Domino C–H Functionalization Reactions of *gem*-Dibromoolefins: Synthesis of *N*-Fused Benzo[*c*]carbazoles

by

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A thesis submitted in conformity with the requirements
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University of Toronto

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Abstract

The development of a novel palladium-catalyzed domino reaction with indole-based *gem*-dibromoolefin substrates is described. The reaction allowed access to a new class of polycyclic nitrogen heterocycles: *N*-fused benzo[*c*]carbazoles. A key feature of this domino reaction was the participation of both bromides in C–H functionalization processes, a hitherto unprecedented reactivity. Various substituents and substitution patterns were tolerated in this reaction, allowing for a highly modular approach to these challenging synthetic targets. Mechanistic studies were performed to gain further insight into the reactivity of these systems and elucidate the sequence of reaction steps. The results indicate that isomerization of reaction intermediates likely played a key role in promoting a successful reaction.

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List of Abbreviations

Å	Angstrom
Ac	acetyl
Ad	adamantyl
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
Calcd	calculated
Cbz	carbobenzyloxy
conv.	conversion
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift, in parts per million
d	day(s)
CAN	ceric ammonium nitrate
CDI	1,1'-carbonyldiimidazole
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-(dimethylamino)pyridine

DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
eq.	equivalent(s)
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
h	hour(s)
HMDS	hexamethyldisilazane
HRMS	high-resolution mass spectrometry
<i>i</i>	<i>iso</i>
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IR	infrared
L	generic ligand
M	generic metal
Me	methyl
μW	microwave
min	minute(s)
mmol	millimole(s)
MP	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance
OAc	acetate
OPiv	pivalate

OTf	trifluoromethanesulfonate
<i>p</i>	<i>para</i>
Ph	phenyl
pin	pinacolate
Piv	pivaloyl
Pr	propyl
QPhos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
quant.	quantitative
R	generic group
R _f	retention factor
r.t.	room temperature
<i>t</i>	<i>tert</i>
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl or tetramethylsilane
tol	tolyl
Ts	<i>para</i> -toluenesulfonyl
TsOH	<i>para</i> -toluenesulfonic acid
X	generic halide/atom
Y	generic atom
Z	generic atom

Chapter 1 Introduction

1.1 Palladium-Catalyzed Cross Coupling Reactions

Over the past thirty years, palladium-catalyzed cross coupling reactions have arguably emerged as one of the most important and versatile methods for the formation of carbon-carbon and carbon-heteroatom bonds.¹ This is due largely in part to palladium's unique electronic and chemical properties, which enables it to act as both an oxidant and reductant under a variety of reaction conditions, satisfying a fundamental requirement of catalytic cross coupling reactions. Attesting to its importance and contribution to the field of organic chemistry, the 2010 Nobel Prize in Chemistry was awarded to researchers Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for “palladium-catalyzed cross couplings in organic synthesis”.

The suite of cross coupling reactions developed in the latter half of the 20th century trace their roots back to the 1960's, when Heck laid the groundwork with a series of papers published in 1968 describing the Pd-catalyzed arylation reactions of olefins with organomercury compounds.² Shortly thereafter in 1971, Mizoroki described an improved version utilizing aryl iodides in place of the organomercurial,³ and Heck followed up with his own findings a year after.⁴ From this point onwards, further examples of metal-catalyzed cross couplings continued to appear in the literature. In 1972, Kumada⁵ and Corriu⁶ independently reported the Ni-catalyzed cross coupling between organomagnesium reagents and sp² carbon halides, now known as the “Kumada-Corriu coupling”, while Murahashi described the Pd-catalyzed version

¹ For a comprehensive discussion on organopalladium chemistry, see: a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i.; de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Volumes 1 & 2. b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Volumes 1 & 2.

² a) Heck, R. F.; *J. Am. Chem. Soc.* **1968**, *90*, 5518. b) Heck, R. F.; *J. Am. Chem. Soc.* **1968**, *90*, 5531. c) Heck, R. F.; *J. Am. Chem. Soc.* **1968**, *90*, 5538. d) Heck, R. F.; *J. Am. Chem. Soc.* **1968**, *90*, 5542.

³ Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

⁴ Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

⁵ Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

⁶ Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Commun* **1972**, 144.

of the Kumada-Corriu coupling in 1975.⁷ These pioneering studies paved the way for a variety of other Pd-catalyzed cross couplings, and marked the beginning of the rise of palladium. In the years that followed, research focused on improving the original Kumada-Corriu coupling through substitution of the Grignard reagent with milder and more functional group tolerant variants. This led to the discovery that organometallic species derived from Zn,⁸ Sn,⁹ B¹⁰, and Si¹¹ were all effective coupling partners (Table 1.1). Further studies in the field led to the realization that heteroatom based nucleophiles such as amines could also be effectively coupled,¹² thus greatly enhancing the utility of cross coupling chemistry. Today, palladium-catalyzed cross couplings have risen to the forefront, and become an indispensable tool in modern synthetic chemistry.

Table 1.1 Common Pd-catalyzed cross coupling reactions

Name Reaction	Nucleophilic Partner		Year of Discovery
	R'	M	
Buchwald-Hartwig	Amine	Li, Na, K, Cs	1994
Hiyama	Alkyl, alkynyl, aryl	Si	1988
Kosugi-Migita-Stille	Alkyl, alkenyl, aryl	Sn	1977
Kumada-Corriu	Alkyl, alkenyl, aryl	Mg	1972
Mizoroki-Heck	Alkene	-	1968
Negishi	Alkyl, alkenyl, aryl	Zn	1977
Suzuki-Miyaura	Alkyl, alkenyl, aryl	B	1979

⁷ Yamamura, M.; Moritani, I.; Murahashi, S.-I.; *J. Organomet. Chem.* **1975**, 91, C39.

⁸ Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, 42, 1821.

⁹ a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301. b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, 100, 3636.

¹⁰ Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 20, 3437.

¹¹ Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, 53, 918.

¹² a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, 116, 5969. b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 7901.

At its core, a cross coupling reaction involves the union of an electrophilic partner **1.1** with its nucleophilic counterpart **1.2** to form the ligated species **1.3**. Although dozens of Pd-catalyzed cross coupling reactions have been developed over the past few decades, most of these could nonetheless be considered as “variations on a theme”, and thus follow the same elementary steps as outlined in Scheme 1.1 (ligand exchange processes have been omitted for clarity).

Scheme 1.1 Generalized catalytic cycle for Pd-catalyzed cross coupling reactions

Typically, Pd(II) precursor **1.4** undergoes *in situ* reduction to a Pd(0) source (**1.5**), although stable Pd(0) sources such as $\text{Pd}_2(\text{dba})_3$ may also be directly utilized. The cycle is initiated via oxidative addition of **1.5** into electrophilic partner **1.1** to give charge-neutral Pd(II) species **1.6**. In cases where the electrophilic partner is an organotriflate ($\text{X} = \text{OTf}$), or if silver salts are added to sequester the halide, a cationic Pd(II) complex results, so named because of the formal positive charge on Pd. Depending upon the nature of the nucleophilic partner (**1.2**), **1.6** can undergo either transmetalation or 1,2-insertion, ultimately resulting in the formation of a second Pd-carbon bond. Except for the Heck reaction, the cycle almost always follows the left path, where transmetalation with $\text{R}'\text{-M}$ (**1.2**) leads to the Pd(II) complex **1.7**, from which reductive elimination can occur to forge the coupled product $\text{R-R}'$ (**1.3**) with concomitant regeneration of active Pd(0) species **1.5**. In cases where the nucleophilic partner is an olefin (**1.8**), the right path

is followed, whereby migratory insertion occurs subsequent to formation of π -complex **1.9** to give the Pd(II) σ -complex **1.10**. Following β -hydride elimination, the π -complexed product **1.11** is formed. Subsequent de-complexation extrudes olefin **1.12**, and hydridopalladium(II) species **1.13** results. Finally, the catalytically active Pd(0) species **1.5** is regenerated via base-promoted reductive elimination of **1.13**.

1.2 Direct Arylation

1.2.1 Background

There is no doubt that Pd-catalyzed cross couplings, as described previously, are among the most reliable and versatile methods for carbon-carbon bond formation. Despite their utility, one major drawback common to all these reactions is the requirement that both coupling partners be pre-activated. This is undesirable from the perspectives of cost, as well as atom and step economy, since it requires the installation and subsequent removal of stoichiometric activating groups. The installation of activating groups adds several steps to the overall sequence, and may in itself be non-trivial. Thus, a process wherein a simple C–H bond could be utilized directly as a functional handle without pre-activation would be highly desirable (Scheme 1.2).

Scheme 1.2 Traditional cross coupling versus direct arylation processes

Because such processes formally represent the direct conversion of a carbon-bound hydrogen atom into a new functionality, they are referred to as “C–H functionalizations”. The term “C–H activation” is sometimes used interchangeably in this context; this should be discouraged however, as “C–H activation” implies the C–H bond in question is broken or “activated” via an

organometallic intermediate containing a C-M bond, rather than a reactive species formed oxidatively.¹³ Since the vast majority of studies performed on C-H functionalization pertain to aromatic C-H bonds, the term “direct arylation” is preferred as it is specific and makes no inferences to any particular reaction mechanism.¹⁴

Conceptually, three direct arylation processes could be envisioned, differentiated only by the nature of the second coupling partner. In the most ideal scenario, the biaryl product **1.16** would be generated through direct coupling of *two* unactivated arenes (process (d), Scheme 1.2). Because hydrogen is formally eliminated in the process, such reactions are also referred to as “dehydrogenative arylations”.^{14b} While the most appealing in terms of chemical ideality, issues associated with regioselectivity limit the scope to mainly heteroarenes or molecules containing a directing group.¹⁵ As a compromise between ideality and practicality, most direct arylations fall into either process (b) or (c) (Scheme 1.2), whereby only one coupling partner is an unactivated arene. However, regiocontrol still remains a major challenge, due to the ubiquity of C-H bonds with comparable dissociation energies present in such systems. For example, in the direct arylation between 4-bromotoluene and anisole, all three regioisomers of **1.20** were obtained in a nearly statistical mixture, in line with predictions based on steric bias alone (Scheme 1.3).¹⁶

Scheme 1.3 Direct arylation between 4-bromotoluene and anisole

¹³ Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, 97, 2879.

¹⁴ For selected reviews on direct arylation, see: a) Bellina, F.; Rossi, R. *Tetrahedron*, **2009**, 65, 10269. b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, 48, 9792. c) McGlacken, P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, 38, 2447. d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, 107, 174. e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, 36, 1173. f) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, 345, 1077. g) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, 102, 1731. h) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, 34, 633. i) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, 38, 1698.

¹⁵ a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, 111, 1215. b) Scheuermann, C. J.; *Chem. Asian. J.* **2010**, 5, 436.

¹⁶ Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 16496.

1.2.2 Regiocontrol in Direct Arylation

As appealing as direct arylation is, it would be of little synthetic value if it could not be performed in a controlled and selective manner. In order to overcome the issue of regioselectivity, various strategies have been devised over the years, and can be broadly classified into one of three categories: (i) use of a (potentially removable) directing group, (ii) use of electronically biased substrates, typically heterocycles; and (iii) intramolecular direct arylation employing tethers to limit the degrees of freedom in a system (Scheme 1.4).

Scheme 1.4 Strategies for regiocontrol in direct arylation

It should be noted that these strategies are by no means mutually exclusive, and indeed in many instances, they have been used synergistically in order to achieve the best possible regiocontrol and chemical yields.

1.2.2.1 Use of Directing Groups

As early as 1963, Kleiman and Dubeck observed the cleavage of *ortho* C–H bonds in azobenzene when it was heated in the presence of nickelocene (Scheme 1.5).¹⁷ Although this was a stoichiometric process, as a proof of concept it demonstrated the feasibility of regioselective C–H activation through use of a suitable directing group.

Scheme 1.5 Nickelocene mediated *ortho* C–H activation of azobenzene

The first example of catalytic direct arylation employing a directing group strategy came from the group of Miura and co-workers. They reported in 1997 that 2-phenylphenols could be arylated with very high regioselectivity via the directing effect of the phenolic hydroxyl group (Scheme 1.6).¹⁸ Using a slight excess of iodobenzene lead to monoarylated product **1.21** in good yield, while the diarylated product **1.22** was produced in moderate yield under slightly different conditions and using a large excess of iodobenzene. The authors rationalized the regioselectivity by postulating that after oxidative addition of Pd into iodobenzene, coordination of the phenolic oxygen leads to intermediate **1.23**. Since Pd is spatially proximate to the indicated C–H bond, facile C–H functionalization occurs, leading to the arylated products as shown. This strategy has since been successfully applied to other directing groups, including anilines,¹⁹ carbonyl derivatives,²⁰ and nitrogen-containing heterocycles.²¹

¹⁷ Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, 85, 1544.

¹⁸ Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* **1997**, 36, 1740.

¹⁹ Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, 44, 4046.

²⁰ a) Aldehydes: Gurbuz, N.; Ozdemir, I.; Cetinkaya, B. *Tetrahedron Lett.* **2005**, 46, 2273. b) Amides: Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, 41, 2655. c) Carbamates: Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, 132, 5837. d) Ketones: Satoh, T.; Miura, M.; Nomura, M. *J. Organomet. Chem.* **2002**, 653, 151.

²¹ a) Pyrazoles: Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, 7, 3657. b) Pyridines and Quinolines: Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 7330.

Scheme 1.6 Direct arylation using phenol as a directing group

1.2.2.2 Use of Heterocycles

Prior to the advent of directing groups, heterocycles were attractive targets for catalytic direct arylation, since in many cases the inherent electronic bias present in such systems was often sufficient to achieve good regioselectivity. Furthermore, as heterocycles are important structural motifs found in many natural products and pharmaceuticals, direct arylation represented an attractive method for functionalizing the heterocyclic core without the hassle of installing activating groups. An early example of intermolecular direct arylation of heterocycles came from the group of Ohta. They found that *N*-substituted indoles could be regioselectively arylated at the C-2 or C-3 position, depending on the substituent on the indole nitrogen (Scheme 1.7).²² Unsubstituted and *N*-alkyl indoles gave exclusively C-2-arylation product **1.26**, while tosyl substituted indole gave a mixture in favour of the C-3 product **1.28**. The observed regioselectivity had a dependence on the steric bulk of R', with bulkier R' groups on pyrazine **1.27** leading to higher selectivities. More recently, the scope of C-2 arylation of indoles has been

²² Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, 37, 1477.

significantly expanded by the groups of Sames and Sanford,²³ and protocols for selective C-3 arylation of indoles have also been developed.²⁴

Scheme 1.7 Regioselective direct arylation of *N*-substituted indoles

Ohta's pioneering work demonstrated that good regiocontrol could arise solely from the electronic bias intrinsic to heterocyclic substrates. In the years that followed, advances in the field have allowed a remarkably diverse array of heterocycles to undergo efficient direct arylation with good regiocontrol (Figure 1.1).²⁵

²³ a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

²⁴ a) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415. b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. c) Cusati, G.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 2499. d) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. e) Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929.

²⁵ Selected examples of direct arylation with heterocycles: a) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677. b) Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Organometallics* **2007**, *26*, 472. c) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. d) Gozzi, C.; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867. e) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685. f) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042. g) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. h) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. i) Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Wilson, J. E. *Org. Lett.* **2010**, *12*, 3578. j) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. k) Ranjit, S.; Liu, X. *Chem. Eur. J.* **2011**, *17*, 1105. l) Carrer, A.; Brinet, D.; Florent, J.-C.; Rousselle, P.; Bertounesque, E. *J. Org. Chem.* **2012**, *77*, 1316. m) Zhuravlev, F. A. *Tetrahedron Lett.* **2006**, *47*, 2929.

Figure 1.1 Heterocycles involved in direct arylation with reactive C–H bonds indicated

Significantly, it was shown that in heterocycles with more than one reactive site, regioselectivity could be controlled through changing certain reaction parameters. For example, Wilson and co-workers found that in the direct arylation between oxazole and bromobenzene, the C-2/C-5 selectivity could be altered simply by changing the ligand and the solvent.²⁵ⁱ Using ligand **L1** and DMA as the solvent, C-5 arylation product **1.29** was obtained in good yield with 58:1 selectivity. Changing the solvent to toluene and using RuPhos as the ligand led instead to C-2 arylation product **1.30** as the exclusive regioisomer in 75% yield (Scheme 1.8).

Scheme 1.8 Regioselective C-2 and C-5 direct arylation of oxazole

1.2.2.3 Intramolecular Direct Arylation

Intramolecular direct arylation represents one of the oldest strategies for controlling regioselectivity. By conjoining the reactive components in the same molecule through use of a tether, the degrees of freedom are greatly reduced, often leading to very high selectivities. One of the earliest examples of intramolecular direct arylation came about as the result of a

serendipitous discovery. During investigations into the Mizoroki-Heck reaction between bromocinnoline **1.31** and ethyl acrylate, Ames and Bull discovered that fused tetracycle **1.32** was obtained as the sole product in 55% yield with no traces of the expected Heck product (Scheme 1.9).²⁶

Scheme 1.9 Intramolecular direct arylation of a bromocinnoline

Further studies revealed that ethyl acrylate was not necessary for efficient reaction, and this insight set the stage for extension of this strategy to the synthesis of other carbocycles and heterocycles, such as dibenzofurans (**1.34**),²⁷ and polycyclic aromatic hydrocarbons (**1.36**) via direct arylation and concomitant dehydrogenation (Scheme 1.10).²⁸

Scheme 1.10 Synthesis of heterocycles and carbocycles via intramolecular direct arylation

²⁶ Ames, D. E.; Bull, D. *Tetrahedron* **1982**, 38, 383.

²⁷ Ames, D. E.; Opalko, A. *Synthesis* **1983**, 234.

²⁸ Gonzalez, J. J.; Garcia, N.; Gomez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, 62, 1286.

1.2.3 Direct Arylation in Total Synthesis

Significant progress has been achieved in the field of direct arylation since Ames' report and turned it into a viable alternative to traditional cross-coupling, as witnessed by its numerous applications in total synthesis. Fagnou and Leblanc successfully applied intramolecular direct arylation to aryl chloride **1.37** to forge the key biaryl carbon-carbon bond and form seven-membered intermediate **1.38** en route to their synthesis of Allocolchicine **1.39** (Scheme 1.11).²⁹

Scheme 1.11 Intramolecular direct arylation in the synthesis of Allocolchicine

In a similar vein, Trauner and co-workers utilized the same strategy in their synthesis of Rhazinilam. Direct arylation between the aryl iodide and the tethered pyrrole in intermediate **1.40** successfully furnished the biaryl bond, leading to the rather impressive looking nine-membered lactam **1.41** in 47% yield (Scheme 1.12).³⁰

Scheme 1.12 Intramolecular direct arylation in the synthesis of Rhazinilam

²⁹ Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, 7, 2849.

³⁰ Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, 7, 5207.

More impressive still however is the concise total synthesis of racemic Dragmacidin D by Itami and co-workers, in which *three* carbon-carbon bonds were constructed via direct arylation methods (Scheme 1.13).³¹ Using the steric bulk of the TIPS protecting group to their advantage, a Pd-catalyzed regioselective arylation between iodoindole **1.43** and thiophene **1.44** was achieved in 60% yield. Unwanted C-2 arylation was completely suppressed due to the steric encumbrance of the TIPS group, leading to the expected C-4 arylation product based on previous studies.³² After a series of manipulations, another Pd-catalyzed dehydrogenative arylation between MOM-protected indole **1.46** and pyrazine *N*-oxide set the first biaryl bond and furnished indole **1.47** in 50% yield. Although the yield for this dehydrogenative arylation was relatively modest, excellent regioselectivity was achieved as **1.47** was obtained as the sole regioisomer. A further 4 steps from indole **1.47** completed the synthesis of racemic Dragmacidin D. It is worth noting that the second biaryl bond in Dragmacidin D (indicated in Scheme 1.13) was formed via triflic acid promoted dehydrogenative arylation. Although this was not a Pd-catalyzed direct arylation process, it nevertheless still showcases the utility of direct arylation in the context of complex molecule synthesis.

Scheme 1.13 Total synthesis of racemic Dragmacidin D via direct arylation methods

³¹ Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660.

³² Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 8946.

1.2.4 Mechanistic Aspects of Direct Arylation

Palladium-catalyzed direct arylation with aryl halides typically initiate with oxidative addition of a Pd(0) species into the halide. At this point, several divergent mechanisms have been proposed for the subsequent C–H activation step,^{14b, d} and are outlined in Scheme 1.14.

Scheme 1.14 Proposed mechanisms for C–H activation in direct arylation reactions

These include (a) electrophilic aromatic substitution (S_EAr), (b) concerted metallation-deprotonation (CMD) via an S_E3 or σ -bond metathesis process, (c) Heck-type carbopalladation, and (d) oxidative addition into a C–H bond. In the S_EAr process, nucleophilic attack of the arene onto Pd(II) species **1.49** generates the Wheland intermediate **1.50**, which undergoes deprotonation and re-aromatization to organopalladium species **1.51**. Reductive elimination of

1.51 then leads to desired product **1.52**. For the CMD process, two related but distinct pathways have been proposed. The first involves η^1 coordination of Pd to the π -system of the arene (**1.53**), followed by simultaneous metallation and arene deprotonation by an external base in an S_E3 process (**1.54**). Alternatively Pd could also coordinate in an η^2 fashion (**1.55**), followed by σ -bond metathesis in which metallation and intramolecular proton abstraction by the halide take place at the same time (**1.56**). In the Heck-type mechanism, carbopalladation of **1.49** onto the arene gives intermediate **1.57**. From there, isomerization usually follows to allow for *syn* β -hydride elimination from **1.58**, although **1.57** may also undergo *anti* β -hydride elimination³³ to give **1.52** without prior isomerization. Finally, direct oxidative addition into the C–H bond could also occur, leading to high oxidation state Pd(IV) intermediate **1.59**. Subsequent reductive elimination from **1.59** then gives biaryl product **1.52**.

While the exact mechanism depends heavily on the substrate and reaction conditions, S_EAr , Heck-type, and oxidative addition processes have historically been favoured. However, recent investigations have pointed to S_E3 or σ -bond metathesis, collectively termed as concerted metallation-deprotonation (CMD), as being operative in most cases. Intermolecular competition experiments performed by Fagnou and co-workers between electronically differentiated pyridine *N*-oxides **1.60** and **1.61** showed that product **1.62** arising from arylation with the more electron-deficient substrate **1.60** was obtained in preference by a factor of greater than 20:1 (Scheme 1.15).³⁴ In addition, a large primary kinetic isotope effect (KIE) of 4.7 was observed when pyridine *N*-oxide and pyridine-*d*₅ *N*-oxide were subjected to the reaction conditions. These results were clearly in contravention with S_EAr being the operative mechanism.

Scheme 1.15 Intermolecular competition experiment between pyridine *N*-oxides

³³ Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, 5, 3679.

³⁴ Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, 127, 18020.

Similar trends were observed in intramolecular studies performed by Echavarren and co-workers. They observed that arylation occurred preferentially on the less nucleophilic, yet more C–H acidic trifluorophenyl ring of substrate **1.64** to give phenanthrene **1.65** with a selectivity of 25:1 (Scheme 1.16).³⁵

Scheme 1.16 Intramolecular competition experiment using a fluorinated substrate

Further investigations revealed that electron-withdrawing substituents facilitated the reaction, and additionally a large KIE of 5.0 was observed in a competition experiment using deuterated substrate **1.67** (Scheme 1.17).³⁶ As with Fagnou's observations, these results were clearly incompatible with an $\text{S}_{\text{E}}\text{Ar}$ process.

Scheme 1.17 Intramolecular competition experiment using a deuterated substrate

On the basis of these experimental findings, the authors propose that C–H activation most likely occurs via a CMD mechanism, in which proton abstraction from the aryl ring is assisted by

³⁵ Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, 128, 1066.

³⁶ García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, 129, 6880.

carbonate or a related anionic ligand. To further distinguish between the two subtypes of CMD, namely S_E3 and σ -bond metathesis, computational studies were undertaken. The results indicated that the site selectivity observed with substrate **1.64** could be much better explained by an intermolecular rather than an intramolecular process. Thus the authors conclude that an S_E3 mechanism is likely operative in their reactions.

