N,N*-dimethylacrylamide at 90 °C, the reaction was complete in 1.5 h and a 70 % yield of isoquinoline **39** was isolated as a 91:9 *E/Z* mixture (entry 32). While the introduction of a *meta*-dimethylamino group shortens the reaction time, the introduction of a dimethylamino group *para* to the alkynyl moiety slows the reaction down. Thus, arylaldimine **40** has been allowed to react with *t*-butyl acrylate and *N,N*-dimethylacrylamide at 90 °C affording a 71 % yield of isoquinoline **41** in 12 h (entry 33) and a 70 % yield of isoquinoline **42** in 16 h (entry 34). The reason for the slow reactions is apparently because the dimethylamino group *para* to the alkynyl group in arylaldimine **40** significantly increases the electron density on the carbon-carbon triple bond and has little influence on the electron density of the imine nitrogen, disfavoring attack of the imine nitrogen on the triple bond. However, the dimethylamino group in arylaldimine **37** significantly increases the electron density on the imine nitrogen, favoring attack of the imine nitrogen on the carbon-carbon triple bond. Thus, the reactions of arylaldimine **37** reach completion in shorter reaction times.

The reactions of arylaldimine **43** with *n*-butyl acrylate, *t*-butyl acrylate, *N,N*-dimethylacrylamide, and styrene gave the corresponding isoquinolines **44-47** in 51-78 % yields (entries 35-38). Similar to the reactions of arylaldimine **29**, the reactions of

arylaldimine **43** with olefins also involve electronic effects and facilitation by the *ortho*-methoxy group (Scheme 4). However, the reactions of aarylaldimine **43**, having an *ortho*-methoxy group on the benzylidene moiety, are very slow. For example, when benzaldimine **43** was allowed to react with *n*-butyl acrylate or *N,N*-dimethylacrylamide, the reactions are not complete even in 48 h at 90 °C (entries 35 and 37). The reason is probably because the intermediate **F** (Scheme 4) is quite hindered, preventing approach of the olefins. Comparing the results from aarylaldimine **29** (entries 23 and 24) with those of aarylaldimine **43** (entries 36 and 37), we conclude that the introduction of an *ortho*-methoxy group onto the phenyl moiety promotes this isoquinoline olefination better than the introduction of an *ortho*-methoxy group onto the benzylidene moiety.

Scheme 4

To further test the effect of oxygen substituents in this isoquinoline olefination process, aarylaldimine **48** has been prepared and allowed to react with olefins. The reaction of aarylaldimine **48** and styrene afforded none of the desired product for reasons which are not obvious. When 3-buten-2-ol and 1-phenyl-2-propen-1-ol have been allowed to react with aarylaldimine **48**, a 50 % yield of ketone **49** (entry 39) and a 36 % yield of ketone **50** were

obtained, respectively. Using procedure B, the reaction of arylaldimine **48** and 5-hexen-2-ol afforded compound **51** by palladium migration, albeit in a low yield (entry 41).¹⁷

Conclusions

An efficient and straightforward route to synthesize 4-(1-alkenyl)isoquinolines and 4-alkyl-3-arylisoquinolines containing a ketone group has been developed using a palladium(II)-catalyzed cyclization, followed by olefination (Heck reaction). A wide variety of olefins undergo this process in moderate to excellent yields with high regioselectivity being observed. The introduction of an *ortho*-methoxy group on the benzaldimine moiety promotes the Pd-catalyzed cyclization and stabilizes the resulting Pd(II) intermediate, improving the yields of the desired isoquinoline products. Moreover, the introduction of an *ortho*-methoxy group onto the phenyl moiety has been shown to promote this isoquinoline olefination more efficiently than the introduction of an *ortho*-methoxy group onto the benzyldiene moiety. To form isoquinolines in high yields, both electronic effects and facilitation by an *ortho*-methoxy group are necessary.

Experimental Section

General. ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and a basic KMnO₄ solution [3 g of KMnO₄ + 20 g of K₂CO₃ + 5 mL of NaOH (5 %) + 300 mL of H₂O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass

spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.

Compounds **1**,^{1a} **10**,^{1a} **12**,^{1a} **14**,^{1a} **20**,^{1a} **52**,^{1a} **53**,¹² **54**,^{1a} 4-dimethylamino-2-iodobenzaldehyde,^{8b} 5-dimethylamino-2-iodobenzaldehyde,^{8b} 2-iodo-3,4,5-trimethoxybenzaldehyde,^{8b} and *N*-(benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine¹⁴ were prepared according to previous literature procedures.

2-Methoxyphenyl trimethylsilyl acetylene. To a solution of the 2-iodoanisole (4.68 g, 20 mmol) and trimethylsilylacetylene (24 mmol, 1.2 equiv) in Et₃N (60 mL) were added PdCl₂(PPh₃)₂ (0.281 mg, 2 mol %) and CuI (38.2 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 55 °C. The reaction was complete in 2 h. The mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (15:1 hexane/EtOAc) to afford 4.05 g of the indicated product in 100 % yield as a yellow liquid: ¹H NMR (CDCl₃) δ 0.27 (s, 9H), 3.87 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.89 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.25-7.30 (m, 1H), 7.44 (dd, *J* = 1.6, 7.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 0.3, 56.0, 98.7, 101.4, 110.8, 112.4, 120.5, 130.2, 134.4, 160.5.

2-Methoxyphenylacetylene. A solution of KOH (5.06 g, 10 mmol) in 4 mL of water was added dropwise to 2-methoxyphenyl trimethylsilyl acetylene (2.04 g, 10 mmol) in 40 mL of CH₃OH under an Ar atmosphere at 25 °C. The mixture was stirred for another 0.5 h at 25 °C, and the CH₃OH was removed under vacuum. The residue was added to 20 mL of brine solution, and the mixture was extracted with EtOAc (3 x 20 mL), dried (Na₂SO₄),

filtered, and the solvent removed under vacuum. Purification by flash chromatography (7:1 hexane/EtOAc) afforded 1.15 g (10 mmol) of the indicated compound in a 100 % yield as a yellow liquid: ^1H NMR (CDCl_3) δ 3.31 (s, 1H), 3.88 (s, 3H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.90 (dd, $J = 0.8, 7.6$ Hz, 1H), 7.28-7.32 (m, 1H), 7.46 (dd, $J = 1.6, 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 55.9, 80.2, 81.3, 110.7, 111.3, 120.5, 130.4, 134.3, 160.7.

***N*-[4,5-Dimethoxy-2-(phenylethynyl)benzylidene]-*tert*-butylamine (16).** To a solution of 2-bromo-4,5-dimethoxybenzaldehyde (1.23 g, 5.0 mmol) and phenylacetylene (0.62 g, 6.0 mmol) in Et_3N (20 mL) were added $\text{PdCl}_2(\text{PPh}_3)_2$ (70 mg, 2 mol %) and CuI (10 mg, 1 mol %). The resulting mixture was then heated under an Ar atmosphere at 55 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the reaction mixture was allowed to cool to 25 °C, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding arylalkyne. To the purified arylalkyne in a 4 dram vial was added *t*-BuNH₂ (12 equiv). The mixture was then stirred under an Ar atmosphere at 25 °C for 24 h. The resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of the solvent afforded 1.32 g of the indicated arylaldimine in a 82 % overall yield as a yellow solid: mp 137-140 °C; ^1H NMR (CDCl_3) δ 1.35 (s, 9H), 3.95 (s, 3H), 4.00 (s, 3H), 7.01 (s, 1H), 7.36-7.38 (m, 3H), 7.52-7.55 (m, 2H), 7.63 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.1, 56.2, 56.3, 57.8, 86.9, 93.8, 107.9, 113.9, 117.1, 123.5, 128.5, 128.7, 131.5, 132.1, 149.9, 150.5, 153.9; IR (CHCl_3 , cm^{-1}) 3019, 2969, 1681, 1593, 1507; HRMS Calcd for $\text{C}_{21}\text{H}_{23}\text{O}_2\text{N}$: 321.1729. Found: 321.1735.

***N*-[2-(*p*-Methoxyphenylethynyl)benzylidene]-*tert*-butylamine (22).** Using the procedure used to prepare arylaldimine **16**, 2-bromobenzaldehyde (0.93 g, 5.0 mmol) and *p*-methoxyphenylacetylene (0.79 g, 6.0 mmol) were employed to afford 1.06 g of the indicated arylaldimine in a 90 % overall yield as a yellow oil: ^1H NMR (CDCl_3) δ 1.34 (s, 9H), 3.84 (s, 3H), 6.90 (td, $J = 2.1, 9.0$ Hz, 2H), 7.32-7.36 (m, 2H), 7.47 (td, $J = 2.1, 9.0$ Hz, 2H), 7.50-7.54 (m, 1H), 8.04-8.07 (m, 1H), 8.92 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.0, 55.6, 58.1, 85.7, 95.2, 114.4, 115.4, 124.5, 126.1, 128.5, 129.9, 132.3, 133.2, 137.7, 154.7, 160.0; IR (neat, cm^{-1}) 2963, 2836, 1699; HRMS Calcd for $\text{C}_{20}\text{H}_{21}\text{ON}$: 291.1623. Found: 291.1626.

***N*-[4,5-Dimethoxy-2-(*o*-methoxyphenylethynyl)benzylidene]-*tert*-butylamine (29).** Using the procedure used to prepare arylaldimine **16**, 2-bromo-4,5-dimethoxybenzaldehyde (1.23 g, 5.0 mmol) and *o*-methoxyphenylacetylene (0.79 g, 6.0 mmol) were employed to afford 1.23 g of the indicated arylaldimine in a 70 % overall yield as a yellow solid: mp 124-126 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.35 (s, 9H), 3.92 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 6.92-6.98 (m, 2H), 7.03 (s, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.50 (d, $J = 7.5$ Hz, 1H), 7.61 (s, 1H), 8.94 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.2, 55.9, 56.2, 57.6, 90.2, 91.3, 107.8, 110.8, 112.7, 113.9, 117.6, 120.7, 129.9, 132.0, 133.4, 149.8, 150.5, 154.6, 160.0 (one methoxy carbon is missing due to overlap); IR (CHCl_3 , cm^{-1}) 3019, 2967, 2838, 1634, 1598, 1507; HRMS Calcd for $\text{C}_{22}\text{H}_{25}\text{O}_3\text{N}$: 351.1834. Found: 351.1839.

***N*-[6-(*o*-Methoxy)phenylethynylbenzo[1,3]dioxol-5-ylmethylene]-*tert*-butylamine (33).** Using the procedure used to prepare arylaldimine **16**, 6-bromo-1,3-benzodioxole-5-carboxaldehyde (1.15 g, 5 mmol) and *o*-methoxyphenylacetylene (0.70 g, 6 mmol) were employed to afford 1.12 g of the indicated arylaldimine in a 67 % overall yield after recrystallization (EtOAc /hexane) as a yellow solid: mp 87-89 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.33

(s, 9H), 3.90 (s, 3H), 5.99 (s, 2H), 6.91 (d, $J = 8.8$ Hz, 1H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.98 (s, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.57 (s, 1H), 8.92 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.1, 55.9, 57.7, 90.2, 90.9, 101.8, 105.7, 110.8, 111.3, 112.6, 119.0, 120.7, 129.9, 133.4, 133.8, 148.6, 149.1, 154.3, 160.1; IR (CHCl_3 , cm^{-1}) 3017, 2968, 1612, 1476; HRMS Calcd for $\text{C}_{21}\text{H}_{21}\text{O}_3\text{N}$: 335.1521. Found: 335.1526.

***N*-[4-Dimethylamino-2-(*o*-methoxyphenylethynyl)benzylidene]-*tert*-butylamine**

(37). Using the procedure used to prepare arylaldimine **16**, 4-dimethylamino-2-iodobenzaldehyde^{8b} (1.38 g, 5 mmol) and *o*-methoxyphenylacetylene (0.70 g, 6 mmol) were employed to afford 1.57 g of the indicated arylaldimine in a 94 % overall yield as a yellow solid: mp 102-104 °C; ^1H NMR (CDCl_3) δ 1.34 (s, 9H), 3.02 (s, 6H), 3.92 (s, 3H), 6.71 (dd, $J = 2.4, 8.8$ Hz, 1H), 6.82 (d, $J = 2.8$ Hz, 1H), 6.91-6.97 (m, 2H), 7.32 (dt, $J = 1.6, 8.0$ Hz, 1H), 7.51 (dd, $J = 1.6, 7.6$ Hz, 1H), 8.00 (br s, 1H), 8.90 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.2, 40.5, 55.9, 57.3, 90.2, 91.8, 110.8, 112.6, 113.1, 114.5, 120.7, 125.6, 126.1, 127.2, 130.0, 133.6, 151.4, 155.0, 160.2; IR (CHCl_3 , cm^{-1}) 3018, 2968, 2400, 1596; HRMS Calcd for $\text{C}_{22}\text{H}_{16}\text{ON}_2$: 334.02045. Found: 334.2050.

***N*-[5-Dimethylamino-2-(*o*-methoxyphenylethynyl)benzylidene]-*tert*-butylamine**

(40). Using the procedure used to prepare arylaldimine **16**, 5-dimethylamino-2-iodobenzaldehyde^{8b} (1.38 g, 5 mmol) and *o*-methoxyphenylacetylene (0.70 g, 6 mmol) were employed to afford 1.48 g of the indicated arylaldimine in a 89 % overall yield as a yellow solid: mp 118-120 °C; ^1H NMR (CDCl_3) δ 1.35 (s, 9H), 3.03 (s, 6H), 3.92 (s, 3H), 6.72 (dd, $J = 2.8, 8.4$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.94 (dd, $J = 0.8, 7.6$ Hz, 1H), 7.27 (dt, $J = 1.6, 7.6$ Hz, 1H), 7.38 (br s, 1H), 7.44 (d, $J = 8.8$ Hz, 1H), 7.47 (dd, $J = 1.6, 7.6$ Hz, 1H), 8.98 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.1, 40.6, 55.9, 57.7, 89.1, 92.3, 108.4, 110.8, 112.2, 113.5,

114.2, 120.7, 129.2, 133.2, 133.5, 138.7, 150.4, 155.8, 159.7; IR (CHCl₃, cm⁻¹) 3017, 2969, 1638, 1602; HRMS Calcd for C₂₂H₁₆ON₂: 334.2045. Found: 334.2050.

***N*-[2-(Phenylethynyl)-3,4,5-trimethoxybenzylidene]-*tert*-butylamine (43).** Using the procedure used to prepare arylaldimine **16**, 2-iodo-3,4,5-trimethoxybenzaldehyde^{8b} (1.61 g, 5.0 mmol) and phenylacetylene (0.62 g, 6.0 mmol) were employed to afford 1.42 g of the indicated arylaldimine in a 81 % overall yield as a yellow oil: ¹H NMR (CDCl₃) δ 1.33 (s, 9H), 3.92 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 7.35-7.37 (s, 3H), 7.43 (s, 1H), 7.52-7.55 (m, 2H), 8.85 (s, 1H); ¹³C NMR (CDCl₃) δ 30.1, 56.4, 58.0, 61.4, 61.7, 82.8, 98.1, 104.6, 112.4, 123.7, 128.5, 128.7, 131.5, 134.5, 144.1, 153.9, 154.3, 154.6; IR (neat, cm⁻¹) 3079, 3056, 2966, 2872, 2837, 1687, 1640, 1585, 1493; HRMS Calcd for C₂₂H₂₅O₃N: 351.1834. Found: 351.1839.

4-Iodo-1,3-benzodioxole-5-carboxaldehyde. To a solution of *N*-(benzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine¹⁴ (1.03 g, 5.0 mmol) in 40 mL of THF at -78 °C was added 5.25 mmol of *n*-BuLi (2.5 M in hexane) dropwise over a 5 min period. The solution was stirred for 30 min at -78 °C and a solution of I₂ (2.68 g, 7.5 mmol) in 15 mL of THF was added dropwise. The resulting solution was warmed to 25 °C and stirred for 2 h. The reaction mixture was then quenched with water, extracted with ether, washed with satd aq Na₂S₂O₃, dried (NaSO₄), filtered, and the solvent was removed under reduced pressure. The residue was chromatographed using 3:1 hexane/EtOAc to afford 1.01 g of the indicated compound in a 70 % yield as a white solid: mp 130-132 °C; ¹H NMR (CDCl₃) δ 6.16 (s, 2H), 6.86 (dd, *J* = 0.3, 8.1 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 9.90 (d, *J* = 0.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 76.0, 101.5, 108.3, 127.5, 128.8, 150.3, 150.9, 192.8.

***N*-(4-Phenylethynylbenzo[1,3]dioxol-5-ylmethylene)-*tert*-butylamine (48).** Using the procedure used to prepare arylaldimine **16**, 4-iodo-1,3-benzodioxole-5-carboxaldehyde (1.45 g, 5 mmol) and phenylacetylene (0.61 g, 6 mmol) were employed to afford 1.52 g of the indicated arylaldimine in a 100 % overall yield as a yellow solid: mp 128-129 °C; ¹H NMR (CDCl₃) δ 1.34 (s, 9H), 6.10 (s, 2H), 6.84 (d, J = 8.0 Hz, 1H), 7.37-7.38 (m, 3H), 7.55-7.57 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 8.77 (s, 1H); ¹³C NMR (CDCl₃) δ 30.0, 57.8, 80.8, 98.8, 102.1, 106.1, 109.0, 120.6, 122.9, 128.6, 128.9, 131.7, 131.8, 148.9, 153.4 (one sp² carbon missing due to overlap); IR (CHCl₃, cm⁻¹) 3018, 2969, 1644, 1616, 1458; HRMS Calcd for C₂₀H₁₉O₂N: 305.1416. Found: 305.1420.

General procedure A for the palladium-catalyzed formation of isoquinolines.

Dried DMSO (3 mL), PdBr₂ (6.7 mg, 0.025 mmol), Cu(OAc)₂ (0.091 g, 0.50 mmol), NaOAc (0.062 g, 0.75 mmol) and the benzaldimine (0.25 mmol) were placed in a 4 dram vial. The contents were then stirred for 1 min, and the appropriate olefin (1.25 mmol) was added. The vial was sealed carefully and heated in an oil bath at 70 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled to 25 °C, diluted with 20 mL of EtOAc, washed with 20 mL of brine, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

General procedure B for the palladium-catalyzed formation of isoquinolines.

Dried DMSO (3 mL), PdBr₂ (6.7 mg, 0.025 mmol), CuCl₂ (3.4 mg, 0.025 mmol), NaHCO₃ (0.063 g, 0.75 mmol) and the benzaldimine (0.25 mmol) were placed in a 4 dram vial. The contents were then stirred for 1 min, and the appropriate olefin (1.25 mmol) was added. The vial was flushed with O₂ and heated in an oil bath at 70 °C or 90 °C under an O₂ balloon for

the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled to 25 °C, diluted with 20 mL of EtOAc, washed with 20 mL of brine, dried (Na₂SO₄), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

Methyl (*E*)-3-(3-phenylisoquinolin-4-yl)acrylate (2). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 44 mg of the indicated compound in a 61 % yield as a yellow oil: ¹H NMR (CDCl₃) δ 3.81 (s, 3H), 6.31 (d, *J* = 16.4 Hz, 1H), 7.41-7.49 (m, 3H), 7.61-7.63 (m, 2H), 7.67 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.78 (dt, *J* = 1.6, 8.4 Hz, 1H), 8.02 (d, *J* = 16.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.24 (dd, *J* = 0.8, 8.8 Hz, 1H), 9.30 (s, 1H); ¹³C NMR (CDCl₃) δ 52.1, 123.9, 124.4, 126.3, 127.5, 127.6, 128.5, 128.5, 128.6, 130.6, 131.5, 134.5, 140.2, 141.6, 152.0, 152.9, 166.8; IR (CHCl₃, cm⁻¹) 3018, 2924, 2852, 1717, 1638; HRMS Calcd for C₁₉H₁₅O₂N: 289.1103. Found: 289.1108.

***n*-Butyl (*E*)-3-(3-phenylisoquinolin-4-yl)acrylate (5).** The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 51 mg (Table 3, entry 2) or 46 mg (entry 3) of the indicated compound as a yellow oil in a 61 % or a 56 % yield using Procedure A or B, respectively: ¹H NMR (CDCl₃) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.37-1.46 (m, 2H), 1.64-1.72 (m, 2H), 4.43 (t, *J* = 6.8 Hz, 2H), 6.33 (d, *J* = 16.4 Hz, 1H), 7.42-7.49 (m, 3H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 16.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 9.31 (s, 1H); ¹³C NMR (CDCl₃) δ 13.9, 19.4, 30.9, 64.8, 123.9, 124.4, 126.6, 127.4, 127.6, 128.4, 128.5, 128.5, 130.6, 131.5, 134.4, 140.2, 141.3, 152.0, 152.8, 166.4; IR (neat, cm⁻¹) 3412, 3058, 2958, 2872, 1716, 1636, 1570; HRMS Calcd for C₂₂H₂₁O₂N: 331.1572. Found: 331.1577.

***t*-Butyl (*E*)-3-(3-phenylisoquinolin-4-yl)acrylate (6).** The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 41 mg of the indicated compound as a yellow oil in a 50 % yield: ^1H NMR (CDCl_3) δ 1.50 (s, 9H), 6.22 (d, $J = 16.4$ Hz, 1H), 7.38-7.49 (m, 3H), 7.62-7.67 (m, 3H), 7.75 (dt, $J = 0.8, 6.8$ Hz, 1H), 7.86 (d, $J = 16.4$ Hz, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (CDCl_3) δ 28.4, 81.0, 124.1, 124.6, 127.4, 127.6, 128.3, 128.4, 128.5, 130.6, 131.4, 134.4, 140.2, 140.3, 151.9, 152.7, 165.7 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3400, 3058, 2977, 2931, 1708, 1634, 1617, 1572, 1553; HRMS Calcd for $\text{C}_{22}\text{H}_{21}\text{O}_2\text{N}$: 331.1572. Found: 331.1577.

3-Phenyl-4-[(*E*)-2-phenylethen-1-yl]isoquinoline (7). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 41 mg of the indicated compound as a yellow oil in a 53 % yield: ^1H NMR (CDCl_3) δ 6.89 (d, $J = 16.8$ Hz, 1H), 7.25-7.47 (m, 9H), 7.62 (dt, $J = 1.2, 8.1$ Hz, 1H), 7.71-7.74 (m, 3H), 8.02 (d, $J = 7.8$ Hz, 1H), 8.38 (d, $J = 8.4$ Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (CDCl_3) δ 124.7, 125.2, 126.6, 126.7, 127.1, 127.9, 127.9, 128.2, 128.2, 128.2, 128.9, 130.6, 130.8, 135.1, 136.8, 137.3, 141.1, 150.8, 151.4; IR (CHCl_3 , cm^{-1}) 3058, 3024, 2972, 1697, 1666, 1617, 1495; HRMS Calcd for $\text{C}_{23}\text{H}_{17}\text{N}$: 307.1361. Found: 307.1366.

(*E*)-2-Methyl-4-(3-phenylisoquinolin-4-yl)-3-buten-2-ol (8). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 26 mg of the indicated compound as a white solid in a 34 % yield: mp 178-179 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.34 (s, 6H), 1.60 (br s, 1H), 5.92 (d, $J = 16.5$ Hz, 1H), 6.72 (d, $J = 16.2$ Hz, 1H), 7.34-7.37 (m, 1H), 7.40-7.45 (m, 2H), 7.59-7.64 (m, 3H), 7.73 (dd, $J = 1.2, 6.9$ Hz, 1H), 8.01 (d, $J = 7.8$ Hz, 1H), 8.17 (d, $J =$

5.4 Hz, 1H), 9.25 (s, 1H); ^{13}C NMR (CDCl_3) δ 29.6, 71.5, 121.7, 124.8, 126.7, 127.1, 127.6, 127.7, 128.1, 128.1, 130.7, 130.7, 135.3, 141.2, 145.9, 150.9, 151.2; IR (CHCl_3 , cm^{-1}) 3650, 3019, 2975, 2400, 1521; HRMS Calcd for $\text{C}_{20}\text{H}_{19}\text{ON}$: 289.1467. Found: 289.1471.

4-(1-*n*-Butoxyethen-1-yl)-3-phenylisoquinoline (9). The reaction mixture was chromatographed using 7:1 hexane/EtOAc to afford 24 mg of the indicated compound as a yellow oil in a 31 % yield: ^1H NMR (CDCl_3) δ 0.92 (t, $J = 7.6$ Hz, 3H), 1.33-1.43 (m, 2H), 1.64-1.72 (m, 2H), 3.78 (t, $J = 2.8$ Hz, 2H), 4.12 (d, $J = 2.4$ Hz, 1H), 4.48 (d, $J = 2.4$ Hz, 1H), 7.35-7.45 (m, 3H), 7.61 (dt, $J = 1.6, 8.4$ Hz, 1H), 7.74 (dt, $J = 1.6, 8.4$ Hz, 1H), 7.78 (tt, $J = 1.2, 6.8$ Hz, 2H), 8.00 (d, $J = 8.0$ Hz, 1H), 8.08 (dd, $J = 0.8, 8.8$ Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.1, 19.6, 31.2, 67.7, 89.6, 125.5, 127.2, 127.2, 127.4, 127.7, 127.9, 128.1, 129.4, 130.9, 135.9, 141.2, 151.4, 152.5, 157.5; IR (CHCl_3 , cm^{-1}) 3060, 3015, 2960, 2873, 1621, 1564, 1497; HRMS Calcd for $\text{C}_{21}\text{H}_{21}\text{ON}$: 303.1623. Found: 303.1627.

***n*-Butyl (*E*)-3-(3-cyclohexen-1-ylisoquinolin-4-yl)acrylate (11).** The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 34 mg of the indicated compound as a yellow oil in a 41 % yield: ^1H NMR (CDCl_3) δ 0.99 (t, $J = 7.2$ Hz, 3H), 1.43-1.53 (m, 2H), 1.68-1.76 (m, 4H), 1.83-1.86 (m, 2H), 2.24-2.27 (m, 2H), 2.45-2.50 (m, 2H), 4.27 (t, $J = 7.2$ Hz, 2H), 5.85 (t, $J = 1.6$ Hz, 1H), 6.39 (d, $J = 16.4$ Hz, 1H), 7.59 (dt, $J = 0.8, 7.2$ Hz, 1H), 7.73 (dt, $J = 1.2, 7.2$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 16.4$ Hz, 1H), 8.21 (d, $J = 8.4$ Hz, 1H), 9.19 (s, 1H); ^{13}C NMR (CDCl_3) δ 13.9, 19.5, 22.2, 23.1, 25.9, 28.8, 30.9, 64.7, 122.9, 124.4, 124.9, 126.9, 127.4, 128.4, 131.2, 132.7, 134.4, 138.0, 141.6, 152.5, 155.1, 166.8; IR (neat, cm^{-1}) 2932, 2872, 1712, 1632; HRMS Calcd for $\text{C}_{22}\text{H}_{25}\text{O}_2\text{N}$: 335.1885. Found: 335.1892.

***n*-Butyl (*E*)-3-(3-phenyl-2,6-naphthyridin-4-yl)acrylate (13).** The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 42 mg of the indicated compound as a yellow solid in a 51 % yield: mp 86-88 °C; ¹H NMR (CDCl₃) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.37-1.46 (m, 2H), 1.57-1.62 (m, 2H), 4.24 (t, *J* = 6.9 Hz, 2H), 6.43 (d, *J* = 16.5 Hz, 1H), 7.44-7.51 (m, 3H), 7.64 (dd, *J* = 1.5, 8.1 Hz, 2H), 7.85 (d, *J* = 5.7 Hz, 1H), 7.97 (d, *J* = 16.5 Hz, 1H), 8.78 (d, *J* = 5.7 Hz, 1H), 9.39 (s, 1H), 9.74 (s, 1H); ¹³C NMR (CDCl₃) δ 13.9, 19.4, 30.8, 65.0, 119.4, 123.7, 128.1, 128.6, 128.7, 129.0, 129.2, 130.5, 139.2, 139.3, 144.8, 150.0, 152.0, 153.4, 165.9; IR (CHCl₃, cm⁻¹) 3019, 2965, 2874, 1712, 1638; HRMS Calcd for C₂₁H₂₀O₂N₂: 332.1525. Found: 332.1531.

***n*-Butyl (*E*)-3-(7-phenyl-1,3-dioxolo[4,5-*g*]isoquinolin-8-yl)acrylate (15).** The reaction mixtures were chromatographed using 2:1 hexane/EtOAc to afford 40 mg or 45 mg of the indicated compound as a yellow solid in a 43 % (entry 10) or 48 % (entry 11) yield: mp 73-76 °C; ¹H NMR (CDCl₃) δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.36-1.44 (m, 2H), 1.62-1.70 (m, 2H), 4.20 (t, *J* = 6.8 Hz, 2H), 6.14 (s, 2H), 6.22 (d, *J* = 16.4 Hz, 1H), 7.24 (s, 1H), 7.38-7.47 (m, 3H), 7.51 (s, 1H), 7.56-7.58 (m, 2H), 7.92 (d, *J* = 16.4 Hz, 1H), 9.02 (s, 1H); ¹³C NMR (CDCl₃) δ 13.9, 19.3, 30.8, 64.8, 101.1, 102.1, 103.8, 123.7, 125.1, 126.1, 128.3, 130.4, 132.8, 140.3, 141.8, 148.4, 150.4, 151.3, 152.2, 166.4 (one sp² carbon missing due to overlap); IR (CHCl₃, cm⁻¹) 3018, 2962, 1708, 1615; HRMS Calcd for C₂₃H₂₁O₄N: 375.1471. Found: 375.1475.

***t*-Butyl (*E*)-3-(6,7-dimethoxy-3-phenylisoquinolin-4-yl)acrylate (17).** The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 50 mg of the indicated compound as a yellow solid in a 51 % yield: mp 157-159 °C; ¹H NMR (CDCl₃) δ 1.51 (s, 9H), 4.04 (s, 3H), 4.06 (s, 3H), 6.20 (d, *J* = 16.4 Hz, 1H), 7.26 (s, 1H), 7.37-7.47 (m, 4H),

7.60 (d, $J = 6.8$ Hz, 2H), 7.86 (d, $J = 16.4$ Hz, 1H), 9.08 (s, 1H); ^{13}C NMR (CDCl_3) δ 28.4, 56.3, 56.3, 80.9, 103.0, 106.0, 123.0, 123.8, 127.6, 128.2, 130.5, 131.0, 140.5, 140.9, 150.0, 150.4, 150.9, 153.8, 165.8 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3020, 2972, 2934, 2840, 1700, 1503; HRMS Calcd for $\text{C}_{24}\text{H}_{25}\text{O}_4\text{N}$: 391.1784. Found: 391.1792.

***N,N*-Dimethyl (*E*)-3-(6,7-dimethoxy-3-phenylisoquinolin-4-yl)acrylamide (18).** The reaction mixture was chromatographed using 1:3 hexane/EtOAc and 50:1 $\text{CHCl}_3/\text{CH}_3\text{OH}$ to afford 46 mg of the indicated compound as a yellow solid in a 51 % yield: mp 150-151 °C; ^1H NMR (CDCl_3) δ 2.72 (s, 3H), 3.00 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.41 (d, $J = 16.0$ Hz, 1H), 7.26 (s, 1H), 7.32-7.38 (m, 2H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.57-7.59 (m, 2H), 8.07 (d, $J = 16.0$ Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (CDCl_3) δ 35.9, 37.0, 56.3, 56.4, 102.7, 105.8, 123.6, 124.0, 126.8, 127.7, 128.3, 130.3, 131.7, 137.9, 141.3, 149.5, 150.4, 150.8, 153.6, 166.2; IR (CHCl_3 , cm^{-1}) 3444, 3006, 2934, 1649, 1618, 1505, 1467; HRMS Calcd for $\text{C}_{22}\text{H}_{22}\text{O}_3\text{N}_2$: 362.1630. Found: 362.1635.

6,7-Dimethoxy-3-phenyl-4-[(*E*)-2-methylsulfonylethen-1-yl]isoquinoline (19). The reaction mixture was chromatographed using 1:3 hexane/EtOAc to afford 25 mg of the indicated compound as a yellow solid in a 27 % yield: mp 196-198 °C; ^1H NMR (CDCl_3) δ 2.80 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.47 (d, $J = 15.6$ Hz, 1H), 7.24 (s, 1H), 7.28 (s, 1H), 7.39-7.42 (m, 1H), 7.47 (t, $J = 8.0$ Hz, 2H), 7.53 (dd, $J = 1.2, 7.6$ Hz, 2H), 8.02 (d, $J = 16.0$ Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (CDCl_3) δ 42.6, 56.4, 56.5, 101.9, 106.1, 120.8, 123.6, 128.5, 128.6, 130.4, 131.1, 134.4, 140.4, 140.8, 150.7, 150.8, 151.3, 154.3; IR (CHCl_3 , cm^{-1}) 3019, 2974, 2399, 1621, 1508; HRMS Calcd for $\text{C}_{20}\text{H}_{19}\text{O}_4\text{SN}$: 369.1035. Found: 369.1041.

***n*-Butyl (*E*)-3-[3-(*p*-methoxyphenyl)isoquinolin-4-yl]acrylate (21).** The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 32 mg of the indicated

compound as a yellow oil in a 35 % yield: ^1H NMR (CDCl_3) δ 0.96 (t, $J = 7.5$ Hz, 3H), 1.36-1.49 (m, 2H), 1.64-1.74 (m, 2H), 3.87 (s, 3H), 4.24 (t, $J = 6.6$ Hz, 2H), 6.36 (d, $J = 16.5$ Hz, 1H), 7.00 (tt, $J = 1.8, 7.8$ Hz, 2H), 7.57-7.66 (m, 3H), 7.76 (dt, $J = 1.8, 7.8$ Hz, 1H), 8.97 (d, $J = 16.5$ Hz, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 8.25 (d, $J = 8.7$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.0, 19.4, 30.9, 55.6, 64.8, 113.9, 123.4, 124.4, 126.3, 127.2, 127.4, 128.5, 131.5, 132.1, 132.7, 134.5, 141.7, 151.7, 152.8, 160.0, 166.6; IR (neat, cm^{-1}) 3057, 2958, 2872, 2836, 1708, 1633, 1607, 1552, 1463; HRMS Calcd for $\text{C}_{23}\text{H}_{23}\text{O}_3\text{N}$: 361.1678. Found: 361.1682.

***n*-Butyl (*E*)-3-[3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylate (23).** The reaction mixtures were chromatographed using 2:1 hexane/EtOAc to afford 59 mg (entry 16) or 58 mg (entry 17) of the indicated compound as a yellow oil in a 65 % or a 64 % yield, respectively: ^1H NMR (CDCl_3) δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.31-1.36 (m, 2H), 1.57-1.64 (m, 2H), 3.72 (s, 3H), 4.13 (t, $J = 6.8$ Hz, 2H), 6.07 (d, $J = 16.4$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 7.04 (t, $J = 7.6$ Hz, 1H), 7.35-7.39 (m, 2H), 7.62 (t, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.92 (d, $J = 16.0$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 8.14 (d, $J = 8.8$ Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (CDCl_3) δ 13.9, 19.3, 30.8, 55.5, 64.6, 111.2, 121.0, 124.3, 125.3, 125.6, 127.4, 127.6, 128.3, 129.4, 130.1, 131.2, 131.6, 134.2, 141.2, 149.7, 152.6, 156.4, 166.6; IR (neat, cm^{-1}) 3059, 2958, 2872, 2835, 1716, 1638, 1601, 1494; HRMS Calcd for $\text{C}_{23}\text{H}_{23}\text{O}_3\text{N}$: 361.1678. Found: 361.1682.