During the development of an efficient catalytic system for direct arylation between aryl halides and benzene,¹⁶ Fagnou and Lafrance noted that the use of pivalate as an additive was uniquely effective in promoting catalytic turnover and achieving good yields. Use of other carboxylates such as acetate, propionate, isobutyrate, and 1-adamantanecarboxylate led to incomplete conversion and less than 40% yields (Scheme 1.18). Likewise, similar trends were observed for intramolecular direct arylations.³⁷

Scheme 1.18 Effect of additives in the direct arylation of benzene with 4-bromotoluene

In accordance with previous investigations by Echavarren and co-workers,³⁵ these findings strongly hinted at the involvement of pivalate in the C–H activation step, its role akin to that of carbonate. In the proposed catalytic cycle for pivalate assisted direct arylation, following oxidative addition of Pd(0) into the aryl bromide, two pathways may be followed. The first involves ligand exchange between pivalate and the bromide on **1.71** to give pivalate ligated Pd(II) species **1.73**. This can then metallate benzene in an intramolecular CMD process via transition state **1.74** to generate biaryl Pd(II) intermediate **1.75**, which reductively eliminates to product **1.76**. Alternatively, a second intermolecular pathway may involve pivalate acting as an external base at the C–H bond cleavage step via transition state **1.72** to intercept intermediate

³⁷ Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

1.75 without prior ligand exchange (Scheme 1.19). The authors propose that the superior reactivity of pivalate compared to other carboxylates may be attributed to both its steric bulk as well as the increased basicity of its conjugate base.

Scheme 1.19 Proposed catalytic cycle for direct arylation of benzene in the presence of pivalate

1.3 The *gem*-Dihalovinyl System³⁸

1.3.1 Properties and Preparation of *gem*-Dihaloolefins

The *gem*-dihalovinyl (1,1-dihalo-1-alkenyl) moiety scarcely occurs in nature, yet is often found in the chemical literature due to its versatility as a synthetic intermediate. Owing to the presence of two reactive vinylic halides, it serves as a useful bidentate electrophile in transition metal catalyzed reactions, as well as partaking in a variety of non-metal catalyzed processes. Apart from being synthetically valuable, the motif proves to be useful in its own right. The insecticide Deltamethrin (**1.77**) is perhaps the most widely used chemical to contain this structure (Figure 1.2). With an astonishing LD₅₀ of 0.03 mg/kg for insects, it possesses an insecticidal potency three orders of magnitude above the naturally occurring pyrethrin I, and is more than 30 times as active as earlier insecticides such as Parathion and DDT.³⁹ First synthesized in 1974, it has been applied to a range of commercial crops and still enjoys widespread use to this day. Around the same time Deltamethrin was being developed, a series of polybrominated butenolides were isolated from the dichloromethane soluble extracts of the red algae *Delisa fimbriata* found off the coasts of Sydney.⁴⁰ These butenolides were collectively named “Fimbrilides”, and stimulated much interest due to the significant antimicrobial activities they displayed.⁴¹ One such fimbrilide (**1.78**) was found to contain the *gem*-dihalovinyl motif, and is a rare example of a naturally occurring *gem*-dibromoolefin.

Figure 1.2 Examples of the *gem*-dihalovinyl motif in synthetic and natural products

³⁸ For an excellent and comprehensive review on this topic, see: Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344.

³⁹ a) Elliot, M.; Farnham, A. W.; James, N. F.; Needham, P. H.; Pulman, D. A. *Nature* **1974**, *248*, 710. b) Elliot, M.; James, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.

⁴⁰ Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1977**, *1*, 37.

⁴¹ Reichelt, J. L.; Borowitzka, M. A. *Hydrobiologia* **1984**, *116/117*, 158.

The preparation of *gem*-dihaloolefins typically entails the reaction of an aldehyde or ketone (**1.79**) with a dihalomethylene ylid (**1.80** or **1.81**), generally prepared *in situ* as they are quite reactive (Scheme 1.20). The first reported synthesis of a *gem*-dichloroolefin (**1.82**, R = R' = Ph) was achieved by reacting benzophenone with ylid **1.80** in a pentane-ether mixture. The ylid was generated from the reaction of triphenylphosphine and dichlorocarbene; the carbene being formed by treatment of chloroform with potassium *tert*-butoxide.^{42a} Subsequently it was found that using heptane as the solvent allowed for azeotropic removal of the *tert*-butanol generated from the deprotonation step, and led to an improvement in yields.^{42b} The authors also successfully extended the methodology to the synthesis of the *gem*-dibromoolefins of benzaldehyde and benzophenone, although in rather modest yields of 42% and 9% respectively. However, the need for prior removal of stoichiometric quantities of *tert*-butanol through azeotropic distillation rendered the synthesis rather inconvenient.

Scheme 1.20 Synthesis of *gem*-dihaloolefins from dihalomethylene ylids

Rabinowitz and Marcus reported that ylid **1.80** could be formed directly by refluxing the reaction mixture in carbon tetrachloride, obviating the need for removal of *tert*-butanol (Scheme 1.21).⁴³ Although the reaction setup was simplified, the yield of dichloroolefin **1.84** suffered due to the low reactivity of carbon tetrachloride, and benzal chloride (**1.85**) was formed as a side product in equal amounts. Around the same time, the bromo-version of this improvement was independently reported by Ramirez and co-workers.⁴⁴ Due to the much higher reactivity of

⁴² a) Speziale, A. J.; Marco, G. J.; Ratts, K. W. *J. Am. Chem. Soc.* **1960**, 82, 1260. b) Speziale, A. J.; Ratts, K. W. *J. Am. Chem. Soc.* **1962**, 84, 854.

⁴³ Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.* **1962**, 84, 1312.

⁴⁴ Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, 84, 1745.

carbon tetrabromide, the reaction was extremely facile even at room temperature, being complete in just 5 minutes, and providing dibromoolefin **1.86** in excellent yield. Two equivalents of triphenylphosphine was found to be necessary, as one equivalent was needed to scavenge Br_2 formally generated in the reaction. This led to an incompatibility with certain functional groups such as amines, due to the Lewis acidic nature of Br_2PPh_3 . To address these issues, the use of sacrificial scavengers such as Et_3N ⁴⁵ or Zn powder⁴⁶ has been reported.

Scheme 1.21 Improved synthesis of *gem*-dihaloolefins using tetrahalomethanes

Although Ramirez's conditions gave fairly good yields with aldehydes, ketones were much less reactive, often leading to incomplete conversions and low yields. To overcome this reactivity issue, Rezaei and Normant developed a three-step, non-ylid protocol utilizing organometallic reagents (Scheme 1.22).⁴⁷ Reaction of ketone **1.79** with the organolithium derived from bromoform gives alcohol **1.87**, which is acetylated (**1.88**) and finally deacetoxybrominated with a Grignard reagent to give dibromoolefin **1.89**. An alternative redox-based strategy reported by Korotchenko involves a Cu-catalyzed redox reaction between carbon tetrabromide and hydrazones **1.91** formed from ketones and hydrazine hydrate.⁴⁸ While the yields of the dibromoolefins were much improved, both of these methods involved multistep syntheses, and lacked the convenience afforded by Ramirez's single step, one-pot protocol.

⁴⁵ Grandjean, D.; Pale, P. Chuche, J. *Tetrahedron Lett.* **1994**, 35, 3529.

⁴⁶ Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 13, 3769.

⁴⁷ Rezaei, H.; Normant, J. *Synthesis*, **2000**, 139.

⁴⁸ Korotchenko, V. N.; Shastin, A. V.; Nenajdenko, V. G.; Balenkova, E. S. *J. Chem. Soc., Perkin Trans. I* **2002**, 883.

Scheme 1.22 Non-ylid approaches to *gem*-dibromoolefins of ketones

Seeking to develop a high-yielding approach to dibromoolefins of ketones that retained the operational simplicity of Ramierz's method, alternatives to triphenylphosphine were studied by undergraduate Olga Lifchits under the supervision of Eric Fang, a former graduate student.⁴⁹ Of the phosphorus reagents screened, triisopropyl phosphite was found to be uniquely effective in promoting the dibromoolefination reaction. Compared to triphenylphosphine, reaction with aldehydes gave comparable yields, while much improved and synthetically useful yields were obtained with ketones (Scheme 1.23). In addition, purification of the products was also made easier since all of the phosphorus byproducts were oils, and a simple recrystallization was often sufficient to obtain analytically pure product. This was especially important for large scale reactions, as the highly crystalline triphenylphosphine oxide produced in triphenylphosphine mediated reactions often made product isolation difficult.

Scheme 1.23 Synthesis of *gem*-dibromoolefins using triisopropyl phosphite

⁴⁹ Fang, Y.-Q.; Lifchits, O.; Lautens, M. *Synlett* **2008**, 413.

The synthetic potential of these *gem*-dibromoolefins was first realized in 1972. Corey and Fuchs discovered that dibromoolefins **1.95** underwent initial elimination to bromoalkyne **1.96** when treated with *n*-butyllithium. Under the reaction conditions, rapid *in situ* lithium-halogen exchange followed and led to the production of alkynyllithium **1.97**, which could be quenched with water or carbon dioxide to give terminal alkynes and propargylic acids (Scheme 1.24).⁴⁶ This discovery popularized the use of *gem*-dibromoolefins as intermediates in the synthesis of alkynes, and the conversion of aldehydes to alkynes is now known as the “Corey-Fuchs reaction”.⁵⁰

Scheme 1.24 The Corey-Fuchs alkyne synthesis reaction

1.3.2 Palladium-Catalyzed Reactions of *gem*-Dihaloolefins

The presence of two geminally bound halogen atoms on the alkenyl carbon render *gem*-dihaloolefins more reactive toward oxidative addition than their mono-halogenated counterparts. Capitalizing on this increased reactivity, various Pd-catalyzed reactions with *gem*-dihaloolefins have been developed. In 1987, Minato and Tamao described the first (*E*)-selective cross coupling between dichloroolefins **1.99** and Grignards or organozinc reagents (Scheme 1.25).⁵¹ By careful control of stoichiometry, mono-coupling products **1.100** could be achieved in excellent yields. Further coupling could be realized under slightly modified conditions to give bis-coupling products **1.101** in moderate to good yields. Most notably, trichloroethylene **1.102** which contains three reactive vinyl chlorides, underwent cross coupling with 4-chlorophenylmagnesium bromide exclusively at the (*E*)-chloride of the disubstituted carbon to give **1.103** in 90% yield. The authors noted that use of dppb as a ligand was crucial for selective

⁵⁰ The “Corey-Fuchs reaction” is really a two-step sequence rather than one single reaction, although literature often indiscriminately applies the term to describe the initial dibromoolefination step as well. The synthesis of dibromoolefins was well preceded, and acknowledged as such by Corey and Fuchs. Thus the term “Ramirez olefination” will be used hereafter to describe the dibromoolefination step.

⁵¹ Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257.

mono-coupling, and that the observed *E/Z* selectivity in these dichloroolefins was likely a result of the (*E*)-chloride being more sterically accessible, since the parent 1,1-dichloroethene (**1.99**, R = H) gave an almost 1:1 mixture of the mono- and bis-coupling products, while no reaction took place with the dichloroolefin derived from benzophenone. Since then, a number of (*E*)-selective Pd-catalyzed cross couplings with dichloro or dibromoolefins have been published.^{38, 52}

Scheme 1.25 (*E*)-selective cross coupling of *gem*-dichloroolefins

While investigating the reductive cyclization of aryl and vinyl bromides, Trost and Walchli observed that the dibromo substrate **1.104** cyclized to the *cis*-fused product **1.105** in 50% yield (Scheme 1.26).⁵³ Despite the higher reactivity and usual selectivity for the (*E*)-bromide, this appears to be the first reported example of selective reaction at the (*Z*)-bromide.

Scheme 1.26 Intramolecular reductive cyclization of a *gem*-dibromoolefin

Soderquist and co-workers reported that six-membered rings of type **1.107** containing a trisubstituted exocyclic double bond could be obtained via a double Suzuki coupling between

⁵² For a review of cross coupling reactions of dibromoolefins, see: Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405.

⁵³ Trost, B. M.; Walchli, R. *J. Am. Chem. Soc.* **1987**, *109*, 3487.

dibromoolefin **1.95** and the bis-9-BBN compound **1.106** (Scheme 1.27).⁵⁴ This demonstrated that both bromides of the *gem*-dibromoolefin moiety could be reacted in a one-pot fashion.

Scheme 1.27 Double Suzuki couplings of *gem*-dibromoolefins

During their studies on the stereoselective Stille coupling of aryl dibromoolefins, Wang and Shen discovered that if the dibromoolefin contained an *ortho*-substituted methyl ester (**1.108**), an isocoumarin (**1.109**) was isolated rather than the expected mono-coupling product (Scheme 1.28).⁵⁵ The authors noted that the (*E*) mono-coupling product could be isolated in some instances, and subjecting them to the reaction conditions led to the isocoumarin in good yields. Based on this, the authors reason that Stille coupling with the (*E*)-bromide should take place prior to cyclization with the (*Z*)-bromide.

Scheme 1.28 Synthesis of isocoumarins via domino reactions of *gem*-dibromoolefins

A few years later, Bissert and co-workers disclosed a domino C-O or C-N bond formation and Suzuki coupling sequence between dibromoolefins **1.110** and **1.111** and a suitable organoboron reagent for the synthesis of benzofurans and indoles (Scheme 1.29).⁵⁶ However, the scope of

⁵⁴ Soderquist, J. A.; Leon, G.; Colbert, J. C.; Martinez, I. *Tetrahedron Lett.* **1995**, 36, 3119.

⁵⁵ Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, 39, 7625.

⁵⁶ Thielges, S.; Meddah, E.; Bissert, P.; Eustache, J. *Tetrahedron Lett.* **2004**, 45, 907.

this transformation was not studied in any detail, and the authors noted that in the case of indole synthesis, the protecting group on the aniline nitrogen must be carefully selected, since both Boc-protected and unprotected aniline yielded only complex mixtures.

Scheme 1.29 Synthesis of heterocycles via domino reactions of *gem*-dibromoolefins

Inspired by this work, former graduate student Eric Fang set out to expand the scope and utility of this interesting transformation. He found that when SPhos was used as the ligand, the *N*-acetyl group was no longer necessary for the reaction to proceed with high yields and broad scope. In fact, *N*-protection proved detrimental to the yields under his conditions. With a set of optimized conditions in hand, Fang sought to extend this to a broader range of transformations (Scheme 1.30).⁵⁷ By varying the coupling partner and fine-tuning reaction conditions, the C-N coupling step could be paired with either a Suzuki coupling (Scheme 1.30a and b), Heck reaction (Scheme 1.30c), or a Sonogashira coupling (Scheme 1.30d) to produce indoles with varying functionality at the 2-position. Phenols were found to be reactive under the conditions for Sonogashira coupling and gave 2-alkynylbenzofurans in good yields. Further extension of the strategy to pyridines and thiophenes afforded azaindoles and thienopyrroles respectively (Scheme 1.30e). Following up on these promising results, another former student, Chris Bryan, successfully combined C-N amination with a direct arylation step to produce polycyclic indole derivatives (Scheme 1.30f). Later, he showed that thiophenols were also viable substrates, and developed a highly modular synthesis of benzothiophenes functionalized at the 2-position (Scheme 1.30g). Finally, by using an alkene as the *ortho* substituent, functionalized methyleneindenes could be synthesized (Scheme 1.30h). This represented the first synthesis of

⁵⁷ a) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, 7, 3549. b) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, 73, 538. c) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, 8, 4203. d) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, 9, 2955. e) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, 72, 5152. f) Bryan, C. S.; Lautens, M. *Org. Lett.* **2008**, 10, 4633. g) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, 48, 7064. h) Bryan, C. S.; Lautens, M. *Org. Lett.* **2010**, 12, 2754.

carbocycles using Pd-catalyzed domino chemistry on *gem*-dibromoolefins, and also demonstrated the feasibility of domino reactions in which C–heteroatom coupling did not constitute part of the sequence.

Scheme 1.30 Palladium catalyzed domino reactions of *gem*-dihaloolefins

The Lautens group has long sought to develop domino reactions of *gem*-dibromoolefins in which direct arylation constitutes one of the steps. As mentioned previously, the first such example came from Bryan's synthesis of polycyclic indoles in which catalytic amination was paired with direct arylation (Scheme 1.30f). By modification of the substrate structure (**1.115**), former graduate student David Chai was able to synthesize polycyclic pyrroles (**1.116**) by union

of a Suzuki coupling with direct arylation (Scheme 1.31).⁵⁸

Scheme 1.31 Synthesis of polycyclic pyrroles via domino Suzuki coupling and direct arylation

Subsequently, this avenue of research was continued by extending the scope of this chemistry to other heterocycles, as they are known to be excellent substrates for direct arylation. To this end, two former postdoctoral fellows, Dr. Norman Nicolaus and Dr. Patrick Franke, reported a highly modular synthesis of naphthothiophenes **1.118** by utilizing thiophene-containing substrates **1.117** and subjecting them to domino Suzuki coupling-direct arylation (Scheme 1.32).⁵⁹

Scheme 1.32 Synthesis of naphthothiophenes via domino Suzuki coupling and direct arylation

Clearly, *gem*-dihalovinyl systems of the type depicted in Scheme 1.30 are remarkably versatile building blocks, lending themselves well to a seemingly endless combination of domino reactions. Thus far, domino reactions in which direct arylation constitutes part of the sequence remain the least explored. Given the utility of these *gem*-dibromoolefins, and the advantages of direct arylation, additional work in the area to identify further applications would greatly enhance their synthetic appeal.

⁵⁸ Chai, D. I.; Lautens, M. J. *Org. Chem.* **2009**, 74, 3054.

⁵⁹ Nicolaus, N.; Franke, P. T.; Lautens, M. *Org. Lett.* **2011**, 13, 4236.

Chapter 2

Results and Discussion

2.1 Origin of Current Project and Proposed Research

During their studies on the synthesis of naphthothiophenes via a domino Suzuki coupling-direct arylation approach, Dr. Nicolaus and Dr. Franke attempted to extend the chemistry to indole derivatives. This was met with very limited success, as complex mixtures often resulted. Fortuitously, it was found that *N*-tosyl substituted indole **2.1a** could react with 4-methoxyphenylboronic acid, an electron-rich boronic acid, to give the desired product (**2.2**) in 50% yield (Scheme 2.1).

Scheme 2.1 Domino Suzuki coupling-direct arylation of an *N*-tosylated indole

A very interesting discovery was made when **2.1a** was reacted with an electron-poor boronic acid (Scheme 2.2). Although the reaction was rather messy, careful chromatography allowed isolation of a high melting solid (MP > 200 °C) in 21% yield. Curiously, the NMR spectra of the isolated material did not match that of the expected product, and high resolution mass spectrometry indicated that the boronic acid was not incorporated. In order to unambiguously determine the structure of this material, X-ray crystallography was performed. The isolated solid was found to be the *N*-fused benzo[*c*]carbazole **2.3a**, resulting from two-fold C–H functionalization first at the C-2 position of indole, followed by the position *ortho* to the sulfonyl moiety of the tosyl group (Figure 2.1).

Scheme 2.2 Serendipitous synthesis of a double C–H functionalization product

Figure 2.1 Crystal structure of *N*-fused benzo[*c*]carbazole **2.3a**

Although synthetically useful double C–H functionalization reactions (excluding dehydrogenative arylations) are known,⁶⁰ to the best of our knowledge, double C–H functionalization involving *gem*-dibromovinyl systems in a domino, one-pot fashion has never been reported. Despite the very modest yield, the novel reactivity exhibited is quite interesting

⁶⁰ By definition, dehydrogenative arylation between two unactivated arenes is a double C–H functionalization process; see Ref 15 for comprehensive reviews. Double C–H functionalization not involving dehydrogenative arylation: a) Dyker, G. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 103. b) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, 127, 13148. c) Liu, R.; Zhang, J. *Adv. Synth. Catal.* **2011**, 353, 36. d) Samanta, R.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2011**, 50, 5217. e) Wong, N. W. Y.; Forgiione, P. *Org. Lett.* **2012**, 14, 2738.

and worth exploring in its own right. Thus, our objective at the outset of this project was to optimize the conditions for the domino C–H functionalization reaction to assess its synthetic viability. Following successful optimization, a streamlined and divergent route to the starting materials would be developed, and the scope of this domino reaction would be examined (Scheme 2.3). Points of diversity would include variations on the heterocyclic nucleus (R^1), the aryl group containing the dibromoolefin (R^2) and the linker (R^3), as well as the linker itself (X).

Scheme 2.3 Proposed points of diversity for the domino C–H functionalization reaction

2.2 Optimization of the Domino C–H Functionalization Reaction

We began our optimization of the domino reaction by looking at different ligands and solvents (Table 2.1). For all optimization reactions, the yield of the crude reaction mixture was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. We started by attempting the reaction using previously established conditions for the domino Suzuki coupling–direct arylation of thiophenes⁵⁹ but without the boronic acid component. (entry 1). An NMR yield of 27% was obtained, which was more or less comparable to that obtained during the serendipitous discovery, although the reaction appeared to be cleaner by TLC. We next screened several monodentate, highly electron-rich phosphines, as well as the bidentate ligand dppf (entries 2–5) as David Chai had previously shown these to be the most effective in promoting the direct arylation of pyrroles.⁵⁸ Unfortunately, none of them proved to be as effective as PCy_3 .

Prior to a solvent screen, we decided to investigate whether the additives TBAB and CsOPiv were really necessary for efficient reaction. We found that omission of TBAB had little effect (entry 6), while a large decrease in yield resulted if CsOPiv was omitted (entry 7). Interestingly, omission of both additives had little effect when dioxane was used as the solvent (entry 8). However, only 10% conversion was achieved when the solvent was switched to the much more

apolar toluene (entry 9). Addition of both TBAB and CsOPiv still only gave 70% conversion and a complex mixture (entry 10), but the yield improved substantially when only CsOPiv was used (entry 11). Benzene was shown to be equally effective (entry 12), while other polar solvents gave inferior results (entries 13-16). Due to the toxicity of benzene and the deleterious effect of TBAB when used in toluene, we chose toluene as the solvent and CsOPiv as the sole additive in going forward.

Table 2.1 Optimization of ligand and solvent in the domino reaction

Entry	Ligand	Solvent	NMR Yield (%)
1 ^a	PCy ₃	Dioxane	27
2 ^a	SPhos	Dioxane	6
3 ^a	XPhos	Dioxane	19
4 ^a	<i>t</i> -Bu ₃ P ⁺ HB ⁻ F ₄	Dioxane	12
5 ^a	dppf	Dioxane	18
6	PCy ₃	Dioxane	27
7 ^{a,b}	PCy ₃	Dioxane	4
8 ^b	PCy ₃	Dioxane	25
9 ^b	PCy ₃	Toluene	10% conv.
10 ^a	PCy ₃	Toluene	70% conv.
11	PCy₃	Toluene	38
12	PCy₃	Benzene	38
13	PCy ₃	MeCN	10
14	PCy ₃	DMF	Trace
15	PCy ₃	DME	15
16	PCy ₃	DCE	17

^a TBAB (1 equiv.) was added. ^b CsOPiv was omitted.

We then examined the effects of palladium catalysts and bases (Table 2.2). Of the non-palladacyclic catalysts screened, only $\text{Pd}(\text{PPh}_3)_4$ had comparable efficiency to $\text{Pd}(\text{OAc})_2$ (entry 2), while all other $\text{Pd}(0)$ and $\text{Pd}(\text{II})$ sources gave much reduced yields (entries 3-5). The yield improved when Buchwald palladacycle **Pd-1** containing SPhos pre-ligated to the palladium was used (entry 6), while XPhos palladacycle **Pd-2** proved inferior (entry 7). Using **Pd-1** as the catalyst, several bases were screened. For the carbonate bases, K_2CO_3 was more effective than Cs_2CO_3 (entry 10), possibly due to a favourable combination of solubility and basicity, which helped to suppress unwanted elimination of the dibromoolefin to the bromoalkyne. Phosphate and acetate bases were less effective under the reaction conditions (entries 11 and 12).

Table 2.2 Optimization of the catalyst and base in the domino reaction

Entry	Catalyst	Base	NMR Yield (%)
1 ^a	$\text{Pd}(\text{OAc})_2$	Cs_2CO_3	38
2	$\text{Pd}(\text{PPh}_3)_4$	Cs_2CO_3	41
3 ^a	$\text{Pd}_2(\text{dba})_3$	Cs_2CO_3	21
4 ^a	PdCl_2	Cs_2CO_3	8
5	$\text{Pd}(\text{IMes})(\text{Allyl})\text{Cl}$	Cs_2CO_3	4
6	Pd-1	Cs_2CO_3	48
7	Pd-2	Cs_2CO_3	26
9	Pd-1	Na_2CO_3	8
10	Pd-1	K_2CO_3	62 (54 isolated)
11	Pd-1	K_3PO_4	26
12	Pd-1	KOAc	15

^a Exogenous PCy_3 (20 mol %) was added as the ligand

Reasoning that product **2.3a** might be decomposing under the rather strenuous conditions used in all optimizations thus far, we proceeded to investigate the effects of temperature and reaction

time (Table 2.3). Decreasing the temperature to 80 °C led to lower yields due to incomplete reaction (entry 1), while a shorter reaction time of 8 instead of 18 hours decreased the yield slightly (cf. entries 2 and 3). When the temperature was increased to 120 °C, complete conversion occurred in just 6 hours, albeit with slightly diminished yield (entry 4). Thus, it appeared that previously established conditions (18 hours at 100 °C) were actually optimal.

Table 2.3 Optimization of the temperature and reaction time in the domino reaction

2.1a $\xrightarrow[\text{Toluene, temp, time}]{\text{Pd-1 (10 mol \%), K}_2\text{CO}_3 \text{ (2 equiv), CsOPiv (50 mol \%)} }$ **2.3a**

Entry	Temperature (°C)	Time (h)	NMR Yield (%)
1	80	18	46
2	100	18	62
3	100	8	55
4	120	6	56

During the early stages of the optimization process, we demonstrated the dramatic influence CsOPiv had on the course of the reaction, whereby in its absence the reaction completely shut down and only 10% conversion was observed (Table 2.1, entry 9). With most of the reaction parameters set, we thought it wise to turn our attention to the role of additives (Table 2.4). As a starting point we altered the amount of CsOPiv to test whether it might affect reactivity, as Fagnou had observed that as low as 30 mol % was sufficient for direct arylation with most heterocycles.⁶¹ In our hands, comparable results were achieved with 30 mol % and stoichiometric amounts of CsOPiv (entries 2 and 3), indicating that beyond a certain threshold, CsOPiv simply acted as a spectator. For consistency we continued optimization with a loading of 50 mol %. The use of *in situ* generated pivalate from pivalic acid and excess base sometimes

⁶¹ Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

conferred an advantage over direct addition of pivalate;¹⁶ however this proved to make little difference (entry 4). Likewise, addition of water⁵⁸ provided no benefit (entry 5).

Table 2.4 Optimization of additives in the domino reaction

Entry	Additive	NMR Yield (%)
1	CsOPiv (50 mol %)	62
2	CsOPiv (30 mol %)	59
3	CsOPiv (100 mol %)	57
4 ^a	PivOH (50 mol %)	58
5	CsOPiv (50 mol %) + H ₂ O (5 equiv.)	58
6 ^a	<i>o</i> -NO ₂ -Ph-COOH (50 mol %)	10% conv.
7 ^a	2,4,6-Me-Ph-COOH (50 mol %)	31
8 ^b	2,4,6-Me-Ph-COOH (100 mol %)	64
9	CsOPiv (50 mol %) + AgOAc (1 equiv.)	48
10	CsOPiv (50 mol %) + Ag ₂ CO ₃ (50 mol %)	60

^a 2.5 equiv. of K₂CO₃ was used. ^b 3 equiv. of K₂CO₃ was used.

Larossa found that use *o*-nitrobenzoic acid was crucial for efficient phosphine-free direct C-2 arylation of indoles,⁶² when applied to the current reaction however only 10% conversion was achieved (entry 6). Ackermann noted that 2-mesitylenecarboxylic acid exhibited superior reactivity compared to pivalic acid in the direct arylation of triazoles.⁶³ This was not the case for us, as sub-stoichiometric amounts led to poorer yields due to incomplete conversion (entry 7), and only when used in stoichiometric quantities was a very slight improvement seen (cf. entries

⁶² Lebrasseur, N.; Larrosa, I.; *J. Am. Chem. Soc.* **2008**, *130*, 2926.

⁶³ Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922.

1 and 8). Previously, we observed that addition of exogenous halide such as TBAB was very detrimental, inhibiting product formation and leading to significant quantities of unreacted starting material (Table 2.1, entry 10). We hypothesized that the added bromide ions might be binding to palladium and inhibiting catalysis. However, it seemed plausible that bromide generated from the dibromoolefin could also be poisoning the catalyst. To test whether this was the case, we sought to sequester the *in situ* generated bromide by addition of a silver salt. Based on previous reports,^{57f, 64} one equivalent of silver in the form of Ag₂CO₃ and AgOAc was added. Unfortunately, use of AgOAc only led to diminished yields (Table 2.4, entry 9), while Ag₂CO₃ did not seem to impart any impact on the reaction (entry 10). We concluded that CsOPiv was an optimal additive and moved on.

It is worth mentioning that the Buchwald palladacycle **Pd-1** used in the current reaction was originally developed to be a stable Pd(II) precatalyst with the desired phosphine already ligated to palladium.⁶⁵ This would circumvent the complexities associated with generating a phosphine-ligated Pd(0) species from a Pd(II) source, as well as the issue of coordinating ligands if a stable Pd(0) precatalyst such as Pd₂(dba)₂ was to be utilized. Buchwald noted that these palladacycles were readily activated in about 3 minutes by alkoxides at room temperature, or by weak bases such as K₂CO₃ at 80 °C in dioxane. Considering the apolar nature of toluene used in the current reaction, K₂CO₃ is likely to be much less soluble. Additionally, *gem*-dibromoolefin **2.1a** had a propensity to undergo base-induced elimination to the bromoalkyne at elevated temperatures (10-20% of bromoalkyne was observed as the major byproduct in most reactions). These considerations prompted us to investigate whether modifying the reaction setup could suppress unwanted elimination (Table 2.5). We attempted to pre-activate the catalyst without dibromoolefin **2.1a** by stirring **Pd-1**, K₂CO₃, and CsOPiv in half the volume of toluene for 10 minutes at 100 °C (entry 2). The substrate was then introduced as a solution in toluene and the reaction continued as usual. However, this did not seem to make any notable difference. Reasoning that catalytic turnover may not be fast enough to completely outcompete elimination, we tried to limit the amount of dibromoolefin **2.1a** present at any one time through controlled addition via a syringe pump. Slow addition of **2.1a** into the reaction mixture over 4 hours had no

⁶⁴ Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

⁶⁵ Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

bearing on the outcome of the reaction (entry 3). Increasing the addition time to 8 hours caused substantial diminishment of the yield due to incomplete reaction (entry 4). The effect of overall reaction concentration was then examined. Two-fold dilution led to a small but noticeable drop in yield (entry 5), while performing the reaction at a higher concentration decreased the yield further (entry 6). Due to the rather unfruitful results, additional experiments were not attempted.

Table 2.5 Optimization of the domino reaction by modification of reaction setup

Entry	Modification	NMR Yield (%)
1	None ([Reaction] at 0.04M)	62
2	Catalyst pre-activation: 10 minutes at 100 °C	57
3	Slow addition over 4 hours	60
4	Slow addition over 8 hours	43
5	[Reaction] at 0.02M	56
6	[Reaction] at 0.1M	49

Finally, we decided to look into conducting the reactions in a Biotage microwave (Table 2.6), since it had been demonstrated that heating by means of microwave irradiation was beneficial in certain C–H functionalization reactions.⁶⁶ Due to the apolar nature of toluene, it is a very poor microwave absorber, and the maximum obtainable temperature within safety limits was estimated to be around 170 °C. After multiple rounds of trial and error, we discovered that the practical limit was closer to 160 °C, and even then the microwave struggled in bringing the reaction to temperature. At a temperature of 160 °C, irradiation for 35 minutes led to around 90% conversion and an isolated yield of 46% (entry 2), which increased to 51% if the irradiation

⁶⁶ a) Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, 72, 775. b) De Luca, L.; Porcheddu, A. *Eur. J. Org. Chem.* **2011**, 5791.

out the synthesis on a large scale, this would be wasteful from both an economical and environmental standpoint. Thus, concurrent with optimization studies on the domino reaction, general and high yielding conditions were developed for each individual step.

Scheme 2.4 Outline of the synthetic strategy

2.3.2 Synthesis of *N*-Sulfonylated Substrates

2.3.2.1 Iodination

Using conditions established by Palla and Bocchi,⁶⁷ the iodination of free indoles was a very facile and high yielding process (Table 2.7). The products could be isolated by precipitation with water, and did not require any purification. For the parent free indole, a reaction performed on 100 mmol scale gave a 95% yield (entry 1), demonstrating excellent scalability. We did find that 3-iodoindoles prepared in such a manner contained small amounts of DMF even when left under high vacuum overnight. If desired, the DMF could be removed by washing a diethyl ether solution of **2.5** with water. However this was not necessary as the residual DMF did not interfere with subsequent reactions. These 3-iodoindoles proved to be extremely acid sensitive, and had limited thermal stability, as they slowly decomposed when stored at room temperature. Thus they were prepared and used immediately, or if absolutely necessary, stored at -20 °C under an inert atmosphere.

⁶⁷ Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096.

Table 2.7 Synthesis of 3-iodoindoles

Entry	R ¹	Product	Yield (%) ^a	Entry	R ¹	Product	Yield (%) ^a
1	H	2.5a	95	5	6-CO ₂ Me	2.5e	95
2	5-Me	2.5b	96	6	5-CN	2.5f	93
3	7-Me	2.5c	87	7	5-NO ₂	2.5g	77
4	5-OMe	2.5d	64	8	7-azaindole	2.5h	79

^a Isolated yields.

2.3.2.2 Sulfonylation

Due to the sensitivity of **2.5**, a procedure for *N*-sulfonylation of 3-iodoindoles **2.5** that avoided the use of highly reactive bases such as *n*-butyllithium or sodium hydride was desired. The tosylation of indole **2.4** under pseudo-phase transfer conditions using NaOH in conjunction with Bu₄NHSO₄ in dichloromethane was preceded.⁶⁸ After some experimentation, we found that KOH gave improved reactivity with 3-iodoindoles **2.5**. These conditions allowed the reaction to

⁶⁸ Ramalingan, C.; Lee, I.-S.; Kwak, Y.-W. *Chem. Pharm. Bull.* **2009**, 57, 591.

be performed in an open flask under ambient conditions, offering great operational simplicity. With a few exceptions, excellent yields of sulfonylated products **2.6** were obtained (Table 2.8).

Table 2.8 *N*-Sulfonylation of 3-iodoindoles

Entry	2.5	Product	Yield (%) ^a	Entry	2.5	Product	Yield (%) ^a
1	2.5a	2.6a	quant.	7 ^b	2.5g	2.6g	87
2	2.5b	2.6b	97	8 ^b	2.5h	2.6h	97
3	2.5c	2.6c	59	9	2.5a	2.6i	55
4	2.5d	2.6d	48	10	2.5a	2.6j	97
5	2.5e	2.6e	91	11	2.5a	2.6k	62
6	2.5f	2.6f	87				

^a Isolated yields. ^b Brief refluxing was required to completely solubilize starting material **2.5**

Some of the products were poorly soluble in common chromatography solvents, and had a tendency to crystallize on the chromatography column, leading to substantial loss of yields, such as in the cases of **2.6d** and **2.6k** (entries 4 and 11). Complicating matters further, the excess sulfonyl chlorides tended to co-elute with the products during chromatographic purification. Therefore except for benzylsulfonyl product **2.6i** (entry 9), only a very slight excess (1.03 equiv.) of sulfonyl chlorides was used. Even then, the excess sulfonyl chlorides were remarkably recalcitrant to hydrolysis, as they remained intact even after stirring the crude mixture with excess aqueous 1M NaOH for 30 minutes. Gratifyingly, when the reactions were quenched with aqueous 1M NH₃ instead, complete aminolysis occurred within 20 minutes. Reactions quenched in such a manner also proved to be exceptionally clean, as the crude products were often >95% pure by NMR, containing 2-4% of tetrabutylammonium salts as the only visible impurity. The presence of these quaternary ammonium salts proved to be of no consequence for the subsequent Suzuki coupling, and thus in the vast majority of cases, crude **2.6** could be directly utilized. This reaction was also highly scalable, yielding nearly 20 grams of **2.6a** in a single reaction performed with **2.5a** on 50 mmol scale (entry 1).

2.3.2.3 Suzuki Coupling

The most straightforward approach towards aldehydes **2.7** would involve a Suzuki coupling between iodide **2.6** and commercially available 2-formylphenylboronic acid. Unfortunately, this step proved to be the bottleneck, as previously established conditions for benzothiophenes⁵⁹ did not lend itself well to *N*-tosyl indole **2.6a**, resulting in a rather poor yield of 36%. Thus some optimization was required in order to proceed. A literature survey revealed that Larock achieved a selective cross coupling between **2.6a** and 2-bromophenylboronic acid in 82% yield by employing a Pd(dba)₂/PPh₃ catalyst system using CsF as the base.⁶⁹ Larock's original conditions called for 5 mol % of the palladium catalyst, but after a few trial reactions, we found that 2 mol % was sufficient for complete conversion and excellent yields (Table 2.9).

⁶⁹ Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 5616.

Table 2.9 Fine-tuning of Larock's Suzuki coupling conditions

Entry	Catalyst Loading	Boronic Acid Amount	Time (h)	Conv. (%)	Yield (%) ^a
1	1 mol %	1.5 equiv.	23	75	64
2	2 mol %	1.5 equiv.	17	85	68
3	2 mol %	2 equiv.	16	100	92

^a Isolated yields.

With optimal conditions in hand, we pushed on with the synthesis of aldehydes **2.7** (Table 2.10). Except for nitrile-containing substrate **2.6f** (entry 6) and substrate **2.6i** bearing a benzylsulfonyl group (entry 9), the yields generally ranged from decent to excellent, although some fluctuation was seen. The modest yield observed for **2.6f** may be due to coordination of the nitrile group to palladium, thus causing catalyst inhibition. For certain substrates (**2.6g**, entry 7; **2.6h**, entry 8; **2.6i**, entry 9) a higher catalyst loading was needed to achieve complete turnover. Unfortunately, thiophene-containing boronic acid **2.8** did not couple well under the current conditions, and only partial conversion was achieved (Scheme 2.5).

Scheme 2.5 Attempted Suzuki coupling with a thiophene-containing boronic acid

As with previous reactions, scalability was good, and yields in excess of 90% for **2.7a** were routinely obtained when the reaction was performed on a 6 g scale.

Table 2.10 Suzuki coupling of *N*-sulfonyl indoles

Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a
1		5		9 ^d	
2		6		10	
3		7 ^b		11	
4		8 ^c		12	

^a Isolated yields. ^b 5 mol % Pd(dba)₂ used. ^c 8 mol % Pd(dba)₂ used. ^d 4 mol % Pd(dba)₂ used.

2.3.2.4 Ramirez Olefination

Previously, it had been shown that aldehyde **2.7a** was reactive under standard conditions ($\text{CBr}_4/\text{PPh}_3$), yielding the corresponding *gem*-dibromoolefin **2.1a** in 70% yield.⁵⁹ Given Eric Fang's success in replacing PPh_3 with $\text{P}(\text{O}i\text{-Pr})_3$, we applied his conditions to aldehyde **2.7a** and were delighted to find that **2.1a** was obtained in 85% yield on the first run (Scheme 2.6).

Scheme 2.6 Comparison of Ramirez olefination of **2.7a** by PPh_3 and $\text{P}(\text{O}i\text{-Pr})_3$

More importantly however, all the phosphorus byproducts were now oils. This proved to be a significant advantage due to the highly crystalline nature of **2.1a**, as it was observed to crystallize out during rotary evaporation of the crude mixture in subsequent reactions, and could be isolated by simple trituration. Using this method of purification, **2.1a** was obtained in a yield of 83% (Table 2.11, entry 1), comparable to the 85% achieved by chromatographic means. The yields obtained with this $\text{P}(\text{O}i\text{-Pr})_3$ mediated Ramirez olefination were generally good; significantly, trituration of the crude product was sufficient to produce analytically pure **2.1** in half the cases (entries 1 and 2, 5-8), providing a very convenient and economical alternative to traditional column chromatography.

Table 2.11 P(Oi-Pr)₃ mediated Ramirez olefination of *N*-sulfonyl aldehydes **2.7**

Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a
1 ^b	2.1a 83%	5 ^b	2.1e 73%	9 ^c	2.1i 60%
2 ^b	2.1b 82%	6 ^b	2.1f 53%	10 ^c	2.1j 84%
3 ^c	2.1c 82%	7 ^b	2.1g 75%	11 ^c	2.1k 80%
4 ^c	2.1d 62%	8 ^b	2.1h 69%	12 ^c	2.1l 65%

^a Isolated yields. ^b Purified by trituration. ^c Purified by column chromatography.

2.3.3 Synthesis of Other *N*-Substituted Substrates

2.3.3.1 Initial Results

As efficient as the streamlined route to **2.7** may be, it was nevertheless still completely linear, and offered no points for either convergence or divergence. Starting from free indole **2.4**, preparation of one single *N*-fused benzo[*c*]carbazole **2.3** required a linear sequence of five steps (Scheme 2.4). Admittedly, this was inevitable if one wanted to alter the substituent R¹ on the indole core. However, the inadequacy of this linear approach was fully exposed when we attempted to prepare various non-sulfonyl based *N*-substituted substrates. More specifically, previously optimized conditions for the Suzuki coupling were not as general as we had hoped, and yields decreased sharply when other substituents were utilized (Table 2.12).

Table 2.12 Effect of different *N*-substituents on yield of Suzuki coupling

Entry	R	2.7	Yield (%) ^a	[Pd] Loading
1		2.7a	92	2 mol %
2		2.7q	66	2 mol %
3		2.7r	54	4 mol %
4		2.7w	29	6 mol %

^a Isolated yields.

Interestingly, yields varied in accordance with the electron-withdrawing power of the substituent: more electron-withdrawing groups gave better yields and required less catalyst. In the extreme case of the slightly electron-donating benzyl group (entry 4), full conversion was

not achieved even when catalyst loading was tripled, and a poor yield of 29% was obtained. These results as well as the desire for divergence prompted us to investigate a new route.

2.3.3.2 Evolution of a Diversity-Oriented Synthesis

Since the Suzuki coupling seemed to be the most problematic, we envisaged that an intermediate of type **2.10** with the requisite aldehyde already installed would completely bypass the coupling step (Scheme 2.7). Further, since **2.10** is unsubstituted, it can now serve as a common entry point, expediting the synthesis of substrate **2.1** bearing different *N*-substituents.

Scheme 2.7 Proposed strategy for a divergent route

The most straightforward approach to **2.10** would involve direct C-3 arylation of indole **2.4a** with commercially available aryl bromide **2.11**, followed by acetal deprotection (Scheme 2.8). Unfortunately, literature conditions reported by Rossi^{24d} (Condition **A**) and Djakovitch^{24e} (Condition **B**) resulted only in extensive decomposition.

Scheme 2.8 Attempted direct arylation approach to intermediate **2.10**

We then realized if one started with aldehyde **2.7a** instead, the synthesis of **2.10** was now simply a matter of removing the *N*-tosyl group in the highest yield possible. After a bit of

experimentation, we found that by using slightly modified literature conditions,⁷⁰ the tosyl group could be cleaved very smoothly by refluxing **2.7a** with excess cesium carbonate in methanol. Two runs on a 10 g scale both gave an identical yield of 95% for **2.10**. Thus, an optimized route to **2.10** with an overall efficiency of 83% over four steps was established (Scheme 2.9).

Scheme 2.9 Highly efficient route to intermediate **2.10**

To test the efficacy of intermediate **2.10**, we first subjected it to previously developed conditions for *N*-sulfonylation with several sulfonyl chlorides (Table 2.13, entries 1-3). We were very pleased to find that the conditions translated well when applied to **2.10**, and the *N*-substituted aldehydes were produced in excellent yields. Encouraged by these results, we reacted **2.10** with a variety of other electrophiles, such as carbamoyl chlorides (entries 6 and 7), chloroformates (entries 8 and 9), and even a phosphinic chloride (entry 4). Mild heating was required in a few cases (entries 2, 6 and 7), but most reactions could be carried out at room temperature. Except for thiophene-containing substrate **2.7o**, all yields were in excess of 90%, demonstrating the synthetic utility of **2.10**. Since *N*-benzoyl aldehyde **2.7q** had already been prepared by Suzuki coupling in an acceptable yield (entry 4; see also Table 2.12, entry 2), sufficient quantities were available for subsequent steps, and thus it was not re-synthesized via the current method in order to conserve the highly valuable building block **2.10**.

⁷⁰ Bajwa, J. S.; Chen, G. P.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, 47, 6425

Table 2.13 Diversity-oriented approach to *N*-substituted aldehydes **2.7**

Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a
1		4		7 ^b	
2 ^b		5 ^c		8	
3		6 ^b		9	

^a Isolated yields. ^b Refluxed at 50 °C. ^c Synthesized by conventional Suzuki coupling.

Although the sulfonylation conditions worked well with hard electrophiles, soft electrophiles such as alkyl halides proved to be much less reactive, and required alternative conditions for good yields. Fortunately, **2.10** reacted smoothly with benzyl bromide in DMSO, affording benzylated product **2.7w** in 94% yield (Scheme 2.10, equation 2). However, very forcing

conditions had to be utilized in order to synthesize the one carbon homologue **2.7x** (equation 3), since the alkyl bromide was unactivated and reacted very sluggishly. A modest yield was obtained and multiple byproducts were observed. Finally, a Cu-catalyzed Ullmann coupling⁷¹ between **2.10** and iodobenzene allowed easy access to the *N*-phenyl derivative **2.7v** in moderate yield (equation 1), which would have been difficult to prepare via the linear route due to competing homocoupling and polymerization of 3-iodoindole.

Scheme 2.10 Reaction of **2.10** with aryl and alkyl halides

The P(Oi-Pr)_3 mediated Ramirez olefination for these differentially *N*-substituted aldehydes were in general quite high yielding (Table 2.14), although a diminished yield was seen for some substrates (entries 5, 8 and 9). Once again, trituration was a sufficient means of purification for nearly half of the compounds (entries 3-5, 8 and 9), demonstrating the superiority of P(Oi-Pr)_3 over PPh_3 in the Ramirez olefination for aldehydes of type **2.7**.

⁷¹ Xu, X.-H.; Liu, G.-K.; Azuma, A.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 4854.

Table 2.14 Ramirez olefination of differentially *N*-substituted aldehydes **2.7**

Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a	Entry	Product/Yield (%) ^a
1 ^c	 2.1m 96%	5 ^b	 2.1q 55%	9 ^b	 2.1u 45%
2 ^c	 2.1n 75%	6 ^c	 2.1r 78%	10 ^c	 2.1v quant.
3 ^b	 2.1o 96%	7 ^c	 2.1s 92%	11 ^c	 2.1w 76%
4 ^b	 2.1p 90%	8 ^b	 2.1t 57%	12 ^c	 2.1x 89%

^a Isolated yields. ^b Purified by trituration. ^c Purified by column chromatography.

2.3.4 Scope of the Domino C–H Functionalization Reaction

We began our study of the domino reaction by examining the effect of different substituents on the indole core (Table 2.15).

Table 2.15 Variation of the indole substituent

Entry	Product	Yield (%) ^a	Entry	Product	Yield (%) ^a
1		54	5		31
2		52	6		decomp.
3		42	7		decomp.
4		36	8		60% conv.

^a Isolated yields.

The results were somewhat surprising, as the reaction seemed to be sensitive to electronic effects quite remote from the site of C–H functionalization. Any substituent other than a methyl group led to a rather significant decrease in yield compared to the parent example (cf. entries 1, 4 and 5). Furthermore, the reaction appeared to be incompatible with certain functional groups, as both nitrile and nitro groups (entries 6 and 7) only gave decomposition products, although the dibromoolefin substrate was fully consumed in those cases. When the indole phenyl ring was replaced with a pyridine ring, as in the case of 7-azaindole (entry 8), the reaction failed to reach completion under the optimized conditions, and multiple products were observed by both TLC and NMR. Interestingly, substrate **2.3c** bearing a methyl group in proximity to the sulfonyl moiety (entry 2) gave a 10% lower yield compared to **2.3b** with a spatially distant methyl group (entry 3), suggesting that steric effects may also play a role in the reaction.