***t*-Butyl (*E*)-3-[3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylate (24).** The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 61 mg of the indicated compound as a yellow oil in a 68 % yield: ^1H NMR (CDCl_3) δ 1.47 (s, 9H), 3.74 (s, 3H), 6.04 (d, $J = 16.4$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.07 (dt, $J = 0.8, 7.4$ Hz, 1H), 7.38-7.42

(m, 2H), 7.63 (dt, $J = 0.8, 7.6$ Hz, 1H), 7.75 (dt, $J = 1.2, 8.4$ Hz, 1H), 7.83 (d, $J = 16.4$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 28.3, 55.5, 80.7, 111.2, 121.0, 124.4, 125.7, 127.0, 127.3, 127.6, 128.3, 129.5, 130.0, 131.1, 131.6, 134.2, 140.1, 149.7, 152.4, 156.4, 165.8; IR (neat, cm^{-1}) 3400, 3059, 2977, 2934, 2835, 1708, 1636, 1601, 1494; HRMS Calcd for $\text{C}_{23}\text{H}_{23}\text{O}_3\text{N}$: 361.1678. Found: 361.1682.

3-(*o*-Methoxyphenyl)-4-[(*E*)-2-phenylethen-1-yl]isoquinoline (25). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 54 mg of the indicated compound as a yellow oil in a 64 % yield: ^1H NMR (CDCl_3) δ 3.71 (s, 3H), 6.71 (d, $J = 16.4$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 7.05 (t, $J = 8.4$ Hz, 1H), 7.21-7.26 (m, 2H), 7.31-7.35 (m, 5H), 7.40 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.62 (t, $J = 8.4$ Hz, 1H), 7.72 (dt, $J = 1.2, 8.4$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 8.29 (d, $J = 8.8$ Hz, 1H), 9.25 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.7, 111.3, 120.9, 124.3, 124.9, 126.5, 127.0, 127.9, 128.1, 128.2, 128.8, 129.6, 130.4, 130.6, 131.7, 134.9, 135.8, 137.6, 149.1, 151.0, 156.6 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3057, 3025, 2957, 2935, 2833, 2214, 1617, 1494; HRMS Calcd for $\text{C}_{24}\text{H}_{19}\text{ON}$: 337.1467. Found: 337.1473.

3-(*o*-Methoxyphenyl)-4-[(*E*)-2-phenylsulfonylethen-1-yl]isoquinoline (26). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 20 mg of the indicated compound as a yellow oil in a 20 % yield: ^1H NMR (CDCl_3) δ 3.58 (s, 3H), 6.45 (d, $J = 15.6$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 6.98 (t, $J = 7.2$ Hz, 1H), 7.27-7.31 (m, 2H), 7.50 (t, $J = 8.0$ Hz, 2H), 7.61-7.70 (m, 4H), 7.80 (dd, $J = 0.8, 7.6$ Hz, 1H), 8.02-8.08 (m, 3H), 9.30 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.5, 111.3, 121.1, 123.6, 123.7, 127.4, 127.7, 127.8, 128.5, 128.9, 129.5, 130.1, 131.3, 131.7, 133.4, 133.8, 134.0, 139.0, 140.4, 149.5, 153.3,

155.8; IR (neat, cm^{-1}) 3060, 2938, 2836, 1619, 1600, 1494; HRMS Calcd for $\text{C}_{24}\text{H}_{19}\text{O}_3\text{NS}$: 401.1086. Found: 401.1093.

***N,N*-Dimethyl (*E*)-3-[3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylamide (27).** The reaction mixture was chromatographed using 1:1 hexane/EtOAc and pure EtOAc to afford 54 mg of the indicated compound as a yellow oil in a 65 % yield: ^1H NMR (CDCl_3) δ 2.66 (s, 3H), 2.96 (s, 3H), 3.74 (s, 3H), 6.33 (d, $J = 15.6$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.06 (t, $J = 7.2$ Hz, 1H), 7.36 (dt, $J = 1.6, 8.0$ Hz, 1H), 7.41 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.64 (t, $J = 8.0$ Hz, 1H), 7.75 (dt, $J = 1.2, 7.2$ Hz, 1H), 8.01 (d, $J = 7.6$ Hz, 1H), 8.03 (d, $J = 15.6$ Hz, 1H), 8.16 (d, $J = 8.8$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 35.8, 37.0, 55.7, 111.3, 121.0, 124.3, 125.3, 126.7, 127.3, 127.4, 128.1, 129.6, 130.3, 130.9, 131.4, 134.7, 137.3, 148.8, 151.9, 156.3, 166.3; IR (CHCl_3 , cm^{-1}) 3468, 3058, 3004, 2935, 2835, 2234, 1651, 1613; HRMS Calcd for $\text{C}_{21}\text{H}_{20}\text{O}_2\text{N}_2$: 332.1525. Found: 332.1531.

(*E*)-2-Methyl-4-[3-(*o*-methoxyphenyl)isoquinolin-4-yl]-3-buten-2-ol (28). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 20 mg of the indicated compound as a yellow oil in a 25 % yield: ^1H NMR (CDCl_3) δ 1.20 (s, 6H), 3.74 (s, 3H), 5.75 (d, $J = 16.0$ Hz, 1H), 6.77 (d, $J = 16.0$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 7.02 (t, $J = 7.6$ Hz, 1H), 7.32-7.37 (m, 2H), 7.60 (d, $J = 7.2$ Hz, 1H), 7.70 (dt, $J = 1.2, 7.6$ Hz, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 9.24 (s, 1H) (the hydrogen from the OH group is missing); ^{13}C NMR (CDCl_3) δ 29.6, 55.6, 71.2, 111.0, 120.7, 121.1, 124.6, 127.0, 127.6, 128.1, 128.3, 129.3, 130.5, 130.7, 131.6, 134.9, 144.8, 148.9, 150.9, 156.5; IR (CHCl_3 , cm^{-1}) 3018, 2973, 1496; HRMS Calcd for $\text{C}_{21}\text{H}_{21}\text{O}_2\text{N}$: 319.1572. Found: 319.1576.

***t*-Butyl (*E*)-3-[6,7-dimethoxy-3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylate (30).**

The reaction mixture was chromatographed using 1:3 hexane/EtOAc to afford 94 mg of the

indicated compound as a yellow oil in a 92 % yield: ^1H NMR (CDCl_3) δ 1.46 (s, 9H), 3.74 (s, 3H), 4.04 (s, 6H), 6.00 (d, $J = 16.4$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.25 (s, 1H), 7.36-7.40 (m, 3H), 7.82 (d, $J = 16.4$ Hz, 1H), 9.08 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.3, 28.3, 55.4, 56.2, 56.3, 80.6, 102.8, 105.8, 111.0, 120.9, 123.8, 124.5, 126.2, 129.7, 130.8, 131.5, 140.6, 148.6, 149.8, 150.3, 153.6, 156.3, 165.9; IR (neat, cm^{-1}) 3400, 3060, 3004, 2975, 2835, 2255, 2211, 1701, 1624, 1578, 1505; HRMS Calcd for $\text{C}_{25}\text{H}_{27}\text{O}_5\text{N}$: 421.1889. Found: 421.1895.

***N,N*-Dimethyl (*E*)-3-[6,7-dimethoxy-3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylamide (31).** The reaction mixture was chromatographed using pure EtOAc and 50:1 $\text{CHCl}_3/\text{CH}_3\text{OH}$ to afford 95 mg of the indicated compound as a yellow solid in a 97 % yield: mp 124-126 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 2.63 (s, 3H), 2.96 (s, 3H), 3.74 (s, 3H), 4.05 (s, 6H), 6.29 (d, $J = 15.6$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.25 (s, 1H), 7.30-7.37 (m, 2H), 7.41 (dd, $J = 1.6, 7.2$ Hz, 1H), 8.02 (d, $J = 15.6$ Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (CDCl_3) δ 35.7, 36.9, 55.7, 56.2, 56.4, 102.5, 105.7, 111.2, 121.0, 123.6, 124.7, 125.5, 129.3, 130.7, 131.4, 131.4, 137.6, 147.8, 149.4, 150.4, 153.4, 156.2, 166.3; IR (CHCl_3 , cm^{-1}) 3547, 3011, 2937, 2836, 1649, 1618, 1499; HRMS Calcd for $\text{C}_{23}\text{H}_{24}\text{O}_4\text{N}_2$: 392.1736. Found: 392.1742.

6,7-Dimethoxy-3-phenyl-4-[(*E*)-2-methanesulfonylethen-1-yl]isoquinoline (32).

The reaction mixture was chromatographed using 1:3 hexane/EtOAc to afford 51 mg of the indicated compound as a pale yellow solid in a 52 % yield: mp 212-214 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 2.66 (s, 3H), 3.77 (s, 3H), 4.06 (s, 3H), 4.06 (s, 3H), 6.34 (d, $J = 15.6$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.09 (t, $J = 7.2$ Hz, 1H), 7.14 (s, 1H), 7.27 (s, 1H), 7.37-7.43 (m,

2H), 8.02 (d, $J = 15.6$ Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (CDCl_3) δ 42.7, 55.8, 56.3, 56.5, 101.9, 105.9, 111.3, 121.3, 122.3, 123.6, 129.6, 130.0, 130.8, 131.6, 132.5, 140.5, 148.1, 150.6, 150.7, 154.0, 156.0; IR (CHCl_3 , cm^{-1}) 3020, 2963, 2838, 1622, 1579; HRMS Calcd for $\text{C}_{21}\text{H}_{21}\text{O}_5\text{SN}$: 399.1140. Found: 399.1148.

***t*-Butyl (*E*)-3-{7-(*o*-methoxyphenyl)-1,3-dioxolo[4,5-*g*]isoquinolin-8-yl}acrylate**

(34). The reaction mixtures were chromatographed using 1:1 hexane/EtOAc to afford 62 mg or 83 mg of the indicated compound as a yellow oil in a 61 % (entry 26) or an 82 % (entry 27) yield: ^1H NMR (CDCl_3) δ 1.47 (s, 9H), 3.74 (s, 3H), 5.97 (d, $J = 16.4$ Hz, 1H), 6.11 (s, 2H), 6.94 (d, $J = 8.0$ Hz, 1H), 7.05 (t, $J = 7.2$ Hz, 1H), 7.23 (s, 1H), 7.36 (d, $J = 7.6$ Hz, 1H), 7.37 (dt, $J = 1.2, 8.0$ Hz, 1H), 7.44 (s, 1H), 7.73 (d, $J = 16.4$ Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (CDCl_3) δ 28.3, 55.4, 80.6, 101.0, 101.9, 103.6, 111.1, 120.9, 125.1, 125.4, 126.6, 129.5, 129.9, 131.5, 132.6, 140.5, 148.3, 148.9, 150.1, 151.8, 156.4, 165.8; IR (CHCl_3 , cm^{-1}) 2977, 2835, 1704, 1640; HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{O}_5\text{N}$: 405.1576. Found: 405.1584.

***N,N*-Dimethyl (*E*)-3-{7-(*o*-methoxyphenyl)-1,3-dioxolo[4,5-*g*]isoquinolin-8-yl}acrylamide (35).** The reaction mixture was chromatographed using 1:3 hexane/EtOAc and pure EtOAc to afford 61 mg of the *E* isomer as a yellow oil and 23 mg of the *Z* isomer as a yellow oil in a 89 % overall yield. The following characterization data is for the pure major *E* isomer: ^1H NMR (CDCl_3) δ 2.64 (s, 3H), 2.95 (s, 3H), 3.74 (s, 3H), 6.12 (s, 2H), 6.26 (d, $J = 15.6$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 7.05 (dt, $J = 0.8, 7.6$ Hz, 1H), 7.23 (s, 1H), 7.34 (dt, $J = 1.2, 8.0$ Hz, 1H), 7.38 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.41 (s, 1H), 7.90 (d, $J = 15.6$ Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (CDCl_3) δ 35.8, 37.0, 55.8, 100.9, 102.0, 103.5, 111.3, 121.0, 124.9, 125.1, 126.5, 129.5, 130.5, 131.4, 133.3, 137.7, 148.2, 148.5, 149.7, 151.8, 156.3, 166.3; IR

(CHCl₃, cm⁻¹) 3006, 2937, 2836, 1650, 1614; HRMS Calcd for C₂₂H₂₀O₄N₂: 376.1423.

Found: 376.1431.

4-{7-(*o*-Methoxyphenyl)-1,3-dioxolo[4,5-*g*]isoquinolin-8-yl}butan-2-one (36). The reaction mixture was chromatographed using 1:3 hexane/EtOAc to afford 42 mg of the indicated compound as a yellow solid in a 48 % yield: mp 174-175 °C; ¹H NMR (CDCl₃) δ 2.02 (s, 3H), 2.58-2.65 (m, 2H), 2.92-3.00 (m, 1H), 3.06-3.13 (m, 1H), 3.75 (s, 3H), 6.12 (s, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.23-7.25 (m, 3H), 7.38 (dt, *J* = 1.2, 8.0 Hz, 1H), 8.94 (s, 1H); ¹³C NMR (CDCl₃) δ 23.3, 29.8, 43.7, 55.6, 99.8, 101.8, 104.0, 111.2, 120.9, 125.4, 128.5, 129.6, 130.3, 130.9, 133.3, 148.0, 148.5, 149.4, 151.6, 156.7, 207.9; IR (CHCl₃, cm⁻¹) 3018, 2963, 2837, 1713, 1603; HRMS Calcd for C₂₁H₁₉O₄N: 349.1314. Found: 349.1320.

***t*-Butyl (*E*)-3-[6-dimethylamino-3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylate (38).** The reaction mixtures were chromatographed using pure EtOAc to afford 70 mg or 68 mg of the indicated compound as a yellow oil in a 69 % (entry 30) or a 67 % (entry 31) yield: ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 3.14 (s, 6H), 3.74 (s, 3H), 6.02 (d, *J* = 16.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 7.02-7.06 (m, 2H), 7.19 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.34-7.38 (m, 2H), 7.79 (d, *J* = 16.4 Hz, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 8.99 (s, 1H); ¹³C NMR (CDCl₃) δ 28.3, 40.5, 42.8, 55.5, 80.3, 101.0, 111.0, 116.2, 120.9, 123.5, 125.3, 129.6, 129.6, 130.2, 131.5, 136.2, 141.1, 150.1, 151.3, 151.8, 156.4, 166.3; IR (CHCl₃, cm⁻¹) 2975, 2834, 1698, 1613; HRMS Calcd for C₂₅H₂₈O₃N₂: 404.2100. Found: 404.2107.

***N,N*-Dimethyl 3-[6-dimethylamino-3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylamide (39).** The reaction mixture was chromatographed using pure EtOAc and 10:1 CHCl₃/CH₃OH to afford 65 mg of a 91:9 *E/Z* mixture as determined by ¹H NMR

spectroscopy of a yellow oil in 89 % overall yield. ^1H NMR (CDCl_3) for the major *E* isomer: δ 2.63 (s, 3H), 2.95 (s, 3H), 3.13 (s, 6H), 3.72 (s, 3H), 6.28 (d, J = 15.6 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.93 (s, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.19 (dd, J = 1.6, 9.2 Hz, 1H), 7.33 (dt, J = 1.2, 8.0 Hz, 1H), 7.38 (dd, J = 1.6, 7.6 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.98 (d, J = 15.6 Hz, 1H), 8.96 (s, 1H); additional ^{13}C NMR (CDCl_3) for the *E/Z* mixture δ 35.7, 36.9, 40.5, 40.6, 41.1, 55.7, 100.7, 111.3, 116.3, 120.7, 120.8, 120.9, 124.0, 124.5, 129.3, 129.4, 131.3, 136.8, 138.1, 149.1, 150.8, 151.7, 156.3, 166.6 (except for two sp^3 carbons from the minor *Z* isomer, all other carbons are from the major *E* isomer); IR (CHCl_3 , cm^{-1}) for the *E/Z* mixture 3006, 2937, 2836, 1650, 1614; HRMS Calcd for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{N}_3$: 375.1947. Found: 375.1953.

***t*-Butyl (*E*)-3-[7-dimethylamino-3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylate (41).**

The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 71 mg of the indicated compound as a yellow solid in a 71 % yield: mp 163-166 °C; ^1H NMR (CDCl_3) δ 1.47 (s, 9H), 3.09 (s, 6H), 3.73 (s, 3H), 6.05 (d, J = 16.4 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 7.05 (t, J = 7.2 Hz, 1H), 7.36-7.38 (m, 3H), 7.78 (d, J = 16.4 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 9.10 (s, 1H); ^{13}C NMR (CDCl_3) δ 28.3, 40.7, 55.4, 80.5, 105.4, 111.1, 120.7, 120.9, 125.2, 125.3, 126.3, 126.7, 129.6, 129.6, 129.8, 131.8, 140.8, 146.1, 149.1, 150.9, 156.6, 166.1; IR (CHCl_3 , cm^{-1}) 3018, 2979, 2836, 1702, 1621; HRMS Calcd for $\text{C}_{25}\text{H}_{28}\text{O}_3\text{N}_2$: 404.2100. Found: 404.2107.

***N,N*-Dimethyl (*E*)-3-[7-dimethylamino-3-(*o*-methoxyphenyl)isoquinolin-4-yl]acrylamide (42).** The reaction mixture was chromatographed using pure EtOAc and 20:1 $\text{CHCl}_3/\text{CH}_3\text{OH}$ to afford 66 mg of the indicated compound yield as a yellow solid in a 70 % yield: mp 171-174 °C; ^1H NMR (CDCl_3) δ 3.27 (s, 3H), 2.95 (s, 3H), 3.09 (s, 6H), 3.73 (s, 3H), 6.30 (d, J = 15.6 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 7.04 (t, J =

7.6 Hz, 1H), 7.31-7.40 (m, 3H), 7.98 (s, 1H), 8.02 (t, $J = 4.8$ Hz, 1H), 9.09 (s, 1H); ^{13}C NMR (CDCl_3) δ 35.8, 37.0, 40.7, 55.7, 105.2, 111.2, 120.5, 120.9, 124.7, 125.1, 126.2, 127.3, 129.2, 129.3, 130.7, 131.6, 137.8, 145.1, 149.2, 150.4, 156.4, 166.5; IR (CHCl_3 , cm^{-1}) 3017, 2837, 2399, 1650, 1621, 1581; HRMS Calcd for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{N}_3$: 375.1947. Found: 375.1953.

***n*-Butyl (*E*)-3-(3-phenyl-5,6,7-trimethoxyisoquinolin-4-yl)acrylate (44).** The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 52 mg of the indicated compound as a yellow oil in a 51 % yield: ^1H NMR (CDCl_3) δ 0.93 (t, $J = 7.6$ Hz, 3H), 1.32-1.39 (m, 2H), 1.57-1.63 (m, 2H), 3.81 (s, 3H), 4.02 (s, 3H), 4.04 (s, 3H), 4.12 (t, $J = 6.4$ Hz, 2H), 5.49 (d, $J = 16.0$ Hz, 1H), 7.12 (s, 1H), 7.31 (t, $J = 6.8$ Hz, 1H), 7.38 (t, $J = 7.2$ Hz, 2H), 7.52 (d, $J = 7.6$ Hz, 2H), 8.57 (d, $J = 16.4$ Hz, 1H), 9.09 (s, 1H); ^{13}C NMR (CDCl_3) δ 13.9, 19.3, 30.9, 56.3, 61.0, 61.4, 64.3, 102.6, 123.3, 123.7, 125.0, 127.1, 127.7, 128.2, 130.5, 140.8, 145.7, 146.6, 149.0, 150.3, 150.7, 154.0, 166.8; IR (CHCl_3 , cm^{-1}) 3058, 2960, 2871, 1709, 1636, 1612, 1483; HRMS Calcd for $\text{C}_{25}\text{H}_{27}\text{O}_5\text{N}$: 421.1889. Found: 421.1897.

***t*-Butyl (*E*)-3-(3-phenyl-5,6,7-trimethoxyisoquinolin-4-yl)acrylate (45).** The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 63 mg of the indicated compound as a yellow oil in a 62 % yield: ^1H NMR (CDCl_3) δ 1.45 (s, 9H), 3.81 (s, 3H), 4.02 (s, 3H), 4.03 (s, 3H), 5.41 (d, $J = 16.0$ Hz, 1H), 7.11 (s, 1H), 7.31 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 7.6$ Hz, 2H), 7.54 (d, $J = 7.2$ Hz, 2H), 8.46 (d, $J = 16.4$ Hz, 1H), 9.07 (d, 1H); ^{13}C NMR (CDCl_3) δ 28.3, 56.3, 60.9, 61.3, 80.2, 102.5, 123.8, 124.9, 125.0, 127.2, 127.6, 128.1, 130.6, 140.9, 144.6, 146.5, 149.0, 150.2, 150.6, 154.0, 166.0; IR (neat, cm^{-1}) 3392, 3058, 2976, 2937, 2840, 2253, 1698, 1636, 1611, 1484; HRMS Calcd for $\text{C}_{25}\text{H}_{27}\text{O}_5\text{N}$: 421.1889. Found: 421.1895.

***N,N*-Dimethyl (*E*)-3-[3-phenyl-5,6,7-trimethoxyisoquinolin-4-yl]acrylamide (46).**

The reaction mixture was chromatographed using 1:1 hexane/EtOAc and 20:1 CHCl₃/CH₃OH to afford 49 mg of the indicated compound as a white solid in a 50 % yield: mp 169-171 °C; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 2.92 (s, 3H), 3.90 (s, 3H), 4.02 (s, 3H), 4.04 (s, 3H), 5.90 (d, *J* = 15.6 Hz, 1H), 7.11 (s, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 8.43 (d, *J* = 15.6 Hz, 1H), 9.07 (s, 1H); ¹³C NMR (CDCl₃) δ 35.6, 36.7, 56.3, 61.3, 61.3, 102.4, 124.7, 124.9, 125.1, 127.3, 127.3, 128.2, 130.7, 141.7, 141.8, 146.6, 149.4, 150.0, 150.8, 154.0, 166.8; IR (CHCl₃, cm⁻¹) 3017, 2941, 1648, 1611, 1580; HRMS Calcd for C₂₃H₂₄O₄N₂: 392.1736. Found: 392.1742.

5,6,7-Trimethoxy-3-phenyl-4-[(*E*)-2-phenylethen-1-yl]isoquinoline (47). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 77 mg of the indicated compound as a yellow solid in a 78 % yield: mp 133-135 °C; ¹H NMR (CDCl₃) δ 3.74 (s, 3H), 4.02 (s, 3H), 4.03 (s, 3H), 6.12 (d, *J* = 16.4 Hz, 1H), 7.11 (s, 1H), 7.17-7.28 (m, 6H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.60 (dd, *J* = 1.2, 8.0 Hz, 2H), 7.86 (d, *J* = 16.4 Hz, 1H), 9.06 (s, 1H); ¹³C NMR (CDCl₃) δ 56.2, 61.4, 61.4, 102.7, 125.4, 126.1, 126.2, 127.1, 127.3, 127.6, 128.0, 128.3, 128.7, 130.6, 133.9, 138.2, 141.9, 146.6, 149.4, 149.7, 151.0, 153.7; IR (CHCl₃, cm⁻¹) 3018, 2940, 1612, 1482; HRMS Calcd for C₂₆H₂₃O₃N: 397.1678. Found: 397.1685.

4-{8-Phenyl-1,3-dioxolo[4,5-*f*]isoquinolin-9-yl}butan-2-one (49). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 41 mg of the indicated compound as a yellow solid in a 50 % yield: mp 161-164 °C; ¹H NMR (CDCl₃) δ 2.06 (s, 3H), 2.69 (dd, *J* = 6.0, 8.1 Hz, 2H), 3.31-3.36 (m, 2H), 6.17 (s, 2H), 7.30 (t, *J* = 7.2 Hz, 1H),

7.40-7.47 (m, 5H), 7.62 (d, $J = 8.4$ Hz, 1H), 9.04 (s, 1H); ^{13}C NMR (CDCl_3) δ 23.5, 28.6, 44.5, 100.6, 110.6, 121.6, 122.9, 123.2, 124.2, 126.8, 127.3, 128.1, 139.6, 139.7, 146.8, 149.5, 151.5, 206.6; IR (CHCl_3 , cm^{-1}) 3018, 1709, 1632, 1572, 1503; HRMS Calcd for $\text{C}_{20}\text{H}_{17}\text{O}_4\text{N}$: 319.1208. Found: 319.1212.

1-Phenyl-3-{8-phenyl-1,3-dioxolo[4,5-*f*]isoquinolin-9-yl}propan-1-one (50). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 34 mg of the indicated compound as a yellow solid in a 36 % yield: mp 184-186 °C; ^1H NMR (CDCl_3) δ 3.20-3.34 (m, 2H), 3.50-3.54 (m, 2H), 6.10 (s, 2H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.37-7.54 (m, 8H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.81 (dd, $J = 1.2, 8.0$ Hz, 2H), 9.06 (s, 1H); ^{13}C NMR (CDCl_3) δ 25.3, 40.8, 101.9, 111.8, 122.9, 124.1, 124.7, 125.4, 128.0, 128.2, 128.6, 128.7, 129.3, 133.1, 136.8, 140.9, 140.9, 148.0, 150.7, 152.8, 199.1; IR (CHCl_3 , cm^{-1}) 3018, 1685, 1632, 1598, 1580, 1503; HRMS Calcd for $\text{C}_{25}\text{H}_{19}\text{O}_3\text{N}$: 381.1365. Found: 381.1373.

6-{8-Phenyl-1,3-dioxolo[4,5-*f*]isoquinolin-9-yl}hexan-2-one (51). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 24 mg of the indicated compound as a yellow oil in a 27 % yield: ^1H NMR (CDCl_3) δ 1.54-1.58 (m, 4H), 2.06 (s, 3H), 2.29 (t, $J = 7.2$ Hz, 2H), 3.04 (t, $J = 7.6$ Hz, 2H), 6.20 (s, 2H), 7.29 (t, $J = 8.4$ Hz, 1H), 7.41-7.50 (m, 5H), 7.60 (d, $J = 8.4$ Hz, 1H), 9.02 (s, 1H); ^{13}C NMR (CDCl_3) δ 23.6, 29.7, 29.8, 31.4, 43.1, 101.5, 111.5, 122.8, 123.7, 125.2, 125.7, 127.6, 128.1, 129.3, 140.8, 141.0, 147.7, 150.1, 152.0, 208.9; IR (CHCl_3 , cm^{-1}) 3017, 2959, 1711, 1632, 1571, 1503, 1503; HRMS Calcd for $\text{C}_{22}\text{H}_{21}\text{O}_3\text{N}$: 347.4130. Found: 347.4136.

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**CHAPTER 3. SYNTHESIS OF SUBSTITUTED NAPHTHALENES AND
CARBAZOLES BY THE PALLADIUM-CATALYZED ANNULATION OF
INTERNAL ALKYNES**

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Abstract

An efficient synthesis of highly substituted naphthalenes has been developed by the palladium-catalyzed annulation of a variety of internal alkynes, in which two new carbon-carbon bonds are formed in a single step under relatively mild reaction conditions. This method has also been used to synthesize carbazoles although a higher reaction temperature is necessary. The process involves arylpalladation of the alkyne, followed by intramolecular Heck olefination and double bond isomerization. This method accommodates a variety of functional groups and affords the anticipated highly substituted naphthalenes and carbazoles in good to excellent yields.

Introduction

Highly substituted naphthalenes are common structural units in numerous biologically significant natural products and pharmaceuticals,¹ and improved methods for their construction are highly desirable.²⁻⁶ Among the most important synthetic routes to such compounds are annulation via Fischer carbenes (the Dötz reaction)³ and the palladium-

catalyzed cyclization of alkynes by arylsilyl triflates via *in situ* generation of highly reactive benzyne.⁴ Another method of synthesis is based on the cyclopropane-shift reaction of diaryl(2-halogenocyclopropyl)methanols.⁵ Very recently, substituted naphthalenes have been prepared using the gallium-catalyzed cyclization of carbonyl compounds or epoxides with alkynes.⁶

Annulation processes have proven quite valuable in organic synthesis because of the ease with which a variety of complicated hetero- and carbocycles can be rapidly constructed.⁷ In our own laboratories, it has been demonstrated that palladium-catalyzed annulation⁸ can be effectively employed for the synthesis of indoles,⁹ isoindolo[2,1-*a*]indoles,¹⁰ benzofurans,¹¹ benzopyrans,¹² isocoumarins,^{11,12} α -pyrones,^{12,13} indenones,¹⁴ isoquinolines,¹⁵ carbolines,¹⁶ and polycyclic aromatic hydrocarbons¹⁷ (eq 1). More recently, Takahashi et al. have reported that pentasubstituted fulvene derivatives can be prepared using the palladium-catalyzed annulation of disubstituted alkynes (eq 2).¹⁸

Due to our continuing interest in the palladium-catalyzed annulation of internal alkynes, we have investigated the reaction of internal alkynes and *o*-(2-alkenyl)aryl halides

derived from aldehydes and ylides and have fully detailed this new naphthalene synthesis and its extension to the formation of substituted carbazoles (Scheme 1).

Scheme 1

Results and Discussion

Our initial studies focused on achieving optimal reaction conditions for the palladium-catalyzed annulation employing ethyl (*E*)-4-(2-iodophenyl)-2-butenolate (**1**). The reaction of aryl halide **1** and diphenylacetylene was chosen as the model system for optimization of this process (eq 3) and the results are summarized in Table 1.

Table 1. Optimization of the Synthesis of Naphthalene **2** (eq 3)^a

entry	alkyne (equiv)	catalyst	ligand	base	time (h)	% yield
1	2	10 % Pd(OAc) ₂	--	3 NaOAc	12 h	58
2	2	10 % Pd(OAc) ₂	--	3 Na ₂ CO ₃	12 h	40
3	2	10 % Pd(OAc) ₂	--	3 NaHCO ₃	8 h	49
4	2	10 % Pd(PPh ₃) ₄	--	3 Na ₂ CO ₃	24 h	trace
5	2	10 % Pd(OAc) ₂	--	3 Bu ₃ N	10 h	71
6	2	10 % Pd(OAc) ₂	--	3 Et ₃ N	12 h	76
7	2	10 % Pd(OAc) ₂	--	3 pyridine	24 h	trace
8	2	5 % Pd(OAc) ₂	--	3 Et ₃ N	10 h	80
9	1.2	5 % Pd(OAc) ₂	--	3 Et ₃ N	12 h	58
10	5	5 % Pd(OAc) ₂	--	3 Et ₃ N	12 h	81
11	2	5 % Pd(OAc) ₂	--	3 Et ₃ N	12 h	80 ^b
12	2	5 % Pd(OAc) ₂	--	1.5 Et ₃ N	12 h	70
13	2	5 % Pd(OAc) ₂	--	2 Et ₃ N	12 h	79
14	2	5 % Pd(OAc) ₂	10 % PPh ₃	2 Et ₃ N	12 h	86
15	2	5 % Pd(OAc) ₂	10 % PPh ₃	1.5 Et ₃ N	12 h	78

^a All reactions were run under the following reaction conditions, unless otherwise specified: 0.25 mmol of aryl halide **1** and the indicated amount of diphenylacetylene were stirred in 3 mL of DMF at 80 °C in the presence of the specified amount of the indicated base, Pd(OAc)₂, and PPh₃. ^b One equiv of *n*-Bu₄NCl was added.

Using 10 mol % of Pd(OAc)₂ and 3 equiv of NaOAc afforded the desired naphthalene product **2** in a 58 % yield (entry 1, Table 1). Carbonate bases, such as Na₂CO₃ and NaHCO₃, gave naphthalene **2** in 40 % and 49 % yields respectively (entries 2 and 3). However, the use of Pd(PPh₃)₄ as a catalyst and Na₂CO₃ as a base gave only a trace of the desired product (entry 4). Our previous work has shown that carbonate bases usually work better for palladium-catalyzed annulation chemistry than organic bases.⁹⁻¹⁷ However, it turned out that

organic bases work better than carbonate salts in this annulation chemistry. For example, when the organic bases *n*-Bu₃N and Et₃N were employed, the reaction of halide **1** gave 71 % and 76 % yields of naphthalene **2**, respectively, in the presence of 10 mol % of Pd(OAc)₂ (entries 5 and 6). This is probably because the ester group can be hydrolyzed in the presence of the carbonate bases and the resulting yield of naphthalene suffers. The use of pyridine afforded only a trace of the desired product (entry 7). Further optimization work showed that 5 mol % of Pd(OAc)₂ and 2 equiv of diphenylacetylene are necessary to achieve decent yields of naphthalene **2** (entries 8-10). In entry 11, the addition of 1 equiv of *n*-Bu₄NCl gave an 80 % yield, which is the same yield as the reaction without *n*-Bu₄NCl (entry 8). We have also explored the effects on the yield of other variables, such as the ligand and the amount of the base (entries 12-15). The optimal reaction conditions thus far developed employ 0.25 mmol of aryl halide **1**, 2 equiv of diphenylacetylene, 5 mol % of Pd(OAc)₂, 10 mol % of PPh₃ and 2 equiv of Et₃N as a base in 3 mL of DMF stirred at 80 °C. This afforded an 86 % yield of naphthalene **2** (entry 14).