We next turned our attention to varying the substitution on the aromatic containing the dibromoolefin as well as the sulfonyl moiety (Table 2.16). We anticipated that variations on the sulfonyl-containing aromatic (R^3) should affect the reaction outcome significantly, since the electronics in close proximity to the reactive site is being altered. Once again, the nitro group proved to be very detrimental, as extensive decomposition resulted when substrate **2.3k** was subjected to the reaction conditions (entry 2). As expected, the electron-donating methoxy group had a minor impact when placed at a remote location (entry 3), but exerted a very negative influence when placed near the reaction centre (entry 2). Curiously however, an electron-withdrawing CF_3 group at the same position seemed to have no impact on the reaction outcome (entry 4), yet substitution of a fluorine was less effective (entry 5). We were pleased to see that replacement of the phenyl ring by thiophene was tolerated, and it underwent direct arylation at the normally less reactive C3 position with moderate efficiency (entry 6).

Table 2.16 Variation of other aromatic substituents

Entry	Product	Yield (%) ^a	Entry	Product	Yield (%) ^a
1		13	4		53
2		decomp.	5 ^b		41
3		44	6		42

^a Isolated yields. ^b Heated to 100 °C for 15 h.

As all examples thus far had an arylsulfonyl group as the *N*-substituent (the “linker”), we sought to investigate the compatibility of different linkers with this domino process (Table 2.17). Additionally, since the arylsulfonyl group limited the synthesis to only 6-membered rings, changing the nature of the linker could potentially allow access to different ring sizes.

microwave conditions were applied, the reaction reached half conversion, although multiple byproducts were observed, presumably due to decomposition of **2.1q** under the very strenuous reaction conditions. Since the sulfonyl group was an established linker, we wondered whether a 7-membered ring could be made by employing a benzylsulfonyl linker which contains a phenyl ring extended by one methylene unit (entry 1). Such an alteration proved to be completely ineffective, as the reaction barely proceeded. Presumably, the linker simply had too much rotational freedom about the carbon-sulfur bond and was therefore too flexible. Gratifyingly, use of the conformationally restricted diphenylcarbamoyl linker successfully furnished the 7-membered product **2.3r** in 60% yield (entry 4), the highest achieved to date. Efforts to synthesize the 8-membered ring product **2.3s** were frustrated by the fact that the product could not be isolated pure. However the yield as determined by NMR was around 25% (entry 5), indicating that replacement of the phenyl ring by a benzyl group, and thus introducing more conformational flexibility, was less effective. Since the diphenylcarbamoyl linker proved to be very effective, we decided to test its oxygen analogue (entry 6). In this case however, only 20% conversion was observed, and NMR of the crude mixture indicated that no desired product had formed. This may be caused by the fact that the oxygen linker of the carbamate moiety prefers to be in the *s*-cis conformation for both electronic and steric reasons (Scheme 2.11, **2.1t-c**). Unfortunately this would appear to be the unreactive conformation, since the phenyl ring seems well out of reach, and product **2.3t** has the linker locked in the *s*-trans conformation.

Scheme 2.11 Rationale for diminished reactivity of substrate **2.1t**

Use of the Cbz group, which circumvents this conformational issue by having a methylene unit between the oxygen and the phenyl ring, appeared to be more effective, even though this now required the formation of an 8-membered ring (entry 7). The reaction nearly reached half-

conversion, and 8-membered product **2.3u** was formed in around 15% yield by NMR (akin to **2.3s**, the product could not be isolated pure, thus the yield was determined by NMR). To probe this conformational issue further, we subjected three substrates bearing hydrocarbon linkers of incremental length to the reaction conditions (Table 2.17).

Table 2.17 Effect of linker length on the reaction outcome

Entry	n	Product	Yield (%) ^a
1	0	2.3v	decomp.
2	1	2.3w	55
3	2	2.3x	(25; 80% conv.) (30; 100% conv.) ^b

^a Isolated yields; NMR yields in parentheses. ^b μ W conditions: 75 min at 160 °C

Not too surprisingly, dibromoolefin **2.1v** with a phenyl ring fused directly to the indole nitrogen gave no productive reaction and led only to decomposition products (entry 1). With a one carbon linker, just the right amount of conformational flexibility was introduced, and the desired

product was formed in 55% yield (entry 2). Imparting further conformational flexibility with a two carbon linker was counterproductive, as the reaction did not even reach completion when under conventional heating (entry 3). Use of a microwave did succeed in driving the reaction to completion; however the yield was still significantly lower when compared to the 6-membered analogue **2.3w**, and **2.3x** could not be isolated pure due to multiple co-eluting impurities.

It should be said that all these results need to be interpreted with some degree of caution, since the electronics directly adjacent to the site of C–H functionalization are necessarily altered when changes are made to the linker. Thus any conformational effects will inevitably be confounded with electronic effects. All this notwithstanding, there is no doubt that conformation certainly plays a role in the outcome of this domino reaction, as evidenced by the results in Table 2.17.

Finally, we attempted a competition experiment with substrate **2.1y** bearing two potentially reactive C–H bonds in order to test whether the 6-membered product **2.3y** or 7-membered **2.3z** would be favoured (Scheme 2.12).⁷² However, only decomposition products were observed, including around 20% of free indole, indicating that hydrolysis of the urea linkage by adventitious water was a major competing process. This result was not entirely surprising, seeing that substrate **2.1y** was essentially the indole equivalent of CDI.

Scheme 2.12 Attempted competition experiment for 6 and 7-membered ring formation

⁷² For synthetic details of **2.1y**, please refer to Chapter 3.

2.4 The Azole Family and Carbocyclic Substrates

Since all the examples thus far had dealt with indole-containing substrates, we sought to extend the scope to other nitrogen-containing heterocycles. To this end, we realized that if the phenyl ring of the indole nucleus was removed, it would potentially allow access to four members of the azole family (Scheme 2.13), namely pyrrole (**2.13**), pyrazole (**2.14**), imidazole (**2.15**), and 1,2,3-triazole (**2.16**).

Scheme 2.13 The azole family of *gem*-dibromoolefin substrates

The pyrrole based substrate was synthesized as outlined in Scheme 2.14. Starting from commercial *N*-tosylpyrrole **2.17**, regioselective bromination at the C3 position was achieved in an apparently decent yield under literature conditions.⁷³ Upon close examination of the NMR however, it was clear that the isolated material was actually an inseparable mixture of product **2.18** along with unreacted **2.17** in a 65:35 ratio. Reasoning that **2.17** should not interfere with the Suzuki coupling, we subjected this mixture to the conditions developed for indole substrates and isolated aldehyde **2.19** in a decent 83% yield, confirming our initial hypothesis. Subsequent Ramirez olefination then afforded the desired *gem*-dibromoolefin **2.13**.

⁷³ Zonta, C.; Fabris, F.; De Lucchi, O. *Org. Lett.* **2005**, 7, 1003.

Scheme 2.14 Synthesis of pyrrole-containing *gem*-dibromoolefin **2.13**

The pyrazole substrate was prepared in a similar manner (Scheme 2.15). Regioselective C4 iodination of pyrazole **2.20** was achieved using sub-stoichiometric amounts of iodine and CAN as the *in situ* oxidant to recycle the iodide produced.⁷⁴ Tosylation of **2.21** then proceeded very smoothly under the standard *N*-sulfonylation conditions. However, the Suzuki coupling was quite problematic, leading to aldehyde **2.23** in only 28% yield. The low yield of the subsequent Ramirez olefination was due to difficulties associated with the isolation of **2.14**, as the reaction was observed to reach full conversion by TLC.

Scheme 2.15 Synthesis of pyrazole-containing *gem*-dibromoolefin **2.14**

The imidazole and 1,2,3-triazole substrates proved to be the real stumbling blocks however. While iodoimidazole **2.25** was easily prepared by a literature procedure,⁷⁵ the conditions for the Suzuki coupling appeared to be completely ineffective (Scheme 2.16). Not only did the reaction

⁷⁴ Sammelson, R. E.; Casida, J. E. *J. Org. Chem.* **2003**, *68*, 8075.

⁷⁵ Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1995**, *60*, 2378-2383.

reach less than half conversion, more than 4 byproducts were observed by TLC, including significant amounts of benzaldehyde, the product of protodeboronation.

Scheme 2.16 Attempted synthesis of imidazole-containing aldehyde **2.23**

Likewise, synthesis of triazole-containing *gem*-dibromoolefin **2.16** was met with a lot of frustration (Scheme 2.17). Ironically, while precursors alkyne **2.28** and tosyl azide⁷⁶ for the “click reaction” were fairly easy to prepare, triazole **2.29** itself was not. Very disappointingly, even though **2.29** is a literature known compound,⁷⁷ applying the reported conditions gave only 20% conversion in our hands. After trying several other literature conditions without success, we were finally able to access **2.29** in moderate yield using the protocol developed by Sharpless and co-workers.⁷⁸ Unfortunately, only decomposition products were observed when **2.29** was subjected to $\text{P}(\text{O}i\text{-Pr})_3$ mediated Ramirez olefination. Additionally, **2.29** appeared to have limited stability, and had degraded into a brown gum when we attempted to re-examine this reaction several weeks later.

Scheme 2.17 Attempted synthesis of 1,2,3-triazole-containing *gem*-dibromoolefin **2.16**

⁷⁶ Presset, M.; Mailhol, D.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2011**, 16, 2549.

⁷⁷ Wang, K.; Bi, X.; Xing, S.; Liao, P.; Fang, Z.; Meng, X.; Zhang, Q.; Liu Q.; Ji, Y. *Green Chem.*, **2011**, 13, 562.

⁷⁸ Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, 46, 1730.

Under the optimized conditions for the domino reaction, pyrrole substrate **2.13** reacted smoothly to give the desired product **2.30** in 53% yield, demonstrating that the phenyl ring was not necessary for productive reaction (Scheme 2.18). However, pyrazole substrate **2.14** remained largely unreactive, reaching only 20% conversion even when the reaction temperature was increased to 120 °C. This lack of reactivity may have been due to the pyridine-like nitrogen in pyrazole, which could potentially coordinate to palladium and inhibit catalysis.

Scheme 2.18 Domino reaction of pyrrole and pyrazole substrates

Our final attempt at pushing the envelope involved us examining whether carbocycles could also be utilized for this domino reaction. In designing a suitable substrate, we envisioned that *gem*-dibromoolefin of type **2.32** could potentially undergo two C–H functionalizations if an appropriate linker (X) was used (Scheme 2.19). Since the sulfonyl group had enjoyed the greatest success as a linker thus far in this domino reaction, we decided to focus our attention on sulfone-containing dibromoolefin **2.34**.

Scheme 2.19 Design of a carbocyclic substrate for domino C–H functionalization

The synthesis of **2.34** is outlined in Scheme 2.20. After evaluating several strategies for the preparation of sulfone **2.37**, we finally settled on the sulfonyl fluoride route as presented in the

scheme since it appeared to be the most robust.⁷⁹ The requisite sulfonyl fluoride **2.36** was synthesized in 82% yield via halogen exchange using excess KF and catalytic amounts of 18-crown-6 as the phase-transfer catalyst. The reaction could be conveniently monitored by IR, as both $\nu_{\text{asym}}(\text{S}=\text{O})$ ($\sim 1420\text{ cm}^{-1}$) and $\nu_{\text{sym}}(\text{S}=\text{O})$ ($\sim 1215\text{ cm}^{-1}$) of the product were about 40 cm^{-1} higher compared to the starting material. When this sulfonyl fluoride (**2.36**) was treated with phenylmagnesium bromide, sulfone **2.37** was isolated in almost quantitative yield. Additionally, the reaction was extremely clean, as the crude material was shown to be >98% pure by NMR, and could be used directly without any purification. The Suzuki coupling also worked extremely well, and the Ramirez olefination similarly gave a good yield of dibromoolefin **2.34**.

Given that this synthetic sequence worked very well on the first run, it was naturally very disappointing to find that dibromoolefin **2.34** only gave decomposition products when subjected to the conditions for the domino reaction. However, complete conversion was achieved, indicating that lack of reactivity did not seem to be the issue. Conceivably, functionalization simply does not occur at the two *ortho* C–H bonds due to steric crowding (see **2.32**, Scheme 2.18), and catalytic turnover is achieved through numerous off-pathway processes that lead to eventual degradation of the starting material.

Scheme 2.20 Synthesis of carbocyclic substrate **2.34** and attempted domino reaction

⁷⁹ Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M. *J. Org. Chem.* **1992**, 57, 697.

2.5 Mechanistic Studies

Having studied the reaction scope in quite some detail, we deemed it appropriate to conclude with some mechanistic investigations in order to gain some insight into this interesting reaction. From our optimization studies we found that CsOPiv was required for achieving productive reaction, as in its absence only 10% conversion was observed. This dependency indicates that the C–H activation step may very well proceed via a CMD mechanism, with pivalate assisting in deprotonating the aryl ring as depicted in Scheme 1.19. However, one important question remained: what is the exact sequence of events? Theoretically speaking, the first C–H functionalization could occur at either H^a or H^b (Scheme 2.21); however, any mechanistic scenario involving initial functionalization at H^b would necessarily lead to formation of the highly strained 10-membered intermediate **2.40**, which seems quite implausible. On the other hand, functionalization at H^a leads to the much more reasonable benzo[*c*]carbazole **2.39**, and would seem more likely as the first site of reaction. A third possibility exists however. Dibromoolefin **2.1a** is known to undergo base-promoted elimination to bromoalkyne **2.41**, and this could potentially converge on intermediate **2.39** via a 6-endo-dig cyclization process.

Scheme 2.21 Potential intermediates in the domino reaction

To determine whether bromoalkyne **2.41** is on the productive pathway, it was synthesized independently via TBAF-promoted dehydrohalogenation of **2.1a** (Scheme 2.22).⁸⁰

Scheme 2.22 Synthesis of bromoalkyne **2.41**

The deuterated analogue (**2.45**) of **2.1a** was also prepared as shown in Scheme 2.23 in order to provide complementary information. A noteworthy aspect of the synthesis is that deuterium was incorporated to an extent of 95% at the desired position through a simple, one step H/D exchange process via a cyanohydrin intermediate,⁸¹ using only the relatively cheap D₂O as the deuterium source.

Scheme 2.23 Synthesis of deuterated *gem*-dibromoolefin analogue **2.45**

Subjecting bromoalkyne **2.41** to the conditions for the domino reaction resulted only in extensive decomposition (Scheme 2.24). Though no identifiable product was isolated, **2.41** was

⁸⁰ Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442.

⁸¹ Chancellor, T.; Quill, M.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1978**, *43*, 1245.

completely consumed, indicating that although it is not on the productive pathway, its presence under the reaction conditions is unlikely to cause catalyst inhibition. The deuterated analogue **2.45** led to the expected product (**2.46**) with no leaching of deuterium (within integration error), reinforcing the conclusion that **2.41** is not a productive intermediate.

Scheme 2.24 Reactivity of potential intermediates in the domino reaction

With bromoalkyne **2.41** eliminated as a potential intermediate, the question now became one of whether C–H functionalization occurred at H^a or H^b first (Scheme 2.20). Since functionalization of H^a and H^b correspond to reaction with the (*Z*) and (*E*)-bromide respectively, one could probe this indirectly by synthesizing both stereoisomers and evaluating their reactivity in the domino reaction. Thus, both vinyl bromides were prepared as outlined in Scheme 2.25. After an initial unsuccessful attempt at preparing the (*Z*)-bromide by Pd-catalyzed (*E*)-selective reduction of *gem*-dibromoolefin **2.1a**,⁸² we found that **2.47** could be prepared in almost exclusive (*Z*)-selectivity by performing a bromo-Wittig reaction⁸³ on aldehyde **2.7a**. The (*Z*)-geometry was confirmed by the small ³*J* value of 8 Hz of the olefinic protons. The synthesis of (*E*)-bromide **2.50** was accomplished from the same aldehyde in three steps using Charette’s protocol.⁸⁴ Pleasingly, the desired (*E*)-bromide was obtained as the exclusive stereoisomer, as confirmed by the large vicinal coupling constant of 13.9 Hz for the two vinylic protons.

⁸² Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, 63, 8965.

⁸³ Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, 21, 4021.

⁸⁴ Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, 10, 5485.

Scheme 2.25 Synthesis of (*E*) and (*Z*)-vinyl bromides

When subjected to the reaction conditions, (*Z*)-bromide **2.47** led to benzo[*c*]carbazole **2.51** as the only observable product in 80% yield, with no traces of terminal alkyne **2.52** (Scheme 2.26). Under identical conditions, (*E*)-bromide **2.50** gave only a complex mixture of more than 6 products, none of which corresponded to **2.51** as judged by TLC and NMR.

Scheme 2.26 Reactivity of (*E*) and (*Z*)-vinyl bromides in the domino reaction

These results have several important implications. First, it appears that (*E*)-bromide **2.50** by itself does not isomerize under the reaction conditions, as product **2.51** arising from reaction of

(*Z*)-bromide **2.47** was not detected. Second, as in the case of bromoalkyne **2.41**, (*E*)-bromide **2.50** was completely consumed even though no identifiable product could be isolated. This indicates that while insertion into the (*E*)-bromide does not cause catalyst inhibition, it is nevertheless a deleterious process since it only results in decomposition of the starting material, decreasing the amount available for productive reaction. Third, the fact that terminal alkyne **2.52** was not formed to any extent implies that the kinetics of insertion into the (*Z*)-bromide, however slow it may be, still far outcompeted that of base-promoted dehydrohalogenation of **2.47**. Most importantly however, these results indicate that it is H^a which first undergoes functionalization. This in turn implies that the (*Z*)-bromide of the *gem*-dibromoolefin must react in preference to the (*E*)-bromide for a productive reaction to occur. Though this goes against the natural reactivity of such systems, it could nevertheless be achieved in one of three ways: (i) directed oxidative addition into the (*Z*)-bromide, (ii) reversible oxidative addition, and (iii) isomerization of the vinylpalladium complex. Each of these will be addressed briefly.

Since the (*E*)-bromide of *gem*-dibromoolefins is more sterically accessible, oxidative addition is generally (*E*)-selective. Nonetheless, it has been shown that if appropriate functional groups such as amines,^{57b} thiols,^{57f} or olefins^{57h} are placed *ortho* to the dibromoolefin moiety (Scheme 2.27, **2.53**), they can coordinate to palladium (**2.54**) and direct insertion into the now spatially proximate (*Z*)-bromide (**2.55**), leading to a reversal in selectivity. Seeing as no such directing groups are present in dibromoolefins of type **2.1**, this mode of reactivity appears unlikely.

Scheme 2.27 Functional group directed insertion into (*Z*)-bromide

Oxidative addition of Pd(0) into an aryl or vinyl halide has traditionally been viewed as being an irreversible process for thermodynamic reasons. However, Hartwig has shown that in the case of aryl bromides, the reverse process, *viz.* the reductive elimination of arylpalladium(II) halide complexes could indeed be achieved if certain bulky, electron-rich phosphines, such as P(*t*-Bu)₃,

1-AdP(*t*-Bu)₃, and QPhos are used.⁸⁵ We have demonstrated that for our *gem*-dibromoolefin system, initial oxidative addition into the (*E*)-bromide is a non-productive process (Scheme 2.26). Yet if this oxidative addition was reversible, it would allow regeneration of the starting material, and a productive reaction would eventually result when addition into the (*Z*)-bromide occurs. However, graduate student Stephen Newman has shown that in the synthesis of 2-bromoindole **2.57**, use of any ligand other than P(*t*-Bu)₃ led to less than 5% of **2.57**, due to irreversible oxidative addition of the Pd(0) species into the resulting product, which shuts down the catalytic cycle (Scheme 2.28).⁸⁶ Noteworthy is the fact that SPhos was among the unsuccessful ligands, yet we employ SPhos palladacycle **Pd-1** as both the source of palladium and ligand for all our reactions. Admittedly, a direct comparison cannot be drawn since our substrates are *gem*-dibromoolefins rather than aryl bromides, but this does call into question the ability of SPhos to promote reversible oxidative addition.

Scheme 2.28 Effects of phosphine ligands in the synthesis of 2-bromoindole

If oxidative addition is always (*E*)-selective in the absence of directing groups, and assuming the process is unlikely to be reversible under our reaction conditions, then in order for productive reaction to occur, vinylpalladium(II) complex **2.58** must somehow isomerize to complex **2.59**, the product of addition into the (*Z*)-bromide (eqn. 4).

⁸⁵ a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232. b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944. c) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533.

⁸⁶ Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416.

Precedence exists for the isomerization of vinylpalladium intermediates derived from alkyne carbopalladation.⁸⁷ Jutand and co-workers reported that in the reaction between *trans*-PhPdI(PPh₃)₂ **2.60** and ethyl propiolate **2.61**, the product arising from *syn*-carbopalladation (**2.62**) was observed initially, and had a ³¹P NMR signal at 22.02 ppm (Scheme 2.29). Over the course of the reaction, that signal gradually diminished in intensity, and a new peak was seen at 20.40 ppm, which they correctly hypothesized was the *anti*-adduct **2.63**. To confirm their hypothesis, they treated a mixture of the corresponding vinyl iodides composing of 66% of the (*Z*)-isomer (**2.64**) and 34% of the (*E*)-isomer (**2.65**) to stoichiometric amounts of Pd(PPh₃)₄. Monitoring the reaction by ³¹P NMR, the signal at 20.40 ppm was first observed, due to faster oxidative addition with (*E*)-iodide **2.65**. After a longer period of time, a new peak appeared at 22.02 ppm, which corresponded to **2.62**, the product of insertion into (*Z*)-iodide **2.64**. Most tellingly, the intensities changed gradually and eventually stabilized at a ratio of 36:64 in favour of **2.63**, exactly matching that obtained in the first carbopalladation reaction with ethyl propiolate.

Scheme 2.29 Observation of isomerization products in alkyne carbopalladation

The authors propose that isomerization of the vinylpalladium species could proceed through one of either two resonance structures (**2.67** or **2.68**, Scheme 2.30), wherein rotation about the newly created C–C single bond would now lead to the observed isomerization.

⁸⁷ Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A. *J. Organomet. Chem.* **2004**, 689, 4642 and references therein.

Scheme 2.30 Isomerization of vinylpalladium species through zwitterionic intermediates

It is conceivable that *gem*-dibromoolefins could isomerize via similar structures as shown in Scheme 2.30. For these systems however a further possibility exists – the cationic vinylidene **2.71**⁸⁸ could arise via departure of the vinylic bromide from (*E*)-isomer **2.70**. This bromide could then attack the carbene-like carbon from the more sterically open side opposite the R group to afford (*Z*)-isomer **2.72** (Scheme 2.31). The fact that (*E*)-bromide **2.50** failed to undergo any productive reaction (see Scheme 2.26) lends credence to this being a viable process, since it requires the presence of a decent leaving group alpha to palladium. In the case of **2.50**, this necessitates that hydride act as a leaving group, which would be very unfavourable.

Scheme 2.31 Isomerization of vinylpalladium species through a palladium carbenoid

Combining all of the above, a plausible catalytic cycle can now be drawn (Scheme 2.32). The cycle initiates with generation of an active Pd(0) species, which would first insert into the (*E*)-bromide of **2.1a** to give (*E*)-complex **2.58**. This could now undergo *E-Z* isomerization, possibly via cationic carbenoid **2.71**, to (*Z*)-complex **2.59**, which goes on to give palladacycle **2.73** after the first C–H activation event. Reductive elimination then generates the benzo[*c*]carbazole intermediate **2.39**, which gives arylpalladium(II) species **2.74** following oxidative addition. A second C–H activation onto the tethered tosyl group, and subsequent reductive elimination then finally affords the domino C–H functionalization product **2.3a**.

⁸⁸ Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.

Scheme 2.32 Proposed catalytic cycle for the domino C-H functionalization reaction

2.6 Conclusions and Future Outlook

Building upon the serendipitous discovery of an intriguing reactivity of *gem*-dibromoolefins, we have developed a novel synthesis of substituted *N*-fused benzo[*c*]carbazoles, which proceeds via a key step involving two C–H functionalizations in a domino fashion. Although the yields of these reactions were often moderate, the current procedure allows for a highly modular approach to these polycyclic nitrogen heterocycles, for which few general preparative methods exist.

The results from our mechanistic studies indicate that the reaction does not proceed via alkyne carbopalladation. Rather, it is likely to follow a pathway in which preferential functionalization of the (*Z*)-bromide is achieved through isomerization of the initial (*E*)-vinylpalladium(II) complex, possibly through a cationic palladium carbenoid intermediate. Pivalate was also found to be essential for productive reaction, strongly implying that the C–H activation step proceeds via a concerted metallation-deprotonation process.