Using our optimal reaction conditions, the scope of the annulation process has been explored using a variety of substrates carefully selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems (Table 2). While the reaction of aryl halide **1** and diphenylacetylene afforded naphthalene **2** in an 86 % yield (entry 1), only a 61 % yield of naphthalene **3** was obtained from the reaction of aryl halide **1** and di(*p*-methoxyphenyl)acetylene (entry 2). The decrease in the yield of the reaction indicates that electron-rich diarylacetylenes disfavor the annulation chemistry. However, when an electron-deficient diarylacetylene, such as di(*p*-ethoxycarbonylphenyl)acetylene was allowed to react with aryl halide **1**, an 83 % yield of

Table 2. Synthesis of Substituted Naphthalenes and Carbazoles by the Palladium-Catalyzed Annulation of Internal Alkynes^a

entry	haloalkene	alkyne	time (h)	product(s)	% isolated yield
1		Ph—C≡C—Ph	12	2	86
2		<i>p</i> -MeOC ₆ H ₄ —C≡C—C ₆ H ₄ OMe- <i>p</i>	24	3	61
3		<i>p</i> -EtO ₂ CC ₆ H ₄ —C≡C—C ₆ H ₄ CO ₂ Et- <i>p</i>	30	4	83
4		<i>n</i> -Pr—C≡C— <i>n</i> -Pr	48	5	60
5		Me—C≡C—Ph	24	 + 6 + 7	75 ^b (53 : 47)
6		Ph—C≡C—CO ₂ Et	12	 + 8 + 9	88 ^b (76 : 24)

Table 2 continued

7		$\text{Ph} \equiv \text{Ph}$	40	2	75
8	10	$n\text{-Pr} \equiv n\text{-Pr}$	72	5	46
9		$\text{Et} \equiv \text{CO}_2\text{Et}$	72		52 ^b (60 : 40)
10		$\text{Ph} \equiv \text{Ph}$	26	14	72
11		$\text{Ph} \equiv \text{CO}_2\text{Et}$	5		86 ^b (67 : 33)

Table 2 continued

12	$\text{BnOCH}_2\text{---}\equiv\text{---CH}_2\text{OBn}$	12	17	56
13	18	8	19	48
14	20	24	21	0
15	22	12	23	73

Table 2 continued

16		$n\text{-Pr}-\text{C}\equiv\text{C}-n\text{-Pr}$	7		74
17		$n\text{-Pr}-\text{C}\equiv\text{C}-n\text{-Pr}$	7		45
18		$\text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$	16		
19		$\text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$	12		
20		$\text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$	16		32

Table 2 continued

21		$\text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$	24		71
22		$n\text{-Pr}-\text{C}\equiv\text{C}-n\text{-Pr}$	16		73
23		$\text{BnOCH}_2-\text{C}\equiv\text{C}-\text{CH}_2\text{OBn}$	7		60
24		$\text{Ph}-\text{C}\equiv\text{C}-\text{CO}_2\text{Et}$	12		73 + 8
25		$\text{Ph}-\text{C}\equiv\text{C}-\text{Ph}$	18		66 ^b (83 : 17)

Table 2 continued

26		$\text{HOCH}_2\text{---}\equiv\text{---CH}_2\text{OH}$	16		73
				39	
27		$\text{HOCH}_2\text{---}\equiv\text{---Ph}$	8		31
				40	
28		$\text{Ph---}\equiv\text{---CO}_2\text{Et}$	8		76 + 8
				41 + 42	
29		$n\text{-Pr---}\equiv\text{---n-Pr}$	24		33 ^d
				44	

Table 2 continued

30	$\text{BnOCH}_2\text{---}\equiv\text{CH}_2\text{OBn}$	4	<p>45</p>	56 ^c
31	$\text{HOCH}_2\text{---}\equiv\text{CH}_2\text{OH}$	12	<p>46</p>	41 ^e
32	$\text{Ph---}\equiv\text{Ph}$	24	<p>47</p>	Trace ^{ef}
33	$\text{Ph---}\equiv\text{CO}_2\text{Et}$	16	<p>48 + 49</p>	91 ^{b,d} (60 : 40)

Table 2 continued

34		72		78 ^{b,d} (82 : 18)
35		7		42
36		12		0

^a All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the aryl halide, 0.5 mmol of the alkyne, 0.5 mmol of Et₃N, 5 mol % of Pd(OAc)₂ and 10 mol % of PPh₃ were stirred in 3 mL of DMF at 80 °C under an Ar atmosphere. ^b The products are inseparable. ^c Compound 34 was prepared and utilized as a 55:45 mixture of *E/Z* isomers. ^d The reaction was run at 100 °C. ^e The reaction was run at 120 °C. ^f Sixty five percent of the starting materials were recovered.

naphthalene **4** was obtained (entry 3), comparable to the yield obtained from the reaction of aryl halide **1** and diphenylacetylene (entry 1). When 4-octyne, a dialkylacetylene, was allowed to react with aryl halide **1**, a 60 % yield of naphthalene **5** was obtained (entry 4).

To test the regioselectivity of this annulation process, 1-phenylpropyne was allowed to react with aryl halide **1** and a 53:47 mixture of two regioisomers **6** and **7** was obtained in a 75 % overall yield (entry 5). According to our previous work,⁹⁻¹⁷ the bulkiness of the substituents on the acetylene plays a major role in determining the regioselectivity of alkyne insertion. The aryl moiety of the arylpalladium intermediate adds preferentially to the less hindered end of the carbon-carbon triple bond. In this naphthalene synthesis, the regioselectivity appears to be significantly lower than we have normally observed in the annulation of unsymmetrical alkynes. Similarly, the reaction of aryl halide **1** and ethyl phenylpropiolate afforded a 76:24 mixture of two regioisomers **8** and **9** (entry 6). In this case, the major product **8** results from aryl addition to the 3-position of the phenylpropiolate. Electronic effects appear to play a major role here. As in most Heck reactions, the aryl group of the initial Pd intermediate is more likely to add to the end of the carbon-carbon multiple bond furthest from the electron-withdrawing ester moiety, which results in naphthalene **8** as the major product.

The reactions of aryl halide **1** and 2-butyne-1,4-diol or 3-phenyl-2-propyn-1-ol failed to afford any recognizable product. It appears that the problem may be transesterification of the ester group by the acetylenic alcohols, which is further supported by the results described later. No recognizable naphthalene products could be obtained when bulky symmetrical or unsymmetrical alkynes, like di-*t*-butylacetylene, phenyl(trimethylsilyl)acetylene and 4,4-dimethyl-2-pentyne, were allowed to react with aryl halide **1**. Presumably, the problem here

is the difficulty in adding the hindered vinylic palladium intermediate across the relatively hindered internal alkene to place three bulky substituents in contiguous positions on the resulting carbocyclic ring.

A synthetically interesting question is whether aryl bromides can also undergo this palladium-catalyzed annulation chemistry. To answer this question, compound **10** was prepared and employed in reactions with various alkynes. Generally, compared to the results from aryl iodide **1**, the annulation reactions of aryl bromide **10** with alkynes result in a longer reaction time and lower yields, although the reactions proceed smoothly (entries 7 and 8). The observed lower reactivity of the aryl bromide **10** is consistent with our other annulation chemistry.⁹⁻¹⁷ Notice that the reaction of compound **10** and ethyl 2-pentynoate gave a 60:40 mixture of regioisomers **11** and **12** (entry 9).

In order to vary the linkage between the alkene and the iodoarene unit, substrates **13**, **18** and **20** have been prepared and employed in this annulation chemistry. The reaction of aryl iodide **13** and diphenylacetylene afforded a 72 % yield of the expected product (entry 10), a little lower than the yield from the reaction of aryl halide **1** and diphenylacetylene (entry 1). When ethyl phenylpropiolate was allowed to react with compound **13**, a 67:33 mixture of regioisomers **15** and **16** was obtained in an 86 % overall yield (entry 11). Comparing the results from entries 6 and 11, it is clear that the introduction of a methyl group into the starting material decreases the regioselectivity of the annulation chemistry. When aryl halide **13** was allowed to react with 2-butyne-1,4-diol, none of desired product was obtain. However, the use of a benzyl protected 2-butyne-1,4-diol resulted in a 56 % yield (entry 12). While compound **13** underwent the annulation chemistry very well and gave good to excellent yields, the annulation reaction of aryl halides **18** and **20** gave none of the desired

products (entries 13 and 14). It is not too surprising that aryl halide **18** was isomerized to the more stable trisubstituted alkene **19** which was isolated in a 48 % yield after 8 h. Note that compound **19**, which is a possible starting material for this annulation chemistry, is relatively unstable under the reaction conditions employed. If the reaction of compound **18** is allowed to proceed for 28 h, compound **19** disappeared and no other significant product was observed. The readily prepared aryl halide **20** may also be undergoing double bond isomerization because no recognizable products could be isolated from its reaction with diphenylacetylene.

It is interesting that the reaction of aryl halide **22** and diphenylacetylene afforded compound **23** in a 73 % yield (entry 15). A mechanism for the formation of product **23** is shown in Scheme 2. From the intermediate **A** that is formed, there are two possible pathways for palladium β -hydride elimination to occur. Intermediate **A** can eliminate H_b on the ring and eventually generate the naphthalene product after isomerization. The other pathway involves elimination of H_a from the methyl group which would afford compound **23** bearing a disubstituted terminal alkene. The result indicates that the elimination of H_a is much faster than that of H_b . This may be because the methyl group has three hydrogens increasing the chances of elimination. Alternatively, when the vinylic palladium iodide adds *cis* to the alkene, H_b is not *syn* to the alkylpalladium iodide generated. To undergo β -hydride elimination, rotation of the C-C bond is necessary before H_b and PdI are aligned *cis* to each other for elimination. Thus, the elimination of H_a may be achieved before this rotation can actually occur.

Scheme 2

To examine whether the geometry of the carbon-carbon double bond affects the annulation process, nitriles **24** and **27**, which are *E/Z* isomers, were prepared and allowed to react with 4-octyne and diphenylacetylene (entries 16-19). When 4-octyne was employed, both reactions reached completion in 7 h and afforded very similar yields (entries 16 and 17). The reactions of nitriles **24** and **27** with diphenylacetylene also resulted in very similar yields (entries 18 and 19), although they gave lower yields than the reactions of 4-octyne. Notice that the reactions of diphenylacetylene also required a longer reaction time. This is probably because 4-octyne, which is an electron-rich alkyne, is more reactive than diphenylacetylene.

These results (entries 16-19) indicate that the geometry of the carbon-carbon double bond has little effect on this annulation process.

Since aryl halides bearing electron-deficient olefins work very well in this annulation chemistry, it was important to determine if the introduction of an electron-withdrawing group on the alkene is really necessary to achieve success. To answer this question, compound **28** was prepared and allowed to react with diphenylacetylene. Only a 32 % yield of naphthalene **29** was isolated (entry 20). It appears that the presence of an electron-withdrawing group, which presumably makes the olefin a better acceptor for the Heck reaction, facilitates this chemistry. In this comparison, however, we cannot rule out the possibility that the terminal alkene in aryl iodide **28** may be undergoing intermolecular Heck processes resulting in a lower yield.

The reactions of aryl halide **30**, bearing two methoxy groups on the aromatic ring, with symmetrical alkynes, such as diphenylacetylene, 4-octyne and 1,4-di(benzyloxy)-2-butyne afforded the corresponding naphthalenes **31-33** in 71 %, 73 % and 60 % yields, respectively (entries 21-23). When aryl halide **30** was allowed to react with ethyl phenylpropiolate, two regioisomers **34** (73 %) and **35** (8 % yield) were isolated (entry 24). Comparing this result with that from the reaction of aryl halide **1** and ethyl phenylpropiolate (entry 6), it appears that the introduction of electron-donating substituents, like methoxy groups, onto the arene moiety increases the regioselectivity in this annulation process. The use of a diyne afforded an 83:17 mixture of alkynes **36** and **37** in a 66 % overall yield (entry 25).

The phenyl-substituted aryl iodide **38** has been found to react well with 2-butyne-1,4-diol to produce naphthalene **39** in a 73 % yield (entry 26). This result confirms our suspicion that the earlier problem with alkynols had more to do with transesterification of the ester

group than any inherent problems with the alcohol functionality. Surprisingly, only one regioisomer **40** was isolated, when 3-phenyl-2-propyn-1-ol was allowed to react with aryl halide **38** (entry 27), although the yield of 31 % was not very good. The reaction of aryl iodide **38** and ethyl phenylpropiolate afforded two regioisomers **41** (76 %) and **42** (8 %) with a yield and ratio of the two regioisomers similar to those from the reaction of **30** and ethyl phenylpropiolate (entry 24).

Carbazoles have attracted much attention due to their biological activity¹⁹ and their potential as functional materials,²⁰ and the synthesis of carbazoles has been extensively studied.²¹ Our palladium-catalyzed annulation chemistry provides an alternative, very efficient method to synthesize substituted carbazoles. Iodoindole **43** was first prepared using iodocyclization chemistry currently under investigation in our group.²² This compound was allowed to react with a variety of alkynes, including symmetrical and unsymmetrical alkynes. While the reactions of 4-octyne, 2-butyne-1,4-diol and 1,4-di(benzyloxy)-2-butyne gave moderate yields ranging from 33 % to 56 %, the use of diphenylacetylene gave only a trace of the desired product (entries 29-32). The failure of the reaction of diphenylacetylene is probably a result of the fact that this alkyne appears to be less reactive than most other alkynes. Notice that for the carbazole synthesis, a higher reaction temperature is also required. There was no reaction at 80 °C when iodoindole **43** was employed. This may indicate that 5,6-fused ring systems are more difficult to form than 6,6-fused ring systems when employing this annulation chemistry. More reactive alkynes, such as ethyl phenylpropiolate and ethyl 2-butynoate have also been allowed to react with iodoindole **43** and better yields have been obtained (entries 33 and 34). The use of ethyl phenylpropiolate gave a 60:40 mixture of regioisomers **48** and **49** in a 91 % overall yield, which indicates that

the electronic effects appear to be more important than steric effects in this system (entry 33). Ethyl 2-butynoate, a less bulky alkyne, was allowed to react with iodoindole **43** and a 82:18 mixture of isomers **50** and **51** was isolated in a 78 % overall yield (entry 34). The results from entries 33 and 34 indicate that both electronic and steric effects play a role in the regioselectivity of the alkyne insertion and the electronic effect apparently outweighs the steric effect.

When compound **52** was allowed to react with two alkynes, the reaction of the more reactive ethyl phenylpropiolate gave a 42 % yield of compound **53** as a single isomer, while use of the less reactive diphenylacetylene results in none of the desired product (entries 35 and 36).

A mechanism for the reaction of aryl halide **1** and diphenylacetylene is proposed in Scheme 3. First of all, Pd(0) oxidatively inserts into the carbon-iodide bond of the aryl iodide to generate an arylpalladium species. Addition of the arylpalladium species to the carbon-carbon triple bond, followed by an intramolecular *cis*-addition to the carbon-carbon double bond, generates an alkylpalladium species **B**. Intermediate **B** can undergo *E*-hydride elimination forming intermediate **C**, which subsequently isomerizes to naphthalene **2**. Alternatively, the intermediate **B** may undergo reversible palladium hydride elimination to an alkene complex **D**, which undergoes readdition of the palladium hydride to the double bond with the opposite regiochemistry. Further palladium hydride elimination would produce the observed aromatic product.

Scheme 3

Conclusions

An efficient synthesis of highly substituted naphthalenes and carbazoles has been developed in which two new carbon-carbon bonds are formed in a single step under relatively mild reaction conditions. Both electronic and steric effects play a role in the regioselectivity of this process and the electronic effect predominates over the steric effect with certain ester-containing alkynes. The introduction of an electron-rich group onto the aryl halide increases the regioselectivity of this annulation process. When this method was employed to synthesize carbazoles, a higher reaction temperature was necessary due to the lower reactivity of the iodoindoles. This method accommodates a variety of functional

groups and generally affords the anticipated highly substituted naphthalenes and carbazoles in good to excellent yields.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and a basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. All reagents were used directly as obtained commercially unless otherwise noted. Compounds **20**,²³ **28**,²⁴ (2-iodophenyl)acetaldehyde,²⁵ *N,N*-dimethylaniline,²⁶ and 2-iodoindole²⁷ were prepared according to previous literature procedures. The following starting materials were prepared as indicated.

Preparation of *o*-(2-Alkenyl)aryl halides.

Ethyl (*E*)-4-(2-iodophenyl)-2-butenolate (1). To a suspension solution of (carboethoxymethylene)triphenylphosphorane (5.22 g, 15.0 mmol) in 100 mL of CH_2Cl_2 was added dropwise a solution of 2-iodophenylacetaldehyde²⁵ (2.46 g, 10.0 mmol) in 20 mL of CH_2Cl_2 at 0 °C under an Ar atmosphere. The resulting mixture was stirred at 25 °C for 3 h and the solvent (CH_2Cl_2) was evaporated under reduced pressure. The solid residue was dissolved in 50 mL of hexane and the mixture was then stirred at 25 °C for 0.5 h. The Ph_3PO was filtered and the solvent (hexane) was removed under the reduced pressure. The oily residue was purified by flash chromatography (10:1 hexane/EtOAc) to afford 2.65 g of the

indicated compound as a colorless oil in an 84% yield: ^1H NMR (CDCl_3) δ 1.27 (t, $J = 7.2$ Hz, 3H), 3.65 (dd, $J = 1.5, 6.3$ Hz, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 5.78 (td, $J = 1.8, 15.6$ Hz, 1H), 6.94 (dt, $J = 1.8, 8.4$ Hz, 1H), 7.06 (td, $J = 6.3, 15.9$ Hz, 1H), 7.19 (dd, $J = 1.5, 7.5$ Hz, 1H), 7.31 (dt, $J = 1.2, 7.5$ Hz, 1H), 7.84 (dd, $J = 1.2, 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.5, 43.5, 60.6, 100.9, 123.2, 128.8, 128.9, 130.2, 139.9, 140.9, 145.8, 166.6; IR (neat, cm^{-1}) 3058, 2978, 2923, 2850, 1717, 1652; HRMS Calcd for $\text{C}_{12}\text{H}_{13}\text{IO}$: 315.9960. Found: 315.9965.

Ethyl (*E*)-4-(2-bromophenyl)-2-butenolate (10). Using the procedure used to prepare aryl halide 1, 2-bromophenylacetaldehyde²⁸ (2.01 g, 10.0 mmol) and (carboethoxymethylene)triphenylphosphorane (5.22 g 15.0 mmol) were employed to afford 1.82 g of the indicated compound as a colorless oil in a 68% yield: ^1H NMR (CDCl_3) δ 1.27 (t, $J = 6.8$ Hz, 3H), 3.65 (dd, $J = 1.2, 6.4$ Hz, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 5.78 (td, $J = 1.6, 15.6$ Hz, 1H), 7.04-7.13 (m, 2H), 7.20 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.26 (t, $J = 7.2$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 38.7, 60.5, 123.1, 127.8, 127.9, 128.7, 130.9, 133.2, 137.5, 145.6, 166.6; IR (neat, cm^{-1}) 3058, 2980, 1719, 1654; HRMS Calcd for $\text{C}_{12}\text{H}_{13}\text{BrO}$: 268.0099. Found: 268.0103.

2-(2-Iodophenyl)propanal. To a suspension of (methoxymethyl)triphenylphosphonium chloride (2.87 g, 8.4 mmol) in dry THF (15 mL) was added KO-*t*-Bu (0.90 g, 8.0 mmol) portionwise under an Ar atmosphere at 25 °C. The resulting red suspension was stirred for 30 min at 25 °C and a solution of 2-iodoacetophenone (0.98 g, 4.0 mmol) in dry THF (5 mL) was added dropwise. After the reaction mixture was stirred at 25 °C for 1 h, the THF was removed under reduced pressure and hexane (30 mL) was added to the residue. The resulting suspension was stirred for 20

min and the Ph_3PO was removed by filtration. The filtrate was collected, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (20:1 hexane/EtOAc) on silica gel to afford 1.10 g of 2-(2-iodophenyl)-1-methoxypropene ($E/Z = 90:10$) in a 100 % yield as a yellow oil. To a solution of 2-(2-iodophenyl)-1-methoxypropene ($E/Z = 90:10$) (0.55 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was added 1.2 mL of 47 % hydroiodic acid and the mixture was stirred under an Ar atmosphere at 25 °C for 40 min. The reaction was then diluted with 30 mL of CH_2Cl_2 and the excess acid was carefully neutralized by 30 mL of satd aq NaHCO_3 , during which lots of bubbles were generated. The organic layer was collected, washed with 20 mL of brine, dried over Na_2SO_4 , and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (20:1 hexane/EtOAc) on silica gel to afford 0.36 g of 2-(2-iodophenyl)propanal in a 69 % yield as a colorless liquid: ^1H NMR (CDCl_3) δ 1.40 (d, $J = 6.8$ Hz, 3H), 4.08 (q, $J = 6.8$ Hz, 1H), 6.99-7.03 (m, 1H), 7.06 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.35-7.39 (m, 1H), 7.93 (dd, $J = 1.2, 8.0$ Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.7, 56.9, 102.3, 128.6, 129.2, 129.5, 140.3, 141.4, 200.5.

Ethyl (*E*)-4-(2-iodophenyl)-2-pentenoate (13). To a suspension of (carboethoxymethylene)triphenylphosphorane (0.69 g, 1.95 mmol) in 5 mL of CH_2Cl_2 was added dropwise a solution of 2-(2-iodophenyl)propanal (0.34 g, 1.3 mmol) in 5 mL of CH_2Cl_2 at 0 °C under an Ar atmosphere. The resulting mixture was stirred at 25 °C for 3 h and the solvent (CH_2Cl_2) was evaporated under reduced pressure. The solid residue was dissolved in 20 mL of hexane and the mixture was then stirred at 25 °C for 0.5 h. The Ph_3PO was filtered and the solvent was removed under reduced pressure. The oily residue was purified by flash chromatography (20:1 hexane/EtOAc) to afford 0.41 g of the indicated

compound as a colorless oil in a 95 % yield: ^1H NMR (CDCl_3) δ 1.28 (t, $J = 7.2$ Hz, 3H), 1.39 (d, $J = 7.2$ Hz, 3H), 3.97-4.04 (m, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 5.84 (dd, $J = 2.0, 16.0$ Hz, 1H), 6.90-6.95 (m, 1H), 9.08 (dd, $J = 5.6, 16.0$ Hz, 1H), 7.15 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.30-7.34 (m, 1H), 7.85 (dd, $J = 1.2, 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.5, 19.7, 45.9, 60.6, 101.3, 121.0, 127.9, 128.8, 129.0, 140.0, 145.8, 151.3, 166.9; IR (neat, cm^{-1}) 3058, 2976, 2933, 2902, 1716, 1465; HRMS Calcd for $\text{C}_{13}\text{H}_{15}\text{IO}_2$: 330.0117. Found: 330.0123.

(2-Iodophenyl)phenylacetaldehyde. To a suspension of (methoxymethyl)triphenylphosphonium chloride (5.76 g, 16.8 mmol) in dry THF (25 mL) was added KO-*t*-Bu (1.80 g, 16.0 mmol) portionwise under an Ar atmosphere at 25 °C. The resulting reddish suspension was stirred for 30 min at 25 °C and a solution of 2-iodobenzophenone (2.46 g, 8.0 mmol) in THF (10 mL) was added dropwise. After the reaction mixture was stirred at 25 °C for 1 h, the solvent was removed under reduced pressure and hexane (50 mL) was added to the residue. The suspension was stirred for 20 min and the Ph_3PO was removed by filtration. The filtrate was collected, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford 2.68 g of 1-(2-iodophenyl)-2-methoxy-1-phenylethene ($E/Z = 61:39$) in 100 % yield as a pale yellow oil. To a solution of 1-(2-iodophenyl)-2-methoxy-1-phenylethene ($E/Z = 61:39$) (1.68 g, 5.0 mmol) in CH_2Cl_2 (15 mL) was added 3.0 mL of 47 % hydroiodic acid and the mixture was stirred under an Ar atmosphere at 25 °C for 3 h. Then the excess acid was carefully destroyed by 60 mL of satd aq NaHCO_3 , during which lots of bubbles were generated. The organic layer was collected, washed with 50 mL of brine, dried over Na_2SO_4 , and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (15:1 hexane/EtOAc) on silica

gel to afford 0.91 g of (2-iodophenyl)phenylacetaldehyde in a 57 % yield as a pale yellow oil: ^1H NMR (CDCl_3) δ 5.39 (s, 1H), 6.98-7.02 (m, 1H), 7.12 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.22-7.24 (m, 2H), 7.30-7.40 (m, 4H), 7.92 (dd, $J = 1.2, 8.0$ Hz, 1H), 9.98 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 68.1, 102.7, 128.0, 128.7, 129.2, 129.5, 129.7, 130.3, 135.4, 139.8, 140.4, 198.1.

Ethyl (*E*)-4-(2-iodophenyl)-4-phenyl-2-butenolate (18). Using the procedure used to prepare aryl halide **13**, (2-iodophenyl)phenylacetaldehyde (0.84 g, 2.6 mmol) and (carboethoxymethylene)triphenylphosphorane (1.36 g, 3.9 mmol) were employed to afford 1.01 g of the indicated compound in a 100 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.28 (t, $J = 7.2$ Hz, 3H), 4.19 (q, $J = 7.2$ Hz, 2H), 5.27 (dd, $J = 1.6, 6.0$ Hz, 1H), 5.64 (dd, $J = 1.6, 15.6$ Hz, 1H), 6.93-6.97 (m, 1H), 7.11 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.15-7.17 (m, 2H), 7.23-7.38 (m, 5H), 7.87 (dd, $J = 1.2, 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.5, 57.2, 60.7, 102.1, 123.8, 127.2, 128.7, 128.8, 129.0, 129.2, 130.1, 140.2, 140.4, 144.0, 149.2, 166.6; IR (neat, cm^{-1}) 3060, 2980, 1716, 1650, 1494; HRMS Calcd for $\text{C}_{18}\text{H}_{17}\text{IO}_2$: 392.0273. Found: 392.0279.

Ethyl (*E*)-4-(2-iodophenyl)-2-methyl-2-butenolate (22). Using the procedure used to prepare aryl halide **13**, (2-iodophenyl)acetaldehyde²⁵ (0.89 g, 3.6 mmol) and (carboethoxyethylene)triphenylphosphorane (1.67 g, 4.3 mmol) were employed to afford 1.19 g of the indicated compound in a 100 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.29 (t, $J = 7.2$ Hz, 3H), 1.97-1.98 (m, 3H), 3.62 (d, $J = 7.5$ Hz, 2H), 4.20 (q, $J = 7.2$ Hz, 2H), 6.78-6.84 (m, 1H), 6.90-6.95 (m, 1H), 7.18 (dd, $J = 1.5, 7.5$ Hz, 1H), 7.27-7.32 (m, 1H), 7.84 (dd, $J = 1.2, 7.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 13.1, 14.5, 40.4, 60.8, 100.8, 128.5, 128.8,

129.5, 129.7, 138.8, 139.8, 142.2, 168.2; IR (neat, cm^{-1}) 3054, 2979, 2930, 1708, 1648, 1251; HRMS Calcd for $\text{C}_{13}\text{H}_{15}\text{IO}_2$: 330.0117. Found: 330.0123.

(Z)-4-(2-Iodophenyl)-2-butenenitrile (24). Using the procedure used to prepare aryl halide **1**, 2-iodophenylacetaldehyde²⁵ (2.46 g, 10.0 mmol) and (triphenylphosphoranylidene)acetonitrile (4.52 g 15.0 mmol) were employed to afford 1.02 g of aryl halide **24** as a colorless oil in a 38 % yield and 1.10 g of aryl halide **27** as a colorless oil in a 41 % yield. Aryl halide **24**: ^1H NMR (CDCl_3) δ 3.88 (d, $J = 11.2$ Hz, 2H), 5.47 (td, $J = 1.2, 12.0$ Hz, 1H), 6.60 (td, $J = 7.6, 10.8$ Hz, 1H), 6.97 (dt, $J = 1.6, 7.6$ Hz, 1H), 7.25 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.33 (dt, $J = 1.2, 8.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 43.1, 100.3, 100.9, 116.1, 129.1, 129.1, 130.1, 139.9, 140.2, 151.5; IR (neat, cm^{-1}) 3062, 2219, 1619; HRMS Calcd for $\text{C}_{10}\text{H}_8\text{IN}$: 268.9702. Found: 268.9705.

(E)-4-(2-Iodophenyl)-2-butenenitrile (27). ^1H NMR (CDCl_3) δ 3.67 (dd, $J = 2.4, 8.0$ Hz, 2H), 5.25 (td, $J = 2.8, 22.0$ Hz, 1H), 6.84 (td, $J = 8.4, 29.6$ Hz, 1H), 6.98 (dt, $J = 2.0, 16.0$ Hz, 1H), 7.17 (dd, $J = 2.0, 10.0$ Hz, 1H), 7.34 (dt, $J = 1.6, 10.0$ Hz, 1H), 7.86 (dd, $J = 1.6, 10.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 44.3 100.7, 101.7, 117.4, 129.1, 129.3, 130.2, 139.4, 140.1, 152.5; IR (CHCl_3 , cm^{-1}) 3017, 2224, 1631; HRMS Calcd for $\text{C}_{10}\text{H}_8\text{IN}$: 268.9702. Found: 268.9705.

(2-Iodo-4,5-dimethoxyphenyl)acetaldehyde. To a solution of (2-iodo-4,5-dimethoxyphenyl)acetic acid²⁹ (14.5 mmol) in dried THF (50 mL) was added dropwise 8.0 mL of 2.0 M $\text{BH}_3\cdot\text{SMe}_2$ (16.0 mmol) in THF at 0 °C. Considerable gas was generated during addition of the $\text{BH}_3\cdot\text{SMe}_2$. The resulting mixture was stirred for 12 h at 25 °C and the solvent was removed under reduced pressure to afford crude 2-(2-iodo-4,5-dimethoxyphenyl)ethanol.

DMSO (2.06 mL, 31.9 mmol) was added dropwise into a solution of $(\text{COCl}_2)_2$ (1.39 mL, 16.0 mmol) in CH_2Cl_2 (20 mL) at -60°C (CHCl_3 and dry ice), in which considerable gas was generated. The colorless mixture was stirred for 10 min at -60°C . Then, a solution of the crude 2-(2-iodo-4,5-dimethoxyphenyl)ethanol in 10 mL CH_2Cl_2 was added dropwise to the reaction vessel and the reaction mixture turned a cloudy white. The resulting reaction mixture was further stirred for 30 min at -60°C and Et_3N (72.5 mmol) was added. After being stirred for 10 min, the reaction mixture was then diluted with water (50 mL) at -60°C , warmed up to 25°C , washed with 1N HCl (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The extracts were combined and dried over Na_2SO_4 . The solvent was removed and the liquid chromatographed (3:1 hexane/EtOAc) to afford 1.11 g of the desired compound as a yellow solid in a 25 % overall yield: mp $53\text{--}56^\circ\text{C}$; ^1H NMR (CDCl_3) δ 3.82 (s, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.71 (s, 1H), 7.28 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (CDCl_3) δ 54.5, 56.2, 56.4, 89.1, 113.6, 122.0, 128.4, 149.2, 149.9, 198.9.

Ethyl (*E*)-4-(2-iodo-4,5-dimethoxyphenyl)-2-butenolate (30). Using the procedure used to prepare aryl iodide **1**, (2-iodo-4,5-dimethoxyphenyl)acetaldehyde (1.53 g, 5.0 mmol) and (carboethoxymethylene)triphenylphosphorane (2.61 g, 7.5 mmol) were employed to afford 1.37 g of the indicated compound as a pale yellow oil in a 73% yield: ^1H NMR (CDCl_3) δ 1.28 (t, $J = 6.8$ Hz, 3H), 3.59 (dd, $J = 2.0, 6.0$ Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 5.76 (td, $J = 1.6, 15.6$ Hz, 1H), 6.69 (s, 1H), 7.01 (td, $J = 9.2, 21.6$ Hz, 1H), 7.23 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 43.1, 56.2, 56.4, 60.5, 88.5, 112.7, 121.9, 122.8, 133.1, 146.1, 148.6, 149.8, 166.7; IR (neat, cm^{-1}) 2977, 2904, 2839, 1715, 1651; HRMS Calcd for $\text{C}_{14}\text{H}_{17}\text{IO}_4$: 376.0171. Found: 376.0177.

1-(2-Iodo-4,5-dimethoxyphenyl)-3-phenylpropene (38). To a white suspension of benzyltriphenylphosphonium chloride (2.92 g, 7.5 mmol) in 100 mL of dried THF was added dropwise 2.5 M of *n*-BuLi (3.0 mL, 7.5 mmol) at 0 °C. The resulting reddish solution was then warmed up to 25 °C and stirred for 30 min before use. Using the procedure used to prepare aryl iodide **1**, (2-iodo-4,5-dimethoxyphenyl)acetaldehyde (1.53 g, 5.0 mmol) and (phenylmethylene)triphenylphosphorane (7.5 mmol) were employed to afford 1.71 g of a 55:45 mixture of *E/Z* stereoisomers as a colorless oil in a 90 % overall yield: ¹H NMR (CDCl₃) δ 3.59 (dd, *J* = 1.2, 6.0 Hz, 2H), 3.69 (dd, *J* = 2.0, 7.2 Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 5.76 (td, *J* = 6.4, 11.2 Hz, 1H), 6.29 (td, *J* = 6.4, 16.0 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.64 (d, *J* = 11.6 Hz, 1H), 6.73 (s, 1H), 6.77 (s, 1H), 7.18-7.39 (m, 12H); additional ¹³C NMR (CDCl₃) δ 39.8, 44.0, 56.1, 56.2, 56.4, 88.3, 88.5, 112.2, 112.7, 121.8, 126.3, 126.3, 126.4, 127.1, 127.4, 128.0, 128.5, 128.7, 128.7, 128.9, 130.0, 130.8, 131.7, 135.3, 136.0, 137.3, 137.6, 148.1, 148.2, 149.6, 149.7 (one sp³ carbon from one of the methoxy groups is missing due to overlap); IR (neat, cm⁻¹) 3079, 3055, 3002, 2933, 2905, 2837, 1596, 1567; HRMS Calcd for C₁₇H₁₇IO₂: 380.0273. Found: 380.0280.

(*E*)-1-Phenyl-1-penten-4-yne. To a stirred mixture of cinnamyl bromide (1.97 g, 10.0 mmol) and CuCl (0.099 g, 1.0 mmol) in dry THF (40 mL) was added dropwise a solution of ethynylmagnesium bromide in THF (0.5 M, 20 mL) at 25 °C. The resulting mixture was then stirred at 25 °C for 5 min and at 50 °C for 14 h. It was allowed to cool to room temperature and washed with 50 mL of brine. The organic layer was collected, dried over Na₂SO₄, and filtered, and the solvent was removed under reduced pressure. The oily residue was purified by flash chromatography (hexane) on silica gel to afford 0.67 g (47 % yield) of the indicated compound as a colorless liquid: ¹H NMR (CDCl₃) δ 2.18 (t, *J* = 2.4 Hz, 1H), 3.13-3.15 (m,

2H), 6.16 (td, $J = 5.6, 16.0$ Hz, 1H), 6.67 (d, $J = 16.0$ Hz, 1H), 7.22-7.24 (m, 1H), 7.29-7.32 (m, 2H), 7.36-7.38 (m, 2H); ^{13}C NMR (CDCl_3) δ 22.2, 70.9, 81.4, 123.8, 126.5, 127.6, 128.7, 131.8, 137.2.

***N,N*-Dimethyl-2-(*E*-5-phenyl-4-penten-1-ynyl)aniline.** To a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (42.1 mg, 0.06 mmol), *N,N*-dimethyl-2-iodoaniline²⁶ (0.74 g, 3.0 mmol) and (*E*)-1-phenyl-1-penten-4-yne (0.51 g, 3.6 mmol) in Et_3N (15 mL) was added CuI (5.71 mg, 0.03 mmol). The resulting mixture was stirred for 10 min under an Ar atmosphere and was heated to 50 °C. After 6 h, the reaction was allowed to cool to 25 °C. The ammonium salt was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (20:1 hexane/EtOAc) on silica gel to afford 0.64 g (92 % yield) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 2.93 (s, 6H), 3.44 (dd, $J = 2.0, 5.6$ Hz, 2H), 6.27 (td, $J = 5.6, 16.0$ Hz, 1H), 6.76 (d, $J = 16.0$ Hz, 1H), 6.86-6.90 (m, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 7.20-7.25 (m, 2H), 7.29-7.33 (m, 2H), 7.37-7.39 (m, 2H), 7.43 (dd, $J = 1.6, 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 23.7, 43.9, 82.1, 92.2, 116.4, 117.3, 121.0, 124.6, 126.4, 127.5, 128.7, 128.9, 131.6, 134.6, 137.4, 155.0.

3-Iodo-1-methyl-2-[*E*-3-phenylpro-2-enyl]-1*H*-indole (43). To a solution of *N,N*-dimethyl-2-(*E*-5-phenyl-4-penten-1-ynyl)aniline (0.58 g, 2.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of I_2 (0.67 g, 1.2 equiv) in CH_2Cl_2 (15 mL) under an Ar atmosphere at 25 °C. The reaction mixture was stirred at 25 °C for 3 h and diluted with 30 mL of CH_2Cl_2 . The excess I_2 was destroyed by adding 50 mL of satd aq $\text{Na}_2\text{S}_2\text{O}_3$. The organic layer was washed with 50 mL of brine, dried over Na_2SO_4 , and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) to afford 0.73 g of the indicated compound as a

yellow solid: mp 85-87 °C; ^1H NMR (CDCl_3) δ 3.72 (s, 3H), 3.79 (dd, $J = 1.2, 5.6$ Hz, 2H), 6.24 (td, $J = 5.6, 16.0$ Hz, 1H), 6.33 (d, $J = 16.0$ Hz, 1H), 7.17-7.31 (m, 8H), 7.43 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 31.0, 59.0, 109.5, 120.5, 121.0, 122.4, 125.4, 126.3, 127.6, 128.7, 130.1, 131.8, 137.1, 137.8, 138.8 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3055, 3025, 2929, 1674, 1386; HRMS Calcd for $\text{C}_{18}\text{H}_{16}\text{IN}$: 373.0328. Found: 373.0332.

2-Iodo-1-(*E*-3-phenylprop-2-enyl)-1*H*-indole (52). To a suspension of NaH (0.18 g, 4.5 mmol) in dry DMF (15 mL) was added dropwise a solution of 2-iodoindole²⁷ (0.73 g, 3.0 mmol) in THF (10 mL) at 0 °C, during which lots of bubbles were generated. The resulting yellow suspension was stirred at 0 °C for 1 h and a solution of cinnamyl bromide (0.59 g, 3.0 mmol) in dry THF (2 mL) was added dropwise at 0 °C. After the reaction mixture was stirred at 0 °C for 20 min, it was warmed up to 25 °C, diluted with 50 mL of Et_2O , and washed with 50 mL of brine. The organic layer was collected, dried over Na_2SO_4 , and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (30:1 hexane/ EtOAc) on silica gel to afford 0.61 g of the compound **52** as a white solid: mp 99-101 °C; ^1H NMR (CDCl_3) δ 4.95 (d, $J = 4.8$ Hz, 2H), 6.24 (td, $J = 4.8, 16.0$ Hz, 1H), 6.36 (d, $J = 16.0$ Hz, 1H), 6.84 (s, 1H), 7.07-7.11 (m, 1H), 7.12-7.16 (m, 1H), 7.21-7.29 (m, 5H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 49.2, 83.3, 110.1, 112.6, 119.8, 120.2, 122.1, 124.3, 126.7, 128.0, 128.7, 130.1, 132.4, 136.4, 137.7; IR (CHCl_3 , cm^{-1}) 3077, 3019, 2913, 1455, 1434; HRMS Calcd for $\text{C}_{17}\text{H}_{14}\text{IN}$: 359.0171. Found: 359.0179.

General procedure for preparation of the naphthalenes and carbazoles. To a mixture of the alkyne (0.50 mmol), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.025 mmol), PPh_3 (6.6 mg, 0.05

mmol), and Et₃N (55.0 mg, 0.5 mmol) in 2 mL of DMF was added dropwise a solution of the aryl halide (0.25 mmol) in 1 mL of DMF. The resulting mixture was then stirred under an Ar atmosphere at the indicated temperature (see Table 2 in the text). The reaction was monitored by TLC to establish completion. When the reaction was complete, the reaction mixture was allowed to cool to 25 °C, poured into brine (25 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated and the residue was purified by column chromatography on silica gel to afford the corresponding naphthalene(s) or carbazole(s).

Ethyl (1,2-diphenylnaphth-3-yl)acetate (2). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 79 mg or 69 mg of the indicated product as a white solid in an 86 % (entry 1) or a 75 % (entry 7) yield, respectively: mp 85-87 °C; ¹H NMR (CDCl₃) δ 1.15 (t, *J* = 7.2 Hz, 3H), 3.61 (s, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 7.02 (d, *J* = 6.8 Hz, 2H), 7.09-7.22 (m, 8H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.45-7.49 (m, 2H), 7.85 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.3, 40.5, 60.9, 126.1, 126.2, 126.6, 126.7, 127.0, 127.6, 127.7, 127.8, 128.9, 130.6, 131.2, 132.2, 133.0, 139.4, 139.5, 139.6, 139.8, 172.1 (one sp² carbon is missing due to overlap); IR (CHCl₃, cm⁻¹) 3056, 3021, 2982, 2933, 1950, 1731, 1601; HRMS Calcd for C₂₆H₂₂O₂: 366.1620. Found: 366.1620.

Ethyl [1,2-di(4-methoxyphenyl)naphth-3-yl]acetate (3). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 65 mg of the indicated compound as a yellow oil in a 61 % yield: ¹H NMR (CDCl₃) δ 1.15 (t, *J* = 7.2 Hz, 3H), 3.61 (s, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 4.02 (q, *J* = 9.6 Hz, 2H), 6.69-6.77 (m, 2H), 6.93 (dd, *J* = 2.8, 8.8 Hz, 2H), 7.00 (dd, *J* = 1.6, 11.2 Hz, 2H), 7.34 (dt, *J* = 1.6, 9.2 Hz, 1H), 7.45-7.51 (m, 2H), 7.82 (s, 1H), 7.86 (d, *J* = 10.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.3, 40.6, 55.2, 55.3, 60.7, 113.2,

113.2, 126.0, 126.1, 127.1, 127.8, 128.6, 131.6, 131.8, 132.1, 132.3, 132.6, 132.9, 139.4, 139.6, 158.1, 172.2 (two sp^2 carbons are missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3015, 2958, 2933, 2836, 1893, 1731, 1609; HRMS Calcd for $C_{28}H_{26}O_4$: 426.1831. Found: 426.1837.

Ethyl [1,2-di(4-ethoxycarbonylphenyl)naphth-3-yl]acetate (4). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 106 mg of the indicated compound as a yellow oil in an 83 % yield: 1H NMR ($CDCl_3$) δ 1.14 (t, $J = 7.2$ Hz, 3H), 1.38 (t, $J = 6.8$ Hz, 3H), 1.38 (t, $J = 7.2$ Hz, 3H), 3.58 (s, 2H), 4.01 (q, $J = 7.2$ Hz, 2H), 4.32-4.38 (m, 4H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.35-7.40 (m, 2H), 7.48-7.52 (m, 1H), 7.85-7.91 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 40.2, 61.0, 61.1, 126.6, 126.6, 126.7, 128.0, 129.1, 129.1, 129.6, 130.5, 130.6, 131.1, 131.6, 133.1, 138.3, 138.4, 144.0, 144.3, 166.5, 166.6, 171.7 (two sp^3 carbons from ethoxy groups and two sp^2 carbons are missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3021, 2983, 2937, 2906, 2872, 1716, 7608; HRMS Calcd for $C_{32}H_{30}O_6$: 510.2042. Found: 510.2049.

Ethyl (1,2-di-*n*-propylnaphth-3-yl)acetate (5). The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 45 mg or 35 mg of the indicated product as a yellow in a 60 % (entry 4) or a 46 % (entry 8) yield, respectively: 1H NMR ($CDCl_3$) δ 1.08 (t, $J = 7.5$ Hz, 3H), 1.11 (t, $J = 7.5$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.48-1.61 (m, 2H), 1.62-1.75 (m, 2H), 2.74-2.79 (m, 2H), 3.01-3.06 (m, 2H), 3.80 (s, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 7.35-7.46 (m, 2H), 7.57 (s, 1H), 7.73 (dd, $J = 1.5, 8.4$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 15.0, 24.5, 24.7, 31.2, 32.4, 40.1, 61.0, 124.2, 125.0, 125.8, 128.3, 128.5, 131.5, 131.9, 132.5, 136.7, 137.0, 172.2 (one sp^3 carbon is missing due

to overlap); IR (neat, cm^{-1}) 3069, 2958, 2870, 1735, 1597; HRMS Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_2$: 298.1933. Found: 298.1937.

Ethyl (1-methyl-2-phenylnaphth-3-yl)acetate (6) and ethyl (2-methyl-1-phenylnaphth-3-yl)acetate (7). The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 57 mg of a 53:47 mixture of regioisomers **6/7** as determined by ^1H NMR spectral analysis of the yellow oil in a 75 % overall yield. ^1H NMR (CDCl_3) for the major regioisomer **6**: δ 1.26 (t, $J = 7.2$ Hz, 3H), 2.16 (s, 3H), 3.86 (s, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 7.20-7.52 (m, 8H), 7.73 (s, 1H), 7.79 (d, $J = 4.8$ Hz, 1H). ^1H NMR (CDCl_3) for the minor regioisomer **7**: δ 1.13 (t, $J = 7.2$ Hz, 3H), 2.37 (s, 3H), 3.51 (s, 2H), 3.99 (q, $J = 7.2$ Hz, 2H), 7.20-7.52 (m, 7H), 7.67 (s, 1H), 7.83 (dd, $J = 1.2, 4.8$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (CDCl_3) for the mixture δ 14.3, 14.4, 16.8, 17.7, 40.6, 40.6, 60.8, 61.1, 124.6, 125.3, 125.8, 125.9, 126.2, 126.5, 127.2, 127.2, 127.3, 127.6, 128.4, 128.5, 128.6, 128.9, 129.9, 130.4, 131.2, 131.9, 132.0, 132.2, 132.5, 132.6, 132.9, 132.9, 139.3, 139.8, 140.4, 140.8, 171.9, 172.1; IR (neat, cm^{-1}) for the mixture 3056, 3022, 2981, 2934, 2870, 1731, 1599, 1572; HRMS Calcd for $\text{C}_{21}\text{H}_{20}\text{O}_2$: 304.1463. Found: 304.1467.

Ethyl (2-ethoxycarbonyl-1-phenylnaphth-3-yl)acetate (8) and ethyl (1-ethoxycarbonyl-2-phenylnaphth-3-yl)acetate (9). The reaction mixture was chromatographed using 7:1 hexane/EtOAc to afford 80 mg of a 76:24 mixture of regioisomers **8/9** as determined by ^1H NMR spectroscopy of the yellow oil in an 88 % overall yield. ^1H NMR (CDCl_3) for the major regioisomer **8**: δ 0.87 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 6.8$ Hz, 3H), 3.94 (s, 2H), 3.95 (q, $J = 7.2$ Hz, 2H), 4.16 (q, $J = 6.8$ Hz, 2H), 7.28-7.59 (m, 8H), 7.79-7.87 (m, 2H). ^1H NMR (CDCl_3) for the minor regioisomer **9**: δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 6.8$ Hz, 3H), 3.61 (s, 2H), 3.98-4.10 (m, 4H), 7.28-7.59 (m, 8H), 7.79-

7.87 (m, 2H). ^{13}C NMR (CDCl_3) for the mixture δ 13.6, 13.8, 14.2, 14.3, 39.7, 39.7, 60.9, 61.0, 61.1, 61.2, 125.0, 126.7, 127.0, 127.2, 127.3, 127.7, 127.8, 127.9, 128.0, 128.1, 128.1, 128.5, 129.0, 129.6, 129.8, 130.3, 130.8, 130.9, 131.4, 131.8, 132.3, 132.7, 133.7, 138.3, 138.4, 138.5, 139.2, 169.0, 169.2, 171.3, 171.5 (one sp^2 carbon is missing due to overlap); IR (neat, cm^{-1}) for the mixture 3057, 2981, 2936, 2903, 2872, 1731, 1622, 1596; HRMS Calcd for $\text{C}_{23}\text{H}_{22}\text{O}_4$: 362.1518. Found: 362.1522.

Ethyl 3-(2-ethoxy-2-oxoethyl)-1-ethyl-2-naphthoate (11) and ethyl 3-(2-ethoxy-2-oxoethyl)-2-ethyl-1-naphthoate (12). The reaction mixture was chromatographed using 7:1 hexane/EtOAc to afford 41 mg (52 % yield) of a 60:40 mixture of regioisomers **11/12** as determined by ^1H NMR spectroscopic analysis of the yellow oil. ^1H NMR (CDCl_3) for the major regioisomer **11**: δ 1.22-1.27 (m, 3H), 1.34-1.48 (m, 6H), 3.09 (q, $J = 7.5$ Hz, 2H), 3.81 (s, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 4.44 (q, $J = 7.2$ Hz, 2H), 7.41-7.56 (m, 2H), 7.64 (s, 1H), 7.76-7.82 (m, 1H), 8.05-8.09 (m, 1H). ^1H NMR (CDCl_3) for the minor regioisomer **12**: δ 1.22-1.27 (m, 6H), 1.34-1.48 (m, 3H), 2.82 (q, $J = 7.5$ Hz, 2H), 3.83 (s, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 4.54 (q, $J = 7.2$ Hz, 2H), 7.41-7.56 (m, 2H), 7.68-7.71 (m, 1H), 7.76-7.82 (m, 2H). ^{13}C NMR (CDCl_3) for the mixture δ 14.4, 14.4, 14.4, 14.6, 15.5, 15.9, 24.2, 24.7, 39.0, 40.0, 61.2, 61.3, 61.5, 61.6, 124.5, 124.6, 126.0, 126.7, 126.9, 127.0, 128.0, 128.2, 128.6, 128.8, 129.6, 130.7, 131.0, 131.5, 131.6, 131.8, 132.0, 134.1, 137.9, 138.7, 170.0, 170.2, 171.3, 171.6; IR (neat, cm^{-1}) for the mixture 3060, 2979, 2937, 1728, 1449; HRMS Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4$: 314.1518. Found: 314.1522.

Ethyl (1-methyl-3,4-diphenyl-2-naphthyl)acetate (14). The reaction mixture was chromatographed using 30:1 hexane/EtOAc to afford 68 mg (72 % yield) of the indicated compound as a white solid: mp 80-82 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.18 (t, $J = 7.1$ Hz, 3H), 2.72

(s, 1H), 3.69 (s, 2H), 4.08 (q, $J = 7.1$ Hz, 2H), 7.01-7.21 (m, 10H), 7.32-7.38 (m, 1H), 7.48-7.54 (m, 2H), 8.16 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 15.8, 38.0, 60.8, 124.3, 125.8, 126.0, 126.4, 126.6, 127.6, 127.7, 127.7, 129.3, 130.5, 131.3, 132.1, 132.3, 133.0, 137.5, 139.9, 140.1, 141.0, 171.9; IR (CHCl_3 , cm^{-1}) 3018, 1729, 1216; HRMS Calcd for $\text{C}_{27}\text{H}_{24}\text{O}_2$: 380.1776. Found: 380.1781. Anal. Calcd: C, 85.22; H, 6.35. Found: C, 84.83; H, 6.49.

Ethyl 3-(2-ethoxy-2-oxoethyl)-4-methyl-1-phenyl-2-naphthoate (15) and ethyl 3-(2-ethoxy-2-oxoethyl)-4-methyl-2-phenyl-1-naphthoate (16). The reaction mixture was chromatographed using 7:1 hexane/EtOAc to afford 64 mg (86 % yield) of a 67:33 mixture of regioisomers **15/16** as determined by ^1H NMR spectroscopic analysis of the yellow oil. ^1H NMR (CDCl_3) for the major regioisomer **15**: δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 3.95 (s, 2H), 3.96 (q, $J = 7.2$ Hz, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 7.26-7.59 (m, 8H), 8.12-8.14 (m, 1H). ^1H NMR (CDCl_3) for the minor regioisomer **16**: δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.18 (t, $J = 7.2$ Hz, 3H), 3.67 (s, 2H), 4.02 (q, $J = 7.2$ Hz, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 7.26-7.59 (m, 7H), 7.85-7.87 (m, 1H), 8.12-8.14 (m, 1H). ^{13}C NMR (CDCl_3) for the mixture δ 13.7, 13.9, 14.4, 14.4, 15.5, 15.9, 37.1, 37.5, 60.9, 61.1, 61.1, 61.2, 124.5, 124.6, 125.7, 125.9, 126.2, 126.6, 126.9, 127.0, 127.7, 127.7, 127.8, 128.1, 128.1, 128.8, 129.1, 129.9, 130.7, 130.8, 131.5, 132.1, 133.1, 133.2, 133.9, 135.5, 136.4, 138.5, 138.6, 139.6, 169.5, 169.9, 171.0, 171.5; IR (neat, cm^{-1}) for the mixture 3059, 2980, 2937, 1717, 1228; HRMS Calcd for $\text{C}_{24}\text{H}_{24}\text{O}_4$: 376.1675. Found: 376.1680.

Ethyl {3,4-bis[(benzyloxy)methyl]-1-methyl-2-naphthyl}acetate (17). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 65 mg of the indicated compound as a yellow solid in a 56 % yield: mp 82-83 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.18 (t, $J =$

7.2 Hz, 3H), 2.64 (s, 3H), 4.01 (s, 2H), 4.05 (q, $J = 7.2$ Hz, 2H), 4.49 (s, 2H), 4.55 (s, 2H), 4.70 (s, 2H), 4.91 (s, 2H), 7.23-7.36 (m, 10H), 7.47-7.50 (m, 2H), 8.04-8.07 (m, 1H), 8.11-8.14 (m, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 15.8, 36.2, 60.9, 65.4, 66.6, 72.8, 72.9, 124.7, 125.3, 126.1, 126.2, 128.0, 128.3, 128.4, 128.6, 128.6, 130.4, 131.6, 132.2, 133.2, 134.4, 134.9, 138.2, 138.4, 171.7 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3065, 3026, 2975, 2867, 1728, 1326; HRMS Calcd for $\text{C}_{31}\text{H}_{32}\text{O}_4$: 468.2301. Found: 468.2312.

Ethyl *E*-4-(2-iodophenyl)-4-phenyl-3-butenate (19). The reaction mixture was chromatographed using 15:1 hexane/EtOAc to afford 47 mg (48 % yield) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 1.25 (t, $J = 7.2$ Hz, 3H), 2.92 (dd, $J = 8.0$, 16.4 Hz, 1H), 3.05 (dd, $J = 6.4$, 16.4 Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 6.44-6.47 (m, 1H), 7.02-7.06 (m, 1H), 7.19 (dd, $J = 1.6$, 7.6 Hz, 1H), 7.24-7.30 (m, 5H), 7.39-7.43 (m, 1H), 7.92 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.5, 35.6, 60.9, 100.0, 121.7, 126.8, 127.7, 128.5, 128.6, 129.2, 130.8, 139.4, 139.7, 144.1, 146.0, 171.6; IR (neat, cm^{-1}) 3059, 2981, 1717; HRMS Calcd for $\text{C}_{18}\text{H}_{17}\text{IO}_2$: 392.0273. Found: 392.0279.

Ethyl 2-(3,4-diphenyl-1,2-dihydronaphthalen-2-yl)acrylate (23). The reaction mixture was chromatographed using 15:1 hexane/EtOAc to afford 69 mg (73 % yield) of the indicated compound as a yellow solid: mp 135-137 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 3H), 2.99 (dd, $J = 2.4$, 16.0 Hz, 1H), 3.47 (dd, $J = 7.2$, 16.0 Hz, 1H), 4.01 (dd, $J = 1.6$, 7.2 Hz, 1H), 4.20-4.25 (m, 2H), 5.80-5.81 (m, 1H), 6.28 (d, $J = 1.2$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 7.00-7.13 (m, 10H), 7.20-7.22 (m, 3H); ^{13}C NMR (CDCl_3) δ 14.4, 34.5, 41.3, 61.1, 126.5, 126.5, 126.6, 126.8, 127.0, 127.6, 127.7, 128.3, 128.4, 128.8, 131.2, 133.6, 136.9, 137.2, 138.6, 138.9, 139.7, 142.0, 167.1; IR (CH_2Cl_2 , cm^{-1}) 3054, 3020, 2981, 2899, 1709, 1264; HRMS Calcd for $\text{C}_{27}\text{H}_{24}\text{O}_2$: 380.1776. Found: 380.1784.

(3,4-Di-*n*-propylnaphthyl)acetonitrile (25). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 46 mg or 45 mg of the indicated compound as a yellow solid in a 74 % (entry 16) or a 72 % (entry 17) yield, respectively: mp 76-78 °C; ^1H NMR (CDCl_3) δ 1.10 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.52-1.62 (m, 2H), 1.63-1.72 (m, 2H), 2.71-2.75 (m, 2H), 3.01-3.06 (m, 2H), 3.88 (s, 2H), 7.44 (dt, $J = 0.8$, 7.6 Hz, 1H), 7.50 (dt, $J = 1.2$, 7.6 Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.79 (s, 1H), 7.99 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 15.0, 15.0, 22.8, 24.4, 24.7, 31.1, 32.1, 118.4, 124.2, 125.6, 126.6, 126.8, 126.8, 128.6, 132.2, 132.4, 135.3, 137.6; IR (CHCl_3 , cm^{-1}) 3065, 3019, 2960, 2872, 2251, 1598; HRMS Calcd for $\text{C}_{18}\text{H}_{21}\text{N}$: 251.1674. Found: 251.1679.

(3,4-Diphenyl-2-naphthyl)acetonitrile (26). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 36 mg or 34 mg of the indicated compound as a yellow solid in 45 % (entry 18) or 43 % (entry 19) yield: mp 193-195 °C; ^1H NMR (CDCl_3) δ 3.61 (d, $J = 0.9$ Hz, 2H), 7.02-7.10 (m, 4H), 7.17-7.25 (m, 6H), 7.38-7.44 (m, 1H), 7.49-7.57 (m, 2H), 7.95 (d, $J = 8.1$ Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (CDCl_3) δ 23.5, 118.4, 126.6, 126.8, 126.9, 127.1, 127.2, 127.3, 127.8, 127.9, 128.4, 130.2, 131.0, 132.4, 132.9, 138.2, 138.7, 138.7, 140.1 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3020, 2254, 1487, 1442; HRMS Calcd for $\text{C}_{24}\text{H}_{17}\text{N}$: 319.1361. Found: 319.1366.

3-Methyl-1,2-diphenylnaphthalene (29). The reaction mixture was chromatographed using hexane to afford 24 mg (32 % yield) of the indicated compound as a white solid: mp 147-148 °C; ^1H NMR (CDCl_3) δ 2.26 (d, $J = 0.6$ Hz, 3H), 7.01-7.05 (m, 2H), 7.08-7.24 (m, 8H), 7.28-7.34 (m, 1H), 7.42-7.48 (m, 2H), 7.77 (s, 1H), 7.82-7.85 (m, 1H); ^{13}C NMR (CDCl_3) δ 22.1, 125.5, 125.9, 126.3, 126.5, 127.0, 127.3, 127.6, 127.6, 127.7, 130.3, 131.2,

131.5, 133.1, 134.6, 138.8, 139.6, 140.1, 140.8; IR (CHCl₃, cm⁻¹) 3019, 1489, 1442, 1215; HRMS Calcd for C₂₃H₁₈: 294.1408. Found: 294.1413.

Ethyl (6,7-dimethoxy-1,2-diphenylnaphth-3-yl)acetate (31). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 75 mg of the indicated compound as a white solid in a 71 % yield: mp 142-145 °C; ¹H NMR (CDCl₃) δ 1.15 (t, *J* = 7.2 Hz, 3H), 3.57 (s, 2H), 3.69 (s, 3H), 4.02 (s, 3H), 4.03 (q, *J* = 7.2 Hz, 2H), 6.76 (s, 1H), 7.01-7.03 (m, 2H), 7.08-7.21 (m, 9H), 7.71 (s, 1H); ¹³C NMR (CDCl₃) δ 14.3, 40.3, 55.8, 56.1, 60.8, 105.8, 106.2, 126.5, 126.6, 127.2, 127.6, 127.7, 127.7, 128.9, 129.3, 130.7, 131.0, 138.0, 138.1, 139.7, 140.1, 149.6, 149.7, 172.3; IR (CHCl₃, cm⁻¹) 3057, 3020, 2982, 2956, 2831, 1733, 1623, 1599, 1566; HRMS Calcd for C₂₈H₂₆O₄: 426.1831. Found: 426.1837.

Ethyl (6,7-dimethoxy-1,2-dipropyl-3-naphthyl)acetate (32). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 66 mg (73 % yield) of the indicated compound as a pale yellow solid: mp 94-96 °C; ¹H NMR (CDCl₃) δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.47-1.60 (m, 2H), 1.63-1.77 (m, 2H), 2.71-2.76 (m, 2H), 2.95-3.01 (m, 2H), 3.76 (s, 2H), 3.96 (s, 3H), 4.00 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 7.04 (s, 1H), 7.22 (s, 1H), 7.44 (s, 1H); ¹³C NMR (CDCl₃) δ 14.4, 15.0, 15.1, 24.2, 24.6, 31.5, 32.3, 40.0, 55.9, 55.9, 61.0, 103.4, 106.9, 126.8, 127.4, 128.3, 129.8, 135.3, 135.3, 148.8, 149.4, 172.5; IR (CHCl₃, cm⁻¹) 3020, 2958, 2871, 1729, 1510, 1473; HRMS Calcd for C₂₂H₃₀O₄: 358.2144. Found: 358.2148.

Ethyl [1,2-di(benzyloxy)methyl-6,7-dimethoxy-3-naphthyl]acetate (33). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 72 mg (60 % yield) of the indicated compound as a white solid: mp 83-85 °C; ¹H NMR (CDCl₃) δ 1.20 (t, *J* = 7.2 Hz, 3H), 3.84 (s, 2H), 3.86 (s, 3H), 3.97 (s, 3H), 4.07 (q, *J* = 7.2 Hz, 2H), 4.52 (s, 2H),

4.53 (s, 2H), 4.70 (s, 2H), 4.88 (s, 2H), 7.04 (s, 1H), 7.30-7.37 (m, 11H), 7.58 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.4, 39.5, 55.9, 56.0, 61.0, 65.6, 66.1, 72.7, 72.8, 103.8, 106.5, 128.0, 128.0, 128.2, 128.4, 128.4, 128.6, 128.6, 129.5, 129.7, 130.4, 132.4, 132.5, 138.4, 138.4, 149.8, 149.9, 172.1; IR (CHCl_3 , cm^{-1}) 3019, 2939, 1727, 1509, 1259; HRMS Calcd for $\text{C}_{32}\text{H}_{34}\text{O}_6$: 514.2355. Found: 514.2362.

Ethyl (2-ethoxycarbonyl-6,7-dimethoxy-1-phenylnaphth-3-yl)acetate (34). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 77 mg of naphthalene **34** as a colorless oil in 73 % yield and 8 mg of naphthalene **35** as a pale yellow oil in an 8 % yield. Naphthalene **34**: ^1H NMR (CDCl_3) δ 0.86 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H), 3.72 (s, 3H), 3.89 (s, 2H), 3.93 (q, $J = 7.2$ Hz, 2H), 4.00 (s, 3H), 4.16 (q, $J = 7.2$ Hz, 2H), 6.85 (s, 1H), 7.12 (s, 1H), 7.37 (d, $J = 7.6$ Hz, 2H), 7.40-7.46 (m, 3H), 7.64 (s, 1H); ^{13}C NMR (CDCl_3) δ 13.7, 14.4, 39.7, 55.8, 56.1, 61.0, 61.0, 105.7, 106.2, 127.1, 127.7, 128.0, 128.2, 130.1, 130.2, 130.2, 137.8, 139.1, 150.0, 150.5, 169.6, 171.6 (one sp^2 carbon is missing due to overlap); IR (CHCl_3 , cm^{-1}) 3021, 2981, 2937, 1731, 1625; HRMS Calcd for $\text{C}_{25}\text{H}_{26}\text{O}_2$: 422.1729. Found: 422.1734. Naphthalene **35**: ^1H NMR (CDCl_3) δ 0.89 (dt, $J = 1.5, 7.2$ Hz, 3H), 1.15 (dt, $J = 1.5, 7.2$ Hz, 3H), 3.56 (s, 2H), 3.96-4.05 (m, 5H), 4.08-4.19 (m, 5H), 7.13 (s, 1H), 7.19 (s, 1H), 7.27-7.47 (m, 5H), 7.73 (s, 1H).

Ethyl [6,7-dimethoxy-2-phenyl-1-(phenylethynyl)-3-naphthyl]acetate (36) and ethyl [6,7-dimethoxy-1-phenyl-2-(phenylethynyl)-3-naphthyl]acetate (37). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 74 mg (66 % yield) of a 83:17 mixture of regioisomers **36/37** as determined by ^1H NMR spectroscopic analysis of the yellow oil. ^1H NMR (CDCl_3) for the major regioisomer **36**: δ 1.23 (t, $J = 7.2$ Hz, 3H), 3.74 (s, 2H), 4.00 (s, 3H), 4.04 (s, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 6.89 (s, 1H), 7.12 (s, 1H), 7.14-

7.55 (m, 10H), 7.63 (s, 1H). ^1H NMR (CDCl_3) for the minor regioisomer **37**: δ 1.16 (t, J = 7.2 Hz, 3H), 3.59 (s, 2H), 4.00-4.05 (m, 5H), 4.08 (s, 3H), 7.14-7.55 (m, 11H), 7.67 (s, 1H), 7.77 (s, 1H). Additional ^{13}C NMR (CDCl_3) for the mixture δ 14.3, 14.4, 39.9, 41.1, 55.8, 56.0, 56.1, 60.9, 61.1, 87.9, 88.3, 97.1, 98.2, 105.4, 105.5, 106.5, 106.5, 119.4, 119.5, 123.8, 127.0, 127.2, 127.5, 127.6, 128.1, 128.2, 128.3, 128.4, 128.6, 129.1, 129.3, 130.3, 130.8, 131.3, 131.3, 131.4, 139.6, 140.3, 142.3, 142.5, 149.8, 150.2, 150.2, 150.7, 171.9, 172.0 (five sp^2 carbons and one sp^3 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3057, 3020, 2980, 1731, 1506, 1255; HRMS Calcd for $\text{C}_{30}\text{H}_{26}\text{O}_4$: 450.1831. Found: 450.1839.

3-Benzyl-1,2-di(hydroxymethyl)-6,7-dimethoxynaphthalene (39). The reaction mixture was chromatographed using 1:3 hexane/EtOAc to afford 63 mg of the indicated compound as a white solid in a 73 % yield: mp 170-172 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 2.28 (br s, 2H), 4.00 (s, 3H), 4.03 (s, 3H), 4.26 (s, 2H), 4.83 (s, 2H), 5.15 (s, 2H), 7.08 (s, 1H), 7.14 (d, J = 6.8 Hz, 2H), 7.20 (dt, J = 2.0, 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.28 (dt, J = 2.0, 8.4 Hz, 1H), 7.49 (s, 1H), 7.54 (s, 1H); ^{13}C NMR (CDCl_3) δ 40.4, 56.1, 56.1, 58.9, 59.8, 103.0, 106.7, 126.6, 127.4, 128.7, 128.9, 129.0, 129.9, 134.9, 135.1, 136.0, 141.4, 150.0, 150.1; IR (CHCl_3 , cm^{-1}) 3415 (br), 3019, 2972, 2953, 2903, 2829, 1625, 1602; HRMS Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_4$: 338.1518. Found: 338.1525.

(3-Benzyl-6,7-dimethoxy-2-phenyl-1-naphthyl)methanol (40). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 30 mg (31 % yield) of the indicated compound as a yellow solid: mp 144-146 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.45 (br s, 1H), 3.80 (s, 2H), 4.00 (s, 3H), 4.04 (s, 3H), 4.75 (s, 2H), 6.88-6.91 (m, 2H), 7.05-7.20 (m, 6H), 7.34-7.38 (m, 3H), 7.48 (s, 1H), 7.54 (s, 1H); ^{13}C NMR (CDCl_3) δ 40.5, 56.1, 56.2, 60.5, 103.7, 106.8,

125.9, 126.7, 127.3, 127.8, 128.3, 128.3, 129.2, 129.4, 129.9, 132.7, 135.7, 139.4, 139.9, 141.1, 149.7, 150.0; IR (CHCl₃, cm⁻¹) 3354 (br), 3016, 2940, 1509; HRMS Calcd for C₂₆H₂₄O₃: 384.1725. Found: 384.1731.

Ethyl 3-benzyl-6,7-dimethoxy-1-phenyl-2-naphthoate (41) and ethyl 3-benzyl-6,7-dimethoxy-2-phenyl-1-naphthoate (42). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford 81 mg of compound **41** (76 % yield) as a pale yellow solid and 9 mg of compound **42** (8 % yield) as a yellow oil. Naphthalene **41**: mp 129-131 °C; ¹H NMR (CDCl₃) δ 0.77 (t, *J* = 7.2 Hz, 3H), 3.71 (s, 3H), 3.80 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 4.19 (s, 2H), 6.83 (s, 1H), 7.05 (s, 1H), 7.18-7.33 (m, 5H), 7.36-7.47 (m, 6H); NOE: H^a-H^b; ¹³C NMR (CDCl₃) δ 13.7, 39.6, 55.8, 56.1, 60.8, 105.5, 106.3, 126.3, 126.4, 126.9, 127.7, 128.2, 128.5, 129.6, 130.0, 130.3, 131.2, 133.5, 136.9, 138.7, 140.4, 149.7, 150.3, 169.9; IR (CHCl₃, cm⁻¹) 3057, 3024, 2962, 1713, 1507; HRMS Calcd for C₂₈H₂₆O₄: 426.1831. Found: 426.1831. Anal. Calcd: C, 78.85; H, 6.15. Found: C, 78.69; H, 6.18. Naphthalene **42**: ¹H NMR (CDCl₃): δ 0.89 (t, *J* = 7.2 Hz, 3H), 3.90 (s, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 4.01 (q, *J* = 7.2 Hz, 2H), 6.91-6.93 (m, 2H), 7.07 (s, 1H), 7.14-7.21 (m, 6H), 7.30-7.34 (m, 3H), 7.55 (s, 1H); ¹³C NMR (CDCl₃) δ 13.9, 39.8, 56.1, 56.1, 61.2, 103.7, 106.4, 124.4, 126.0, 127.4, 128.0, 128.4, 129.0, 129.2, 130.0, 130.5, 135.4, 137.2, 139.4, 141.0, 150.0, 150.4, 169.7 (one sp² carbon missing due to overlap); IR (CHCl₃, cm⁻¹) 3021, 2937, 1714, 1506; HRMS Calcd for C₂₈H₂₆O₄: 426.1831. Found: 426.1831.