In developing the current methodology, we have also demonstrated the feasibility of having both bromides of the *gem*-dibromoolefin moiety undergo C–H functionalization processes. Such reactivity is unprecedented, and opens up avenues for further exploration. In particular, extending the scope of this transformation to include carbocycles would enhance its versatility and appeal. As well, development of intermolecular variants would be highly desirable, although their realization may prove to be difficult.

Chapter 3

Experimental Procedures

3.1 General

Unless otherwise stated, reactions were carried out under an inert atmosphere in oven or flame-dried glassware with magnetic stirring. Organic solutions were concentrated using a Buchi rotary evaporator at 40 – 45 °C under reduced pressure. Analytical thin layer chromatography (TLC) was performed on EMD Silica Gel 60 F₂₅₄ plates (0.2 mm, 60 Å pore size). Visualization was done under a 254 nm UV light source or by anisaldehyde stain. Flash chromatography was performed employing Silicycle Ultra-Pure 230-400 mesh silica gel.

Materials: All reagents were purchased from commercial sources; catalysts and ligands were purchased from Strem, boronic acids were purchased from CombiBlocks and used as received. Diethyl ether, THF, and toluene were distilled over Na/benzophenone prior to use. 1,2-dimethoxyethane (DME) was distilled over CaH₂. Dichloromethane (DCM) was dried using an MBraun solvent purification system. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were dried over activated 4Å molecular sieves. SPhos palladacycle **Pd-1**,⁶⁵ 3-iodoindoles **2.5**,⁶⁷ starting materials **2.18**,⁷³ **2.21**,⁷⁴ **2.25**,⁷⁵ tosyl azide,⁷⁶ *N,N*-dibenzylcarbamoyl chloride,⁸⁹ and indole-1-carboxylic acid⁹⁰ were synthesized according to literature procedures.

Instrumentation: ¹H, ¹³C, ¹⁹F, and ³¹P NMR were recorded at 25 °C on a Varian Mercury 400 MHz or Bruker Avance III 400 MHz spectrometer. ¹H spectra were referenced to solvent residual resonances relative to TMS (CDCl₃: δ 7.26). ¹³C spectra were referenced to solvent carbon resonances (CDCl₃: δ 77.16). Chemical shifts are reported in parts per million (ppm) and coupling constants as scalar values in Hz. Data for ¹H NMR are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*, Hz), and integration. High resolution mass spectra (HRMS) were obtained using an AB/Sciex QStar or AB/Sciex QStar/XL spectrometer operating in positive

⁸⁹ Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. *J. Org. Chem.* **2007**, 72, 5898.

⁹⁰ Boger, D. L.; Patel, M. *J. Org. Chem.* **1987**, 52, 3934.

ESI mode. Infrared spectra were recorded using a Shimadzu FTIR 8400S spectrometer as a thin film on NaCl plates. All melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected.

3.2 Synthesis of *gem*-Dibromoolefin Substrates

Note: Compounds failing to undergo the key domino reaction may not have full characterization. All available data are provided.

3.2.1 General Procedure A: *N*-Sulfonylation of Indoles

To a stirred solution of 3-iodoindole, powdered KOH (3 equiv.), and Bu₄NHSO₄ (10 mol %) in dry DCM (0.25M) was added the sulfonyl chloride in one portion. The reaction was stirred at room temperature or heated as necessary. When judged to be complete by TLC, the reaction was quenched with an equal volume of aqueous 1M NH₃ and the biphasic mixture was stirred vigorously at room temperature for 20 minutes. The layers were separated, the organic layer was washed successively with 1M NaOH and distilled water, dried over MgSO₄, and removed *in vacuo*. The crude products were purified by column chromatography or trituration.

3-Iodo-1-tosyl-1*H*-indole (2.6a)

Following general procedure A, 3-iodo-1*H*-indole (12.152 g, 50 mmol), powdered KOH (8.42 g, 150 mmol), and Bu₄NHSO₄ (1.7 g, 5 mmol) were dissolved in dry DCM (200 mL). Tosyl chloride (9.82 g, 51.5 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 30 minutes. Subsequent workup yielded the title compound as a light tan solid in quantitative yield. The crude product thus obtained was judged to be >95% pure by NMR (containing 3-4% tetrabutylammonium salts as the only visible impurity) and was

used without further purification. An analytically pure sample was obtained via column chromatography (hexanes:EtOAc 13:1). The analytical data was consistent with literature.⁹¹ **R_f** = 0.51 (hexanes:EtOAc 4:1). **MP** 136-137 °C (lit. **MP** 138-139 °C⁹¹); **¹H NMR** (400 MHz, CDCl₃) δ 7.96 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.39 – 7.35 (m, 2H), 7.32 – 7.28 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.34 (s, 3H).

3-Iodo-5-methyl-1-tosyl-1*H*-indole (2.6b)

Following general procedure A, 3-iodo-5-methyl-1*H*-indole (3.342 g, 13 mmol), powdered KOH (2.188 g, 39 mmol), and Bu₄NHSO₄ (0.442 g, 1.3 mmol) were dissolved in dry DCM (50 mL). Tosyl chloride (2.555 g, 13.4 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 30 minutes. Subsequent workup yielded the title compound as a tan solid (5.155 g, 97% yield). The crude product thus obtained was judged to be >95% pure by NMR (containing ~2% tetrabutylammonium salts as the only visible impurity) and was used without further purification. **R_f** = 0.5 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.65 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 0.7 Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.3, 135.1, 133.9, 132.7 (2C), 130.1, 129.9, 127.2, 127.0, 121.9, 113.3, 66.9, 21.7, 21.4; **IR** (NaCl, neat): 3132, 2920, 1597, 1456, 1371, 1267, 1175, 1153, 1111, 1090, 1032, 822, 766 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₁₆H₁₅INO₂S: 411.98682; Found. 411.98781.

⁹¹ Witulski, B.; Buschmann, N.; Bergstraber, U. *Tetrahedron* **2000**, 56, 8473.

3-Iodo-7-methyl-1-tosyl-1H-indole (2.6c)

Following general procedure A, 3-iodo-7-methyl-1H-indole (1.285 g, 5 mmol), powdered KOH (0.842 g, 15 mmol), and Bu₄NHSO₄ (0.175 g, 0.5 mmol) were dissolved in dry DCM (20 mL). Tosyl chloride (0.982 g, 5.15 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature. Extra tosyl chloride (95.3 mg, 0.1 equiv.) was added after 1 hour. The reaction was left to stir overnight at room temperature (total reaction time 19 hours). Subsequent workup and column chromatography (pentane:EtOAc 12:1) yielded the title compound as a light pink solid (1.213 g, 59% yield). **R_f** = 0.59 (pentane:EtOAc 4:1). **MP** 108–110 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.93 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 2.54 (s, 3H), 2.37 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.1, 136.7, 134.5, 134.4, 133.4, 130.2, 129.4, 126.7, 125.0, 124.5, 120.3, 67.3, 21.8, 21.6; **IR** (NaCl, neat): 3148, 2973, 2936, 1596, 1456, 1362, 1249, 1173, 1123, 1087, 973, 856, 811, 780, 738 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₁₆H₁₅INO₂S: 411.9862; Found. 411.9849.

3-Iodo-5-methoxy-1-tosyl-1H-indole (2.6d)

Following general procedure A, 3-iodo-5-methoxy-1H-indole (1.038 g, 3.8 mmol), powdered KOH (0.64 g, 11.4 mmol), and Bu₄NHSO₄ (0.133 g, 0.38 mmol) were dissolved in dry DCM (15 mL). Tosyl chloride (0.746 g, 3.914 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature. Subsequent workup and column chromatography (hexanes:EtOAc 12:1) yielded the title compound as white crystals (0.782 g, 48% yield). The analytical data was consistent with literature.⁹¹ **R_f** = 0.47 (hexanes:EtOAc 4:1). **MP** 173–175 °C (lit. MP 174–175 °C⁹¹); **¹H NMR** (400 MHz, CDCl₃) δ 7.85 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.1

Hz, 2H), 7.65 (s, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.96 (dd, $J = 9.0, 1.9$ Hz, 1H), 6.78 (s, 1H), 3.84 (s, 3H), 2.34 (s, 3H).

Methyl 3-iodo-1-tosyl-1*H*-indole-6-carboxylate (2.6e)

Following general procedure A, methyl 3-iodo-1*H*-indole-6-carboxylate (1.5054 g, 5 mmol), powdered KOH (0.842 g, 15 mmol), and Bu₄NHSO₄ (0.175 g, 0.5 mmol) were dissolved in dry DCM (150 mL). Tosyl chloride (1.05 g, 5.5 mmol, 1.1 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 90 minutes. Subsequent workup yielded the crude product as an orange solid. The crude product was suspended in a minimal amount (~4 mL) of DCM and kept at -20 °C overnight. Trituration with ice-cold DCM until the washings were colourless afforded the title compound as an off-white solid (2.061 g, 91% yield). $R_f = 0.44$ (pentane:EtOAc 4:1). **MP** 198-200 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.66 (s, 1H), 8.00 (d, $J = 8.3$ Hz, 1H), 7.83 – 7.80 (m, 3H), 7.41 (d, $J = 8.3$ Hz, 1H), 7.28 – 7.26 (m, 2H), 3.98 (s, 3H), 2.36 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 167.0, 145.9, 136.1, 134.8, 134.0, 132.7, 130.4, 127.7, 127.2, 125.1, 122.0, 115.3, 66.3, 52.5, 21.8; **IR** (NaCl, neat): 3132, 2952, 1713, 1596, 1377, 1291, 1241, 1173, 1135, 1091, 1027, 812, 768, 720, 667, 606 cm⁻¹; **HRMS** (ESI) [M+NH₄]⁺ Calcd for C₁₇H₁₈IN₂O₄S: 473.00385; Found. 473.00441.

3-Iodo-1-tosyl-1*H*-indole-5-carbonitrile (2.6f)

Following general procedure A, 3-iodo-1*H*-indole-5-carbonitrile (1.34 g, 5 mmol), powdered KOH (0.842 g, 15 mmol), and Bu₄NHSO₄ (0.175 g, 0.5 mmol) were dissolved in dry DCM (100 mL). Tosyl chloride (0.982 g, 5.15 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 90 minutes. Subsequent workup yielded the crude product as a tan solid. The crude product was suspended in a minimal amount (~3 mL) of

DCM, and pentane (20 mL) was added. The suspension was kept at $-20\text{ }^{\circ}\text{C}$ for 30 minutes, and then filtered over a medium frit, washing with ice-cold pentane. The title compound was obtained as a slightly off-white solid (1.832 g, 87% yield). $R_f=0.36$ (pentane:EtOAc 4:1). **MP** 173-174 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.05 (d, $J = 8.6$ Hz, 1H), 7.80 – 7.78 (m, 3H), 7.73 (d, $J = 1.0$ Hz, 1H), 7.61 (dd, $J = 8.6, 1.5$ Hz, 1H), 7.29 (d, $J = 8.2$ Hz, 2H), 2.38 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 146.4, 136.3, 134.5, 132.9, 132.0, 130.5, 128.7, 127.2, 127.2, 119.0, 114.5, 107.9, 65.7, 21.8; **IR** (NaCl, neat): 3136, 2226, 1595, 1454, 1381, 1291, 1266, 1173, 1145, 1090, 1026, 815, 806, 763, 670 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{16}\text{H}_{15}\text{IN}_3\text{O}_2\text{S}$: 439.99296; Found. 439.99290.

3-Iodo-5-nitro-1H-indole (2.6g)

Following general procedure A, 3-iodo-5-nitro-1H-indole (3.745 g, 13 mmol), powdered KOH (2.188 g, 39 mmol), and $\text{Bu}_4\text{NH}_4\text{SO}_4$ (0.442 g, 1.3 mmol) were suspended in dry DCM (130 mL). Tosyl chloride (2.555 g, 13.4 mmol, 1.03 equiv.) was then added in one portion, and the reaction was gently heated to reflux with a heat gun and kept at reflux temperature until it became homogeneous. The reaction was then cooled to room temperature and stirred for 30 minutes. Subsequent workup yielded crude product as a brown solid. The crude product was triturated with EtOAc (10 mL x 3) to wash away the brown impurity and afford the title compound as a yellow-tan solid (4.99 g, 87% yield). $R_f = 0.45$ (hexanes:EtOAc 4:1). **MP** 186-187 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.31 (d, $J = 2.1$ Hz, 1H), 8.25 (dd, $J = 9.1, 2.2$ Hz, 1H), 8.08 (d, $J = 9.1$ Hz, 1H), 7.84 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 2.38 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 146.5, 144.8, 137.4, 134.4, 132.9, 132.8, 130.5, 127.2, 120.9, 118.8, 114.0, 66.5, 21.8; **IR** (NaCl, neat): 3136, 1595, 1522, 1438, 1383, 1346, 1292, 1192, 1175, 1123, 1090, 1078, 1026, 957, 816, 727, 665 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{15}\text{H}_{15}\text{IN}_3\text{O}_4\text{S}$: 459.98279; Found. 459.98321.

3-Iodo-1-tosyl-7-azaindole (2.6h)

Following general procedure A, 3-iodo-7-azaindole (3.173 g, 13 mmol), powdered KOH (2.188 g, 39 mmol), and Bu₄NHSO₄ (0.442 g, 1.3 mmol) were suspended in dry DCM (130 mL). Tosyl chloride (2.555 g, 13.4 mmol, 1.03 equiv.) was then added in one portion, and the reaction was gently heated to reflux with a heat gun and kept at reflux temperature until it became homogeneous. The reaction was then cooled to room temperature and stirred for 30 minutes. Subsequent workup yielded crude product as a thick syrup. The crude product was redissolved in EtOAc (40 mL) and any insoluble impurities were removed by filtration. The organic layer was washed with distilled water (120 mL x 3). The aqueous washings were extracted with EtOAc (30 mL x 2), the organic extracts were combined, dried over MgSO₄, and removed *in vacuo* to afford the title compound as a light tan solid (5.018 g, 97% yield). **R_f** = 0.58 (hexanes:EtOAc 6:4). **MP** 123-125 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.44 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.86 (s, 1H), 7.65 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.24 (dd, *J* = 7.9, 4.8 Hz, 1H), 2.36 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 146.5, 146.1, 145.7, 135.1, 130.3, 130.0, 129.9, 128.3, 125.3, 119.6, 62.0, 21.8; **IR** (NaCl, neat): 3134, 1593, 1572, 1391, 1375, 1277, 1175, 1142, 1090, 1024, 1015, 924, 812, 800, 764, 708, 664 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₁₄H₁₂IN₂O₂S: 398.9658; Found. 398.9666.

1-(Benzylsulfonyl)-3-iodo-1*H*-indole (2.6i)

Following general procedure A, 3-iodo-1*H*-indole (1.458 g, 6 mmol), powdered KOH (1.01 g, 18 mmol), and Bu₄NHSO₄ (0.204 g, 0.6 mmol) were dissolved in dry DCM (24 mL). Phenylmethanesulfonyl chloride (1.178 g, 6.18 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 30 minutes. Additional sulfonyl

chloride was added (0.572 g, 3 mmol, 0.5 equiv.), and the reaction stirred for a further 30 minutes at room temperature. TLC indicated reaction was still incomplete, thus additional sulfonyl chloride was added (0.572 g, 3 mmol, 0.5 equiv.), and the reaction stirred a further 30 minutes at room temperature. Subsequent workup and column chromatography (pentane:EtOAc 10 :1) afforded the title compound as a yellow-orange syrup (1.304 g, 55% yield). R_f = 0.49 (hexanes:EtOAc 4:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.77 – 7.73 (m, 1H), 7.44 – 7.41 (m, 1H), 7.38 – 7.34 (m, 2H), 7.30 (ddd, J = 6.9, 4.1, 1.3 Hz, 1H), 7.19 (t, J = 7.6 Hz, 2H), 7.11 (s, 1H), 6.85 (d, J = 7.2 Hz, 2H), 4.47 (s, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 135.0, 132.2, 130.8, 130.6, 129.7, 128.9, 126.5, 125.8, 124.2, 122.2, 113.2, 65.8, 60.2; **IR** (NaCl, neat): 3136, 2924, 1371, 1167, 1125, 1026, 923, 743, 696 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{15}\text{H}_{12}\text{INO}_2\text{SNa}$: 419.9525; Found. 419.9531.

3-Iodo-1-(4-methoxyphenylsulfonyl)-1*H*-indole (2.6j)

Following general procedure A, 3-iodo-1*H*-indole (1.215 g, 5 mmol), powdered KOH (0.842 g, 15 mmol), and Bu_4NHSO_4 (0.175 g, 0.5 mmol) were dissolved in dry DCM (20 mL). 4-methoxybenzenesulfonyl chloride (1.064 g, 5.15 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 4:1) yielded the title compound as a light orange solid (2.00 g, 97% yield). R_f = 0.31 (Hexanes:EtOAc 4:1). **MP** 121-123 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.96 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.9 Hz, 2H), 7.69 (s, 1H), 7.37 (t, J = 6.8 Hz, 2H), 7.32 – 7.29 (m, 1H), 6.89 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 164.2, 134.4, 132.6, 129.9, 129.4 (2C), 125.8, 124.0, 122.1, 114.8, 113.5, 66.8, 55.8; ; **IR** (NaCl, neat): 3132, 2840, 1593, 1576, 1496, 1443, 1373, 1262, 1168, 1093, 1021, 923, 832, 804, 754, 744, 693, 662 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{13}\text{INO}_3\text{S}$: 413.9655; Found. 413.9646.

3-Iodo-1-(4-nitrophenylsulfonyl)-1H-indole (2.6k)

Following general procedure A, 3-iodo-1H-indole (1.215 g, 5 mmol), powdered KOH (0.842 g, 15 mmol), and Bu₄NHSO₄ (0.175 g, 0.5 mmol) were dissolved in dry DCM (20 mL). 4-nitrobenzenesulfonyl chloride (1.165 g, 5.15 mmol, 1.03 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 30 minutes. Subsequent workup and column chromatography (gradient hexanes:EtOAc 9:1 to hexanes:EtOAc 5:1) yielded the title compound as a bright yellow solid (1.334 g, 62% yield). **R_f** = 0.43 (Hexanes:EtOAc 4:1). **MP** 185-187 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H), 7.44 – 7.38 (m, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 150.9, 143.1, 134.4, 132.8, 129.4, 128.3, 126.5, 124.9, 124.8, 122.6, 113.4, 69.2; **IR** (NaCl, neat): 3131, 3118, 1533, 1443 1383, 1348, 1266, 1177, 1125, 1025, 1011, 854, 738, 678 cm⁻¹; **HRMS** (DART-ESI) [M⁺] Calcd for C₁₄H₉IN₂O₄S: 427.93277; Found. 427.93201.

4-Iodo-1-tosyl-1H-pyrazole (2.22)

Following general procedure A, 4-iodo-1H-pyrazole (1.94 g, 10 mmol), powdered KOH (1.683 g, 30 mmol), and Bu₄NHSO₄ (0.34 g, 1 mmol) were suspended in dry DCM (40 mL). Tosyl chloride (2.097 g, 11 mmol, 1.1 equiv.) was then added in one portion, and the reaction was stirred at room temperature for 30 minutes, at which point the reaction became homogenous. Subsequent workup yielded crude **2.11** as a yellow solid. The crude product was redissolved in Et₂O (150 mL) and any insoluble impurities were removed by filtration. The organic layer was washed with distilled water (50 mL x 3), dried over MgSO₄, and removed *in vacuo* to afford the title compound as a white solid (3.072 g, 88% yield). The analytical data was consistent with

literature.⁹² $R_f = 0.39$ (hexanes:EtOAc 4:1). **MP** 83-84 °C (lit. **MP** 89-90 °C⁹²); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.89 (d, $J = 8.2$ Hz, 2H), 7.68 (s, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 2.43 (s, 3H).

3.2.2 General Procedure B: Suzuki-Miyaura Coupling

An oven-dried heavy wall pressure vessel was cooled under Ar. To this flask was sequentially added the aryl halide, boronic acid, catalyst, ligand, and cesium fluoride, all under an Ar atmosphere. The flask was then purged with Ar for an additional 5 minutes, and DME was added via syringe under Ar. The flask was further purged with Ar for 1 minute, then sealed under Ar and placed in an oil bath pre-heated to 90 °C and left overnight. After cooling to room temperature, the reaction was diluted with Et_2O , washed with brine, dried over MgSO_4 , and the solvent removed *in vacuo*. The crude products were purified by column chromatography.

2-(1-Tosyl-1H-indol-3-yl)benzaldehyde (**2.7a**)

Following general procedure B, a mixture of indole **2.6a** (5.96 g, 15 mmol), 2-formylphenylboronic acid (4.5 g, 30 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (172.5 mg, 0.3 mmol, 2 mol %), PPh_3 (157.4 mg, 0.6 mmol, 4 mol %), and CsF (4.557 g, 30 mmol, 2.0 equiv.) in DME (60 mL) was heated to 90 °C for 16 hours. Subsequent workup and column chromatography (15% EtOAc

⁹² Heinisch, G.; Holzer, W.; Obala, C. *Monatsh. Chem.* **1998**, *119*, 253.

in hexanes) gave the title compound as a viscous red-orange gum (5.19 g, 92% yield). The analytical data was consistent with literature.⁵⁹ R_f = 0.34 (hexanes:EtOAc 4:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.90 (s, 1H), 8.09 – 8.06 (m, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.63 (s, 1H), 7.53 (dd, J = 14.9, 7.6 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.26 (t, J = 7.0 Hz, 3H), 2.37 (s, 3H).

2-(5-Methyl-1-tosyl-1*H*-indol-3-yl)benzaldehyde (2.7b)

Following general procedure B, a mixture of indole **2.6b** (2.468 g, 6 mmol), 2-formylphenylboronic acid (1.8 g, 12 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (69 mg, 0.12 mmol, 2 mol %), PPh_3 (63 mg, 0.24 mmol, 4 mol %), and CsF (1.823 g, 12 mmol, 2.0 equiv.) in DME (24 mL) was heated to 90 °C for 17 hours. Subsequent workup and column chromatography (15% EtOAc in hexanes) gave the title compound as a thick yellow gum (1.842 g, 79% yield). R_f = 0.30 (hexanes:EtOAc 4:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.89 (d, J = 0.7 Hz, 1H), 8.07 (dd, J = 7.8, 1.2 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.68 (td, J = 7.5, 1.5 Hz, 1H), 7.59 (s, 1H), 7.56 – 7.49 (m, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.21 (dd, J = 8.5, 1.2 Hz, 1H), 7.15 (d, J = 0.7 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 191.9, 145.4, 136.4, 135.1, 134.6, 134.2, 134.0, 133.2, 131.5, 131.2, 130.1, 128.5, 127.9, 127.0 (2C), 125.8, 119.8, 119.6, 113.7, 21.7, 21.4; **IR** (NaCl, neat): 3061, 2920, 2845, 1692, 1599, 1451, 1371, 1175, 1134, 1090, 812 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$: 407.14294; Found. 407.14290.

2-(7-Methyl-1-tosyl-1*H*-indol-3-yl)benzaldehyde (2.7c)

Following general procedure B, a mixture of indole **2.6c** (1.03 g, 2.5 mmol), 2-formylphenylboronic acid (0.75 g, 5 mmol, 2 equiv.), Pd(dba)₂ (28.8 mg, 0.05 mmol, 2 mol %), PPh₃ (26.2 mg, 0.1 mmol, 4 mol %), and CsF (0.76 g, 5 mmol, 2.0 equiv.) in DME (16 mL) was heated to 90 °C for 19 hours. Subsequent workup and column chromatography (pentane:EtOAc 10:1) gave the title compound as a yellow gum (0.796 g, 82% yield). **R_f** = 0.55 (pentane:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.85 (d, *J* = 0.7 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.82 (s, 1H), 7.69 (td, *J* = 7.5, 1.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.19 – 7.13 (m, 2H), 7.11 (dd, *J* = 6.8, 1.7 Hz, 1H), 2.64 (s, 3H), 2.40 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.8, 145.2, 136.5, 136.4, 135.2, 134.8, 134.2, 133.4, 131.6, 130.1, 129.2 (2C), 128.6, 128.0, 126.7, 125.8, 124.7, 119.8, 118.0, 21.9, 21.8; **IR** (NaCl, neat): 3064, 2925, 2853, 1700, 1693, 1595, 1363, 1174, 1128, 1087, 1000, 871, 786, 747, 672 cm⁻¹; **HRMS** (ESI) [M+NH₄]⁺ Calcd for C₂₃H₂₃N₂O₃S: 407.14294; Found. 407.14184.