2-Benzyl-9-methyl-3,4-dipropyl-9H-carbazole (44). The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 29 mg (33 % yield) of the indicated compound as a pale yellow solid: mp 113-115 °C; ¹H NMR (CDCl₃) δ 1.02 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.46-1.55 (m, 2H), 1.77-1.84 (m, 2H), 2.70-2.74 (m, 2H), 3.19-

3.23 (m, 2H), 3.73 (s, 3H), 4.24 (s, 2H), 7.02 (s, 1H), 7.16-7.24 (m, 4H), 7.25-7.30 (m, 2H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.41-7.45 (m, 1H), 8.07 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 15.1, 15.1, 23.5, 25.3, 29.1, 31.3, 32.7, 40.7, 108.3, 108.5, 118.9, 120.0, 122.4, 123.0, 124.8, 126.1, 128.5, 128.9, 130.3, 136.8, 137.1, 140.0, 141.4, 141.8; IR (CHCl_3 , cm^{-1}) 3018, 2957, 2930, 1597, 1216; HRMS Calcd for $\text{C}_{26}\text{H}_{29}\text{N}$: 355.2300. Found: 355.2310.

2-Benzyl-3,4-bis[(benzyloxy)methyl]-9-methyl-9H-carbazole (45). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 72 mg (56 % yield) of the indicated compound as a pale yellow solid: mp 112-114 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 3.73 (s, 3H), 4.27 (s, 2H), 4.43 (s, 2H), 4.57 (s, 2H), 4.62 (s, 2H), 5.11 (s, 2H), 7.06 (d, $J = 7.2$ Hz, 2H), 7.16-7.25 (m, 5H), 7.28-7.35 (m, 10H), 7.42-7.46 (m, 1H), 8.06 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 29.2, 40.1, 65.7, 66.4, 72.8, 72.8, 108.4, 110.9, 115.5, 119.3, 121.5, 122.6, 123.3, 125.4, 126.1, 127.0, 127.9, 127.9, 128.5, 128.5, 128.5, 128.9, 132.7, 138.4, 138.5, 138.6, 141.5, 141.5, 141.7 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3015, 1597, 1216; HRMS Calcd for $\text{C}_{36}\text{H}_{33}\text{NO}_2$: 511.2511. Found: 511.2520.

2-Benzyl-3,4-bis(hydroxymethyl)-9-methyl-9H-carbazole (46). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 34 mg (41 % yield) of the indicated compound as a yellow solid: mp 191-193 $^{\circ}\text{C}$; ^1H NMR (CD_3OD) δ 3.31 (s, 1H), 3.31 (s, 1H), 3.75 (s, 3H), 4.35 (s, 2H), 4.84 (s, 2H), 5.30 (s, 2H), 7.12-7.23 (m, 6H), 7.27 (s, 1H), 7.38-7.44 (m, 2H), 8.26 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CD_3OD) δ 29.2, 40.9, 58.5, 59.6, 109.6, 111.7, 120.2, 122.1, 123.7, 124.1, 126.5, 127.1, 129.5, 129.8, 130.1, 136.0, 139.7, 142.6, 142.9, 143.1; IR (CHCl_3 , cm^{-1}) 3397 (br), 3060, 3019, 2924, 1598, 1215; HRMS Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_2$: 331.1572. Found: 331.1579.

Ethyl 2-benzyl-9-methyl-4-phenyl-9*H*-carbazole-3-carboxylate (48) and ethyl 2-benzyl-9-methyl-3-phenyl-9*H*-carbazole-4-carboxylate (49). The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 106 mg (91 % yield) of a 60:40 mixture of regioisomers **48/49** as determined by ^1H NMR spectroscopic analysis of the yellow oil.

Carbazole **48**: ^1H NMR (CDCl_3) δ 0.80 (t, $J = 7.2$ Hz, 3H), 3.79 (s, 3H), 3.84 (q, $J = 7.2$ Hz, 2H), 4.30 (s, 2H), 6.91-6.95 (m, 2H), 7.15 (s, 1H), 7.18-7.23 (m, 1H), 7.27-7.40 (m, 6H), 7.46-7.50 (m, 5H); ^{13}C NMR (CDCl_3) δ 13.7, 29.4, 40.3, 60.8, 108.5, 109.0, 119.3, 119.5, 122.3, 122.8, 125.8, 126.1, 126.3, 127.9, 128.4, 128.6, 129.5, 129.6, 135.9, 136.6, 139.4, 140.9, 141.5, 141.9, 170.2; IR (CHCl_3 , cm^{-1}) 3062, 2981, 1709, 1593; HRMS Calcd for $\text{C}_{29}\text{H}_{25}\text{O}_2\text{N}$: 419.1885. Found: 419.1892.

Carbazole **49**: ^1H NMR (CDCl_3) δ 0.94 (t, $J = 7.2$ Hz, 3H), 3.81 (s, 3H), 4.01 (s, 2H), 4.11 (dq $J = 2.0, 7.2$ Hz, 2H), 6.94-6.96 (m, 2H), 7.12-7.25 (m, 6H), 7.29-7.34 (m, 4H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.46-7.50 (m, 1H), 7.97 (d, $J = 8.0$ Hz, 1H). Additional ^{13}C NMR (CDCl_3) for the mixture: δ 13.8, 13.9, 29.4, 29.4, 40.2, 40.3, 60.8, 61.3, 108.5, 108.7, 109.0, 111.1, 117.6, 119.2, 119.5, 121.1, 121.9, 122.3, 122.8, 125.8, 126.0, 126.1, 126.3, 127.2, 127.8, 127.9, 127.9, 128.4, 128.4, 128.5, 129.1, 129.5, 130.6, 131.4, 135.8, 136.6, 137.3, 139.3, 139.4, 140.7, 140.9, 141.4, 141.5, 141.8, 141.9, 169.8, 170.2 (three sp^2 carbons missing due to overlap).

Ethyl 2-benzyl-4,9-dimethyl-9*H*-carbazole-3-carboxylate (50) and ethyl 2-benzyl-3,9-dimethyl-9*H*-carbazole-4-carboxylate (51). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 69 mg (78 % yield) of a 82:18 mixture of regioisomers **50/51** as determined by ^1H NMR spectroscopic analysis of the yellow oil.

Carbazole **50**: ^1H NMR (CDCl_3) δ 1.26 (t, $J = 7.2$ Hz, 3H), 2.85 (s, 3H), 3.77 (s, 3H), 4.23 (s, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 7.03 (s, 1H), 7.20-7.30 (m, 6H), 7.39 (d, $J = 8.4$ Hz, 1H),

7.46-7.49 (m, 1H), 8.18 (d, $J = 7.6$ Hz, 1H); NOE: H^a-H^b ; ^{13}C NMR (CDCl_3) δ 14.3, 18.3, 29.3, 40.5, 61.2, 107.9, 108.6, 119.5, 120.0, 122.8, 123.6, 125.5, 126.3, 126.4, 128.5, 129.3, 131.3, 136.1, 141.0, 141.4, 141.7, 171.0; IR (CHCl_3 , cm^{-1}) 3057, 3027, 2983, 2901, 1710, 1596; HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{O}_2\text{N}$: 357.1729. Found: 357.1734. Carbazole **51**: ^1H NMR (CDCl_3) δ 1.45 (t, $J = 7.2$ Hz, 3H), 2.33 (s, 3H), 3.76 (s, 3H), 4.19 (s, 2H), 4.59 (q, $J = 7.2$ Hz, 2H), 7.13-7.30 (m, 7H), 7.34-7.39 (m, 1H), 7.42-7.49 (m, 1H), 7.89 (dd, $J = 1.2, 10.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.6, 16.4, 29.3, 40.8, 61.7, 108.7, 111.6, 117.8, 119.2, 121.1, 121.4, 124.3, 126.0, 126.3, 127.8, 128.7, 128.9, 137.5, 139.8, 140.4, 141.6.

Ethyl 7-benzyl-9-phenylpyrido[1,2-*a*]indole-8-carboxylate (53). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 34 mg (41 % yield) of the indicated compound as a yellow oil: ^1H NMR (CD_3OD) δ 0.92 (t, $J = 7.2$ Hz, 3H), 4.01 (q, $J = 7.2$ Hz, 2H), 5.28 (d, $J = 2.0$ Hz, 2H), 6.90 (s, 1H), 7.04-7.08 (m, 1H), 7.20-7.28 (m, 3H), 7.33-7.52 (m, 11 H); ^{13}C NMR (CD_3OD) δ 13.8, 43.5, 61.4, 104.2, 109.1, 120.6, 121.7, 123.6, 128.0, 128.2, 128.4, 128.5, 128.6, 128.8, 129.2, 129.3, 129.6, 132.5, 134.4, 136.3, 136.9, 138.5, 168.3 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3056, 3026, 2979, 2933, 1717, 1134; HRMS Calcd for $\text{C}_{28}\text{H}_{23}\text{NO}_2$: 405.1729. Found: 405.1735.

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CHAPTER 4. SYNTHESIS OF FUSED POLYCYCLES BY 1,4-PALLADIUM MIGRATION CHEMISTRY

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Abstract

Novel palladium migration/arylation methodology for the synthesis of complex fused polycycles has been developed, in which one or more sequential Pd-catalyzed intramolecular migration processes involving C-H activation are employed. The chemistry works best with electron-rich aromatics, which is in agreement with the idea that these palladium-catalyzed C-H activation reactions parallel electrophilic aromatic substitution.

Introduction

The ability of palladium to activate C-H bonds has been used extensively in organic synthesis.¹ In recent years, palladium-catalyzed C-H activation has received considerable attention due to the wide variety of reactions this metal will catalyze. For instance, catalytic amounts of Pd salts have been used to effect the addition of C-H bonds of electron-rich arenes to alkenes and alkynes and effect carbonylation.² We have previously reported the synthesis of 9-benzylidene-9*H*-fluorenes by Pd-catalyzed intramolecular C-H activation involving the rearrangement of organopalladium intermediates derived from aryl halides and internal alkynes.³ Similarly, intramolecular C-H activation in organopalladium intermediates

derived from *o*-halobiaryls leads to a 1,4-palladium migration (Scheme 1).⁴ We have already shown that such intermediates can be trapped by Heck, Suzuki and alkyne annulation reactions.^{4,5} We have recently reported that this aryl-to-aryl palladium migration process, followed by arylation, provides a novel, new route to a wide variety of carbo- and heterocycles.⁶ Herein, we now wish to report further details regarding this aryl-aryl migration and also vinylic-aryl migration chemistry, followed by intramolecular arylation.

Scheme 1

Our strategy involves palladium C-H activation and 1,4-palladium migration within a biaryl, which generates key arylpalladium intermediates, which subsequently undergo C-C bond formation by intramolecular arylation producing fused polycycles (Scheme 2). This process represents a very powerful new tool for the preparation of complex molecules, which might be difficult to prepare by any other present methodology.

Scheme 2

Results and Discussion

In order to obtain an optimum set of reaction conditions for migration, we have reinvestigated the palladium-catalyzed transformation of 1-iodo-1,2,2-triphenylethene (**1**) to 9-benzylidene-9*H*-fluorene (**2**) as our model system³ (Table 1). While this system may not be the most obvious for a study of aryl to aryl Pd migrations, we had previously accumulated substantial data on this system. To begin with, we carried out this reaction using our previously reported conditions³ and obtained a 73 % yield of the desired compound **2**, along with a 15 % yield of triphenylethene (**3**) (entry 1). The first variable to be examined was the ligand on palladium. We examined phosphines other than PPh_3 . Entries 2 and 3 indicate that $\text{P}(o\text{-tol})_3$ and $\text{CH}_2(\text{PPh}_2)_2$ (dppm) are superior to PPh_3 in affording higher yields of the fluorene **2**. However, the reactions with all of these phosphine ligands required 3 d to reach completion. In order to shorten this relatively lengthy reaction time, we eliminated $n\text{-Bu}_4\text{NCl}$ (TBAC) and found that the reaction was complete after only 1 d (entry 4). Unfortunately, this led to a much lower yield of the desired compound **2** (47 %), and the

yield of reduced product **3** increased to 47 %. In order to investigate whether DMF was the hydride source for the reduction of **1** to **3**, we carried out this reaction using other solvents,

Table 1. Palladium-catalyzed cyclization of 1-iodo-1,2,2-triphenylethene (**1**) to 9-benzylidene-fluorene (**2**).^a

entry	ligand (mol %)	base	chloride source	solvent	time (d)	% yield 2	% yield 3
1	PPh ₃ (10)	NaOAc	TBAC ^b	DMF	3	73	15
2	P(<i>o</i> -tol) ₃ (10)	NaOAc	TBAC	DMF	3	75	20
3	dppm ^c (5)	NaOAc	TBAC	DMF	3	79	15
4	dppm (5)	NaOAc	-	DMF	1	47	47
5	dppm (5)	NaOAc	-	DMA	1.5	52	48
6	dppm (5)	NaOAc	-	NMP	1	46	46
7	dppm (5)	NaOAc	-	DMSO	1	-	-
8	dppm (5)	pyridine	-	DMF	1	-	-
9	dppm (5)	<i>i</i> -Pr ₂ NEt	-	DMF	1	-	-
10	dppm (5)	Na ₂ CO ₃	-	DMF	1	70	26
11	dppm (5)	NaHCO ₃	-	DMF	1	65	23
12	dppm (5)	Na ₂ CO ₃ ^d	-	DMF	1	-	47
13	dppm (5)	Cs ₂ CO ₃	-	DMF	1	74	22
14	dppm (5)	CsOAc	-	DMF	2	90	4
15	dppm (5)	CsO ₂ CCMe ₃	-	DMF	1	96	4
16	dppm (5)	CsO ₂ CCMe ₃	-	DMA	1	59	17 ^e
17	dppe ^f (5)	CsO ₂ CCMe ₃	-	DMF	1	90	10
18	dppm (5)	<i>n</i> -Bu ₄ NOAc	-	DMF	1	<10	-

^aThe reaction was run using 0.25 mmol of 1-iodo-1,2,2-triphenylethene (**1**), 5 mol % of Pd(OAc)₂ and 4 mL of solvent at 100 °C. ^bTBAC = *n*-Bu₄NCl. ^cDppm = 1,1-bis(diphenylphosphino)methane. ^dOne equiv of NaI was added. ^eTwenty four percent of **1** was recovered. ^fDppe = 1,2-bis(diphenylphosphino)ethane.

such as DMA, NMP, and DMSO (entries 5-7). DMSO gave none of the desired fluorene **2** or any reduction product **3**. The amount of reduction was more or less the same in the other

solvents. Thus, we continued our investigation using DMF as the reaction solvent.

We also examined the effect of various bases on the yields of **2** and **3**, including organic bases, such as pyridine and diisopropylethylamine (entries 8 and 9). These bases were ineffective in promoting the reaction and TLC analysis of the reaction mixtures indicated only the presence of the starting vinylic halide **1**. The use of Na_2CO_3 as the base provided **2** in a 70 % yield, but we also obtained a 26 % yield of reduced product **3** (entry 10). The base NaHCO_3 provided a 65 % yield of **2** and a 23 % yield of **3** (entry 11). We believe that the solubility of these bases in the reaction mixture may be playing a critical role in determining the outcome. Thus, once again we used Na_2CO_3 as the base, but this time we added 1 equiv of NaI , which is completely soluble in DMF, as an additive to promote a sodium common ion effect intended to make Na_2CO_3 less soluble in the reaction mixture. Indeed, this experiment revealed that under such reaction conditions only the reduced product **3** was produced in a 47 % yield (entry 12). None of the desired product **2** was observed (compare entries 10 and 12). Although there may be a number of other effects going on under these reaction conditions, it seemed logical to assume that the yield of the reaction would improve by using more soluble inorganic bases. Thus, the use of Cs_2CO_3 , which presumably has better solubility than other alkali carbonates in DMF,⁷ provided a slightly higher 74 % yield of compound **2**, along with a 22 % yield of the reduced product **3**. Similarly, the use of very soluble CsOAc as the base provided a 90 % yield of the desired product **2**, along with 4 % of the reduced product **3** after 2 d (entry 14). We subsequently found that cesium pivalate ($\text{CsO}_2\text{CCMe}_3$), unlike any other previously studied base, was completely soluble in DMF at 100 °C. In this case, we obtained an impressive 96 % yield of the desired compound **2**, along with only a small amount of the reduced product **3** (4 %) after only 1 d (entry 15). Clearly, cesium pivalate is far superior as

a base in this reaction, and its high solubility in DMF seems to explain this phenomena. To illustrate, we carried out the reaction of **1** under conditions identical to those described in entry 15, but we used DMA instead of DMF as the solvent, in which cesium pivalate is not completely soluble. Under these conditions, we obtained a relatively low 59 % yield of the desired compound **2**, along with a 17 % yield of the reduced product **3** (entry 16). Twenty four percent of the starting vinylic iodide **1** was also obtained. Finally, to test whether dppm was indeed critical to this reaction, we carried out the transformation using another chelating phosphine ligand, namely 1,2-*bis*-(diphenylphosphino)ethane (dppe), and we obtained a 90 % yield of **2**, along with a 10 % yield of the reduced product **3** (entry 17). As a result of this optimization work, our optimal set of reaction conditions for this transformation are those listed in entry 15 of Table 1. Notice that the newly developed conditions catalyze the transformation of **1** to **2** in high yield and much shorter reaction time than our earlier reported procedure (entry 1).³ The variable most critical to the success of this process appears to be the highly soluble cesium pivalate base. Surprisingly, the use of *n*-Bu₄NOAc as the base, which is also completely soluble in DMF under reaction conditions identical to those described in entry 15, failed to promote this reaction, affording only trace amounts of the desired product **2** after 1 d (entry 18). Thus, not only the solubility, but also the exact nature of the base, appears critical in determining the reaction yield. It is interesting to note that the work of Buchwald, Hartwig and Fu has demonstrated that steric congestion imposed on palladium by bulky, electron-rich ligands facilitates both the oxidative addition and reductive elimination steps involving palladium, and gives rise to more effective catalyst systems.⁸ However, nothing is apparently known about the effects of using a sterically hindered base,

such as pivalate, in palladium chemistry, and whether or not it may give similar results to those obtained using bulky ligands.

With an apparently “optimal” set of reaction conditions for palladium migration chemistry at our disposal, we proceeded to study the sequential Pd-catalyzed migration/arylation of various 3'-substituted 2-iodobiphenyls (Table 2). We began by allowing 3'-benzyl-2-iodobiphenyl (**4**) to react under our standard reaction conditions at 100 °C, but after 2 d this substrate failed to react. However, by simply increasing the reaction temperature to 110 °C, we were able to obtain the desired compound **5** in a 40 % yield (entry 1). The disappointingly low yield obtained with this substrate might be explained by the poor reactivity of the benzyl moiety as an intramolecular trap. To test this idea, we carried out the reaction with the more electron-rich 2-iodo-3'-phenoxybiphenyl (**6**) and obtained the desired 4-phenyldibenzofuran (**7**) in an impressive 89 % yield (entry 2). Clearly, these results indicate that the electron-rich oxygen-substituted phenyl ring is superior as an arylating agent. Our finding that electron-rich arenes are superior to electron-neutral arene traps is consistent with literature reports indicating that the ease of C-H activation by palladium parallels electrophilic aromatic substitution.⁹ Similarly, we were able to selectively obtain 3-chloro-5-phenyldibenzofuran (**9**) in an 82 % yield from 3-(*p*-chlorophenoxy)-2-iodobiphenyl (**8**) under our standard conditions, while leaving the chloro functionality intact (entry 3).

Table 2. Sequential 1,4-Palladium Migration, Followed by Intramolecular Arylation^a

entry	substrate	product(s)	time (d)	yield ^b (%)
1			3 ^c	40
2			1 ^c	89
3			1 ^c	82
4			1	70
5			1	71
6		+	2 ^d	75 (60 : 40)
7			1 ^c	81
8			3 ^c	70
9			2 ^c	78 (18)
10			2 ^c	71 (22)
11			2 ^c	50 (20)

Table 2 continued

12		26		27	2°	56 (37)
13		28		29	2°	0
14		30		31	2°	65
15		32		33	2°	0 (80)
16		34		35	2.5°	54
17		36		37	2°	0

Table 2 continued

18		38		39	2 ^c	0
19		40		41	1	92 ^c
20		42		43	0.5	78 + 12
21		44		45	1	33
22		46		47	0.5	65

Table 2 continued

23		49		50	2 ^c	80
24		51		52	2	0
25		53		54	5 ^c	0 (12)
26		55		4	1	88 (^{<} 5)
27		56		57	14	0 (62) ^e

^aThe reaction was carried out under the following standard conditions employing 0.25 mmol of the aryl halide, 5 mol % Pd(OAc)₂, 5 mol % dppm, and 2 equivs of CsO₂CCMe₃ in DMF (4 mL) at 100 °C unless otherwise noted. ^bThe yield in parentheses corresponds to the GC yield of product in which the C-I bond has been reduced to a C-H. ^cThe reaction temperature was increased to 110 °C. ^dThe reaction temperature was increased to 120 °C. ^eThe yield was determined by ¹H NMR spectroscopy.

Motivated by the ease of preparation of the following starting materials and by the knowledge that electron-rich arenes are apparently superior as intramolecular traps for our arylpalladium intermediates, we synthesized the indole derivatives **10** and **12**. To our great satisfaction, compound **10** smoothly underwent the desired reaction, producing the relatively strained isoindoloindole **11** in a 70 % yield (entry 4). Surprisingly, compound **12** produced the strained and sterically congested 2-methylisoindoloindole **13** in a comparable 71 % yield (entry 5). We next examined the possibility of using an intramolecular arylation to form six-membered rings. Unfortunately, 3-(2-iodophenyl)benzyl phenyl ether (**14**) failed to react under our standard reaction conditions. Even at 110 °C, the reaction was sluggish, so the temperature was increased to 120 °C, in which case the reaction was complete after 2 d. Unfortunately, a 60:40 inseparable mixture of the desired compound **15** and the reduced product **16** was obtained in a 75 % overall yield (entry 6). Clearly, the formation of a six-membered ring is not as favorable as five-membered ring formation (compare entries 2 and 6). This might be due to the difficulty in forming a seven-membered ring palladacycle (Figure 1).

Figure 1. Unfavorable seven-membered ring palladacycle intermediates

We proceeded to investigate the sequential migration/arylation reaction of more complex polyaromatic compounds. In theory, 2-iodo-1-phenylnaphthalene (**17**) should afford fluoranthene (**18**) using our methodology. Mechanistically, the palladium must first undergo a 1,4-palladium migration from the 2-position of the naphthalene to the *o*-position of

the phenyl substituent, followed by arylation at the 8-position of the naphthalene (Scheme 3).

Although the reaction did not proceed at 100 °C, at 110 °C compound **17** produced the

Scheme 3

desired compound **18** in an 81 % yield (entry 7). Similarly, 2-bromo-1-phenylnaphthalene (**19**) produced the desired fluorene (**18**) in a 70 % yield, indicating that this aryl bromide also undergoes the desired transformation, but in a somewhat lower yield and a longer reaction time.

Another interesting example of this migration/arylation chemistry involves the rearrangement of easily prepared 9-iodo-10-arylphenanthrenes¹⁰ to benz[*e*]acephenanthrylenes (entries 9-12). In this case, the palladium migrates from the 9 position of the phenanthrene to the *ortho* position of the aryl substituent, followed by cyclization onto the 1 position of the phenanthrene. Indeed, the reaction of 9-iodo-10-phenylphenanthrene (**20**) under our standard reaction conditions at 110 °C produced the

desired benz[*e*]acephenanthrylene (**21**) in a 78 % yield (entry 9). We proceeded to investigate electronic effects in this phenanthrene reaction by looking at different substituents on the phenyl moiety. As expected, the use of an electron-donating methoxy group in compound **22** gave a good yield (71 %) of the corresponding benz[*e*]acephenanthrylene **23**, although the yield was slightly lower than that of the parent system (entry 10). As expected, the introduction of an electron-withdrawing CO₂Et group in the *para* position of the phenyl substituent was detrimental to the reaction, producing compound **25** in only a 50 % yield. All of these phenanthrene reactions gave approximately a 20 % yield of the corresponding reduction product.

We have also studied the regioselectivity of the migration by using an *m*-tolyl moiety in the 10-position of the 9-iodophenanthrene (entry 12). Compound **26** has two available positions for palladium migration, the more sterically-congested neighboring 2 position or the remote 6 position of the phenyl ring. The palladium-catalyzed cyclization of compound **26** generated compound **27** exclusively in a 56 % yield, alongside a significant amount of reduction product (37 %). This result indicates that palladium migration occurs exclusively onto the less sterically-congested 6 position of the phenyl moiety and that the presence of a methyl group apparently completely inhibited migration to the more hindered 2 position or at least cyclization of that intermediate to the corresponding polycyclic product.

We next tried to prepare the more strained fused thiophene **29** from phenanthrene **28**. Unfortunately, this reaction led to a very complex mixture, which produced none of the desired compound **29** as far as we could tell. Besides the unfavorable ring strain associated with the final product **29**, intramolecular sulfur chelation of the intermediate 10-(thiophen-2-

yl)phenanthren-9-ylpalladium iodide might be inhibiting the palladium migration step (Figure 2).

Figure 2. Intramolecular palladium chelation by sulfur.

The relatively electron-rich benzo[*e*]phenanthrene **30** also underwent the migration/arylation reaction, producing the highly conjugated hexacyclic compound **31** in a 65 % yield (entry 14). Unfortunately, compound **32** failed to generate the desired hexacycle **33** under our reaction conditions at 110 °C (entry 15). Only reduction product was isolated in an 80 % yield. This example once again indicates that intramolecular cyclization to form a six membered ring is apparently rather unfavorable.

Having studied the palladium-catalyzed transformation of a variety of polycyclic aromatic halides, we switched our attention to heterocyclic aromatic compounds. To begin with, we carried out the reaction of 3-iodo-4-phenylquinoline (**34**) under our standard reaction conditions at 100 °C, but after 2 d this substrate failed to react. Fortunately, by simply increasing the reaction temperature to 110 °C, we obtained the desired indeno[1,2,3-*de*]quinoline (**35**) in a 54 % yield. Again the modest yield obtained with this electron-deficient substrate is consistent with our previous observations that electron-deficient substrates do not perform as well as more electron-rich substrates (compare entries 7 and 16). We also allowed 2-iodo-1-methyl-3-phenylindole (**36**) to react under our standard reaction

conditions at 110 °C, but failed to obtain the desired tricyclic compound **37** (entry 17). A similar negative result was obtained with iodoindole **38** (entry 18). The poor results obtained with substrates **36** and **38** can be explained in terms of the unfavorable ring strain of the corresponding products **37** and **39**. In addition, we have previously established, using Heck trapping experiments, that palladium prefers to reside on the indole moiety in such substrates.^{4,5}

To confirm our suspicion that the palladium prefers to migrate to a more electron-rich position, because of the relatively easy activation of an electron-rich C-H bond,^{4,5,9} compound **40** was allowed to react under our migration conditions and indole **41** was produced in a 92 % yield in 1 d at 100 °C (entry 19). From the results of entries 1 and 19, it appears that the high efficiency of palladium migration to a relatively electron-rich ring allows the sequential migration/arylation to proceed smoothly at a lower temperature and in a shorter reaction time, although the benzyl group is not a particularly good arylating agent. When a methoxy group was introduced onto the benzyl group, this migration/arylation reaction afforded a mixture of indoles **43** and **44** in 78 % and 12 % yields, respectively (entry 20). This result is consistent with our previous observation (see entry 12) that the palladium intermediate is more likely to form the final carbon-carbon bond at the less hindered position of the aryl terminus. When compound **45**, which has an electron-deficient aryl terminus, was allowed to react under the standard migration conditions, a 33 % yield of product **46** was isolated (entry 21). This is consistent with electron-deficient termini giving lower yields.

We have also examined the possibility of trapping palladium migration species by alkynes. Thus, we have carried out the palladium-catalyzed sequential migration/alkyne insertion/arylation of aryl halide **47** in the hope that the arylpalladium intermediate generated

by a 1,4-Pd shift via through-space C-H activation could be trapped by alkyne insertion-annulation chemistry described earlier by us (Scheme 4).¹¹ The reaction was carried out under our standard migration conditions and carbazole **48** was isolated in a 65 % yield (entry 22). It is important to note that this reaction was complete in 0.5 d at 100 °C, consistent with the particularly facile migration of Pd to the electron-rich indole ring system. Although we cannot rule out the possibility that this reaction is proceeding by direct endocyclic addition of the initial arylpalladium species to the alkyne triple bond and subsequent ring closure onto the indole to give product **48**, this seems unlikely since exocyclic addition is more common. This successful alkyne insertion chemistry suggests that there is the exciting possibility of trapping aryl- and other organopalladium intermediates generated by a 1,4-Pd shift by many other synthetically useful palladium methodologies, such as amination and annulation. We are presently examining such possibilities.

Scheme 4

While our efforts have focused on synthesizing polycyclic compounds in which the key 1,4-palladium shift occurs from an aryl to another aryl position, we wanted to establish that our methodology could also make use of a vinylic to aryl palladium migration to generate the key intermediate for the intramolecular arylation step. We have already shown one example of such a transformation in converting compound **1** to **2** (Table 1). Another illustration of this process involves the use of 9-iodo-10-phenyldibenz[*b,f*]oxepine (**49**). The reaction of this relatively electron-rich substrate produced the desired pentacyclic compound **50** in an 80 % yield (entry 23). On the other hand, treating the electron-deficient 3-iodo-4-phenylisocoumarin (**51**) under our standard reaction conditions gave a complex mixture, and we failed to isolate any of the desired tricyclic compound **52** (entry 24). This disappointing result was not unexpected, since our previous experience with compound **51** has indicated that palladium easily catalyzes its decomposition. Our last attempt to generate polycycles from vinylic iodides involved the use of isoquinolone **53** (entry 25). This substrate suffers the disadvantage that the intramolecular arylation step requires the formation of a six-membered ring. As expected, the reaction of substrate **53** under our standard reaction conditions at 110 °C failed to produce the desired pentacyclic product **54**. After 5 d of reaction, we were only able to isolate the reduction product *N*-phenyl-3-phenylisoquinolone¹² in a 12 % yield.

A mechanistically interesting question is whether the arylpalladium intermediate can migrate more than once and still effect synthetically useful chemistry. To examine this possibility, 2-iodo-5-phenoxybiphenyl (**55**) was allowed to react under our migration conditions and an 88 % yield of double migration product **4** was isolated (entry 26 and

Scheme 5). Mechanistically, the palladium first inserts into the aryl iodide bond to form intermediate **A**, which migrates to the phenyl unit by through-space C-H activation. The metal moiety in the first migration intermediate **B** can return to the original aromatic ring in either the position from which it originally migrated (**A**) or migrate to the position *ortho* to the phenoxy group (**C**), where it can be trapped by arylation. Note that the yield for this double migration chemistry is very similar to that from the single migration chemistry (entry 2) and the success of this double palladium migration indicates that multiple migration processes are entirely feasible.

Scheme 5

One attempt to extend this chemistry to a triple migration process has been unsuccessful. The reaction of idonaphthalene **56** under our standard migration conditions afforded none of the desired triple migration product **57**, producing instead a 62 % yield of the reduction product (entry 27). The reason for this failure to afford compound **57** is

indicated in Scheme 6. While we would anticipate that intermediates **D** and **E** should be easily formed, we believe that the problem lies in getting the relatively unhindered species **E** to migrate the palladium to the more hindered position present in **F**. Instead the palladium presumably migrates back to the less hindered position present in intermediate **D**. This is consistent with our previous observation in entries 12 and 20 that palladium is more likely to migrate to or form a new C-C bond at a less hindered position. Therefore, the palladium intermediates only equilibrate between **D** and **E**, and eventually produce the reduced 1,3-diphenylnaphthalene.

Scheme 6

Conclusions

In conclusion, we have developed novel methodology for the synthesis of complex fused polycycles employing two or more sequential Pd-catalyzed intramolecular processes involving C-H activation. This methodology exploits relatively facile aryl to aryl and vinylic to aryl palladium migrations, followed by intramolecular arylation to prepare a wide variety of carbocycles and heterocycles. This chemistry works best with electron-rich aromatics, which is in agreement with the idea that these palladium-catalyzed C-H activation reactions parallel electrophilic aromatic substitution. The success of our double palladium migration for the conversion of biphenyl **55** to dibenzofuran **4** indicates that multiple migration processes can be employed to produce novel new routes to a variety of polycycles. Finally, our demonstration that this chemistry is applicable to alkyne insertion processes as well opens up still further unique routes to polycyclic products.

Experimental Section

General procedures. All ^1H 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 (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and a basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. Compounds **19**,¹³ **20**,¹³ **36**,¹³ and **49**¹³ were prepared according to literature procedures.

3'-Benzyl-2-iodobiphenyl (4). This biphenyl was prepared from 3'-bromomethyl-2-iodobiphenyl (**58**)¹³ by following a procedure from the literature.¹⁴ To a suspension of AgClO_4 (0.28 g, 1.4 mmol) in benzene (4.0 mL) was added compound **58** (0.261 g, 0.7 mmol) in benzene (4.0 mL) and the resulting mixture was stirred overnight at room temperature in the dark. The reaction mixture was diluted with diethyl ether (50 mL), filtered and washed with brine (25 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 50:1 hexane/EtOAc to afford 0.187 g (72 %) of the indicated compound **4** as a colorless oil: ^1H NMR (CDCl_3) δ 4.03 (s, 3H), 6.97–7.01 (m, 1H), 7.15–7.34 (m, 11H), 7.92 (dd, $J = 1.0, 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 42.0, 98.8, 126.2, 127.1, 128.2, 128.2, 128.3, 128.6, 128.8, 129.1, 130.1, 130.2, 139.6, 140.8, 141.0, 144.3, 146.6; IR (CH_2Cl_2) 3056, 3025, 2917, 1601, 1583, 1494, 1461 cm^{-1} ; HRMS m/z 370.0224 (calcd for $\text{C}_{19}\text{H}_{15}\text{I}$, 370.0218).

2-Iodo-3'-methoxybiphenyl (59). Compound **59** was prepared by a procedure reported by Hart *et al.*¹⁵ A solution of 2-bromoiodobenzene (1.415 g, 5.0 mmol) in THF (10

mL) was added slowly (90 min) to a solution of 3-methoxyphenylmagnesium bromide [prepared from 3-bromoanisole (1.87 g, 10 mmol) and Mg (0.246 g, 10 mmol) in THF (30 mL)], and the mixture was stirred under Ar for an additional 14 h at room temperature. The reaction was quenched by adding I₂ (3.8 g, 15 mmol), and the mixture was stirred for an additional 30 min at room temperature. The excess I₂ was destroyed by adding 10 % aq NaHSO₃ (35 mL) and the organic layer was separated and washed with brine (20 mL). Finally, the organic layer was dried (MgSO₄), filtered, and the solvent removed under reduced pressure. The residue was chromatographed using 30:1 hexane/EtOAc to afford 0.620 g (40 %) of the desired compound **59** as a clear oil: ¹H NMR (CDCl₃) δ 3.84 (s, 3H), 6.88-6.95 (m, 3H), 7.01-7.05 (m, 1H), 7.29-7.38 (m, 3H), 7.95 (dd, *J* = 1.2, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 55.4, 98.5, 113.4, 115.0, 121.8, 128.1, 128.9, 129.1, 130.1, 139.6, 145.5, 146.5, 159.1; HRMS *m/z* 309.9859 (calcd for C₁₃H₁₁IO, 309.9855).

2-Iodo-3'-phenoxybiphenyl (6). This biphenyl was prepared in two steps from 2-iodo-3-methoxybiphenyl (**59**). To a solution of compound **59** (0.97 g, 3.14 mmol) in CH₂Cl₂ (20 mL) at -78 °C was added 1.0 M BBr₃ in CH₂Cl₂ (4.1 mL, 4.1 mmol). The resulting solution was allowed to warm to room temperature and stirred for 2 h. The mixture was worked up with ice (15 g) and extracted with diethyl ether (75 mL). The organic layer was dried (Na₂SO₄), filtered and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 3:1 hexane/EtOAc to afford 0.91 g (98 %) of 3-(2-iodophenyl)phenol (**60**) as a clear oil: ¹H NMR (CDCl₃) δ 5.04 (br s, 1H), 6.80-6.81 (m, 1H), 6.85-6.90 (m, 2H), 7.00-7.05 (m, 1H), 7.25-7.31 (m, 2H), 7.37 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.94 (dd, *J* = 0.8, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 98.4, 114.7, 116.4, 122.0, 128.1, 128.9, 129.3, 130.0, 139.5, 145.8, 146.2, 155.0. 3-(2-Iodophenyl)phenol (**60**) was phenylated

by a literature procedure.¹⁶ A suspension of 3-(2-iodophenyl)phenol (0.222 g, 0.75 mmol), phenylboronic acid (0.183 g, 1.5 mmol), Cu(OAc)₂ (0.163 g, 0.90 mmol), Et₃N (0.38 g, 3.75 mmol), and 5 Angstrom molecular sieves (0.2 g) in CH₂Cl₂ (6.0 mL) was stirred under O₂ (1 atm) for 2 d at room temperature. The reaction mixture was diluted with diethyl ether (50 mL), filtered, and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 15:1 hexane/EtOAc to afford 0.129 g (46 %) of the indicated compound **6** as a clear oil: ¹H NMR (CDCl₃) δ 7.00-7.12 (m, 7H), 7.25-7.40 (m, 5H), 7.92 (dd, *J* = 1.2, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 98.4, 118.2, 119.1, 119.8, 123.4, 124.2, 128.2, 129.0, 129.4, 129.8, 130.0, 139.6, 145.9, 146.0, 156.8, 157.1; IR (CH₂Cl₂) 3058, 1578, 1488, 1460, 1222, cm⁻¹; HRMS *m/z* 372.0020 (calcd for C₁₈H₁₃IO, 372.0011).

2-Iodo-3'-(*p*-chlorophenoxy)biphenyl (8). This biphenyl was prepared by a procedure similar to that used for compound **6**. A suspension of 3-(2-iodophenyl)phenol (**60**) (0.222 g, 0.75 mmol), *p*-chlorophenylboronic acid (0.235 g, 1.5 mmol), Cu(OAc)₂ (0.163 g, 0.90 mmol), Et₃N (0.38 g, 3.75 mmol), and 5 Angstrom molecular sieves (0.2 g) in CH₂Cl₂ (6.0 mL) was stirred under O₂ (1 atm) for 2 d at room temperature. The reaction mixture was diluted with diethyl ether (50 mL), filtered, and the solvent evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column using 30:1 hexanes/ethyl acetate to afford 79.5 mg (26 %) of the indicated compound **8** as a clear oil:

^1H NMR (CDCl_3) δ 6.96-7.09 (m, 6H), 7.27-7.41 (m, 5H), 7.93 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 98.4, 118.2, 119.9, 120.3, 124.6, 128.2, 128.4, 129.1, 129.6, 129.8, 130.0, 139.6, 145.8, 146.0, 155.8, 156.4; IR (CH_2Cl_2) 3057, 1576, 1484, 1460, 1228 cm^{-1} ; HRMS m/z 405.9632 (calcd for $\text{C}_{18}\text{H}_{12}\text{IClO}$, 405.9621).

1-[3-(2-Iodophenyl)benzyl]indole (10). To a suspension of NaH (0.031 g, 1.30 mmol) in DMF (2 mL) at 0 $^{\circ}\text{C}$ was added 1H-indole (0.117 g, 1.0 mmol) in DMF (3 mL) and the mixture was stirred at room temperature for 30 min. At this point 3'-bromomethyl-2-iodobiphenyl (**58**)¹³ (0.347 g, 0.93 mmol) in DMF (3 mL) was added and the reaction mixture was stirred at 50 $^{\circ}\text{C}$ for 3 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with brine (60 mL). The aqueous layer was reextracted with diethyl ether (15 mL) and the organic layers were combined, dried (MgSO_4), and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 12:1 hexanes/ethyl acetate to afford 0.335 g (88 %) of the desired compound **10** as a clear oil: ^1H NMR (CDCl_3) δ 5.34 (s, 2H), 6.54 (d, $J = 2.8$ Hz, 1H), 6.98 (td, $J = 7.6, 1.6$ Hz, 1H), 7.09-7.23 (m, 7H), 7.30-7.34 (m, 3H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.90 (dd, $J = 8.0, 0.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 50.1, 98.6, 101.9, 109.9, 119.6, 121.1, 121.8, 126.2, 128.0, 128.2, 128.4, 128.6, 128.6, 128.9, 129.0, 130.1, 136.4, 137.4, 139.6, 144.6, 146.1; IR (CH_2Cl_2) 3052, 2972, 2922, 2863, 1462, 1437, 1316 cm^{-1} ; HRMS m/z 409.0334 (calcd for $\text{C}_{21}\text{H}_{16}\text{IN}$, 409.0328).

1-[3-(2-Iodophenyl)benzyl]-3-methylindole (12). To a suspension of NaH (0.031 g, 1.30 mmol) in DMF (2 mL) at 0 °C was added 3-methyl-1H-indole (0.131 g, 1.0 mmol) in DMF (3 mL) and the mixture was stirred at room temperature for 30 min. At this point 3'-bromomethyl-2-iodobiphenyl (**58**)¹ (0.347 g, 0.93 mmol) in DMF (3 mL) was added and the reaction mixture was stirred at 50 °C for 3 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with brine (60 mL). The aqueous layer was reextracted with diethyl ether (15 mL) and the organic layers were combined, dried (MgSO₄), and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 12:1 hexanes/ethyl acetate to afford 0.362 g (92 %) of the desired compound **12** as a clear oil: ¹H NMR (CDCl₃) δ 2.33 (d, J = 0.8 Hz, 3H), 5.29 (s, 2H), 6.92-6.92 (m, 1H), 6.97-6.99 (m, 1H), 7.10-7.24 (m, 6H), 7.27-7.34 (m, 3H), 7.56-7.58 (m, 1H), 7.90-7.92 (m, 1H); ¹³C NMR (CDCl₃) δ 10.1, 50.1, 98.8, 109.9, 111.2, 119.1, 119.3, 121.9, 126.2, 126.4, 128.2, 128.4, 128.7, 128.7, 129.2, 129.3, 130.3, 136.9, 137.9, 139.8, 144.7, 146.4; IR (CH₂Cl₂) 3052, 2914, 1611, 1465, 1330, 1012 cm⁻¹; HRMS m/z 423.0491 (calcd for C₂₂H₁₈IN, 423.0484).

3-(2-Iodophenyl)benzyl phenyl ether (14). To a suspension of NaH (0.031 g, 1.30 mmol) in DMF (2 mL) at 0 °C was added phenol (0.094 g, 1.0 mmol) in DMF (3 mL) and the mixture was stirred at room temperature for 30 min. At this point, 3'-bromomethyl-2-iodobiphenyl (**58**)¹³ (0.347 g, 0.93 mmol) in DMF (3 mL) was added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with brine (60 mL). The aqueous layer was reextracted with diethyl ether (15 mL) and the organic layers were combined, dried (MgSO₄), and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using 12:1 hexanes/ethyl acetate to afford 0.359 g (100 %) of the desired compound **14** as a clear oil: ¹H NMR (CDCl₃) δ 5.13 (s, 2H), 6.96-7.04 (m, 4H), 7.26-7.33 (m, 4H), 7.39-7.46 (m, 4H), 7.94-7.96 (m, 1H); ¹³C NMR (CDCl₃) δ 69.9, 98.6, 115.0, 121.1, 126.8, 128.3, 128.4, 128.5, 129.0, 129.0, 129.6, 130.2, 137.0, 139.6, 144.5, 146.4, 158.8; IR (CH₂Cl₂) 3056, 2919, 1598, 1494, 1238 cm⁻¹; HRMS *m/z* 386.0172 (calcd for C₁₉H₁₅IO, 386.0168).

2-Iodo-1-phenylnaphthalene (17). To a solution of 3,4-dihydro-1-phenylnaphthalene (1.30 g, 6.3 mmol) and I₂ (2.24 g, 8.8 mmol) in anhydrous CH₃CN (15 mL) was added dropwise AgOTf (1.75 g, 6.8 mmol) in anhydrous CH₃CN (20 mL). The resulting mixture was stirred at room temperature in the dark for 1 h. The reaction was diluted with diethyl

ether (70 mL) and washed with satd aq $\text{Na}_2\text{S}_2\text{O}_3$ (25 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The residue was dissolved in benzene (25 mL). To this solution was added DDQ (2.86 g, 12.6 mmol) and the reaction was heated at 65 °C for 2 d. The resulting mixture was filtered and washed with 10 % aq Na_2CO_3 (25 mL). The organic layer was filtered, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using 50:1 hexane/EtOAc to afford 1.47 g (70 %) of the indicated compound **17** as a clear oil: ^1H NMR (CDCl_3) δ 7.22-7.26 (m, 2H), 7.32-7.34 (m, 1H), 7.38-7.56 (m, 6H), 7.80-7.83 (m, 1H), 7.95 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 98.7, 126.5, 127.0, 127.4, 128.1, 128.1, 128.7, 129.3, 130.2, 133.1, 133.6, 135.8, 143.5, 144.7; IR (CH_2Cl_2) 3053, 1577, 1502, 1442, 1382, 1306 cm^{-1} ; HRMS m/z 329.9910 (calcd for $\text{C}_{16}\text{H}_{11}\text{I}$, 329.9906).

General procedure for preparation of the 2-(arylethynyl)biphenyls. To a solution of the corresponding aryl iodide (1.0 mmol) and the terminal alkyne (1.2 mmol, 1.2 equiv) in Et_3N (4.0 mL) were added $\text{PdCl}_2(\text{PPh}_3)_2$ (1.4 mg, 2 mol %) and CuI (2.0 mg, 1 mol %). The resulting mixture was then heated under an N_2 atmosphere at 55 °C for 3 h. The mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding product.

2-[(4-Methoxyphenyl)ethynyl]biphenyl (61). 2-Ethynylbiphenyl¹⁷ and 4-iodoanisole were employed. Purification by flash chromatography (30:1 hexane/EtOAc) afforded 0.21 g (74 %) of the product as a clear liquid: ¹H NMR (CDCl₃) δ 3.80 (s, 3H), 6.84 (dd, J = 2.4, 6.9 Hz, 2H), 7.30 (dd, J = 2.1, 6.9 Hz, 2H), 7.34-7.50 (m, 6H), 7.64-7.73 (m, 3H); ¹³C NMR (CDCl₃) δ 55.5, 88.4, 92.5, 114.2, 115.9, 122.2, 127.3, 127.6, 128.1, 128.4, 129.6, 129.7, 132.9, 133.1, 140.9, 143.9, 159.8.

2-[(3-Methylphenyl)ethynyl]biphenyl (62). 2-Ethynylbiphenyl¹⁷ and 3-iodotoluene were employed. Purification by flash chromatography (40:1 hexane/EtOAc) afforded 0.26 g (95 %) of the product as a clear liquid: ¹H NMR (CDCl₃) δ 2.34 (s, 3H), 7.12-7.22 (m, 4H), 7.33-7.53 (m, 6H), 7.67-7.74 (m, 3H); ¹³C NMR (CDCl₃) δ 21.5, 89.3, 92.7, 122.0, 123.5, 127.3, 127.7, 128.2, 128.4, 128.7, 128.7, 129.3, 129.7, 129.7, 132.2, 133.1, 138.2, 140.9, 144.1.

Ethyl 4-(biphen-2-ylethynyl)benzoate (63). 2-Ethynylbiphenyl¹⁷ and ethyl 4-iodobenzoate were employed. Purification by flash chromatography (15:1 hexane/EtOAc) afforded 0.27 g (84 %) of the product as a white solid: mp 58-60 °C; ¹H NMR (CDCl₃) δ 1.38 (t, J = 6.9 Hz, 3H), 4.36 (q, J = 7.2 Hz, 2H), 7.32-7.48 (m, 8H), 7.64-7.66 (m, 3H), 7.96 (d, J = 8.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.6, 61.3, 91.7, 92.6, 121.3, 127.4, 127.9, 128.2, 128.3, 129.3, 129.63, 129.64, 129.8, 129.9, 131.4, 133.2, 140.6, 144.5, 166.3.

2-(Biphen-2-ylethynyl)thiophene (64). 2-Ethynylbiphenyl¹⁷ and 2-iodothiophene were employed. Purification by flash chromatography (15:1 hexane/EtOAc) afforded 0.22 g (85 %) of the product as a light yellow liquid: ¹H NMR (CDCl₃) δ 6.98-7.00 (m, 1H), 7.15-7.17 (m, 1H), 7.25-7.27 (m, 1H), 7.37-7.55 (m, 6H), 7.66-7.75 (m, 3H); ¹³C NMR (CDCl₃) δ 85.9, 93.5, 121.6, 123.8, 127.3, 127.4, 127.5, 127.8, 128.3, 129.0, 129.6, 129.8, 131.8, 132.8, 140.7, 144.0.

2-[(4-Methoxyphenyl)ethynyl]-1-phenylnaphthalene (65). 2-Iodo-1-phenylnaphthalene and 4-ethynylanisole¹⁸ were employed. Purification by flash chromatography (20:1 hexane/EtOAc) afforded 0.27 g (82 %) of the product as a clear oil:

^1H NMR (CDCl_3) δ 3.81 (s, 3H), 6.82 (dd, $J = 6.9, 2.1$ Hz, 2H), 7.17 (dd, $J = 6.9, 2.1$ Hz, 2H), 7.43-7.60 (m, 7H), 7.68-7.72 (m, 2H), 7.83-7.94 (m, 2H); ^{13}C NMR (CDCl_3) δ 55.4, 88.9, 93.5, 114, 115.7, 120.7, 126.4, 126.6, 126.8, 127.6, 127.6, 128.1, 128.2, 128.4, 130.9, 132.4, 133.0, 133.1, 139.3, 142.8, 159.7.

2-[2-(Phenylethynyl)phenyl]naphthalene (66). 2-(2-Iodophenyl)naphthalene¹⁵ and phenylacetylene were employed. Purification by flash chromatography (40:1 hexane/EtOAc) afforded 0.29 g (96 %) of the product as a light yellow liquid: ^1H NMR (CDCl_3) δ 7.24-7.58 (m, 10H), 7.70-7.72 (m, 1H), 7.86-7.97 (m, 4H), 8.17 (s, 1H); ^{13}C NMR (CDCl_3) δ 89.7, 92.7, 122.0, 123.6, 126.2, 126.3, 127.4, 127.5, 127.9, 128.0, 128.3, 128.4, 128.5, 128.9, 130.0, 131.6, 132.9, 133.3, 133.5, 138.3, 144.0 (one sp^2 carbon missing due to overlap).

General procedure for synthesis of the phenanthrenes¹⁰

The following procedure was used to prepare phenanthrenes **22**, **24**, **26**, **28**, **30** and chrysene **32**. To a solution of 2-(arylethynyl)biphenyl (0.30 mmol) in CH_2Cl_2 (3 mL) under N_2 was added ICl (1.2 equiv) in CH_2Cl_2 (0.5 mL) at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h unless otherwise indicated. The reaction mixture was then diluted with diethyl ether (50 mL), washed with 25 mL of satd aq $\text{Na}_2\text{S}_2\text{O}_3$, dried (MgSO_4), and filtered. The solvent was evaporated under reduced pressure and the product was purified by chromatography on a silica gel column.

9-Iodo-10-(4-methoxyphenyl)phenanthrene (22). Purification by flash

chromatography (30:1 hexane/EtOAc) afforded 0.122 g (99 %) of the product as a white solid: mp 170-171 °C; ^1H NMR (CDCl_3) δ 3.94 (s, 3H), 7.09 (dd, $J = 2.1, 6.6$ Hz, 2H), 7.21 (dd, $J = 2.1, 6.6$ Hz, 2H), 7.40-7.49 (m, 2H), 7.64-7.72 (m, 3H), 8.45-8.49 (m, 1H), 8.67-8.78 (m, 2H); ^{13}C NMR (CDCl_3) δ 55.6, 107.7, 114.0, 122.8, 122.9, 127.2, 127.3, 127.7, 128.3, 129.0, 130.5, 130.8, 131.3, 132.7, 132.9, 135.0, 138.2, 145.3, 159.4; IR (neat) 3066, 3024, 2834, 1610 cm^{-1} ; HRMS m/z 410.0172 (calcd for $\text{C}_{21}\text{H}_{15}\text{IO}$, 410.0168).

Ethyl 4-(10-iodophenanthren-9-yl)benzoate (24). The reaction mixture was stirred at

room temperature for 1 h. Purification by flash chromatography (15:1 hexane/EtOAc) afforded 0.136 g (100 %) of the product as a white solid: mp 152-153 °C; ^1H NMR (CDCl_3) δ 1.46 (t, $J = 7.2$ Hz, 3H), 4.47 (q, $J = 7.2$ Hz, 2H), 7.30-7.45 (m, 4H), 7.66-7.75 (m, 3H), 8.26 (dd, $J = 1.8, 6.6$ Hz, 2H), 8.45-8.49 (m, 1H), 8.68-8.78 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.6, 61.4, 106.0, 122.9, 123.0, 127.4, 127.5, 128.0, 128.4, 128.5, 130.1, 130.3, 130.4, 130.5, 130.8, 132.1, 132.5, 134.9, 144.6, 150.0, 166.7; IR (CH_2Cl_2) 3069, 2979, 1714 cm^{-1} ; HRMS m/z 452.0278 (calcd for $\text{C}_{23}\text{H}_{17}\text{IO}_2$, 452.0273).

9-Iodo-10-(3-methylphenyl)phenanthrene (26). Purification by flash chromatography (30:1 hexane/EtOAc) afforded 0.117 g (99 %) of the product as a white solid: mp 134-135 °C; ^1H NMR (CDCl_3) δ 2.44 (s, 3H), 7.07-7.09 (m, 2H), 7.30-7.32 (m, 1H), 7.41-7.45 (m, 3H), 7.63-7.70 (m, 3H), 8.45-8.48 (m, 1H), 8.67-8.73 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.7, 106.5, 122.6, 122.7, 127.1, 127.1, 127.5, 128.1, 128.4, 128.5, 128.8, 130.3, 130.6, 130.6, 132.5, 132.5, 134.7, 138.1, 145.4, 145.5 (one sp^2 carbon missing due to overlap); IR (CH_2Cl_2) 3067, 2971, 2921, 1602, 1563 cm^{-1} ; HRMS m/z 394.0226 (calcd for $\text{C}_{21}\text{H}_{15}\text{I}$, 394.0219).

9-Iodo-10-(thiophen-2-yl)phenanthrene (28). Purification by flash chromatography (30:1 hexane/EtOAc) afforded 0.111 g (96 %) of the product as a white solid: mp 140-142 °C; ^1H NMR (CDCl_3) δ 7.06-7.08 (m, 1H), 7.23-7.26 (m, 1H), 7.45-7.76 (m, 6H), 8.44-8.49 (m, 1H), 8.66-8.75 (m, 2H); ^{13}C NMR (CDCl_3) δ 110.5, 122.7, 122.9, 126.5, 127.2, 127.5, 128.2, 128.4, 128.7, 128.8, 130.3, 131.1, 132.6, 133.2, 135.3, 138.4, 146.5; IR (neat) 2925, 1464, 1216 cm^{-1} ; HRMS m/z 385.9631 (calcd for $\text{C}_{18}\text{H}_{11}\text{IS}$, 385.9626).

6-Iodo-5-(4-methoxyphenyl)benzo[c]phenanthrene (30). Purification by flash chromatography (30:1 hexane/EtOAc) afforded 0.138 g (97 %) of the product as a white solid: mp 186-187 °C; ^1H NMR (CDCl_3) δ 3.94 (s, 3H), 7.08-7.12 (m, 2H), 7.23-7.26 (m, 2H), 7.42-7.47 (m, 1H), 7.57-7.69 (m, 4H), 7.94 (d, $J = 9.0$ Hz, 1H), 8.04-8.06 (m, 1H), 8.42 (d, $J = 9.0$ Hz, 1H), 9.01-9.04 (m, 2H); ^{13}C NMR (CDCl_3) δ 55.6, 107.3, 114.1, 126.4, 126.6, 126.7, 126.8, 128.4, 128.4, 128.6, 128.6, 128.8, 129.0, 129.7, 130.2, 131.3, 131.5, 132.4, 133.8, 133.8, 138.0, 145.0, 159.4; IR (neat) 2950, 1606, 1506 cm^{-1} ; HRMS m/z 460.0330 (calcd for $\text{C}_{25}\text{H}_{17}\text{IO}$, 460.0324).

6-Iodo-5-phenylchrysene (32). Purification by flash chromatography (40:1 hexane/EtOAc) afforded 98 mg (76%) of the product as a yellow solid: mp 168-169 °C; ^1H NMR (CDCl_3) δ 7.07 (t, $J = 6.9$ Hz, 1H), 7.33-7.57 (m, 7H), 7.71-7.76 (m, 2H), 8.89 (d, $J = 6.5$ Hz, 1H), 8.04 (d, $J = 7.6$ Hz, 1H), 8.56-8.60 (m, 1H), 8.78 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 111.5, 121.3, 123.7, 125.4, 126.1, 127.7, 128.2, 128.4, 128.6, 128.9, 129.0, 129.2, 129.3, 130.4, 130.7, 130.8, 131.1, 133.5, 133.8, 135.3, 144.3, 150.0; IR (neat) 2922 cm^{-1} ; HRMS m/z 430.0025 (calcd for $\text{C}_{24}\text{H}_{15}\text{I}$, 430.0219).

3-Iodo-4-phenylquinoline (34). To a solution of *N*-phenylmethanesulfonamide¹⁹ (0.513 g, 3.0 mmol), PPh₃ (1.18 g, 4.5 mmol) and 3-phenylpropargyl alcohol (0.594 g, 4.5 mmol) in anhydrous THF (30 mL) at 0 °C was added DEAD (0.784 g, 4.5 mmol). The resulting solution was stirred at 0 °C for 1 h and an additional 3 h at room temperature. The mixture was washed with brine (30 mL) and the organic layer was dried (Na₂SO₄), filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on a silica gel column using 3:1 hexanes/ethyl acetate to obtain 0.534 g (63 %) of *N*-phenyl-*N*-(3-phenyl-2-propyn-1-yl)methanesulfonamide as a white solid: mp 76-77 °C; ¹H NMR (CDCl₃) δ 3.08 (s, 3H), 4.67 (s, 2H), 7.34-7.46 (m, 8H), 7.62-7.66 (m, 2H); ¹³C NMR (CDCl₃) δ 39.2, 42.3, 84.4, 86.3, 122.3, 127.7, 128.4, 128.7, 129.1, 129.7, 131.9, 140.5. To a solution of *N*-phenyl-*N*-(3-phenyl-2-propyn-1-yl)methanesulfonamide (71.2 mg, 0.25 mmol) in CH₂Cl₂ (3.0 mL) at -78 °C was added ICl (48.7 mg, 0.3 mmol) in CH₂Cl₂ (0.5 mL) and the resulting solution was stirred at this temperature for 1 h. The reaction mixture was washed with satd aq Na₂S₂O₃ (20 mL) and the organic layer dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on a silica gel column using 5:1 hexanes/ethyl acetate to obtain 82.2 mg (80 %) of 3-iodo-1-methanesulfonyl-4-phenyl-1,2-dihydroquinoline as a white solid: mp 173-175 °C; ¹H NMR (CDCl₃) δ 2.89 (s, 3H), 4.82 (s, 2H), 6.80 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.11-7.16 (m, 3H), 7.30-

7.33 (m, 1H), 7.44-7.48 (m, 3H), 7.62 (dd, $J = 8.1, 0.9$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 38.6, 56.7, 92.0, 126.9, 127.2, 127.2, 128.6, 128.8, 129.0, 129.2, 130.7, 134.5, 140.3, 143.9. A solution of 3-iodo-1-methanesulfonyl-4-phenyl-1,2-dihydroquinoline (0.103 g, 0.25 mmol) and NaOH (0.10 g, 2.5 mmol) in EtOH (10 mL) was stirred at 50 °C under O_2 (1 atm) for 12 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column using 5:1 hexanes/ethyl acetate to afford 76.1 mg (92 %) of the desired compound **34** as a white solid: mp 131-132 °C; ^1H NMR (CDCl_3) δ 7.25-7.28 (m, 2H), 7.42-7.48 (m, 2H), 7.52-7.55 (m, 3H), 7.69-7.74 (m, 1H), 8.12 (d, $J = 8.8$ Hz, 1H), 9.24 (s, 1H); ^{13}C NMR (CDCl_3) δ 96.4, 126.8, 127.4, 128.7, 129.0, 129.1, 129.5, 129.8, 140.4, 147.2, 152.4, 156.6 (one sp^2 carbon missing due to overlap); IR (CH_2Cl_2) 3061, 2918, 1566, 1501, 1485 cm^{-1} ; HRMS m/z 330.9864 (calcd for $\text{C}_{15}\text{H}_{10}\text{IN}$, 330.9858).

2-Iodo-3-methylindole. To a solution of 3-methylindole (2.64 g, 20.0 mmol) in 55 mL of dry THF was added dropwise 8.4 mL of *n*-BuLi (2.5 M in hexane) at -78°C under an Ar atmosphere. The resulting suspension was stirred at -78°C for 20 min. Carbon dioxide was bubbled through the reaction mixture for 30 min to form a clear yellow solution. The reaction mixture was allowed to warm to 25°C and the solvent was removed under reduced pressure. To the residue was added 50 mL of dry THF and the suspension was cooled to -78°C . 12.5 mL of *t*-BuLi (1.7 M pentane) was added to the suspension and the resulting orange reaction mixture was stirred at -78°C for 1 h. A solution of $\text{ICH}_2\text{CH}_2\text{I}$ (5.64 g, 20.0 mmol) in 15 mL of dry THF was added dropwise and the resulting yellow solution was stirred at -78°C for 1 h. Then the reaction mixture was allowed to warm to 25°C and washed with 50 mL of satd aqueous NH_4Cl . The organic layer was collected, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column (5:1 hexane/EtOAc) to afford 4.98 g of 2-iodo-3-methylindole as a yellow oil in 97 % yield with spectral properties identical to those previously reported.²⁰

2-Iodo-3-methyl-1-(4-nitrophenyl)indole. To a suspension of NaH (5.5 mmol) in 20 mL of DMF was added 1.28 g of 2-iodo-3-methylindole (5.0 mmol) at 0°C under an Ar atmosphere and lots of bubbles were generated. The resulting yellow suspension was stirred at 0°C for 40 min and a solution of 1-fluoro-4-nitrobenzene (0.846 g, 6.0 mmol) in 10 mL of DMF was added dropwise. After 12 h, the reaction was diluted with 30 mL of Et_2O and washed with 30 mL of brine. The organic layer was collected, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography (15:1 hexane/EtOAc) to afford 1.07 g of the indicated compound in a 57 % yield as a yellow solid: mp $123\text{--}126^{\circ}\text{C}$; ^1H NMR (CDCl_3) 2.39 (s, 3H), 7.13–7.20 (m, 3H), 7.54–7.60 (m, 3H),

8.37-8.42 (m, 2H); ^{13}C NMR (CDCl_3) δ 12.8, 85.2, 110.3, 118.9, 121.1, 121.5, 123.4, 124.9, 129.2, 129.5, 139.3, 144.7, 147.0.

1-(4-Aminophenyl)-2-iodo-3-methylindole. To a 6 dram vial was added 0.80 g of 2-iodo-3-methyl-1-(4-nitrophenyl)indole (2.1 mmol), 17 mL of CH_3OH , 8.5 mg of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (0.32 mmol), 4.3 mg of active carbon (3.6 mmol), and 0.21 mL of $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (4.2 mmol). The resulting mixture was stirred at 25 °C for 5 min and was heated to 70 °C (a sealed tube reaction). After 7 h, the reaction was allowed to cool to 25 °C and filtered. The colorless filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (2:1 hexane/EtOAc) to afford 0.60 g of the indicated compound in an 82 % yield as a yellow oil: ^1H NMR (CDCl_3) 2.38 (s, 3H), 3.94 (br s, 2H), 6.78-6.80 (m, 2H), 7.06-7.10 (m, 5H), 7.54-7.56 (m, 1H); ^{13}C NMR (CDCl_3) δ 12.7, 88.8, 110.9, 115.4, 118.0, 118.2, 119.7, 122.2, 128.5, 130.2, 140.1, 146.7 (one sp^2 carbon missing due to overlap).

1-(4-Dimethylaminophenyl)-2-iodo-3-methylindole (38). To a mixture of formaldehyde (37% of aqueous solution, 0.40 mL, 4.98 mmol) and H_2SO_4 (3 M, 0.69 mL, 2.1 mmol) was added a slurry of NaBH_4 (0.22 g, 5.8 mmol) and 1-(4-aminophenyl)-2-iodo-3-methylindole (0.29 g, 0.83 mmol) in 7 mL of THF at 0 °C. Lots of bubbles were generated in this process and the resulting yellow suspension was stirred at 0 °C for 10 min. The reaction mixture was diluted with 30 mL of Et_2O , and washed with satd aq NaHCO_3 (30 mL) and brine (20 mL). The organic layer was collected, dried over NaSO_4 , and filtered. Removal of solvent under reduced pressure afforded 0.26 g of the indicated compound in an 83 % yield as a yellow solid: mp 149-150 °C; ^1H NMR (CDCl_3) 2.38 (s, 3H), 3.04 (s, 6H), 6.79 (d, J = 8.8 Hz, 2H), 7.05-7.10 (m, 3H), 7.16 (d, J = 8.8 Hz, 2H), 7.54-7.56 (m, 1H); ^{13}C NMR (CDCl_3) δ 12.7, 40.7, 89.3, 111.0, 112.3, 117.8, 118.2, 119.6, 122.1, 128.1, 128.4, 129.9,

140.2, 150.3; IR (CH₂Cl₂) 3053, 2986, 1524 cm⁻¹; HRMS *m/z* 376.0441 (calcd for C₁₇H₁₇IN₂, 376.0437).

3-(2-Iodophenyl)indole (66). To a solution of (2-iodophenyl)acetaldehyde²¹ (0.738 g, 3.0 mmol) in 15 mL of absolute ethanol was added 0.356 g of PhNHNH₂ (3.3 mmol) and 57.6 mg of CH₃SO₃H (0.6 mmol). The resulting yellow solution was then stirred at room temperature for 1 h. Another 0.519 g of CH₃SO₃H (5.4 mmol) was then added to the reaction mixture and the reaction was stirred at 85 °C. After 2 d, the reaction was complete and was allowed to cool to room temperature. The ethanol was removed under reduced pressure and the residue was diluted with Et₂O (30 mL), washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (5:1 hexane/EtOAc) to afford 0.41 g of compound **66** (43 % yield) as a yellow oil: ¹H NMR (CDCl₃) δ 7.01-7.05 (m, 1H), 7.14-7.18 (m, 1H), 7.23-7.27 (m, 1H), 7.38-7.49 (m, 4H), 7.54 (d, *J* = 8.0 Hz, 1H), 8.01 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.27 (br s, 1H); ¹³C NMR (CDCl₃) δ 101.0, 111.5, 120.3, 120.4, 122.6, 123.8, 126.8, 128.2, 128.5, 131.6, 135.8, 140.0, 140.1 (one sp² carbon missing due to overlap).

1-Benzyl-3-(2-iodophenyl)indole (40). To a suspension of 30 mg of NaH (0.75 mmol, 60 % in mineral oil) in DMF (2 mL) was added dropwise a solution of compound **66** (0.16 g, 0.5 mmol) in DMF (4 mL) at 0 °C. A lot of bubbles were generated. The resulting brown

solution was stirred at 0 °C for 45 min and a solution of PhCH₂Cl (0.127 g, 1.0 mmol) in DMF (1 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 12 h. The reaction mixture was diluted with Et₂O (30 mL), washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20:1 hexane/EtOAc) to afford 0.155 g of the indicated compound **40** (76 % yield) as a colorless oil: ¹H NMR (CDCl₃) δ 5.38 (s, 2H), 6.98-7.02 (m, 1H), 7.12-7.16 (m, 1H), 7.18-7.33 (m, 8H), 7.37-7.41 (m, 1H), 7.49 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.54-7.56 (m, 1H), 7.99 (dd, *J* = 1.2, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 50.4, 101.1, 110.1, 119.2, 120.1, 120.4, 122.3, 127.1, 127.5, 127.9, 128.1, 128.2, 128.4, 129.0, 131.6, 136.3, 137.5, 140.0, 140.1; IR (neat) 3055, 3029, 2921, 1613, 1585 cm⁻¹; HRMS *m/z* 409.0335 (calcd for C₂₁H₁₆IN, 409.0328).

1-(3-Methoxybenzyl)-3-(2-iodophenyl)indole (42). Using the procedure to prepare compound **40**, but employing 0.16 g of 3-methoxybenzyl chloride (1.0 mmol) afforded 0.193 g of the indicated compound **42** in an 88 % yield as a yellow oil: ¹H NMR (CDCl₃) δ 3.72 (s, 3H), 5.34 (s, 2H), 6.71 (s, 1H), 6.77-6.81 (m, 2H), 6.98-7.02 (m, 1H), 7.12-7.15 (m, 1H), 7.18-7.24 (m, 2H), 7.31-7.33 (m, 2H), 7.37-7.40 (m, 1H), 7.48-7.50 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 50.3, 55.4, 101.1, 110.1, 112.7, 113.2, 119.2, 119.3, 120.1, 120.4, 122.3, 127.5, 128.1, 128.2, 128.4, 130.0, 131.6, 136.2, 139.1,

140.0, 140.0, 160.2; IR (neat) 3051, 2934, 1586, 1490 cm^{-1} ; HRMS m/z 439.0439 (calcd for $\text{C}_{22}\text{H}_{18}\text{ION}$, 439.0433).