2-(5-Methoxy-1-tosyl-1H-indol-3-yl)benzaldehyde (**2.7d**)

Following general procedure B, a mixture of indole **2.6d** (640.1 mg, 1.5 mmol), 2-formylphenylboronic acid (0.45 g, 3 mmol, 2 equiv.), Pd(dba)₂ (17.3 mg, 0.03 mmol, 2 mol %), PPh₃ (15.8 mg, 0.06 mmol, 4 mol %), and CsF (0.456 g, 3 mmol, 2.0 equiv.) in DME (10 mL) was heated to 90 °C for 16 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:1) gave the title compound as a light orange solid (0.429 g, 71% yield). **R_f** = 0.29 (pentane:EtOAc 4:1). **MP** 148-150 °C; **¹H NMR** (400 MHz, CDCl₃) δ 9.87 (s, 2H), 8.07 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 9.1 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 4H), 7.68 (t, *J* = 7.4 Hz, 2H), 7.58 – 7.49 (m, 6H), 7.25 – 7.27ii (m, 5H), 7.00 (dd, *J* = 9.1, 2.3 Hz, 2H), 6.76 (d, *J* = 2.2 Hz, 2H), 3.73 (s, 6H), 2.37 (s, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.9, 157.3, 145.4, 136.3, 135.1, 134.6, 134.3, 132.0, 131.4, 130.2, 129.6, 128.6, 128.1, 127.0, 126.4, 119.9, 115.0, 114.9, 102.2, 55.8, 21.8; **IR** (NaCl, neat): 2958, 2934, 2836, 1693, 1600, 1469, 1371, 1216, 1174,

1135, 1033, 954, 913, 765, 672 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{20}\text{NO}_4\text{S}$: 406.1107; Found. 406.1110.

Methyl 3-(2-formylphenyl)-1-tosyl-1*H*-indole-6-carboxylate (2.7e)

Following general procedure B, a mixture of indole **2.6e** (1.184 g, 2.6 mmol), 2-formylphenylboronic acid (0.78 g, 5.2 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (30 mg, 0.052 mmol, 2 mol %), PPh_3 (27.3 mg, 0.104 mmol, 4 mol %), and CsF (0.79 g, 5.2 mmol, 2.0 equiv.) in DME (16 mL) was heated to 90 $^\circ\text{C}$ for 17 hours. Subsequent workup and column chromatography (gradient pentane:EtOAc 4:1 to pentane:EtOAc 6:4) gave the title compound as a yellow-orange solid (1.041 g, 92% yield). $R_f = 0.25$ (pentane:EtOAc 4:1). **MP** 158-160 $^\circ\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 9.89 (d, $J = 0.6$ Hz, 1H), 8.77 (d, $J = 0.7$ Hz, 1H), 8.08 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.96 (dd, $J = 8.4, 1.4$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 2H), 7.77 (s, 1H), 7.69 (td, $J = 7.5, 1.4$ Hz, 1H), 7.57 (t, $J = 7.6$ Hz, 1H), 7.50 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.30 (d, $J = 8.1$ Hz, 2H), 3.98 (s, 3H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 191.5, 167.0, 145.9, 135.4, 134.9, 134.6, 134.5, 134.3, 134.2, 131.5, 130.4, 128.8, 128.4, 128.3, 127.5, 127.2, 125.2, 119.9, 119.6, 115.8, 52.5, 21.8; **IR** (NaCl, neat): 3066, 2952, 2925, 2848, 2753, 1717, 1695, 1598, 1434, 1377, 1292, 1250, 1178, 1140, 1090, 1012, 910, 814, 775, 731, 675, 665 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}\text{NO}_5\text{S}$: 434.10872; Found. 434.10756.

3-(2-Formylphenyl)-1-tosyl-1*H*-indole-5-carbonitrile (2.7f)

Following general procedure B, a mixture of indole **2.6f** (1.098 g, 2.6 mmol), 2-formylphenylboronic acid (0.78 g, 5.2 mmol, 2 equiv.), Pd(dba)₂ (30 mg, 0.052 mmol, 2 mol %), PPh₃ (27.3 mg, 0.104 mmol, 4 mol %), and CsF (0.79 g, 5.2 mmol, 2.0 equiv.) in DME (16 mL) was heated to 90 °C for 17 hours. Subsequent workup and column chromatography (pentane:EtOAc 4:1) gave the title compound as a thick orange gum (0.370 g, 36% yield). **R_f** = 0.24 (pentane:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.90 (s, 1H), 8.17 (dd, *J* = 8.7, 0.6 Hz, 1H), 8.10 – 8.08 (m, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.75 – 7.70 (m, 3H), 7.62 (ddd, *J* = 8.2, 4.9, 1.0 Hz, 2H), 7.49 – 7.47 (m, 1H), 7.32 (dd, *J* = 8.0, 0.6 Hz, 2H), 2.40 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.1, 146.4, 136.6, 134.7, 134.6, 134.4, 134.3, 131.5, 130.8, 130.6, 129.2, 129.1, 128.4, 127.5, 127.2, 125.3, 119.0, 114.9, 107.9, 97.0, 21.8; **IR** (NaCl, neat): 3069, 2925, 2854, 1695, 1598, 1456, 1377, 1172, 1134, 1091, 1009, 913, 839, 817, 743, 672 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₇N₂O₃S: 401.0954; Found. 401.0960.

2-(5-Nitro-1-tosyl-1*H*-indol-3-yl)benzaldehyde (**2.7g**)

Following general procedure B, a mixture of indole **2.6g** (4.422 g, 10 mmol), 2-formylphenylboronic acid (3 g, 20 mmol, 2 equiv.), Pd(dba)₂ (0.2875 g, 0.5 mmol, 5 mol %), PPh₃ (0.2623 g, 1 mmol, 10 mol %), and CsF (3.038 g, 20 mmol, 2.0 equiv.) in DME (40 mL) was heated to 90 °C for 18 hours. Subsequent workup yielded 6 g of crude **2.7g** as a red-brown solid. Due to the highly crystalline nature and poor solubility of crude **2.7g**, only ¼ of the crude was purified by column chromatography (hexanes:EtOAc 7:3) to give a light orange solid (1.101 g, 73% yield based on amount purified). **R_f** = 0.35 (hexanes:EtOAc 7:3). **MP** 169-171 °C; **¹H NMR** (400 MHz, CDCl₃) δ 9.92 (s, 1H), 8.31 – 8.27 (m, 2H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.78 (s, 1H), 7.74 (td, *J* = 7.5, 1.4 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.40 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.1, 146.5, 144.9, 137.7, 134.7, 134.6, 134.4, 134.1, 131.6, 130.7, 130.6, 129.4, 129.3, 128.3, 127.2, 120.7, 120.3, 116.8, 114.3, 21.8; **IR** (NaCl,

neat): 3106, 2853, 1694, 1597, 1524, 1441, 1379, 1342, 1179, 1090, 1011, 955, 814, 739, 665 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_5\text{S}$: 438.11237; Found. 438.11355.

2-(1-Tosyl-1*H*-7-azaindol-3-yl)benzaldehyde (**2.7h**)

Following general procedure B, a mixture of indole **2.6h** (2.44 g, 6.13 mmol), 2-formylphenylboronic acid (3 g, 20 mmol, 3.26 equiv.), $\text{Pd}(\text{dba})_2$ (0.2875 g, 0.5 mmol, 8 mol %), PPh_3 (0.2623 g, 1 mmol, 16 mol %), and CsF (3.038 g, 20 mmol, 3.26 equiv.) in DME (40 mL) was heated to 90 °C for 17 hours. Subsequent workup and column chromatography (hexanes:EtOAc 3:1) gave the title compound as a light tan solid (2.08 g, 90% yield). R_f = 0.31 (hexanes:EtOAc 7:3). **MP** 132-134 °C; **^1H NMR** (400 MHz, CDCl_3) δ 9.99 (d, J = 0.5 Hz, 1H), 8.51 (dd, J = 4.8, 1.5 Hz, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.07 (dd, J = 7.8, 1.2 Hz, 1H), 7.81 (s, 1H), 7.73 (dd, J = 7.9, 1.6 Hz, 1H), 7.69 (td, J = 7.5, 1.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.51 (dd, J = 7.7, 0.7 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.22 (dd, J = 7.9, 4.8 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 191.6, 147.0, 145.8, 145.7, 135.6, 135.2, 134.5, 134.3, 131.4, 129.9, 128.7, 128.6, 128.5, 128.4, 125.4, 123.1, 119.6, 116.2, 21.8; **IR** (NaCl, neat): 3125, 3063, 2849, 2751, 1690, 1597, 1549, 1398, 1373, 1256, 1173, 1088, 1011, 932, 827, 763, 669 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_3\text{S}$: 377.0945; Found. 377.0962.

2-(1-(Benzylsulfonyl)-1*H*-indol-3-yl)benzaldehyde (**2.7i**)

Following general procedure B, a mixture of indole **2.6i** (1.192 g, 3 mmol), 2-formylphenylboronic acid (0.9 g, 6 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (69 mg, 0.12 mmol, 4 mol %),

PPh₃ (63 mg, 0.24 mmol, 8 mol %), and CsF (0.911 g, 6 mmol, 2.0 equiv.) in DME (15 mL) was heated to 90 °C for 16 hours. Subsequent workup and column chromatography (pentane:EtOAc 7:1) gave the title compound as a thick, light yellow gum (0.528 g, 47% yield). **R_f** = 0.33 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.74 (d, *J* = 0.6 Hz, 1H), 8.05 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.70 – 7.59 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.38 – 7.29 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.03 (s, 1H), 6.92 (d, *J* = 7.2 Hz, 2H), 4.61 (s, 2H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.8, 136.1, 135.1, 134.6, 134.2, 131.5, 130.6, 130.4, 129.7, 129.0, 128.5, 128.0, 126.9, 126.4, 125.6, 124.2, 120.3, 118.3, 113.4, 59.9; **IR** (NaCl, neat): 2925, 2854, 1691, 1600, 1447, 1371, 1166, 1128, 1016, 913, 748, 667 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₂H₁₈NO₃S: 376.10074; Found. 376.09999.

2-(1-(4-Methoxyphenylsulfonyl)-1*H*-indol-3-yl)benzaldehyde (**2.7j**)

Following general procedure B, a mixture of indole **2.6j** (1.075 g, 2.6 mmol), 2-formylphenylboronic acid (0.78 g, 5.2 mmol, 2 equiv.), Pd(dba)₂ (30 mg, 0.052 mmol, 2 mol %), PPh₃ (27.3 mg, 0.104 mmol, 4 mol %), and CsF (0.79 g, 5.2 mmol, 2.0 equiv.) in DME (16 mL) was heated to 90 °C for 19 hours. Subsequent workup and column chromatography (hexanes:EtOAc 4:1) gave the title compound as a yellow foam (0.845 g, 83% yield). **R_f** = 0.19 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.91 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.63 (s, 1H), 7.53 (dd, *J* = 11.8, 7.7 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.27 – 7.25 (m, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.9, 164.2, 136.3, 135.0, 134.7, 134.2, 131.5, 130.9, 129.5, 129.4, 128.5, 128.1, 125.7, 125.5, 124.1, 120.2, 119.6, 114.8, 114.0, 55.84; **IR** (NaCl, neat): 3066, 2841, 1690, 1683, 1594, 1498, 1447, 1371, 1265, 1189, 1169, 1132, 1089, 1042, 933, 831, 804, 749, 676 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₂H₁₈NO₄S: 392.0951; Found. 392.0948.

2-(1-(4-Nitrophenylsulfonyl)-1*H*-indol-3-yl)benzaldehyde (**2.7k**)

Following general procedure B, a mixture of indole **2.6k** (1.113 g, 2.6 mmol), 2-formylphenylboronic acid (0.78 g, 5.2 mmol, 2 equiv.), Pd(dba)₂ (30 mg, 0.052 mmol, 2 mol %), PPh₃ (27.3 mg, 0.104 mmol, 4 mol %), and CsF (0.79 g, 5.2 mmol, 2.0 equiv.) in DME (16 mL) was heated to 90 °C for 15 hours. Subsequent workup and column chromatography (15% EtOAc in hexanes) gave the title compound as a yellow-orange foam (0.894 g, 85% yield). **R_f** = 0.26 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.92 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.62 (s, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.5, 151.0, 143.3, 135.2, 134.8, 134.7, 134.2, 131.5, 131.1, 128.9, 128.7, 128.4, 126.2, 125.1, 124.9 (2C), 121.5, 120.6, 113.8; **IR** (NaCl, neat): 3106, 1691, 1683, 1600, 1532, 1447, 1403, 1381, 1348, 1183, 1130, 1087, 1010, 934, 854, 827, 738, 682 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₁H₁₅N₂O₅S: 407.0696; Found. 407.0690.

5-Methoxy-2-(1-(tosyl)-1*H*-indol-3-yl)benzaldehyde (**2.7l**)

Following general procedure B, a mixture of indole **2.6a** (1.033 g, 2.6 mmol), boronic acid **3.1** (0.936 g, 5.2 mmol, 2 equiv.), Pd(dba)₂ (30 mg, 0.052 mmol, 2 mol %), PPh₃ (27.3 mg, 0.104 mmol, 4 mol %), and CsF (0.79 g, 5.2 mmol, 2.0 equiv.) in DME (16 mL) was heated to 90 °C for 18 hours. Subsequent workup and column chromatography (pentane:EtOAc 4:1) gave the

title compound as a thick yellow gum (0.977 g, 93% yield). R_f = 0.31 (hexanes:EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3) δ 9.86 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.55 (d, J = 2.8 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.28 – 7.22 (m, 4H), 3.91 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.7, 159.80, 145.5, 135.6, 135.2, 135.0, 132.8, 131.2, 130.2, 129.0, 127.0, 125.5 (2C), 124.1, 122.0, 120.2, 119.5, 114.0, 110.5, 55.8, 21.7; IR (NaCl, neat): 3126, 3066, 2961, 2848, 1684, 1603, 1557, 1494, 1447, 1373, 1276, 1240, 1178, 1130, 1091, 1010, 910, 813, 708, 667 cm^{-1} ; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{20}\text{NO}_4\text{S}$: 406.11130; Found. 406.11082.

Synthesis of Aldehyde 2.7q

(3-Iodo-1H-indol-1-yl)(phenyl)methanone (3.2)

To a stirred solution of 3-iodo-1H-indole (1.215 g, 5 mmol), powdered KOH (0.842 g, 15 mmol), and Bu_4NHSO_4 (0.17 g, 0.5 mmol) in dry DCM (18 mL) was added a solution of benzoyl chloride (0.65 mL, 5.6 mmol, 1.12 equiv.) in dry DCM (2 mL) in one portion. The reaction was stirred at room temperature for 30 minutes, and quenched with 1M NaOH. The layers were separated, the organic layer was washed with brine, dried over MgSO_4 , and concentrated. The residue was suspended in a mixture of DCM (~3 mL) and pentane (~10 mL), and kept at $-20\text{ }^\circ\text{C}$ overnight. The mother liquor was carefully decanted, and the residue redissolved in Et_2O (80 mL). The organic layer was washed with distilled water (30 mL x 3), dried over MgSO_4 , and the solvent removed *in vacuo* to afford **3.2** as a light orange solid (1.456 g, 84% yield). R_f = 0.71 (pentane:EtOAc 4:1). MP 118-119 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.36 (dd, J = 7.6, 1.7 Hz, 1H), 7.75 – 7.72 (m, 2H), 7.66 – 7.62 (m, 1H), 7.55 (ddd, J = 8.1, 6.6, 1.2 Hz, 2H), 7.48 – 7.39 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.8, 135.7, 134.1, 132.5, 132.4, 131.6, 129.3, 128.9, 126.2, 124.7, 121.6, 116.4, 67.5; IR (NaCl, neat): 3141, 3062, 1690,

1600, 1529, 1447, 1354, 1330, 1205, 1151, 1017, 948, 867, 793, 747, 706, 655 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{11}\text{INO}$: 347.98853; Found. 347.98893.

2-(1-Benzoyl-1*H*-indol-3-yl)benzaldehyde (2.7q)

Following general procedure B, a mixture of indole **3.2** (1.042 g, 3 mmol), 2-formylphenylboronic acid (0.9 g, 6 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (34.5 mg, 0.06 mmol, 2 mol %), PPh_3 (31.5 mg, 0.12 mmol, 4 mol %), and CsF (0.911 g, 6 mmol, 2.0 equiv.) in DME (15 mL) was heated to 90 $^\circ\text{C}$ for 15 hours. Subsequent workup and column chromatography (pentane:EtOAc 10:1) gave the title compound as light yellow solid (0.645 g, 66% yield). R_f = 0.25 (pentane:EtOAc 4:1). **MP** 150-151 $^\circ\text{C}$; **^1H NMR** (400 MHz, CDCl_3) 2:1 mixture of rotamers, δ 10.09 (d, J = 0.7 Hz, 2H, rotamer 1), 9.85 (d, J = 0.4 Hz, 1H rotamer 2), 8.49 (d, J = 8.3 Hz, 2H, rotamer 1), 8.12 (dd, J = 8.3, 1.2 Hz, 1H, rotamer 2), 8.07 (dd, J = 7.8, 1.2 Hz, 3H, rotamer 1 and 2), 7.83 – 7.76 (m, 4H, rotamer 1 and 2), 7.71 – 7.45 (m, 24H, rotamer 1 and 2), 7.40 – 7.34 (m, 6H, rotamer 1 and 2); **^{13}C NMR** (100 MHz, CDCl_3) δ 192.0, 191.2, 168.7, 141.4, 136.3, 134.8, 134.3, 134.1, 133.9, 133.6, 132.4, 131.9, 131.5, 130.9, 130.3, 129.4, 129.0 (2C), 128.7, 128.6, 128.5, 128.1, 127.2, 126.0, 124.8, 119.7, 119.2, 116.8; **IR** (NaCl, neat): 3064, 2851, 1690, 1601, 1451, 1362, 1232, 1194, 1180, 953, 873, 773, 751, 715, 698, 677 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{16}\text{NO}_2$: 326.11810; Found. 326.11787.

2-(1-Tosyl-1*H*-pyrrol-3-yl)benzaldehyde (2.19)

Following general procedure B, a mixture of **2.18** (1.5 g, 5 mmol), 2-formylphenylboronic acid (1.5 g, 10 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (0.144 g, 0.25 mmol, 5 mol %), PPh_3 (0.1312 g, 0.5 mmol, 10 mol %), and CsF (1.52 g, 10 mmol, 2 equiv.) in DME (25 mL) was heated to 90 $^\circ\text{C}$ for 16 hours. Subsequent workup and column chromatography (15% EtOAc in hexanes) gave the title compound as a bright yellow gum (1.354 g, 83% yield). R_f = 0.29 (hexanes:EtOAc 4:1). **^1H NMR** (400 MHz, CDCl_3) δ 10.11 (d, J = 0.7 Hz, 1H), 7.95 (dd, J = 7.8, 1.1 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.57 (td, J = 7.5, 1.5 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.26

(dd, $J = 3.2, 2.2$ Hz, 1H), 7.23 (t, $J = 2.0$ Hz, 1H), 6.44 (dd, $J = 3.2, 1.7$ Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.3, 145.6, 138.0, 135.8, 133.9, 133.8, 130.6, 130.3, 127.9, 127.8, 127.2, 125.6, 121.5, 119.9, 115.5, 21.8; **IR** (NaCl, neat): 3135, 2850, 1690, 1686, 1599, 1490, 1373, 1174, 1131, 1067, 763, 672 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{S}$: 326.0845; Found. 326.0838.

2-(1-Tosyl-1H-pyrazol-4-yl)benzaldehyde (**2.23**)

Following general procedure B, a mixture of pyrazole **2.22** (1.741 g, 5 mmol), 2-formylphenylboronic acid (1.5 g, 10 mmol, 2 equiv.), $\text{Pd}(\text{dba})_2$ (0.144 g, 0.25 mmol, 5 mol %), PPh_3 (0.1312 g, 0.5 mmol, 10 mol %), and CsF (1.52 g, 10 mmol, 2 equiv.) in DME (25 mL) were heated to 90 $^\circ\text{C}$ for 16 hours. Subsequent workup and column chromatography (gradient hexanes:EtOAc 4:1 to 100% EtOAc) gave the title compound as a thick yellow gum (0.464 g, 28% yield). $R_f = 0.17$ (hexanes:EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3) δ 10.09 (d, $J = 0.5$ Hz, 1H), 8.23 (d, $J = 0.6$ Hz, 1H), 7.99 – 7.96 (m, 3H), 7.83 (d, $J = 0.5$ Hz, 1H), 7.63 (td, $J = 7.6, 1.5$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 1H), 7.39 (t, $J = 8.0$ Hz, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.4, 146.5, 145.3, 134.2, 133.9, 133.8, 131.0, 130.4, 130.1, 129.1, 128.7, 128.5, 121.5, 21.9; **IR** (NaCl, neat): 3118, 2925, 2854, 1690, 1601, 1381, 1175, 1095, 949, 813, 764, 703, 670 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_3\text{S}$: 327.08034; Found. 327.08121.

Synthesis of Aldehyde **2.29**

2-((Trimethylsilyl)ethynyl)benzaldehyde (**2.27**)

A round bottom flask was purged with N₂ for 10 minutes. Under an N₂ atmosphere, Pd(PPh₃)₂Cl₂ (0.843 g, 1.2 mmol, 3 mol %) and CuI (0.457 g, 2.4 mmol, 6 mol %) were added. Dry triethylamine (80 mL) was cannulated in under N₂, then 2-bromobenzaldehyde (4.7 mL, 40 mmol) and ethynyltrimethylsilane (6.8 mL, 48 mmol, 1.2 equiv.) were added via syringe. The reaction was stirred at room temperature for 3 hours, then heated to 50 °C for 14 hours. The mixture was filtered over a medium frit to remove precipitated salts, the solvent was removed *in vacuo*, and the residue directly chromatographed (hexanes:EtOAc 19:1) to yield **2.27** as a light orange oil (7.036 g, 87% yield). The oil solidified into a beige solid on storing at -20 °C overnight. The analytical data was consistent with literature.⁹³ **R_f** = 0.55 (hexanes:EtOAc 9:1). **MP** 46-47 °C; **¹H NMR** (400 MHz, CDCl₃) δ 10.56 (d, *J* = 0.7 Hz, 1H), 7.90 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.47 – 7.40 (m, 1H), 0.28 (s, 9H).

2-Ethynylbenzaldehyde (**2.28**)

To a stirred solution of **2.27** (4.05 g, 20 mmol) in methanol (40 mL) was added potassium fluoride (0.74 g, 12.7 mmol) in one portion. The suspension was vigorously stirred for 2 hours at room temperature. The reaction was then poured into brine (300 mL), the aqueous layer extracted with Et₂O (100 mL x 2), the organic extracts dried over MgSO₄, and removed *in vacuo* to afford **2.28** as a tan solid (2.52 g, 97% yield). The product thus obtained was judged to be >98% pure by NMR and could be used without further purification. The analytical data was consistent with literature.⁹³ **R_f** = 0.40 (hexanes:EtOAc 9:1). **MP** 58-61 °C. **¹H NMR** (400 MHz, CDCl₃) δ 10.54 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.57 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 3.46 (s, 1H).