1-Benzoyl-3-(2-iodophenyl)indole (45). Using the procedure to prepare compound 40, but employing of 0.14 g of benzoyl chloride (1.0 mmol) afforded 0.190 g of the indicated compound 45 in a 90 % yield as a pale yellow solid: mp 102-103 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 7.04-7.08 (m, 1H), 7.32-7.36 (m, 1H), 7.40-7.46 (m, 5H), 7.51-7.55 (m, 2H), 7.58-7.63 (m, 1H), 7.81-7.84 (m, 2H), 7.98 (d, $J = 7.6$ Hz, 1H), 8.49-8.51 (m, 1H); ^{13}C NMR (CDCl_3) δ 100.2, 116.7, 120.5, 124.3, 125.3, 125.5, 126.5, 128.3, 128.8, 129.6, 129.6, 130.1, 131.3, 132.3, 134.6, 136.1, 138.1, 140.1, 168.9; IR (neat) 3051, 1686, 1450, 1364 cm^{-1} ; HRMS m/z 423.0129 (calcd for $\text{C}_{21}\text{H}_{14}\text{ION}$, 423.0120).

3-(2-Iodophenyl)-1-(5-phenyl-4-pentynyl)indole (47). To a suspension of NaH (45.7 mg, 1.14 mmol, 60 % in mineral oil) in DMF (3 mL) was added dropwise a solution of compound 66 (0.243 g, 0.76 mmol) in DMF (5 mL) at 0 $^{\circ}\text{C}$. A lot of bubbles were generated.

The resulting brown solution was stirred at 0 °C for 45 min and a solution of 5-bromo-1-phenyl-1-pentyne (0.34 g, 1.52 mmol) in DMF (2 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 12 h, diluted with Et₂O (30 mL), washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20:1 hexane/EtOAc) to afford 0.30 g of the indicated compound **47** (85 % yield) as a yellow oil: ¹H NMR (CDCl₃) δ 2.13-2.22 (m, 2H), 2.45 (t, *J* = 8.8 Hz, 2H), 4.41 (t, *J* = 8.8 Hz, 2H), 6.98-7.03 (m, 1H), 7.12-7.23 (m, 1H), 7.23-7.33 (m, 4H), 7.37-7.50 (m, 6H), 7.54-7.56 (m, 1H), 8.00 (dd, *J* = 1.6, 10.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 17.0, 29.1, 45.1, 82.3, 88.6, 101.1, 109.8, 118.7, 120.0, 120.4, 122.1, 123.8, 127.5, 128.0, 128.1, 128.2, 128.3, 128.5, 131.5, 131.8, 135.9, 140.1 (one sp² carbon missing due to overlap); IR (CH₂Cl₂) 3053, 2985, 1613, 1596, 1548 cm⁻¹; HRMS *m/z* 461.0647 (calcd for C₂₅H₂₀IN, 461.0641).

3-Iodo-4-phenylisocoumarin (51). A solution of 4-phenyl-3-(trimethylsilyl)isocoumarin²² (0.435 g, 1.48 mmol), I₂ (1.13 g, 4.45 mmol), and AgOTf (0.76 g, 2.96 mmol) in CH₃CN (20 mL) was heated at 55 °C for 5 d. The reaction mixture was diluted with diethyl ether (100 mL), and washed with satd aq Na₂S₂O₃ (30 mL). The organic layer was dried (Na₂SO₄), filtered, and the solvent removed under reduced pressure to obtain 0.498 g (97 %) of the indicated compound **51** as a yellow solid. Recrystallization from

hexanes/ethyl acetate afforded the indicated compound **51** as a yellow solid: mp 170-171 °C, ^1H NMR (CDCl_3) δ 6.97 (d, J = 8.0 Hz, 1H), 7.26-7.28 (m, 2H), 7.50-7.56 (m, 4H), 7.59-7.63 (m, 1H), 8.31 (dd, J = 8.0, 0.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 107.9, 119.6, 125.6, 127.4, 128.7, 128.9, 129.1, 129.9, 130.5, 135.2, 137.0, 137.3, 161.2; IR (CH_2Cl_2) 1736 cm^{-1} ; HRMS m/z 347.9652 (calcd for $\text{C}_{15}\text{H}_9\text{IO}_2$, 347.9647).

4-Iodo-2,3-diphenyl-2H-isoquinolin-1-one (53). To a solution of *N*-phenyl-2-(phenylethynyl)benzamide²³ (74.2 mg, 0.25 mmol) in CH_2Cl_2 (3.0 mL) at room temperature was added ICl (48.7 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL) and the resulting solution was stirred at this temperature for 1 h. The reaction mixture was washed with satd aq $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and the organic layer dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on a silica gel column using 5:1 hexanes/ethyl acetate to obtain 42.3 mg (40 %) of the indicated compound **53** as a yellow solid: mp 129-130 °C; ^1H NMR (CDCl_3) δ 7.08-7.11 (m, 1H), 7.20-7.30 (m, 3H), 7.33-7.38 (m, 4H), 7.57-7.64 (m, 3H), 7.67-7.72 (m, 1H), 8.03-8.06 (m, 1H), 8.84-8.87 (m, 1H); ^{13}C NMR (CDCl_3) δ 75.2, 124.1, 125.1, 125.1, 125.4, 128.1, 128.7, 128.7, 130.5, 130.9, 132.0, 132.7, 135.7, 140.6, 145.0, 147.8, 152.1; IR (CH_2Cl_2) 2916, 2849, 1642, 1586, 1488, 1445 cm^{-1} ; HRMS m/z 423.0131 (calcd for $\text{C}_{15}\text{H}_9\text{IO}_2$, 423.0120).

***N*-(4-Phenoxyphenyl)-2,2-dimethylpropanamide.** To a solution of 4-phenoxyaniline (3.33 g, 18.0 mmol) in 70 mL of dried THF was added (Boc)₂O (4.71 g, 21.6 mmol) and the resulting yellow solution was refluxed at 80 °C for 6 h. The solvent was removed under reduced pressure and the reddish residue was recrystallized using hexane and EtOAc to afford 4.84 g of the indicated compound (85 % yield) as white needles: mp 109-111 °C; ¹H NMR (CDCl₃) δ 1.52 (s, 9H), 6.43 (br s, 1H), 6.95-6.98 (m, 4H), 7.06 (t, *J* = 3.6 Hz, 1H), 7.29-7.34 (m, 4H); ¹³C NMR (CDCl₃) δ 28.6, 80.7, 118.3, 120.2, 120.5, 123.0, 129.9, 134.2, 152.6, 153.2, 158.1.

***N*-(2-Iodo-4-phenoxyphenyl)-2,2-dimethylpropanamide.** To a solution of *N*-(4-phenoxyphenyl)-2,2-dimethylpropanamide (2.57 g, 9.02 mmol) in 20 mL of dry diethyl ether was added dropwise 10.6 mL of *t*-BuLi (1.7 M in pentane, 18.04 mmol) at -78 °C under Ar. The pale orange solution turned a pale yellow color when half of the *t*-BuLi solution had been added and eventually to yellow when all of the *t*-BuLi solution was added. The resulting yellow solution was then stirred at -78 °C for 30 min. A solution of ICH₂CH₂I (2.81 g, 9.92 mmol, recrystallized from diethyl ether) in 20 mL of dry ether was added dropwise to the reaction mixture and the resulting orange solution was stirred at -78 °C for

another 30 min. The reaction mixture was allowed to warm up to room temperature and quenched by 50 mL of water. The organic layer was separated and dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (15:1 hexane/EtOAc) to afford 2.3 g of the desired compound (62 % yield) as a colorless oil: ^1H NMR (CDCl_3) δ 1.53 (s, 9H), 6.68 (br s, 1H), 6.96-6.98 (m, 2H), 7.02 (dd, J = 2.4, 8.8 Hz, 1H), 7.08-7.12 (m, 1H), 7.30-7.35 (m, 2H), 7.42 (d, J = 2.8 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 28.5, 81.3, 89.5, 118.6, 120.2, 121.6, 123.6, 129.3, 130.0, 134.9, 153.0, 153.0, 157.4.

2-Iodo-4-phenoxyaniline. To a solution of *N*-(2-iodo-4-phenoxyphenyl)-2,2-dimethylpropanamide (0.82 g, 2.0 mmol) in 10 mL of CH_2Cl_2 was added dropwise 2.0 mL of TFA at 0 °C and the reaction was allowed to warm up to room temperature. The resulting colorless mixture was stirred at room temperature for 16 h, diluted with 20 mL of CH_2Cl_2 , washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (5:1 hexane/EtOAc) to afford 0.56 g of the indicated compound (91 % yield) as a pale orange solid: mp 54-56 °C; ^1H NMR (CDCl_3) δ 4.00 (s, 2H), 6.74 (d, J = 8.7 Hz, 1H), 6.88-6.91 (m, 2H), 6.93-6.95 (m, 1H), 7.01-7.07 (m, 1H), 7.26-7.32 (m, 2H), 7.36 (d, J = 2.7 Hz, 1H); ^{13}C NMR (CDCl_3) δ 83.8, 115.2, 117.6, 121.6, 122.8, 129.9, 130.3, 143.5, 148.8, 158.6.

4-Phenoxy-2-phenylaniline. To a 50 mL round-bottom flask was added $\text{PdCl}_2(\text{PPh}_3)_2$ (0.103 g, 0.147 mmol), $\text{PhB}(\text{OH})_2$ (0.358 g, 2.94 mmol), K_2CO_3 (0.406 g, 2.94 mmol), 2-iodo-4-phenoxyaniline (0.457 g, 1.47 mmol), 15 mL of DMF and 3 mL of H_2O . The whole mixture was then stirred at room temperature for 5 min, flushed with Ar and heated to 70 °C for 3 h. The reaction was allowed to cool to room temperature, diluted with diethyl ether (30

mL), washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5:1 hexane/EtOAc) to afford 0.342 g of the indicated compound (88 % yield) as a yellow oil: ^1H NMR (CDCl_3) δ 3.71 (br s, 2H), 6.75-6.77 (m, 1H), 6.87-6.90 (m, 2H), 6.97-7.03 (m, 3H), 7.25-7.35 (m, 3H), 7.41-7.60 (m, 4H); ^{13}C NMR (CDCl_3) δ 116.9, 117.5, 120.4, 122.2, 122.3, 127.6, 129.0, 129.1, 129.2, 129.7, 139.1, 139.9, 148.9, 159.0.

2-Iodo-5-phenoxybiphenyl (55). To a solution of 4-phenoxy-2-phenylaniline (0.383 g, 1.47 mmol) in DME (4 mL) was added dropwise 3 mL of water containing 0.6 mL of conc H_2SO_4 (95 %). The resulting yellow mixture was cooled to 0 °C and a solution of NaNO_2 (0.152 g, 2.21 mmol) in water (1 mL) was added over 10 min. The yellow reaction mixture was stirred at 0 °C for 20 min and a solution of NaI (1.10 g, 7.35 mmol) in water (3 mL) was added dropwise at 0 °C. The reaction mixture turned black when the NaI solution was added. After 10 min, the reaction was diluted with Et_2O (30 mL), and washed by satd $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL), water (30 mL), and brine (30 mL). The organic layer was collected, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (30:1 hexane/EtOAc) to afford 0.44 g of the indicated compound **55** (81 % yield) as a yellow solid: mp 68-70 °C; ^1H NMR (CDCl_3) δ 6.73 (dd, J = 3.0, 8.8 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 7.04-7.06 (m, 2H), 7.11-7.15 (m, 1H), 7.31-7.43 (m, 7H), 7.85 (d, J = 8.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 90.4, 119.4, 119.5, 120.5, 124.1, 128.0, 128.2, 129.4, 130.1, 140.6, 143.9, 148.2, 156.6, 158.0; IR (CH_2Cl_2) 3056, 2981, 1583, 1561, 1490 cm^{-1} ; HRMS m/z 372.0019 (calcd for $\text{C}_{18}\text{H}_{13}\text{IO}$, 372.0011).

1-Iodo-2,4-diphenylnaphthalene (56). To a yellow suspension of $\text{Ph}_3\text{P}=\text{CH}_2$ (1.5 mmol) in THF (8 mL) [prepared by the reaction of 0.57 g of methyltriphenylphosphonium bromide (1.6 mmol) in 8 mL of THF and 0.6 mL of *n*-BuLi (2.5 M in hexane, 1.5 mmol) at 0 °C for 30 min] was added a solution of 2-(phenylethynyl)acetophenone (1.0 mmol) in THF (3 mL). After 1 h, TLC analysis showed that the reaction was not complete and another 1.0 mmol of $\text{Ph}_3\text{P}=\text{CH}_2$ in THF (5 mL) was added to the reaction mixture. The reaction reached completion in 10 min. The solvent was removed under reduced pressure and 30 mL of hexane was added to the residue. After being stirred at 25 °C for 20 min, the mixture was filtered to remove the phosphonium salt. Removal of the solvent under reduced pressure afforded a colorless residue. The colorless residue was added to a stirred mixture of NaHCO_3 (0.25 g, 3.0 mmol), I_2 (1.54 g, 6.0 mmol) and CH_3CN (15 mL). The reaction was complete after 20 min at 25 °C. The reaction mixture was diluted with Et_2O (30 mL) and washed by satd aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL). The organic layer was collected, dried over NaSO_4 , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatograph (50:1 hexane/ EtOAc) to afford 0.39 g of the indicated compound **56** in a 97 % yield as a yellow oil: ^1H NMR (CDCl_3) δ 7.38-7.50 (m, 12H), 7.58-7.63 (m, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 8.43 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 103.6, 126.8, 126.9, 127.8, 128.2, 128.2, 128.6, 128.9, 129.8, 130.2, 131.5, 134.1, 135.3, 139.9, 140.9,

146.0, 146.2 (one sp^2 carbon missing due to overlap); IR (neat) 3058, 3028, 2927, 1599 cm^{-1} ; HRMS m/z 406.0225 (calcd for $\text{C}_{22}\text{H}_{15}\text{I}$, 406.0218).

Representative procedure for the palladium-catalyzed migration reactions. The appropriate aryl iodide (0.25 mmol), $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.0125 mmol), 1,1-*bis*(diphenylphosphino)methane (dppm) (4.8 mg, 0.0125 mmol) and $\text{CsO}_2\text{CCMe}_3$ (CsPiv) (0.117 g, 0.5 mmol) in DMF (4 mL) were stirred under Ar at 100 $^\circ\text{C}$ for the specified period of time. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (35 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried (MgSO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel.

1-Phenyl-9H-fluorene (5). Compound 4 (92.5 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 $^\circ\text{C}$ for 3 d. The reaction mixture was chromatographed using 30:1 hexane/EtOAc to afford 24.2 mg (40 %) of the indicated compound 2 as a colorless oil: ^1H NMR (CDCl_3) δ 3.95 (s, 2H), 6.94 (d, $J = 7.6$ Hz, 1H), 7.05 (t, $J = 7.6$ Hz, 1H), 7.19-7.22 (m, 2H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.45-7.55 (m, 7H); ^{13}C NMR (CDCl_3) δ 37.0, 122.9, 124.0, 124.8, 126.3, 126.4, 127.5, 128.5, 128.8, 129.2, 137.9, 138.7, 141.3, 141.6, 143.7, 143.9 (one sp^2 carbon missing due to overlap); IR (CH_2Cl_2) 3056, 3025, 1454, 1417, 1478 cm^{-1} ; HRMS m/z 242.1101 (calcd for $\text{C}_{19}\text{H}_{14}$, 242.1096).

1-Phenyldibenzofuran (7). Compound **6** (93.0 mg, 0.25 mmol) or compound **55** (93.0 mg, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d. The reaction mixtures were chromatographed using 30:1 hexane/EtOAc to afford 54.4 mg (89 %) (entry 2, Table 2) or 54.0 mg (88 %) (entry 8, Table 2) of the indicated compound **7**, respectively, as a white solid: mp 62-63 °C (lit²⁴ mp 63-64 °C); ¹H NMR (CDCl₃) δ 7.10-7.14 (m, 1H), 7.24-7.26 (m, 1H), 7.37-7.42 (m, 1H), 7.46-7.64 (m, 9H); ¹³C NMR (CDCl₃) δ 110.5, 111.6, 121.8, 122.3, 122.5, 123.9, 124.0, 127.1, 127.1, 127.9, 128.6, 129.0, 138.0, 140.0, 156.4, 156.5. The other spectral properties were identical to those previously reported.²⁴

7-Chloro-1-phenyldibenzofuran (9). Compound **8** (0.101 g, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d. The reaction mixture was chromatographed using 50:1 hexanes/ethyl acetate to afford 57.1 mg (82 %) of the indicated compound **9** as a colorless oil: ¹H NMR (CDCl₃) δ 7.25 (dd, J = 6.8, 1.2 Hz, 1H), 7.34 (dd, J = 8.4, 2.4 Hz, 1H), 7.45-7.60 (m, 9H); ¹³C NMR (CDCl₃) δ 110.7, 112.5, 121.0, 122.1, 124.3, 125.3, 127.1, 127.7, 127.8, 128.3, 128.8, 128.9, 138.2, 139.4, 154.7, 157.1; IR (CH₂Cl₂)

3061, 3032, 1444, 1400, 1199, 1243 cm^{-1} ; HRMS m/z 278.0501 (calcd for $\text{C}_{18}\text{H}_{11}\text{ClO}$, 278.0498).

10-Phenyl-6H-isoindolo[2,1-a]indole (11). Compound **10** (0.102 g, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d. The reaction mixture was chromatographed using 12:1 hexanes/ethyl acetate to afford 49.2 mg (70 %) of the indicated compound **11** as a white solid: mp 139-140 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 5.08 (s, 2H), 6.16 (s, 1H), 7.03-7.07 (m, 1H), 7.14-7.18 (m, 1H), 7.32-7.54 (m, 8H), 7.64-7.66 (m, 2H); ^{13}C NMR (CDCl_3) δ 48.2, 94.3, 109.1, 119.7, 121.7, 122.4, 127.3, 128.0, 128.5, 128.8, 129.3, 131.0, 132.4, 133.7, 137.0, 139.9, 142.5, 143.2 (one sp^2 carbon missing due to overlap); IR (CH_2Cl_2) 3053, 2916, 2850, 1471, 1551, 1446 cm^{-1} ; HRMS m/z 281.1210 (calcd for $\text{C}_{21}\text{H}_{15}\text{N}$, 281.1204).

2-Methyl-10-phenyl-6H-isoindolo[2,1-a]indole (13). Compound **12** (0.106 g, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d. The reaction mixture was chromatographed using 12:1 hexanes/ethyl acetate to afford 52.4 mg (71 %) of the indicated compound **13** as a white solid: mp 143-145 $^{\circ}\text{C}$ (decomposes); ^1H NMR (CDCl_3) δ 1.41 (s, 3H), 5.06 (s, 2H), 7.03-7.07 (m, 1H), 7.16-7.20 (m, 1H), 7.23-7.31 (m,

3H), 7.40-7.50 (m, 7H); ^{13}C NMR (CDCl_3) δ 9.5, 48.1, 104.2, 109.0, 119.1, 120.0, 122.0, 122.4, 126.5, 127.9, 128.7, 129.9, 130.2, 132.6, 133.8, 134.0, 137.0, 140.0, 142.6, 142.8; IR (CH_2Cl_2) 3048, 2976, 2853, 1469, 2976, 2853, 1469, 1411 cm^{-1} ; HRMS m/z 295.1369 (calcd for $\text{C}_{22}\text{H}_{17}\text{N}$, 295.1361).

10-Phenyl-6H-benzo[*c*]chromene (15) and phenyl 3-phenylbenzyl ether (16).

Compound **14** (96.5 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 120 °C for 2 d. The reaction mixture was chromatographed using 50:1 hexanes/ethyl acetate to afford 47.8 mg (75 %) of a 60:40 inseparable mixture of compounds **15** and **16** respectively. Major isomer **15**: ^1H NMR (CDCl_3) δ 5.02 (s, 2H) as a characteristic peak; HRMS m/z 258.1050 (calcd for $\text{C}_{19}\text{H}_{14}\text{O}$, 258.1045). Minor isomer **16**: ^1H NMR (CDCl_3) δ 5.11 (s, 2H) as a characteristic peak; HRMS m/z 260.1206 (calcd for $\text{C}_{19}\text{H}_{16}\text{O}$, 260.1201). Mixture: ^{13}C NMR (CDCl_3) δ 69.9, 70.2, 115.1, 117.6, 121.3, 121.3, 123.6, 124.1, 126.6, 126.7, 127.1, 127.4, 127.4, 127.5, 127.5, 127.7, 128.4, 128.9, 128.9, 128.9, 129.1, 129.1, 129.3, 129.4, 129.4, 129.8, 132.0, 135.5, 137.8, 139.3, 141.2, 141.9, 142.5, 156.6, 159.0; IR (neat) 3058, 3029, 1599, 1495, 1453, 1243 cm^{-1} .

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Fluoranthene (18). Compound 17 (82.5 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 1 d. The reaction mixture was chromatographed using 50:1 hexane/EtOAc to afford 41.0 mg (81 %) of the indicated compound 6 as a white solid: mp 107-108 °C (lit²⁵ mp 106-108 °C). The other spectral properties were identical to those previously reported.²⁶

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Benzo[e]acephenanthrylene (21). Compound 20¹³ (95.0 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2 d. The reaction mixture was chromatographed using 50:1 hexane/EtOAc to afford 49.2 mg (78 %) of the indicated compound 8 as a white solid: mp 166-167 °C (lit²⁷ mp 165-166 °C). The other spectral properties were identical to those previously reported.²⁸

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5-Methoxybenzo[*e*]acephenanthrylene (23). Compound **22** (0.103 g, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2 d. The reaction mixture was chromatographed using 30:1 hexanes/ethyl acetate to afford 50.1 mg (71 %) of the indicated compound **23** as a white solid: mp 188-189 °C (lit²⁸ mp 189-190 °C). The other spectral properties were identical to those previously reported.²⁸

Ethyl benzo[*e*]acephenanthrylene-5-carboxylate (25). Compound **24** (0.113 g, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2 d. The reaction mixture was chromatographed using 9:1 hexanes/ethyl acetate to afford 40.5 mg (50 %) of the indicated compound **25** as a white solid: mp 153-154 °C; ¹H NMR (CDCl₃) δ 1.46 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.63-7.65 (m, 1H), 7.68-7.70 (m, 1H), 7.74-7.78 (m, 1H), 7.98-8.04 (m, 3H), 8.09 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.24 (s, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.54 (d, *J* = 0.8 Hz, 1H), 8.64 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.5, 61.2, 120.1, 121.5, 122.1, 122.5, 123.2, 123.3, 127.0, 127.6, 127.7, 128.5, 129.0, 129.9, 130.6, 131.1, 132.4, 133.8, 134.0, 136.2, 140.7, 142.6, 166.9; IR (CH₂Cl₂) 2979, 1710, 1240, 1290 cm⁻¹; HRMS *m/z* 324.1157 (calcd for C₂₃H₁₆O₂, 324.1150).

6-Methylbenzo[*e*]acephenanthrylene (27). Compound **26** (98.5 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2 d. The reaction mixture was chromatographed using 50:1 hexane/EtOAc to afford 37.2 mg (56 %) of the indicated compound **27** as a white solid: mp 149-151 °C; ^1H NMR (CDCl_3) δ 2.50 (s, 3H), 7.22 (d, $J = 7.6$ Hz, 1H), 7.59-7.80 (m, 5H), 7.91 (d, $J = 7.2$ Hz, 1H), 8.01-8.02 (m, 1H), 8.17 (s, 1H), 8.40 (d, $J = 8.0$ Hz, 1H), 8.63 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.9, 119.2, 121.2, 121.3, 121.3, 122.8, 123.2, 126.8, 127.0, 127.6, 128.3, 129.0, 130.2, 130.8, 132.4, 134.1, 135.3, 137.2, 137.5, 138.2, 138.9; IR (CH_2Cl_2) 2921, 2852, 1460, 1600, 1374 cm^{-1} ; HRMS m/z 266.1099 (calcd for $\text{C}_{21}\text{H}_{14}$, 266.1096).

10-Methoxydibenz[*e,f*]acephenanthrylene (31). Compound **30** (0.115 g, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2 d. The reaction mixture was chromatographed using 50:1 hexanes/ethyl acetate to afford 54.0 mg (65 %) of the indicated compound **31** as a white solid: mp 178-179 °C; ^1H NMR (CDCl_3) δ 3.95 (s, 3H), 6.93 (dd, $J = 8.1, 2.4$ Hz, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.60-7.66 (m, 1H), 7.70-8.03 (m, 7H), 8.11 (s, 1H), 8.98 (d, $J = 8.4$ Hz, 1H), 9.19 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 55.9, 107.4, 113.4, 119.6, 121.0, 122.8, 122.8, 126.0, 126.8, 127.3, 127.5, 127.8, 128.3, 128.4, 128.6, 128.7, 129.0, 131.5, 131.5, 133.8, 133.8, 136.1, 137.4, 142.6, 160.6; IR (CH_2Cl_2) 2921, 2849, 1608, 1461, 1285, 1213 cm^{-1} ; HRMS m/z 332.1209 (calcd for $\text{C}_{25}\text{H}_{16}\text{O}$, 332.1201).

Indeno[1,2,3-*de*]quinoline (35). Compound **34** (82.8 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2.5 d. The reaction mixture was chromatographed using 3:2 hexanes/ethyl acetate to afford 27.4 mg (54 %) of the indicated compound **35** as a white solid: mp 100-101 °C (lit²⁹ mp 102-103 °C); ¹H NMR (CDCl₃) δ 7.35-7.51 (m, 2H), 7.72-7.77 (m, 2H), 7.84-7.91 (m, 3H), 7.99 (d, J = 8.4 Hz, 1H), 9.07 (d, J = 4.2 Hz, 1H); ¹³C NMR (CDCl₃) δ 114.4, 121.0, 122.2, 123.7, 128.2, 128.4, 130.4, 131.7, 135.4, 138.2, 138.2, 140.5, 145.1, 145.7, 152.9. The other spectral properties were identical to those previously reported.³⁰

11-Phenyl-6H-isoindolo[2,1-*a*]indole (41). Compound **40** (103 mg, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d affording a 92 % yield of the indicated compound **41**, which is unstable on silica gel, as determined by ¹H NMR spectroscopy. To obtain pure compound **41**, the crude product was recrystallized (hexane/EtOAc) to afford a pale purple solid: mp 148-151 °C; ¹H NMR (DMSO-*d*₆) δ 5.27 (s, 2H), 7.09-7.13 (m, 1H), 7.21-7.25 (m, 1H), 7.36-7.39 (m, 3H), 7.51-7.58 (m, 3H), 7.63-7.65 (m, 1H), 7.68-7.70 (m, 3H), 7.74-7.76 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 48.2, 108.0,

110.2, 119.5, 120.0, 120.2, 122.0, 124.2, 126.2, 127.6, 128.0, 128.7, 128.9, 130.4, 131.9, 133.5, 134.4, 139.3, 142.7; IR (CH₂Cl₂) 3053, 2985, 1616, 1603, 1497 cm⁻¹; HRMS *m/z* 281.1209 (calcd for C₂₁H₁₅N, 281.1205).

8-Methoxy-11-phenyl-6H-isoindolo[2,1-a]indole (43) and 10-methoxy-11-phenyl-6H-isoindolo[2,1-a]indole (44). Compound **42** (0.110 g, 0.25 mmol) was allowed to react under our standard reaction conditions for 12 h. The reaction mixture was chromatographed using 9:1 hexane/EtOAc to afford 61 mg (78 %) of the compound **43** as a yellow solid and 9 mg (12 %) of the compound **44**. Compound **43**: mp 196-198 °C; ¹H NMR (DMSO-*d*₆) δ 3.83 (s, 3H), 5.23 (s, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.07-7.10 (m, 1H), 7.17-7.21 (m, 1H), 7.27 (s, 1H), 7.34-7.37 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.53-7.57 (m, 2H), 7.66-7.68 (m, 4H); ¹³C NMR (DMSO-*d*₆) δ 48.4, 55.8, 108.1, 109.3, 109.8, 113.7, 120.0, 120.3, 121.9, 122.1, 126.0, 126.2, 128.9, 129.3, 131.6, 134.1, 135.4, 140.3, 144.2, 159.7; IR (CH₂Cl₂) 3051, 1686, 1450 cm⁻¹; HRMS *m/z* 311.1316 (calcd for C₂₂H₁₇ON, 311.1310).

11-Phenyl-6H-isoindolo[2,1-a]indol-6-one (46). Compound **45** (0.106 g, 0.25 mmol) was allowed to react under our standard reaction conditions for 1 d. The reaction mixture

was chromatographed using 10:1 hexane/EtOAc to afford 24 mg (33 %) of the indicated compound **46** as a yellow solid: mp 222-223 °C; ^1H NMR (CDCl_3) δ 7.17-7.21 (m, 1H), 7.31-7.36 (m, 2H), 7.40-7.44 (m, 1H), 7.45-7.49 (m, 1H), 7.54-7.60 (m, 4H), 7.70-7.72 (m, 2H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 113.8, 120.8, 121.4, 121.5, 124.3, 125.6, 127.0, 128.6, 129.0, 129.2, 129.3, 132.4, 133.9, 134.0, 134.1, 134.2, 134.4, 134.9, 162.8; IR (CH_2Cl_2) 3053, 2987, 1731, 1264 cm^{-1} ; HRMS m/z 295.1003 (calcd for $\text{C}_{21}\text{H}_{13}\text{ON}$, 295.0997).

9-Phenyl-7,8-dihydro-6H-benzo[c]pyrido[1,2,3-*lm*]carbazole (48). Compound **47** (116 mg, 0.25 mmol) was allowed to react under our standard reaction conditions for 12 h. The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 54 mg (65 %) of the indicated compound **48** as a yellow solid: mp 239-241 °C; ^1H NMR (CDCl_3) δ 2.21-2.29 (m, 2H), 2.87 (t, $J = 6.0$ Hz, 2H), 4.31 (t, $J = 5.7$ Hz, 2H), 7.28-7.34 (m, 1H), 7.35-7.55 (m, 8H), 7.61-7.65 (m, 2H), 8.58 (d, $J = 7.8$ Hz, 1H), 8.74-8.77 (m, 1H); ^{13}C NMR (CDCl_3) δ 22.8, 24.8, 41.3, 109.1, 112.5, 119.9, 121.1, 122.3, 122.6, 123.2, 123.7, 123.9, 125.9, 127.4, 127.9, 128.5, 129.1, 129.2, 130.8, 135.3, 135.7, 139.1, 139.2; IR (CH_2Cl_2) 3053, 2986, 1421, 1265 cm^{-1} ; HRMS m/z 333.1523 (calcd for $\text{C}_{25}\text{H}_{19}\text{N}$, 333.1518). Anal. Calcd for $\text{C}_{25}\text{H}_{19}\text{N}$: C, 90.06; H, 5.74; N, 4.20. Found: C, 90.27; H, 5.44; N, 4.17.

Benzo[fl]fluoreno[1,9-*bc*]oxepine (50). Compound **49** (99.1 mg, 0.25 mmol) was allowed to react under our standard reaction conditions at 110 °C for 2 d. The reaction mixture was chromatographed using 18:1 hexanes/ethyl acetate to afford 53.6 mg (80 %) of the indicated compound **50** as a white solid: mp 106-107 °C; ^1H NMR (CDCl_3) δ 6.69 (dd, J = 7.6, 0.8 Hz, 1H), 6.83 (s, 1H), 6.93-6.95 (m, 1H), 6.97-6.99 (m, 1H), 7.05-7.07 (m, 1H), 7.16-7.30 (m, 5H), 7.58-7.59 (m, 1H), 7.62-7.64 (m, 1H); ^{13}C NMR (CDCl_3) δ 115.4, 117.2, 120.4, 120.6, 122.3, 124.8, 126.0, 127.2, 128.3, 128.7, 129.1, 131.3, 131.4, 132.4, 137.1, 137.6, 139.9, 141.0, 154.8, 155.6; IR (CH_2Cl_2) 3050, 1580, 1238, 1450, 1426 cm^{-1} ; HRMS m/z 268.0892 (calcd for $\text{C}_{20}\text{H}_{12}\text{O}$, 268.0888).

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CHAPTER 5. SYNTHESIS OF CYCLOPROPANES BY A NOVEL PALLADIUM-CATALYZED ACTIVATION OF ALKYL C-H BONDS

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Abstract

An efficient synthesis of cyclopropanes has been developed using palladium-catalyzed C-H activation in which two new carbon-carbon bonds are formed in a single step. This method involves the palladium-catalyzed activation of unreactive alkyl C-H bonds and provides an efficient way to synthesize cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics.

Introduction

The ability of palladium to activate C-H bonds has been used extensively in organic synthesis.¹ In recent years, palladium-catalyzed C-H activation has received considerable attention due to the wide variety of reactions this metal will catalyze. For instance, catalytic amounts of Pd salts have been used to effect the addition of C-H bonds of electron-rich arenes to alkenes and alkynes, and to effect carbonylation.² We have previously reported the synthesis of 9-benzylidene-9*H*-fluorenes by Pd-catalyzed intramolecular C-H activation involving the rearrangement of organopalladium intermediates derived from aryl halides and internal alkynes.³ Similarly, intramolecular C-H activation in organopalladium intermediates derived from *o*-halobiaryls leads to a 1,4-palladium migration (Scheme 1).⁴ We have already

shown that such intermediates can be trapped by Heck, Suzuki, and alkyne annulation reactions,^{4,5} and intramolecular arylation.⁶ Herein, we wish to report a novel C-H activation using palladium chemistry to synthesize cyclopropanes,⁷ especially cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics.⁸

Results and Discussion

During our investigation of Pd-catalyzed aryl to aryl migration chemistry,⁶ iodoindole **1** was allowed to react under our standard palladium migration conditions, but only trace amounts of the desired migration/arylation product **3** were detected (eq 1). Surprisingly, compound **2** was isolated in a 42 % yield. As shown in Scheme 2, the indolylpalladium iodide **A**, formed by palladium migration from the 2 position of the phenyl group to the 2 position of the indole ring, apparently reacts with the carbon-carbon double bond to generate an alkyl intermediate **B**. Instead of forming a new carbon-carbon bond at the 2 position of the phenyl group by a seven-membered palladacycle **C**, the alkylpalladium iodide apparently forms a cyclopropane ring by activating a relatively unreactive alkyl C-H bond. Due to our interest in the novel palladium-catalyzed activation of alkyl C-H bonds and the substantial biological activity of cyclopropapyrrolo[1,2-*a*]indoles,⁹ we have investigated this novel

palladium-catalyzed C-H activation and have examined its scope by employing various substrates.

Scheme 2

Our initial studies focused on achieving optimal reaction conditions for this novel palladium-catalyzed C-H activation process employing the isomeric iodoindole **4** (eq 2).