2-(1-Tosyl-1*H*-1,2,3-triazol-4-yl)benzaldehyde (**2.29**)

To a stirred solution of **2.28** (0.781 g, 6 mmol, 1.2 equiv.), tosyl azide (0.986 g, 5 mmol), and CuI (95.2 mg, 0.5 mmol, 10 mol %) in CHCl₃ (10 mL) cooled to 0 °C was added 2,6-lutidine (0.7 mL, 6 mmol, 1.2 equiv.) dropwise via syringe pump over 10 minutes. The reaction was

⁹³ Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228.

stirred at 0 °C for 12 hours, then additional CuI (95.2 mg, 0.5 mmol, 10 mol %) was added, and the reaction let warm to room temperature and stirred for an additional 2 hours. Upon completion, DCM (10 mL) and saturated aqueous NH₄Cl (15 mL) were added and the reaction stirred for 30 minutes. The layers were separated, and the aqueous layer extracted with DCM (15 mL x 2). The combined organic extracts were successively washed with 1M citric acid (aq.) and 1M NaOH, then dried over MgSO₄ and the solvent removed *in vacuo*. Crude **2.29** was first purified via column chromatography (hexanes:EtOAc 7:3) to remove bulk impurities, then chromatographed a second time (2.5% EtOAc in DCM) to obtain pure **2.29** as a light yellow solid (0.922 g, 56% yield). The analytical data was consistent with literature.⁷⁷ R_f = 0.28 (hexanes:EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃) δ 10.28 (s, 1H), 8.45 (s, 1H), 8.06 (d, J = 8.5 Hz, 2H), 8.02 (dd, J = 7.7, 1.1 Hz, 1H), 7.72 (dd, J = 7.7, 1.1 Hz, 1H), 7.66 (td, J = 7.5, 1.4 Hz, 1H), 7.56 (td, J = 7.6, 0.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 2.47 (s, 3H).

Synthesis of Aldehyde **2.38**

3-Bromobenzene-1-sulfonyl fluoride (**2.36**)

A mixture of 3-bromobenzenesulfonyl chloride (2.82 mL, 19.6 mmol), potassium fluoride (5.7 g, 98.1 mmol, 5 equiv.), and 18-crown-6 (0.259 g, 0.98 mmol, 5 mol %) in dry acetonitrile (20 mL) was vigorously stirred at room temperature for 34 hours. The solvent was removed *in vacuo*, and the residue resuspended in Et₂O (40 mL). The organics were successively washed with distilled water (2x), brine (1x), dried over MgSO₄, and the solvent removed *in vacuo* to give **2.36** as a light yellow oil (3.847 g, 82% yield). R_f = 0.49 (hexanes:EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃) δ 8.16 (t, J = 1.8 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.91 (dd, J = 8.1, 0.9 Hz, 1H), 7.52 (td, J = 8.0, 0.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 138.8, 134.9 (d, J = 25.6 Hz), 131.4, 131.2, 127.1, 123.7; ¹⁹F NMR (377 MHz, CDCl₃) δ 65.21; IR (NaCl, neat): 1574, 1467, 1415 (S=O), 1212 (S=O), 805 (S-F), 749 (S-F) cm⁻¹.

1-Bromo-3-(phenylsulfonyl)benzene (2.37)

An oven-dried round bottom flask, cooled under N₂, was charged with freshly distilled THF (50 mL) and **2.36** (3.49 g, 14.6 mmol). The mixture was cooled to -78 °C in a dry ice/acetone bath, and phenylmagnesium bromide (14.6 mL of 1M solution in THF, 14.6 mmol) was added dropwise via syringe pump over 25 minutes. Upon completion of addition, the dry ice/acetone bath was removed, and the mixture let warm slowly to room temperature. The mixture was then stirred at room temperature for 2 hours. The reaction was quenched with saturated aq. NH₄Cl (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (30 mL x 2), the organics were combined, dried over MgSO₄, and the solvent removed *in vacuo* to afford **2.37** as a white solid (4.294 g, 99% yield). NMR indicated the product thus obtained was of >98% purity. The analytical data was consistent with literature.⁹⁴ **R_f** = 0.30 (hexanes:EtOAc 4:1). **MP** 118-119 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.08 (t, *J* = 1.8 Hz, 1H), 7.96 – 7.93 (m, 2H), 7.87 (ddd, *J* = 7.9, 1.6, 1.0 Hz, 1H), 7.68 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.55 – 7.51 (m, 2H), 7.38 (t, *J* = 7.9 Hz, 1H).

3'-(Phenylsulfonyl)biphenyl-2-carbaldehyde (2.38)

Following general procedure B, a mixture of sulfone **2.37** (1.486 g, 5 mmol), 2-formylphenylboronic acid (1.5 g, 10 mmol, 2 equiv.), Pd(dba)₂ (0.144 g, 0.25 mmol, 5 mol %), PPh₃ (0.1312 g, 0.5 mmol, 10 mol %), and CsF (1.52 g, 10 mmol, 2 equiv.) in DME (25 mL) were heated to 90 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) gave the title compound as a thick, yellow-orange gum (1.529 g, 95% yield). **R_f** = 0.28 (hexanes:EtOAc 7:3). **¹H NMR** (400 MHz, CDCl₃) δ 9.86 (d, *J* = 0.5 Hz, 1H), 8.04 – 7.97 (m, 5H), 7.67 (td, *J* = 7.5, 1.4 Hz, 1H), 7.63 – 7.51 (m, 6H), 7.40 (dd, *J* = 7.7, 0.8 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.3, 143.5, 142.4, 141.3, 139.5, 134.7, 134.0, 133.7, 133.6, 131.0, 129.6, 129.5, 128.9, 128.7, 128.6, 127.9, 127.3; **IR** (NaCl, neat): 3063, 2850, 2753, 1695, 1596, 1447, 1322, 1306, 1154, 998, 912, 806, 724, 690 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₁₉H₁₅O₃S: 323.0736; Found. 323.0744.

⁹⁴ Bian, M.; Xu, F.; Ma, C. *Synthesis* **2007**, 19, 2951.

3.2.3 General Procedure C: *N*-Substitution of 3-(2-formylphenyl)indole

To a stirred solution of **2.10**, powdered KOH (3 equiv.), and Bu₄NHSO₄ (10 mol %) in dry DCM was added the appropriate electrophile (either as a solid or a solution in DCM). The reaction was stirred at room temperature or heated as necessary. When judged to be complete by TLC, the reaction was quenched with 1M NaOH, and the biphasic mixture stirred vigorously for 15 minutes at room temperature. The layers were separated, the organic layer was washed with distilled water, dried over MgSO₄, and removed *in vacuo*. The products were purified by column chromatography.

2-(1-(4-(Trifluoromethyl)phenylsulfonyl)-1*H*-indol-3-yl)benzaldehyde (**2.7m**)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu₄NHSO₄ (0.102 g, 0.3 mmol) were dissolved in dry DCM (9 mL). 4-(trifluoromethyl)benzenesulfonyl chloride (0.808 g, 3.3 mmol, 1.1 equiv.) was added in one portion, and the reaction stirred at room temperature for 1 hour. Subsequent workup and column chromatography (hexanes:EtOAc 12:1) afforded the title compound as a yellow foam (1.195 g, 93% yield). *R_f* = 0.48 (hexanes:EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃) δ 9.93 (d, *J* = 0.6 Hz, 1H), 8.12 – 8.06 (m, 4H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.69 (td, *J* = 7.5, 1.4 Hz, 1H), 7.64 (s, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.52 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 191.6, 141.4 (q, *J* = 1.2 Hz), 135.8 (q, *J* = 33.3 Hz), 135.5, 134.9, 134.6, 134.2, 131.5, 131.0, 128.8, 128.4, 127.6, 126.8 (q, *J* = 3.7 Hz), 126.0,

125.2, 124.7, 123.0 (q, $J = 273.4$ Hz), 120.8, 120.5, 113.8; **^{19}F NMR** (377 MHz, CDCl_3) δ -64.3; **IR** (NaCl, neat): 3104, 3065, 2845, 2751, 1694, 1601, 1406, 1321, 1182, 1132, 1063, 1011, 934, 843, 750, 714 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{15}\text{NO}_3\text{F}_3\text{S}$: 430.0719; Found. 430.0711.

2-(1-(4-Fluorophenylsulfonyl)-1*H*-indol-3-yl)benzaldehyde (2.7n)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu_4NHSO_4 (0.102 g, 0.3 mmol) were dissolved in dry DCM (9 mL). 4-fluorobenzenesulfonyl chloride (0.876 g, 4.5 mmol, 1.5 equiv.) was added in one portion, and the reaction was refluxed at 50 $^\circ\text{C}$ for 30 minutes. Subsequent workup and column chromatography (15% EtOAc in hexanes) afforded the title compound as a yellow foam (1.13 g, 99% yield). $R_f = 0.35$ (hexanes:EtOAc 4:1). **^1H NMR** (400 MHz, CDCl_3) δ 9.92 (d, $J = 0.5$ Hz, 1H), 8.10 – 8.05 (m, 2H), 8.01 – 7.95 (m, 2H), 7.69 (td, $J = 7.5, 1.4$ Hz, 1H), 7.62 (s, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.44 – 7.38 (m, 2H), 7.32 – 7.27 (m, 1H), 7.20 – 7.13 (m, 2H); **^{13}C NMR** (100 MHz, CDCl_3) δ 191.7, 166.0 (d, $J = 257.8$ Hz), 135.9, 134.9, 134.7, 134.2, 134.1 (d, $J = 3.2$ Hz), 131.5, 131.0, 129.9 (d, $J = 9.7$ Hz), 128.7, 128.2, 125.8, 125.5, 124.4, 120.4, 117.0 (d, $J = 22.9$ Hz), 113.9; **^{19}F NMR** (377 MHz, CDCl_3) δ -102.84 – -102.90 (m); **IR** (NaCl, neat): 3106, 3067, 2847, 2753, 1692, 1589, 1559, 1493, 1447, 1375, 1238, 1182, 1130, 1111, 1089 1011, 934, 837, 748, 677 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{21}\text{H}_{18}\text{FN}_2\text{O}_2\text{S}$: 397.10222; Found. 397.10276.

2-(1-(Thiophen-2-ylsulfonyl)-1*H*-indol-3-yl)benzaldehyde (2.7o)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu₄NHSO₄ (0.102 g, 0.3 mmol) were dissolved in dry DCM (9 mL). 2-thiophenesulfonyl chloride (0.575 g, 3.15 mmol, 1.05 equiv.) was added in one portion, and the reaction was stirred at room temperature for 1 hour. Subsequent workup and column chromatography (hexanes:EtOAc 4:1) afforded the title compound as a thick orange gum (0.943 g, 86% yield). *R*_f = 0.24 (hexanes:EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃) δ 9.93 (d, *J* = 0.7 Hz, 1H), 8.12 – 8.07 (m, 2H), 7.76 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.69 (td, *J* = 7.5, 1.4 Hz, 1H), 7.60 (dd, *J* = 5.5, 1.8 Hz, 2H), 7.55 (ddd, *J* = 8.5, 4.9, 0.9 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.30 (ddd, *J* = 8.0, 7.2, 0.9 Hz, 1H), 7.05 (dd, *J* = 5.0, 3.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 191.8, 138.0, 136.0, 134.9, 134.7, 134.2 (2C), 133.7, 131.5, 131.1, 128.7, 128.1, 127.8, 125.8, 125.5, 124.5, 120.6, 120.3, 114.2; IR (NaCl, neat): 3102, 1690, 1599, 1447, 1379, 1177, 1130, 1022, 748, 675 cm⁻¹; HRMS (ESI) [M+H]⁺ Calcd for C₁₉H₁₄NO₃S₂: 368.04151; Found. 368.04213.

2-(1-(Diphenylphosphoryl)-1*H*-indol-3-yl)benzaldehyde (2.7p)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu₄NHSO₄ (0.102 g, 0.3 mmol) were dissolved in dry DCM (8 mL). A solution of diphenylphosphinic chloride (0.7 mL g, 3.6 mmol, 1.2 equiv.) in DCM (1 mL) was added in one portion, and the reaction was stirred at room temperature for 30 minutes.

TLC indicated the reaction was incomplete, so additional diphenylphosphinic chloride (0.7 mL, 3.6 mmol, 1.2 equiv.) was added neat, and the reaction stirred for a further 10 minutes at room temperature. Upon completion, the reaction was quenched with 1M NaOH and stirred at room temperature for 10 minutes. The layers were separated, the aqueous layer was extracted with DCM, the organics were combined, dried over Na₂SO₄, the solvent removed *in vacuo*, and the residue chromatographed (hexanes:EtOAc 1:1) to afford the title compound as a light yellow foam (1.232 g, 97% yield). **R_f** = 0.28 (hexanes:EtOAc 1:1). **¹H NMR** (400 MHz, CDCl₃) δ 10.02 (d, *J* = 0.6 Hz, 1H), 8.03 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.78 – 7.72 (m, 4H), 7.64 (ddd, *J* = 9.0, 2.7, 1.3 Hz, 4H), 7.55 – 7.46 (m, 7H), 7.25 – 7.18 (m, 2H), 6.84 (d, *J* = 3.3 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 192.2, 138.8 (d, *J* = 3.0 Hz), 137.3, 134.6, 134.0, 133.5 (d, *J* = 2.9 Hz), 132.2 (d, *J* = 10.7 Hz), 131.6, 131.3 (d, *J* = 5.8 Hz), 130.2, 129.3 (d, *J* = 13.5 Hz), 129.0, 128.6 (d, *J* = 5.8 Hz), 127.9 (d, *J* = 12.4 Hz), 124.5, 123.1, 119.8, 118.0 (d, *J* = 6.7 Hz), 115.2 (d, *J* = 1.1 Hz); **³¹P NMR** (162 MHz, CDCl₃) δ 25.3; **IR** (NaCl, neat): 3059, 1690, 1599, 1449, 1437, 1225, 1140, 1125, 1017, 934, 746, 694, 544 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₇H₂₁NO₂P: 422.13099; Found. 422.13189.

3-(2-Formylphenyl)-*N,N*-diphenyl-1*H*-indole-1-carboxamide (**2.7r**)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu₄NHSO₄ (0.102 g, 0.3 mmol) were dissolved in dry DCM (9 mL). Diphenylcarbamoyl chloride (0.72 g, 3.09 mmol, 1.03 equiv.) was added in one portion, and the reaction was refluxed at 50 °C for 20 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) afforded the title compound as a light pink solid (1.16 g, 93% yield). **R_f** = 0.40 (hexanes:EtOAc 4:1). **MP** 80-83 °C; **¹H NMR** (400 MHz, CDCl₃) δ 9.34 (d, *J* = 0.7 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.60 (td, *J* = 7.5, 1.5 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.40 – 7.34 (m, 5H), 7.33 – 7.27 (m, 3H), 7.20 – 7.16 (m, 4H), 7.01 (s, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 191.7, 153.2, 143.4, 136.8, 136.6, 134.6, 133.8,

131.3, 129.9, 129.2, 128.0, 127.8, 127.0, 126.5, 126.3, 125.4, 123.7, 119.6, 117.0, 115.4; **IR** (NaCl, neat): 3065, 2850, 1691, 1599, 1491, 1452, 1362, 1207, 913, 828, 749, 693 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{28}\text{H}_{21}\text{N}_2\text{O}_2$: 417.16030; Found. 417.16229.

***N,N*-Dibenzyl-3-(2-formylphenyl)-1*H*-indole-1-carboxamide (2.7s)**

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu_4NHSO_4 (0.102 g, 0.3 mmol) were dissolved in dry DCM (9 mL). *N,N*-dibenzylcarbamoyl chloride (1.4 g, 5.4 mmol, 1.8 equiv.) was added in one portion, and the reaction was refluxed at 50 $^{\circ}\text{C}$ for 90 minutes. After cooling to room temperature, 1M NaOH was added, and the mixture stirred at room temperature for 10 minutes. The layers were separated, the organic layer was washed with 20% HCl, dried over MgSO_4 , removed *in vacuo*, and chromatographed (hexanes:EtOAc 6:1) to afford the title compound as a yellow solid (1.303 g, 98% yield). R_f = 0.37 (hexanes:EtOAc 4:1). **MP** 133-135 $^{\circ}\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 10.02 (d, J = 0.7 Hz, 1H), 8.05 (dd, J = 7.8, 1.1 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.65 (td, J = 7.5, 1.4 Hz, 1H), 7.54 (dd, J = 7.6, 0.7 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.42 – 7.22 (m, 13H), 4.62 (s, 4H); **^{13}C NMR** (100 MHz, CDCl_3) δ 192.2, 155.1, 137.2, 136.0, 134.6, 134.0, 131.6, 129.5, 129.2, 128.2, 128.1, 128.0, 127.9, 125.8, 124.9, 123.0, 119.9, 117.1, 113.7, 51.2; **IR** (NaCl, neat): 3061, 3028, 2928, 1686, 1599, 1452, 1412, 1350, 1225, 1198, 978, 827, 746, 700 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_2$: 445.19211; Found. 445.19125.

Phenyl 3-(2-formylphenyl)-1*H*-indole-1-carboxylate (2.7t)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu₄NHSO₄ (0.102 g, 0.3 mmol) were dissolved in dry DCM (8 mL). A solution of phenyl chloroformate (0.45 mL g, 3.6 mmol, 1.2 equiv.) in DCM (1 mL) was added in one portion, and the reaction was stirred at room temperature for 1 hour. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) afforded the title compound as a thick, light yellow gum (0.94 g, 92% yield). *R*_f = 0.47 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 10.13 (d, *J* = 0.6 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.85 (s, 1H), 7.72 (td, *J* = 7.5, 1.4 Hz, 1H), 7.62 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.51 – 7.44 (m, 4H), 7.34 (dd, *J* = 11.9, 4.9 Hz, 4H); **¹³C NMR** (100 MHz, CDCl₃) δ 192.1, 150.3, 136.5, 134.9, 134.2, 131.5, 130.8, 129.9, 128.5, 128.1, 126.8, 125.9, 125.1, 124.4, 121.6, 121.0, 120.0, 119.8, 115.8; **IR** (NaCl, neat): 3063, 2849, 1751, 1692, 1601, 1456, 1375, 1229, 1198, 1018, 827, 752 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₂H₁₆NO₃: 342.11302; Found. 342.11415.

Benzyl 3-(2-formylphenyl)-1*H*-indole-1-carboxylate (2.7u)

Following general procedure C, **2.10** (6 mL of 0.5M solution in DCM, 3 mmol), powdered KOH (0.505 g, 9 mmol), and Bu₄NHSO₄ (0.102 g, 0.3 mmol) were dissolved in dry DCM (8 mL). A solution of benzyl chloroformate (0.81 mL g, 5.4 mmol, 1.8 equiv.) in DCM (1 mL) was added in one portion, and the reaction was stirred at room temperature for 30 minutes. Subsequent workup and column chromatography (15% EtOAc in hexanes) afforded the title compound as a white foam (1.058 g, 99% yield). *R*_f = 0.39 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 10.06 (d, *J* = 0.5 Hz, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.71 (s, 1H), 7.68 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.51 (dd, *J* = 7.8, 1.1 Hz, 2H), 7.46 – 7.37 (m, 5H), 7.33 – 7.27 (m, 1H), 5.50 (s, 2H); **¹³C NMR** (100 MHz, CDCl₃) δ 192.2, 136.8, 134.9, 134.8, 134.1, 131.5, 130.6, 129.0 (2C), 128.8, 128.3, 127.9, 125.6, 125.2, 124.0, 119.8, 118.9, 115.6, 69.2; **IR** (NaCl, neat): 3063, 3034, 2845, 1740, 1692, 1601, 1452,

1390, 1358, 1231, 1051, 827, 748 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{18}\text{NO}_3$: 356.12867; Found. 356.12941.

2-(1-Phenyl-1*H*-indol-3-yl)benzaldehyde (2.7v)

A 0.5M stock solution of **2.10** in DCM (8 mL, 4 mmol) was placed on a rotary evaporator to remove DCM. The flask containing the residue was carefully flame-dried and cooled under N_2 . CuI (76.2 mg, 0.4 mmol, 10 mol %), L-proline (92.1 mg, 0.8 mmol, 20 mol %), and Cs_2CO_3 (1.955 g, 6 mmol, 1.5 equiv.) were added and the flask was purged with N_2 for 10 minutes. Dry DMF (12 mL) was added, followed by iodobenzene (0.56 mL, 5 mmol, 1.2 equiv.), and the reaction was heated to 120 $^\circ\text{C}$ for 16 hours under N_2 . The reaction was diluted with Et_2O (40 mL), washed successively with distilled water (60 mL x 2) and brine (60 mL), dried over MgSO_4 , and the solvent removed *in vacuo*. Purification by column chromatography (60% DCM in hexanes) afforded the title compound as a light yellow solid (0.63 g, 53% yield). R_f = 0.27 (hexanes:DCM 1:1). **MP** 138-140 $^\circ\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 10.20 (s, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.71 – 7.61 (m, 4H), 7.57 – 7.53 (m, 4H), 7.51 – 7.47 (m, 1H), 7.43 – 7.38 (m, 2H), 7.33 – 7.29 (m, 1H), 7.26 – 7.22 (m, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ 193.0, 139.2, 138.5, 136.4, 134.6, 134.0, 131.5, 130.0, 128.7, 128.6, 127.9, 127.3, 127.2, 124.6, 123.5, 121.6, 119.8, 114.6, 111.1; **IR** (NaCl, neat): 3059, 2847, 1684, 1597, 1501, 1456, 1377, 1223, 1196, 976, 827, 777, 746, 696 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{16}\text{NO}$: 298.12319; Found. 298.12305.

2-(1-Benzyl-1*H*-indol-3-yl)benzaldehyde (2.7w)

A 0.5M stock solution of **2.10** in DCM (2 mL, 1 mmol) was placed on a rotary evaporator to remove DCM. The residue was redissolved in dry DMSO (2 mL), and to it was added powdered KOH (0.225 g, 4 mmol, 4 equiv.) and benzyl bromide (0.24 mL, 2 mmol, 2 equiv.). The reaction was stirred at room temperature for 30 minutes, and diluted with distilled water (2 mL). The mixture was extracted with Et₂O (10 mL x 2), and each Et₂O extract was washed with distilled water (5 mL x 2). The organics were combined, dried over MgSO₄, the solvent removed *in vacuo*, and chromatographed (hexanes:EtOAc 9:1) to afford the title compound as a yellow-brown syrup (0.294 g, 94%). The analytical data was consistent with literature.⁹⁵ **R_f** = 0.30 (hexanes:EtOAc 9:1). **¹H NMR** (400 MHz, CDCl₃) δ 10.12 (d, *J* = 0.7 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.62 (m, 3H), 7.48 – 7.41 (m, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.24 (m, 4H), 7.21 – 7.15 (m, 4H), 5.39 (s, 2H).

2-(1-Phenethyl-1*H*-indol-3-yl)benzaldehyde (**2.7x**)

A 0.5M stock solution of **2.10** in DCM (6 mL, 3 mmol) was placed on a rotary evaporator to remove DCM. The residue was redissolved in dry DMF (12 mL), and to it was added powdered KOH (0.505 g, 9 mmol, 3 equiv.) and (2-bromoethyl)benzene (0.82 mL, 6 mmol, 2 equiv.). The reaction was heated to 100 °C for 48 hours. TLC indicated the reaction was still incomplete, thus additional KOH (0.168 g, 3 mmol, 1 equiv.) and (2-bromoethyl)benzene (0.41 mL, 3 mmol, 1 equiv.) were added and the reaction heated at 100 °C for a further 18 hours. After cooling to room temperature, EtOAc (40 mL) was added, the organic layer was washed successively with distilled water (60 mL), brine (60 mL), dried over MgSO₄, removed *in vacuo*, and the residue chromatographed (hexanes:EtOAc 9:1) to afford the title compound as a thick orange gum (0.431 g, 44% yield). **R_f** = 0.38 (hexanes:EtOAc 4:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.91 (d, *J* = 0.7 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.56 (dd, *J* = 7.7, 1.0 Hz,

⁹⁵ Li, G.; Wang, E.; Chen, H.; Li, H.; Liu, Y.; Wang, P. G.; *Tetrahedron* **2008**, *64*, 9033.

1H), 7.45 – 7.40 (m, 2H), 7.33 – 7.24 (m, 4H), 7.21 – 7.17(m, 1H), 7.06 (dd, $J = 7.5, 1.8$ Hz, 2H), 6.85 (s, 1H), 4.43 (t, $J = 7.1$ Hz, 2H), 3.16 (t, $J = 7.1$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.2, 139.0, 138.2, 136.1, 134.4, 133.8, 131.4, 129.1, 128.8 (2C), 128.1, 127.7, 127.0, 126.8, 122.6, 120.7, 119.7, 112.0, 109.9, 48.5, 36.6. **IR** (NaCl, neat): 3061, 3028, 2935, 2851, 1684, 1599, 1541, 1466, 1454, 1391, 1267, 1194, 827, 742, 700 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{20}\text{NO}$: 326.15449; Found. 326.15435.