While the reaction of compound 1 generated a 42 % yield of the desired cyclopropane 2 (eq 1), the reaction of compound 4 under the same reaction conditions [5 % Pd(OAc)₂, 5 mol % *bis*(diphenylphosphino)methane (dppm), 2 equiv of CsO₂CCMe₃ (CsPiv) and DMF as the

Table 1. Optimization reactions for the synthesis of compound 2.^{a,b}

entry	catalyst	ligand	base	temperature (°C)	time (h)	% yield of 2 ^c
1	5 % Pd(OAc) ₂	5 % dppm	2 CsPiv	110	6	62 ^d
2		--	2 CsPiv	110	12	37
3		--	2 Bu ₃ N	110	72	15
4		5 % dppm	2 CsPiv	100	24	55 ^e
5		5 % dcpm	2 CsPiv	110	1.5	47 ^e
6		5 % dppm	2 NaOAc	115	24	36 ^e
7		5 % dppm	2 Na ₂ CO ₃	110	72	26 ^e
8		5 % dppm	2 Cs ₂ CO ₃	115	48	52 ^e
9		5 % dppm	2 KO- <i>t</i> -Bu	115	0.5	trace
10	5 % Pd(PPh ₃) ₄	5 % dppm	2 Na ₂ CO ₃	110	72	30 ^e
11	5 % Pd(PPh ₃) ₄	--	2 Na ₂ CO ₃	110	72	27 ^e

^a All reactions were carried out under the following reaction conditions: 0.25 mmol of compound 4, 5 mol % Pd(OAc)₂, 5 mol % dppm, 2 equiv of CsPiv in 4 mL of DMF at the indicated temperature under an Ar atmosphere. ^b Along with cyclopropane 2, another cyclopropane product, generated by having the palladium intermediate close onto the methyl group, has been obtained in a 5-10 % yield. ^c Isolated yield. ^d Compound 3 was isolated in a 15 % yield. ^e The yield is based on gas chromatographic analysis.

solvent] afforded cyclopropane **2** in a 62 % yield and compound **3** in a 15 % yield (entry 1, Table 1). Omitting dppm as the ligand, the yield dropped from 62 % (entry 1) to 37 % (entry 2). When Bu_3N was employed as the base, cyclopropane **2** was isolated in only a 15 % yield (entry 3). When the reaction was carried out at 100 °C, the yield dropped to 55 % (entry 4), and a longer reaction time was required to reach completion. Compared to the reaction using dppm as the ligand (entry 4), when *bis*(dicyclohexylphosphino)methane (dcpm), a more electron-donating ligand, was employed, the C-H activation process was much faster and reached completion in 1.5 h (entry 5). However, the yield decreased to 47 % from 55 % (entry 4). There was no reaction when NaOAc was employed as a base even at 110 °C. However, the reaction did proceed when the reaction temperature was increased to 115 °C, although the yield of cyclopropane **2** was low (entry 6). The bases Na_2CO_3 , Cs_2CO_3 , and KO-*t*-Bu have also been employed and the desired cyclopropane **2** has been obtained in a yield of 26 %, 52 %, and a trace amount, respectively (entries 7-9). When $\text{Pd}(\text{PPh}_3)_4$ was employed as the catalyst with and without the addition of dppm, compound **2** was produced in 30 % and 27 % yields, respectively (entries 10 and 11). Thus, we chose the following conditions as our “optimal” reaction conditions: 0.50 mmol of the substrate, 5 mol % $\text{Pd}(\text{OAc})_2$, 5 mol % dppm, 2 equiv of CsPiv in DMF (4 mL) stirred at 110 °C under an Ar atmosphere.

Using our optimal reaction conditions, the scope of this novel Pd-catalyzed C-H activation process has been explored using a variety of substrates carefully selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems (Table 2). While the reaction of compound **4** afforded cyclopropane **2** in

Table 2. Synthesis of cyclopropanes by Pd-catalyzed activation of unreactive C-H bonds^{a,b}

entry	aryl iodide	time (h)		product	% yield ^c	
1		1	8		2	42
2		4	6		2	62
3		5	12		6	40 (46 ^d)
4		7	12		8	trace
5		9	16		10	31 ^d
6		11	18		12	42

Table 2 continued

7		13	3		14	< 5 %
8		15	12		16	trace
9		17	12		18	0
10		19	12		20	72
11		21	24		22	trace
12		23	12		24	88 ^c

^a All reactions were carried out under the following reaction conditions, unless otherwise specified: 0.5

mmol of the substrate, 5 mol % Pd(OAc)₂, 5 mol % dppm, 2 equiv of CsPiv in 4 mL of DMF at 110 °C

under an Ar atmosphere. ^b For entries 1-3, 5 and 6, along with the desired cyclopropane derivative, another

cyclopropane product has been detected in 5-10 % yields, in which the palladium closes onto the methyl

group. ^c Isolated yield. ^d The yield was determined by gas chromatographic analysis. ^e The reaction was

carried out at 100 °C.

a 62 % yield (entry 2), the reaction of iodoindole **5** generated cyclopropane **6** in a 46 % yield (entry 3). Iodoindole **7**, with no substituent in the 3 position of the indole ring, has been allowed to react under our optimal reaction conditions, but only a trace amount of the desired product was detected. It is quite possible that the alkylpalladium intermediate first produced undergoes palladium migration to the 3 position of the indole ring circumventing cyclopropane formation, although we failed to isolate any recognizable products (Scheme 3). This type of alkyl to aryl palladium migration has been observed previously in our research group under these same reaction conditions.¹⁰

Scheme 3

To test if the C-H activation process occurs when forming a new 6-membered ring, we have prepared compounds **9** and **11** and carried out the corresponding reactions under our optimal reaction conditions (entries 5 and 6). Although the yields are a little lower, those new fused 6-membered ring systems can be generated by this palladium-catalyzed alkyl C-H activation chemistry.

Is the indole nitrogen essential to this C-H activation process? To clarify this question, compounds **13** and **15** were employed under our optimal reaction conditions. Unfortunately, only trace amounts of the desired cyclopropane products **14** and **16** were detected by GC

analysis (entries 7 and 8). It appears that the indole ring system is critical to the formation of the cyclopropanes by this Pd-catalyzed C-H activation process. Consistent with this observation is the fact that the reaction of compound **17** afforded none of the desired cyclopropane product. It is quite possible that compound **17** under our reaction conditions may generate a π -allylpalladium intermediate, which circumvents cyclopropane formation. When compound **19** was employed, the reaction again failed to produce any cyclopropane product. However, 2-iodo-3-phenylindole was isolated in a 72 % yield (entry 10). This product probably arises by simple decomposition of the *N*-(alkoxycarbonyl)indole. When, aryl bromide **21** was allowed to react under our optimal reaction conditions, none of the desired cyclopropane product was detected (entry 11).

When compound **23** was allowed to react under our optimal conditions, instead of obtaining the expected cyclopropane product, compound **24** was isolated in an 88 % yield after 12 h at 100 °C (entry 12). Possible mechanisms for the formation of ether **24** are shown in Scheme 4. Under our reaction conditions, the initial arylpalladium iodide is expected to react with the carbon-carbon double bond to form an alkylpalladium intermediate **D**. Instead of activating a relatively unreactive alkyl C-H bond, the palladium intermediate is more likely to react with a neighboring aromatic C-H bond to generate intermediate **E** or **F**. These species may arise not only because the aromatic C-H bonds are more acidic and thus more reactive, but also because formation of five-membered ring palladacycles is more favorable than formation of four-membered ring palladacycles. Intermediate **E** or **F** can then undergo reductive elimination, followed by intramolecular arylation, to afford the observed product, compound **24**, in a good yield. Thus, this process is another example of an alkyl to aryl palladium migration, similar to others observed recently in our research group.

Scheme 4

Conclusion

A novel palladium-catalyzed activation of simple alkyl C-H bonds has been investigated as a unique new way to form polycyclic cyclopropanes. Our experiments indicate that the indole ring is apparently critical to this activation process. This method provides an efficient synthesis of cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics.⁸

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and a basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. All reagents were used directly as obtained commercially unless otherwise noted. (2-Iodophenyl)acetaldehyde,¹¹ 2-iodo-3-phenylindole¹² and compounds **13**,¹³ **15**,¹⁴ and **17**¹⁴ were prepared according to literature procedures.

3-(2-Iodophenyl)indole. To a solution of (2-iodophenyl)acetaldehyde¹¹ (0.738 g, 3.0 mmol) in 15 mL of absolute ethanol was added 0.356 g of PhNHNH_2 (3.3 mmol) and 57.6 mg of $\text{CH}_3\text{SO}_3\text{H}$ (0.6 mmol). The resulting yellow solution was stirred at 25 °C for 1 h. Another 0.519 g of $\text{CH}_3\text{SO}_3\text{H}$ (5.4 mmol) was then added to the reaction mixture and the reaction was stirred at 85 °C for 2 d. The reaction was then allowed to cool to 25 °C. The ethanol was removed under reduced pressure and the residue was diluted with Et_2O (30 mL), washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5:1 hexane/ EtOAc) to afford 0.41 g of the indicated compound (43 % yield) as an yellow oil: ^1H NMR (CDCl_3) δ 7.01-7.05 (m, 1H), 7.14-7.18 (m, 1H), 7.23-7.27 (m, 1H), 7.38-7.49 (m, 4H), 7.54 (d, J = 8.0 Hz, 1H), 8.01 (dd, J = 1.2, 8.0 Hz, 1H), 8.27 (br s, 1H); ^{13}C NMR (CDCl_3) δ 101.0, 111.5, 120.3,

120.4, 122.6, 123.8, 126.8, 128.2, 128.5, 131.6, 135.8, 140.0, 140.1 (one sp^2 carbon missing due to overlap).

3-Methyl-3-butenyl tosylate.¹⁵ To a mixture of Et_3N (2.026 g, 20 mmol) and 3-methyl-3-buten-1-ol (0.862 g, 10 mmol) in CH_2Cl_2 at 0°C was slowly added *p*-tosyl chloride (1.909 g, 10 mmol). The reaction mixture was stirred at 0°C for 3 h, then diluted with CH_2Cl_2 , washed with 10 % aq HCl, 10 % aq NaHCO_3 , and water and then concentrated, and dried over anhydrous Na_2SO_4 to afford the indicated compound (2.015 g, 84 %) as a yellow oil, which was used without further purification.

***N*-(3-Methyl-3-butenyl)-3-(2-iodophenyl)indole (1).** To a suspension of NaH (0.75 mmol, 60 % in mineral oil) in dry DMF (2 mL) was added dropwise a solution of 3-(2-iodophenyl)indole (0.16 g, 0.50 mmol) in dry DMF (2.5 mL) at 0°C under an Ar atmosphere. Lots of bubbles were generated. The resulting deep yellow suspension was stirred at 0°C for 30 min. A solution of 3-methyl-3-butenyl tosylate (0.24 g, 1.0 mmol) in dry DMF (2.5 mL) was added dropwise and the resulting yellow solution was stirred at 0°C for 14 h. The reaction was diluted with Et_2O (25 mL), washed with brine (30 mL), and the organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was chromatographed (15:1 hexane/ EtOAc) to afford 0.137 g of the indicated compound in a 71 % yield as a yellow oil: ^1H NMR (CDCl_3) δ 1.79 (s, 3H), 2.58 (t, $J = 7.2$ Hz, 2H), 4.27-4.32 (m, 2H), 4.74 (d, $J = 0.6$ Hz, 1H), 4.82-4.83 (m, 1H), 6.96-7.02 (m, 1H), 7.11-7.16 (m, 1H), 7.22-7.29 (m, 1H), 7.29 (s, 1H), 7.35-7.48 (m, 3H), 7.52-7.55 (m, 1H), 7.99 (dd, $J = 1.2, 7.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 22.9, 38.4, 45.3, 100.9, 109.7, 113.0, 118.6, 119.8, 120.5, 122.0, 127.3, 127.5, 128.2, 128.3, 131.6, 135.8, 140.0, 140.2, 142.2; IR

(neat, cm^{-1}) 3048, 2966, 2933, 1649, 1585, 1458; HRMS Calcd for $\text{C}_{19}\text{H}_{18}\text{NI}$: 387.0484.

Found: 387.0490.

***N*-(3-Methyl-3-butenyl)-2-iodo-3-phenylindole (4).** Using the procedure used to prepare compound 1, but employing 2-iodo-3-phenylindole¹² and 3-methyl-3-butenyl tosylate, afforded compound 4 in an 88 % yield as a yellow oil: ^1H NMR (CDCl_3) δ 1.87 (s, 3H), 2.44-2.49 (m, 2H), 4.34-4.39 (m, 2H), 4.84 (d, $J = 0.9$ Hz, 1H), 4.88 (d, $J = 0.9$ Hz, 1H), 7.06-7.11 (m, 1H), 7.17-7.22 (m, 1H), 7.35-7.40 (m, 2H), 7.47-7.50 (m, 2H), 7.56-7.61 (m, 3H); ^{13}C NMR (CDCl_3) δ 23.1, 38.0, 46.8, 85.8, 109.8, 112.7, 119.4, 120.3, 122.5, 123.4, 127.0, 128.2, 128.6, 130.3, 135.4, 137.9, 142.4; IR (neat, cm^{-1}) 3072, 2963, 2936, 1649, 1603, 1530, 1446; HRMS Calcd for $\text{C}_{19}\text{H}_{18}\text{NI}$: 387.0484. Found: 387.0491.

2-Iodo-3-methylindole. This compound was prepared by modifying a reported procedure.¹⁶ To a solution of 3-methylindole (2.64 g, 20 mmol) in dry THF (55 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 8.4 mL, 21 mmol) at -78°C under an Ar atmosphere. The resulting suspension was stirred at -78°C for 20 min. Carbon dioxide was bubbled through the reaction mixture for 30 min. The resulting clear yellow solution was then warmed to 25°C . Lots of bubbles were generated. The solvent was removed under reduced pressure at 25°C . To the residue was added dry THF (50 mL) and the reaction mixture was allowed to cool to -78°C . To the yellow solution was added slowly *t*-BuLi (1.7 M in pentane, 12.5 mL, 21.3 mmol) and the resulting orange solution was stirred at -78°C for 1 h. A solution of $\text{ICH}_2\text{CH}_2\text{I}$ (recrystallized from MeOH) (5.64 g, 20 mmol) in dry THF (15 mL) was added at -78°C . The resulting yellow solution was stirred at -78°C for another 1 hour and was then warmed to 25°C . The reaction mixture was washed with satd aq NH_4Cl (50 mL). The organic layer was dried over Na_2SO_4 and the residue was chromatographed

(5:1 hexane/EtOAc) to afford 5.15 g of the indicated compound in a 97 % yield with spectra identical to those previously reported.¹⁶

***N*-(3-Methyl-3-butenyl)-2-iodo-3-methylindole (5).** Using the procedure used to prepare compound 1, but employing 2-iodo-3-methylindole and 3-methyl-3-butenyl tosylate, afforded compound 5 in a 71 % yield as a yellow oil: ¹H NMR (CDCl₃) δ 1.84 (s, 3H), 2.31 (s, 3H), 2.36-2.40 (m, 2H), 4.23-4.27 (m, 2H), 4.79 (d, *J* = 0.8 Hz, 1H), 4.84 (d, *J* = 0.8 Hz, 1H), 7.05-7.09 (m, 1H), 7.12-7.16 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 0.4, 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 12.6, 23.1, 38.1, 46.4, 86.3, 109.6, 112.5, 117.3, 118.6, 119.3, 121.9, 128.7, 137.7, 142.5; IR (CDCl₃, cm⁻¹) 3074, 3055, 2968, 2912, 1649, 1456; HRMS Calcd for C₁₄H₁₆NI: 325.0328. Found: 325.0334.

***N*-(3-Methyl-3-butenyl)-2-iodoindole (7).** Using the procedure used to prepare compound 1, but employing 2-iodoindole and 3-methyl-3-butenyl tosylate, afforded compound 7 in a 68 % yield as a yellow oil: ¹H NMR (CDCl₃) δ 1.83 (s, 3H), 2.38-2.42 (m, 2H), 4.23-4.27 (m, 2H), 4.77-4.78 (m, 1H), 4.84-4.85 (m, 1H), 6.77 (d, *J* = 0.8 Hz, 1H), 7.04-7.08 (m, 1H), 7.12-7.16 (m, 1H), 7.31-7.33 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.51-7.54 (m, 1H); ¹³C NMR (CDCl₃) δ 23.1, 38.0, 46.3, 82.9, 109.7, 112.3, 112.7, 119.8, 120.0, 121.9, 130.0, 137.3, 142.3; IR (neat, cm⁻¹) 3061, 2962, 1649, 1455; HRMS Calcd for C₁₃H₁₄NI: 311.0171. Found: 311.0178.

4-Methyl-4-penten-1-ol. To 25 mL of dry THF was added slowly *t*-BuLi (1.7 M in pentane, 24.7 mL, 42 mmol) at -78 °C under an Ar atmosphere. The resulting yellow solution was stirred at -78 °C for 5 min, 2-bromopropene (1.86 mL, 21 mmol) was added dropwise, and the resulting suspension was stirred at -78 °C for 30 min. Oxetane (1.30 mL, 20 mmol) was added slowly and the reaction mixture was stirred at -78 °C for another 30

min. Then $\text{BF}_3 \cdot \text{OEt}_2$ (2.52 mL, 20 mmol) was added dropwise, and the clear yellow solution was further stirred at -78°C for 30 min. The reaction was quenched with brine (25 mL) and allowed to warm to 25°C . 10 mL of 10 % aq HCl was added to the reaction mixture and the organic layer was dried over NaSO_4 , and concentrated under reduced pressure. The residue was chromatographed (3:1 hexane/EtOAc) to afford 0.72 g of the indicated compound in a 36 % yield as a yellow oil with spectra identical to those previously reported.¹⁷

4-Methyl-4-pentenyl tosylate. To a mixture of pyridine (2.3 mL, 28.4 mmol) and 4-methyl-4-penten-1-ol (0.71 g, 7.1 mmol) in CH_2Cl_2 (10 mL) at 0°C was slowly added *p*-tosyl chloride (1.36 g, 7.1 mmol). The reaction mixture was stirred at 0°C for 12 h, then diluted with CH_2Cl_2 , washed with 10 % aq HCl (20 mL), 10 % aq NaHCO_3 (20 mL), and water (20 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was chromatographed (9:1 hexane/EtOAc) to afford 1.30 g of the indicated compound in a 72 % yield as a colorless oil: ^1H NMR (CDCl_3) δ 1.66 (s, 3H), 1.74-1.83 (m, 2H), 2.03 (t, $J = 7.5$ Hz, 2H), 2.45 (s, 3H), 4.03 (t, $J = 6.6$ Hz, 2H), 4.59 (d, $J = 0.6$ Hz, 1H), 4.69 (d, $J = 0.6$ Hz, 1H), 7.35 (d, $J = 7.5$ Hz, 2H), 7.78-7.80 (m, 2H); ^{13}C NMR (CDCl_3) δ 21.8, 22.4, 26.9, 33.5, 70.3, 111.1, 128.1, 130.0, 133.4, 144.0, 144.9.

***N*-(4-Methyl-4-pentenyl)-2-iodo-3-methylindole (9).** Using the procedure used to prepare compound **1**, but employing 2-iodo-3-methylindole and 4-methyl-4-pentenyl tosylate, afforded compound **9** in an 82 % yield as a yellow oil: ^1H NMR (CDCl_3) δ 1.75 (s, 3H), 1.84-1.91 (m, 2H), 2.10 (t, $J = 8.0$ Hz, 2H), 2.31 (s, 3H), 4.13-4.16 (m, 2H), 4.74 (s, 1H), 4.78 (s, 1H), 7.04-7.08 (m, 1H), 7.11-7.16 (m, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.50-7.52 (m, 1H); ^{13}C NMR (CDCl_3) δ 12.6, 22.7, 27.9, 35.0, 47.0, 86.5, 109.6, 110.7, 117.2, 118.5,

119.2, 121.8, 128.6, 137.9, 144.7. IR (neat, cm^{-1}) 3074, 3054, 2964, 1648, 1454; HRMS

Calcd for $\text{C}_{15}\text{H}_{18}\text{NI}$: 339.0484. Found: 339.0491.

***N*-(Isopropenyloxycarbonyl)-2-iodo-3-phenylindole (19).** Using the procedure used to prepare compound **1**, but employing 2-iodo-3-phenylindole and isopropenyl chloroformate, afforded compound **11** in a 77 % yield as a yellow solid: mp 85-87 °C; ^1H NMR (CDCl_3) δ 2.18 (d, $J = 0.4$ Hz, 3H), 4.92-4.93 (m, 1H), 5.02 (d, $J = 1.6$ Hz, 1H), 7.20-7.24 (m, 1H), 7.28-7.33 (m, 1H), 7.40-7.46 (m, 2H), 7.48-7.53 (m, 4H), 8.15 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.9, 77.9, 103.6, 115.8, 119.7, 123.8, 125.3, 128.3, 128.8, 130.5, 133.3, 134.2, 138.4, 148.9, 152.6 (one sp^2 carbon missing due to overlap); IR (CHCl_3 , cm^{-1}) 3019, 1746, 1677, 1445; HRMS Calcd for $\text{C}_{18}\text{H}_{14}\text{O}_2\text{NI}$: 403.0069. Found: 403.0076.

2'-(2-Bromophenyl)acetophenone. To a stirred mixture of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.702 g, 0.15 mmol), K_2CO_3 (4.15 g, 30 mmol), 2'-iodoacetophenone (2.46 g, 10 mmol), DMF (80 mL) and H_2O (18 mL) was added slowly a solution of 2-bromoboronic acid (3.01 g, 15 mmol) in DMF (10 mL) at 25 °C under an Ar atmosphere. The resulting mixture was stirred at 80 °C for 6 h and then allowed to cool to 25 °C, diluted with Et_2O (50 mL), and washed with brine (2 x 50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was chromatographed (10:1 hexane/ EtOAc) to afford 1.4 g of the indicated compound in a 52 % yield as a pale red oil: ^1H NMR (CDCl_3) δ 2.02 (d, $J = 0.8$ Hz, 3H), 7.23-7.28 (m, 3H), 7.35-7.37 (m, 1H), 7.45-7.50 (m, 1H), 7.52-7.56 (m, 1H), 7.64-7.66 (m, 1H), 7.73-7.76 (m, 1H); ^{13}C NMR (CDCl_3) δ 29.4, 123.1, 127.6, 128.3, 128.5, 129.4, 131.1, 131.3, 131.3, 132.9, 139.5, 140.3, 142.3, 201.7.

2-Bromo-2'-isopropenylbiphenyl (21). To a suspension of triphenylmethylphosphonium bromide (1.77 g, 4.95 mmol) in dry THF (25 mL) was added

slowly *n*-BuLi (2.5 M in hexane, 2.0 mL, 4.95 mmol) at 0 °C under an Ar atmosphere. The resulting yellow suspension was stirred at 0 °C for 30 min. A solution of 2'-(2-bromophenyl)acetophenone (3.3 mmol) in dry THF (5 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. The solvent was removed under reduced pressure and hexane (40 mL) was added to the residue. The mixture was stirred at 25 °C for 30 min and the phosphonium salt was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was chromatographed (30:1 hexane/EtOAc) to afford 0.90 g of the indicated compound in a 50 % yield as a white solid: mp 58-60 °C; ¹H NMR (CDCl₃) δ 1.77 (s, 3H), 4.82-4.83 (m, 1H), 4.95-4.97 (m, 1H), 7.15-7.23 (m, 2H), 7.24-7.39 (m, 5H), 7.61-7.64 (m, 1H); ¹³C NMR (CDCl₃) δ 23.7, 116.5, 123.9, 126.7, 127.0, 128.0, 128.5, 128.7, 130.7, 131.8, 132.8, 139.0, 142.9, 143.0, 145.1; IR (CHCl₃, cm⁻¹) 3058, 3011, 2969, 1632, 1463; HRMS Calcd for C₁₅H₁₃⁷⁹Br: 272.0201. Found: 272.0207.

3-Phenyl-3-butenyl tosylate. To a solution of TsCl (0.80 g, 4.2 mmol) in CH₂Cl₂ (3 mL) was added dropwise a solution of 3-bromo-3-buten-1-ol (0.302 g, 2.0 mmol) in CH₂Cl₂ (4 mL) at 0 °C under an Ar atmosphere. Pyridine (2.56 mL) was added slowly and the reaction mixture was stirred at 25 °C for 3 h. The reaction was diluted with Et₂O (20 mL), washed with 1N HCl (2 x 20 mL) and brine (20 mL), and the organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude 3-bromo-3-butenyl tosylate was subjected to the following reaction without further purification. To a mixture of PdCl₂(PPh₃)₂ (70.1 mg, 0.1 mmol), K₂CO₃ (0.83 g, 6.0 mmol), 3-bromo-3-butenyl tosylate (crude, 2.0 mmol), DMF (5 mL) and H₂O (3 mL) was added a solution of PhB(OH)₂ (0.36 g, 3.0 mmol) in DMF (10 mL) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at 25 °C for 12 h. The reaction was diluted with Et₂O (20 mL) and washed with brine

(2 x 20 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was chromatographed (5:1 hexane/EtOAc) to afford 0.29 g of the indicated compound in a 48 % overall yield as a brown oil: ¹H NMR (CDCl₃) δ 2.44 (s, 3H), 2.86 (dt, *J* = 0.8, 7.2 Hz, 2H), 4.10 (t, *J* = 7.2 Hz, 2H), 5.08 (s, 1H), 5.34 (s, 1H), 7.25-7.31 (m, 7H), 7.72-7.74 (m, 2H); ¹³C NMR (CDCl₃) δ 21.8, 35.0, 68.9, 115.5, 126.2, 128.0, 128.1, 128.7, 130.0, 133.3, 139.9, 143.0, 144.9.

2-Iodophenyl 3-phenyl-3-butenyl ether (23). To a suspension of NaH (60 % in mineral oil, 44 mg, 1.12 mmol) in dry DMF (1.5 mL) was added a solution of 2-iodophenol (0.23 g, 1.02 mmol) in dry DMF (2 mL) at 0 °C under an Ar atmosphere. Lots of bubbles were generated. After 20 min, a solution of 3-phenyl-3-butenyl tosylate (0.28 g, 0.93 mmol) in dry DMF (2 mL) was added slowly. The reaction mixture was allowed to warm and stirred at 25 °C for 1 d to reach completion. The reaction was diluted with Et₂O (20 mL) and washed with brine (20 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduce pressure. The residue was chromatographed (35:1 hexane/EtOAc) to afford 0.15 g of the indicated compound in a 46 % yield as an yellow oil: ¹H NMR (CDCl₃) δ 3.07 (dt, *J* = 0.9, 6.9 Hz, 2H), 4.10 (t, *J* = 6.9 Hz, 2H), 5.25-5.27 (m, 1H), 5.43 (d, *J* = 1.2 Hz, 1H), 6.65-6.71 (m, 1H), 6.73 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.21-7.37 (m, 4H), 7.45-7.48 (m, 2H), 7.76 (dd, *J* = 2.0, 8.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 35.3, 68.2, 86.9, 112.5, 115.2, 122.7, 126.4, 127.9, 128.7, 129.6, 139.7, 140.8, 144.5, 157.6; IR (neat, cm⁻¹) 3080, 3056, 2946, 1581, 1464; HRMS Calcd for C₁₆H₁₅IO: 350.0168. Found: 350.0171.

General procedure for the synthesis of cyclopropanes by Pd-catalyzed C-H activation. To a 6 dram vial was added Pd(OAc)₂ (6.0 mg, 0.025 mmol), dppm (9.2 mg, 0.025 mmol), CsPiv (234 mg, 1.0 mmol), the substrate (0.50 mmol), and dry DMF (4 mL).

The reaction mixture was stirred at 25 °C under an Ar atmosphere for 5 min, and was then stirred at 110 °C. Completion of the reaction was monitored by thin-layer chromatography and GC-mass spectral analysis. When the reaction was complete, the reaction mixture was allowed to cool to 25 °C, diluted with Et₂O (20 mL), and washed with brine (20 mL). The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to purification by chromatography or gas chromatographic analysis.

8b-Methyl-8-phenyl-1,1a,2,8b-tetrahydrocyclopropa[3,4]pyrrolo[1,2-*a*]indole (1).

White solid: mp 158-160 °C; ¹H NMR (CDCl₃) δ 1.01-1.03 (m, 1H), 1.28 (dd, *J* = 4.8, 8.0 Hz, 1H), 1.46 (s, 3H), 2.08-2.10 (m, 1H), 4.05 (d, *J* = 6.4 Hz, 1H), 4.24 (dd, *J* = 5.6, 10.4 Hz, 1H), 7.06-7.17 (m, 3H), 7.25-7.29 (m, 1H), 7.42-7.46 (m, 2H), 7.61 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 17.5, 23.6, 24.2, 28.8, 46.5, 108.4, 109.2, 119.3, 119.7, 121.2, 125.6, 128.4, 129.5, 131.3, 132.8, 135.2, 145.7; IR (CHCl₃, cm⁻¹) 3018, 2930, 1602, 1478, 1460, 1216; HRMS Calcd for C₁₉H₁₇N: 259.1361. Found: 259.1365.

7a-Methyl-6,7,7a,7b,8,12b-hexahydrobenzo[*c*]pyrrolo[1,2,3-*lm*]carbazole (3).

White solid: mp 154-157 °C; ¹H NMR (CDCl₃) δ 1.37 (s, 3H), 2.61-2.65 (m, 2H), 2.96-3.05 (m, 2H), 4.14-4.19 (m, 1H), 4.33-4.40 (m, 1H), 7.01-7.05 (m, 1H), 7.15-7.17 (m, 2H), 7.20-7.22 (m, 1H), 7.25-7.30 (m, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.85-7.87 (m, 1H); ¹³C NMR (CDCl₃) δ 22.5, 35.9, 45.6, 45.9, 46.9, 104.1, 110.6, 119.8, 120.2, 120.7, 122.7, 124.3, 127.4, 129.0, 129.7, 134.2, 135.0, 136.0, 154.9; IR (CHCl₃, cm⁻¹) 3017, 2959, 1631, 1492, 1433, 1215; HRMS Calcd for C₁₉H₁₇N: 259.1361. Found: 259.1366.

8,8b-Dimethyl-1,1a,2,8b-tetrahydrocyclopropa[3,4]pyrrolo[1,2-*a*]indole (6). White solid: mp 53-55 °C; ¹H NMR (CDCl₃) δ 0.77-0.80 (m, 1H), 1.15 (dd, *J* = 0.8, 8.0 Hz, 1H), 1.66 (s, 3H), 1.98-2.01 (m, 1H), 2.34 (s, 3H), 3.94 (d, *J* = 10.0 Hz, 1H), 4.08-4.12 (m, 1H),

7.00-7.06 (m, 3H), 7.44 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 8.48, 17.8, 23.2, 23.9, 28.5, 46.4, 100.7, 108.7, 118.3, 118.5, 120.5, 132.7, 133.4, 145.1; IR (CHCl_3 , cm^{-1}) 3051, 3007, 2962, 2924, 1619, 1478, 1463; HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{N}$: 197.1205. Found: 197.1208.

10b-Methyl-1,10b-dihydro-2H-indeno[1,2,3-de]chromene (24). White solid: mp 51-53 °C; ^1H NMR (CDCl_3) δ 1.46 (s, 3H), 1.63-1.70 (ddd, $J = 8.0, 11.2, 11.2$ Hz, 1H), 2.29-2.33 (ddd, $J = 0.8, 8.0, 11.2$ Hz, 1H), 4.56 (ddd, $J = 0.8, 8.0, 13.2$ Hz, 1H), 4.65 (ddd, $J = 8.0, 11.2, 13.2$ Hz, 1H), 6.71-6.75 (m, 1H), 7.22-7.26 (m, 2H), 7.29 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.33-7.37 (m, 1H), 7.42-7.44 (m, 1H), 7.69-7.72 (m, 1H); ^{13}C NMR (CDCl_3) δ 25.7, 31.0, 42.6, 65.7, 112.5, 113.8, 121.3, 123.2, 127.1, 127.5, 129.5, 134.9, 140.4, 140.6, 153.0, 153.9; IR (CHCl_3 , cm^{-1}) 3053, 3010, 2963, 2919, 1614, 1592, 1486, 1447; HRMS Calcd for $\text{C}_{16}\text{H}_{14}\text{O}$: 222.1045. Found: 222.1048.

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GENERAL CONCLUSIONS

In this dissertation, the scope and limitations of iodocyclization and several palladium-catalyzed processes have been presented. A wide variety of isoquinolines, naphthyridines, naphthalenes, carbazoles, cyclopropanes and other heterocycles and carbocycles have been synthesized using these new methods.

Chapter 1 describes an efficient synthesis of a wide variety of halo-, selenium-, sulfur-containing substituted isoquinolines and naphthyridines, which employs very mild reaction conditions. This methodology accommodates a variety of iminoalkynes and affords the anticipated substituted isoquinolines and naphthyridines in moderate to excellent yields.

Chapter 2 describes an efficient and straightforward route to synthesize 4-(1-alkenyl)isoquinolines and 4-alkyl-3-arylisoquinolines containing a ketone group, using a palladium(II)-catalyzed cyclization, followed by olefination (Heck reaction). To form isoquinolines in high yields, both electronic effects and facilitation by an *ortho*-methoxy group are necessary.

Chapter 3 describes an efficient palladium-catalyzed synthesis of highly substituted naphthalenes and carbazoles, in which two new carbon-carbon bonds are formed in a single step under relatively mild reaction conditions. This method accommodates a variety of functional groups and generally affords the anticipated highly substituted naphthalenes and carbazoles in good to excellent yields.

Chapter 4 presents a novel method for the synthesis of complex fused polycycles employing two sequential Pd-catalyzed intramolecular processes involving C-H activation. This methodology exploits relatively facile aryl to aryl and vinylic to aryl palladium

migrations, followed by intramolecular arylation to prepare a wide variety of carbocycles and heterocycles.

Chapter 5 presents a novel palladium-catalyzed activation of relatively unreactive alkyl C-H bonds for the synthesis of cyclopropapyrrolo[1,2-*a*]indoles, analogues of the mitomycin antibiotics. Our experiments have shown that the indole ring is critical to this activation process.

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APPENDIX C. CHAPTER 3 ^1H AND ^{13}C NMR SPECTRA

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 Time 14:02
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 G11 0.03920000
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 PL1 0.70
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 LB 2
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 PC 1.00
 P1 - Processing parameters
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 SF 400.1300180
 KW GSINE
 SSB 0.0
 LB 2
 GB 0
 PC 1.00
 2D NMR plot parameters
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 CXL 20.00
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 F2ALO 1321.90
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 F1PH1 90.23
 F2PH1 0.230
 F2PH1 90.23

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APPENDIX D. CHAPTER 4 ^1H AND ^{13}C NMR SPECTRA

APPENDIX E. CHAPTER 5 ^1H AND ^{13}C NMR SPECTRA

data/dat2/nmr400/qh435-10.fid

delta/dx1/nmr400/qh503-1

data/dat2/nmr400/qh505-1.fid

APPENDIX A. CHAPTER 1 ^1H AND ^{13}C NMR SPECTRA

6-iodo-5-phenylchrysene

6-iodo-5-phenylchrysene

150.003
144.299
135.326
133.846
133.536
131.053
130.746
130.715
130.391
129.316
129.187
128.973
128.863
128.561
128.384
128.182
127.725
126.138
125.402
123.669
121.338
111.541

77.689
77.266
76.842

6-methylbenzo[e]acephenanthrylene

6e-1, f, d

APPENDIX B. CHAPTER 2 ^1H AND ^{13}C NMR SPECTRA

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