2-(1-(1H-Indole-1-carbonyl)-1H-indol-3-yl)benzaldehyde (2.7y)

Oxalyl chloride (1.05 mL, 12 mmol, 2 equiv.) was added to a solution of indole-1-carboxylic acid (0.967 g, 6 mmol) in dry THF (4 mL). One drop of DMF was added, and vigorous bubbling was seen. The solution was stirred at room temperature for 10 minutes, at which point bubbling ceased. The mixture was then concentrated *in vacuo*, and the crude acid chloride was taken up in dry THF (8 mL). A 0.5M stock solution of **2.10** in DCM (6 mL, 3 mmol) was placed on a rotary evaporator to remove DCM, the residue was redissolved in dry THF (8 mL), and triethylamine (0.84 mL, 6 mmol, 2 equiv.) was added. The THF solution containing **2.10** was then added to the solution of acid chloride in THF, and DMAP (29.4 mg, 0.24 mmol, 8 mol %) was added to the mixture. The reaction was stirred at room temperature for 1 hour, additional triethylamine (0.42 mL, 3 mmol, 1 equiv.) was added, and then the reaction was heated to 50 °C for 1 hour. THF was then removed *in vacuo*. The residue was suspended in 40 mL distilled water, and the aqueous layer was extracted with DCM (30 mL x 3). The organic extracts were washed with 20% HCl (20 mL), dried over Na_2SO_4 , removed *in vacuo*, and the residue chromatographed (gradient 60% DCM in hexanes to 80% DCM in hexanes) to afford the title compound as an off-white solid (1.052 g, 96% yield). $R_f = 0.38$ (hexanes:EtOAc 4:1). **MP** 168–169 °C; ^1H NMR (400 MHz, CDCl_3) δ 10.14 (d, $J = 0.8$ Hz, 1H), 8.10 (ddd, $J = 7.8, 1.4, 0.5$ Hz, 1H), 8.06 – 8.01 (m, 2H), 7.74 – 7.68 (m, 1H), 7.66 (ddd, $J = 7.7, 1.3, 0.8$ Hz, 1H), 7.61 – 7.51 (m, 5H), 7.46 (ddd, $J = 8.4, 7.3, 1.3$ Hz, 1H), 7.42 – 7.31 (m, 3H), 6.76 (dd, $J = 3.7, 0.7$ Hz,

^1H); ^{13}C **NMR** (100 MHz, CDCl_3) δ 191.8, 148.5, 136.3, 136.2 (2C), 134.8, 134.2, 131.6, 130.5 (2C), 128.6, 128.3, 126.6, 126.3, 125.8, 125.1, 124.6, 124.0, 121.6, 120.1, 119.6, 115.3, 115.0, 109.5; **IR** (NaCl, neat): 3115, 3057, 2847, 1713, 1690, 1601, 1449, 1383, 1362, 1329, 1229, 1196, 1138, 947, 837, 746, 733 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_3\text{O}_2$: 382.15555; Found. 382.15631.

3.2.4 General Procedure D: Ramirez Olefination

To an oven-dried flask cooled under Ar was added CBr_4 (1.5 equiv.) and the aldehyde. Dry DCM was added, and the mixture was cooled to 0 °C. A solution of triisopropyl phosphite (3 equiv.) in dry DCM was added dropwise, and the reaction stirred at 0 °C until judged to be complete by TLC. Upon completion, the reaction was quenched with saturated aqueous NaHCO_3 . The layers were separated, the aqueous layer was extracted with Et_2O . The combined extracts were dried over MgSO_4 , and removed *in vacuo*. The crude products were purified by column chromatography, or by induced crystallization followed by trituration.

NOTE: It has been observed in some instances that the purified *gem*-dibromoolefins fail to properly crystallize on removing the solvent, resulting in an intractable amorphous gum. Should this occur, crystallization can be induced via repeated sonication of a suspension of the gum in hexanes until a solid mass is formed. For a few substrates – particularly those with low melting points – it was necessary to cool the purified products to cryogenic temperatures (-78 °C or -196 °C) in order for proper crystallization to occur.

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1*H*-indole (**2.1a**)

Following general procedure D, aldehyde **2.7a** (1.877 g, 5 mmol) and CBr_4 (2.487 g, 7.5 mmol) were dissolved in dry DCM (20 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (3.7 mL, 15 mmol) in DCM (5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup gave crude **2.1a** as an orange syrup. The syrup was suspended in hexanes (10 mL), and cooled in a liquid N_2 bath for ~1 minute until solidification of the syrup was complete. The solid mass was broken up with a spatula, and kept at -20 °C for 30 minutes. The mother liquor was carefully decanted, and the solids were carefully triturated with hexanes (5 mL x 3) until the washings were colourless. This afforded **2.1a** as an off-white solid (2.206 g, 83% yield) which was of analytical purity by NMR analysis. The analytical data was consistent with literature.⁵⁹ R_f = 0.43 (hexanes:EtOAc 8:1). **MP** 121-122 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.74 (dd, J = 7.2, 1.8 Hz, 1H), 7.56 (s, 1H), 7.51 – 7.34 (m, 5H), 7.29 – 7.23 (m, 3H), 7.19 (s, 1H), 2.35 (s, 3H).

3-(2-(2,2-Dibromovinyl)phenyl)-5-methyl-1-tosyl-1*H*-indole (**2.1b**)

Following general procedure D, aldehyde **2.7b** (1.169 g, 3 mmol) and CBr_4 (1.5 g, 4.5 mmol) were dissolved in dry DCM (12 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (2.22 mL, 9 mmol) in DCM (3 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1b** as an orange syrup. The syrup was cooled in a liquid N_2 bath for ~1 minute until complete solidification occurred, and let slowly warm to room temperature, whereupon seed crystals of **2.1b** started to form. Complete

crystallization was induced by gentle scratching of the flask with a Pasteur pipette. Crude **2.1b** was successively triturated with hexanes (20 mL), 5% EtOAc in hexanes (10 mL), and 10% EtOAc in hexanes (10 mL) until the washings were colourless. This afforded **2.1b** as an off-white solid (1.344 g, 82% yield). $R_f = 0.45$ (hexanes:EtOAc 4:1). **MP** 144-145 °C; **^1H NMR** (400 MHz, CDCl_3) δ 7.93 (d, $J = 8.5$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.73 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.51 (s, 1H), 7.49 – 7.38 (m, 3H), 7.24 (dd, $J = 8.1, 2.0$ Hz, 3H), 7.19 – 7.16 (m, 2H), 2.39 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 145.1, 137.2, 135.2, 134.8, 133.5, 133.4, 131.9, 130.3 (2C), 130.1, 129.7, 128.8, 127.6, 127.1, 126.6, 125.6, 121.4, 120.4, 113.6, 91.5, 21.8, 21.5; **IR** (NaCl, neat): 3061, 2920, 1597, 1464, 1371, 1175, 1134, 1015, 845, 739, 667 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}^{79}\text{Br}_2\text{NO}_2\text{S}$: 543.95815; Found. 543.95959.

3-(2-(2,2-Dibromovinyl)phenyl)-7-methyl-1-tosyl-1*H*-indole (**2.1c**)

Following general procedure D, aldehyde **2.7c** (0.779 g, 2 mmol) and CBr_4 (0.995 g, 3 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.38 mL, 6.3 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (pentane:EtOAc 13:1) afforded the title compound as a white solid (0.898 g, 82% yield). $R_f = 0.39$ (pentane:EtOAc 10:1). **MP** 55-58 °C; **^1H NMR** (400 MHz, CDCl_3) δ 7.76 – 7.73 (m, 2H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.46 – 7.42 (m, 3H), 7.26 (d, $J = 8.05$ Hz, 2H), 7.23 (dd, $J = 7.7, 0.5$ Hz, 1H), 7.17 (s, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.09 (d, $J = 7.2$ Hz, 1H), 2.65 (s, 3H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 144.9, 137.0, 136.6, 135.2, 135.1, 132.4, 132.0, 130.6, 130.1, 129.5, 128.9, 128.8 (2C), 127.8, 126.8, 125.6, 124.2, 121.6, 118.4, 91.5, 22.0, 21.8; **IR** (NaCl, neat): 3133, 3062, 2927, 1595, 1364, 1174, 1128, 1086, 1001, 872, 859, 786, 667 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}^{79}\text{Br}_2\text{NO}_2\text{S}$: 543.95815; Found. 543.95912.

3-(2-(2,2-Dibromovinyl)phenyl)-5-methoxy-1-tosyl-1*H*-indole (2.1d)

Following general procedure D, aldehyde **2.7d** (0.284 g, 0.7 mmol) and CBr_4 (0.35 g, 1.05 mmol) were dissolved in dry DCM (5 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (0.55 mL, 2.1 mmol) in DCM (1 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 14:1) afforded the title compound as a white solid (0.244 g, 62% yield). R_f = 0.42 (hexanes:EtOAc 4:1). **MP** 138-139 °C; ^1H **NMR** (400 MHz, CDCl_3) δ 7.94 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.75 – 7.73 (m, 1H), 7.51 (s, 1H), 7.46 – 7.41 (m, 3H), 7.25 (d, J = 6.3 Hz, 2H), 7.14 (s, 1H), 6.98 (dd, J = 9.0, 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 3.78 (s, 3H), 2.36 (s, 3H); ^{13}C **NMR** (100 MHz, CDCl_3) δ 156.9, 145.2, 137.2, 135.2, 134.8, 131.9, 131.1, 130.3, 130.1, 129.8, 129.7, 128.9, 127.8, 127.0, 126.0, 121.9, 114.9, 114.7, 102.6, 91.5, 55.9, 21.8. **IR** (NaCl, neat): 2935, 2833, 1596, 1467, 1371, 1216, 1174, 1136, 1033, 1012, 852, 761, 666 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}^{79}\text{Br}_2\text{NO}_3\text{S}$: 559.9525; Found. 559.9510.

Methyl 3-(2-(2,2-dibromovinyl)phenyl)-1-tosyl-1*H*-indole-6-carboxylate (2.1e)

Following general procedure D, aldehyde **2.7e** (0.997 g, 2.3 mmol) and CBr_4 (1.144 g, 3.45 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.7 mL, 6.9 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1e** as an orange solid. The solid was suspended in a minimal amount of EtOAc (~5 mL) and pentane (~3 mL) and stored at -20 °C overnight. The mother liquor was carefully decanted, and the solids washed

with ice-cold EtOAc (~10 mL) until the washings were colourless. This afforded **2.1e** as an off-white solid (0.996 g, 73% yield). $R_f = 0.47$ (pentane:EtOAc 4:1). **MP** 175-176 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.75 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 8.3$ Hz, 2H), 7.74 – 7.70 (m, 2H), 7.50 – 7.41 (m, 4H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.16 (s, 1H), 3.98 (s, 3H), 2.37 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.2, 145.6, 136.9, 135.0, 134.9, 134.6, 133.6, 131.1, 130.4, 130.3, 129.8, 128.9, 128.1, 128.0, 127.2, 127.1, 124.8, 121.5, 120.3, 115.7, 92.1, 52.5, 21.8. **IR** (NaCl, neat): 3065, 2951, 1717, 1597, 1434, 1377, 1290, 1249, 1189, 1177, 1163, 1139, 1090, 1012, 912, 774, 731, 668 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{20}^{79}\text{Br}_2\text{NO}_4\text{S}$: 587.94798; Found. 587.94845.

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1H-indole-5-carbonitrile (**2.1f**)

Following general procedure D, aldehyde **2.7f** (0.360 g, 0.9 mmol) and CBr_4 (0.448 g, 1.35 mmol) were dissolved in dry DCM (6.5 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (0.62 mL, 2.7 mmol) in DCM (1 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1f** as an orange syrup, which was kept at -20 °C overnight. Some solids separated the following morning, and the mother liquor was carefully decanted. The solids were chromatographed (pentane:EtOAc 7:1) to afford **2.1f** as an off-white solid (0.265 g, 53% yield). $R_f = 0.50$ (pentane:EtOAc 4:1). **MP** 128-129 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.15 (dd, $J = 8.7, 0.4$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 2H), 7.81 (d, $J = 0.9$ Hz, 1H), 7.73 – 7.70 (m, 1H), 7.68 (s, 1H), 7.62 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.51 – 7.43 (m, 3H), 7.31 (d, $J = 8.1$ Hz, 2H), 7.17 (s, 1H), 2.39 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 146.1, 136.7 (2C), 135.0, 134.7, 130.5, 130.2 (2C), 130.1, 130.0, 129.1, 128.4, 128.1, 127.2 (2C), 125.7, 121.1, 119.3, 114.8, 107.5, 92.5, 21.8; **IR** (NaCl, neat): 2924, 2228, 1596, 1456, 1379, 1307, 1173, 1135, 1097, 1010, 913, 835, 812, 738, 667 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{17}^{79}\text{Br}_2\text{N}_2\text{O}_2\text{S}$: 554.9371; Found. 554.9357.

3-(2-(2,2-Dibromovinyl)phenyl)-5-nitro-1-tosyl-1H-indole (2.1g)

Following general procedure D, aldehyde **2.7g** (0.841 g, 2 mmol) and CBr_4 (0.995 g, 3 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.48 mL, 6 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1g** as an orange syrup. The syrup was cooled in a liquid N_2 bath for ~1 minute until complete solidification occurred. Hexanes was added and the suspension let slowly warm to room temperature. The supernatant was carefully decanted, and the solids were triturated with hexanes (20 mL x 2) and 10% EtOAc in hexanes (20 mL x 2) to afford the title compound as a light tan solid (0.863 g, 75% yield). R_f = 0.50 (hexanes:EtOAc 7:3). **MP** 133-134 °C; ^1H **NMR** (400 MHz, CDCl_3) δ 8.39 (d, J = 2.1 Hz, 1H), 8.26 (dd, J = 9.1, 2.2 Hz, 1H), 8.16 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.73 – 7.71 (m, 2H), 7.53 – 7.45 (m, 3H), 7.32 (d, J = 8.1 Hz, 2H), 7.18 (s, 1H), 2.39 (s, 3H); ^{13}C **NMR** (100 MHz, CDCl_3) δ 146.2, 144.7, 137.8, 136.7, 135.0, 134.6, 130.6, 130.3, 130.1, 130.0 (2C), 129.2, 128.5, 127.9, 127.2, 122.1, 120.4, 117.2, 114.2, 92.7, 21.8; **IR** (NaCl, neat): 3107, 1597, 1522, 1441, 1379, 1344, 1190, 1176, 1151, 1124, 1090, 1011, 907, 860, 813, 785, 741, 671 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{23}\text{H}_{20}^{79}\text{Br}_2\text{N}_3\text{O}_4\text{S}$: 591.95413; Found. 591.95319.

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1H-7-azaindole (2.1h)

Following general procedure D, aldehyde **2.7h** (1.13 g, 3 mmol) and CBr_4 (1.5 g, 4.5 mmol) were dissolved in dry DCM (12 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (2.22 mL, 9 mmol) in DCM (3 mL) was then added dropwise over several minutes. The reaction was stirred

at 0 °C for 30 minutes. Subsequent workup yielded crude **2.59** as an orange solid. Hexanes (~15 mL) was added and the suspension kept at -20 °C for 30 minutes. The supernatant was carefully decanted, and the solids were triturated with Et₂O (~5 mL) and methanol (~1 mL) to afford **2.1h** as a white solid (1.1 g, 69% yield). **R_f** = 0.33 (hexanes:EtOAc 4:1). **MP** 169-170 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.49 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.46 – 7.40 (m, 3H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.23 – 7.20 (m, 2H), 2.39 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 147.3, 145.5 (2C), 137.0, 135.4, 134.8, 131.4, 130.2, 129.9, 129.8, 129.1, 129.0, 128.3, 127.9, 125.1, 122.4, 119.3, 118.2, 92.0, 21.8; **IR** (NaCl, neat): 3131, 3059, 1595, 1549, 1397, 1377, 1256, 1190, 1175, 1140, 1088, 1011, 935, 860, 731, 669 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₂H₁₇⁷⁹Br₂N₂O₂S: 530.9371; Found. 530.9388.

1-(Benzylsulfonyl)-3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole (**2.1i**)

Following general procedure D, aldehyde **2.7i** (0.488 g, 1.3 mmol) and CBr₄ (0.65 g, 1.95 mmol) were dissolved in dry DCM (6.5 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (0.9 mL, 3.9 mmol) in DCM (1.5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 10:1) afforded the title compound as a white foam (0.411 g, 60% yield). **R_f** = 0.24 (hexanes:EtOAc 9:1). **¹H NMR** (400 MHz, CDCl₃) δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.43 – 7.40 (m, 3H), 7.35 – 7.25 (m, 4H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.14 (s, 1H), 7.06 (s, 1H), 6.94 (d, *J* = 7.3 Hz, 2H), 4.56 (s, 2H); **¹³C NMR** (100 MHz, CDCl₃) δ 137.0, 135.5, 135.0, 131.9, 130.6, 130.5, 129.6 (2C), 129.4, 129.0, 128.8, 127.8, 126.9, 125.5, 125.2, 123.7, 120.9, 120.8, 113.3, 91.6, 60.0; **IR** (NaCl, neat): 3064, 3032, 2924, 1447, 1371, 1203, 1165, 1127, 1016, 913, 768, 747, 696 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₈⁷⁹Br₂NO₂S: 529.9419; Found. 529.9428.

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-methoxyphenylsulfonyl)-1*H*-indole (2.1j)

Following general procedure D, aldehyde **2.7j** (0.822 g, 2.1 mmol) and CBr₄ (1.045 g, 3.15 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of P(*Oi*-Pr)₃ (1.64 mL, 6.3 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 12:1) afforded the title compound as an off-white solid (0.963 g, 84% yield). **R_f** = 0.35 (hexanes:EtOAc 4:1). **MP** 140-141 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.73 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.55 (s, 1H), 7.49 – 7.35 (m, 5H), 7.28 – 7.24 (m, 1H), 7.19 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 164.0, 137.1, 135.1, 134.8, 131.8, 130.3, 130.1, 129.7, 129.4, 128.8, 127.7, 125.5, 125.2, 123.7, 121.4, 120.6, 114.8, 113.9, 91.5, 55.8; **IR** (NaCl, neat): 3064, 3015, 2979, 2840, 1594, 1578, 1496, 1371, 1263, 1168, 1089, 1014, 934, 832, 804, 747, 668 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₈⁷⁹Br₂NO₃S: 545.9368; Found. 545.9365.

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-nitrophenylsulfonyl)-1*H*-indole (2.1k)

Following general procedure D, aldehyde **2.7k** (0.853 g, 2.1 mmol) and CBr₄ (1.045 g, 3.15 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of P(*Oi*-Pr)₃ (1.64 mL, 6.3 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography

(hexanes:EtOAc 11:1) afforded the title compound as a bright yellow solid (0.938 g, 80% yield). R_f = 0.50 (hexanes:EtOAc 4:1). **MP** 129-130 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.32 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H), 8.07 (d, J = 8.3 Hz, 1H), 7.73 – 7.71 (m, 1H), 7.53 (s, 1H), 7.49 – 7.40 (m, 5H), 7.31 (t, J = 7.6 Hz, 1H), 7.17 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 150.9, 143.2, 137.0, 135.0, 134.9, 131.0, 130.4, 130.3, 129.8, 128.9, 128.4, 128.1, 125.9, 124.8 (2C), 124.6, 123.3, 121.0, 113.8, 92.0; **IR** (NaCl, neat): 3105, 3066, 1606, 1532, 1447, 1403, 1382, 1348, 1183, 1130, 1010, 935, 854, 738, 682, 644, 612 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{15}^{79}\text{Br}_2\text{N}_2\text{O}_4\text{S}$: 560.91193; Found. 560.91271.

3-(2-(2,2-Dibromovinyl)-4-methoxyphenyl)-1-tosyl-1H-indole (2.11)

Following general procedure D, aldehyde **2.71** (0.933 g, 2.3 mmol) and CBr_4 (1.144 g, 3.45 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.7 mL, 6.9 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (pentane:EtOAc 12:1) afforded the title compound as an off-white solid (0.834 g, 65% yield). R_f = 0.53 (pentane:EtOAc 4:1). **MP** 103-104 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.05 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.29 (d, J = 2.6 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.17 (s, 1H), 6.99 (dd, J = 8.5, 2.7 Hz, 1H), 3.88 (s, 3H), 2.35 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 158.9, 145.2, 136.9, 135.8, 135.2, 135.1, 131.4, 130.4, 130.2, 127.1, 125.2, 125.1, 124.1, 123.7, 121.3, 120.5, 114.8, 114.7, 113.9, 91.6, 55.6, 21.8. **IR** (NaCl, neat): 3129, 3050, 3009, 2937, 2835, 1597, 1565, 1446, 1371, 1241, 1176, 1131, 1010, 909, 813, 711, 665 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}^{79}\text{Br}_2\text{NO}_3\text{S}$: 559.9525; Found. 559.9525.

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-indole (2.1m)

Following general procedure D, aldehyde **2.7m** (1.074 g, 2.5 mmol) and CBr₄ (1.244 g, 3.75 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.85 mL, 7.5 mmol) in DCM (2.5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (7.5% EtOAc in hexanes) afforded the title compound as a thick yellow syrup, which solidified into yellow crystals on cooling in a liquid N₂ bath (1.411 g, 96% yield). **R_f** = 0.55 (hexanes:EtOAc 4:1). **MP** 43-45 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.15 – 8.06 (m, 3H), 7.80 – 7.70 (m, 3H), 7.55 (s, 1H), 7.52 – 7.38 (m, 5H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.18 (s, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 141.4, 137.0, 135.6 (q, *J* = 32.9 Hz), 135.0, 134.8, 131.2, 130.2, 129.7, 128.9, 128.0, 127.6, 126.8 (q, *J* = 3.3 Hz), 125.7, 125.0, 124.3, 123.0 (q, *J* = 273.5 Hz), 122.6, 120.9, 113.8, 91.8; **¹⁹F NMR** (377 MHz, CDCl₃) δ -64.2; **IR** (NaCl, neat): 3063, 1559, 1447, 1406, 1379, 1321, 1182, 1132, 1063, 1011, 936, 841, 746, 721, 710, 644 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₅⁷⁹Br₂F₃NO₂S: 583.91423; Found. 583.91209.

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-fluorophenylsulfonyl)-1*H*-indole (2.1n)

Following general procedure D, aldehyde **2.7n** (0.95 g, 2.5 mmol) and CBr₄ (1.244 g, 3.75 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.85 mL, 7.5 mmol) in DCM (2.5 mL) was then added dropwise over several minutes. The reaction

was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 12:1) afforded the title compound which co-eluted with a yellow impurity. The chromatographed material was triturated with hexanes (5 mL x 3) to wash away the impurity. This afforded **2.1n** as a white solid (1.01 g, 75% yield). R_f = 0.5 (hexanes:EtOAc 4:1). **MP** 92–94 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.06 (d, J = 8.3 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.74 (d, J = 6.8 Hz, 1H), 7.54 (s, 1H), 7.52 – 7.36 (m, 5H), 7.29 (t, J = 7.6 Hz, 1H), 7.21 – 7.12 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.9 (d, J = 257.3 Hz), 137.0, 135.0, 134.8, 134.1 (d, J = 3.4 Hz), 131.5, 130.3, 130.2, 129.9 (d, J = 9.7 Hz), 129.7, 128.9, 127.9, 125.5, 125.2, 124.0, 122.2, 120.7, 117.0 (d, J = 22.9 Hz), 113.8, 91.7; $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ -103.28 – -103.35 (m); **IR** (NaCl, neat): 3104, 3067, 1591, 1559, 1493, 1447, 1375, 1240, 1182, 1130, 1010, 934, 837, 746, 673 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{22}\text{H}_{18}^{79}\text{Br}_2\text{FN}_2\text{O}_2\text{S}$: 550.94398; Found. 550.94321.

3-(2-(2,2-Dibromovinyl)phenyl)-1-(thiophen-2-ylsulfonyl)-1H-indole (2.1o)

Following general procedure D, aldehyde **2.7o** (0.845 g, 2.3 mmol) and CBr_4 (1.145 g, 3.45 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.7 mL, 6.9 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1o** as an orange solid. Crude **2.1o** was suspended in hexanes (~6 mL) and kept at -20 °C for 30 minutes. The supernatant was carefully decanted, and the solids triturated with 10% EtOAc in hexanes (5 mL x 4) until the washings were colourless to afford **2.1o** as an off-white solid (1.157 g, 96% yield). R_f = 0.39 (hexanes:EtOAc 4:1). **MP** 144–145 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 (d, J = 8.3 Hz, 1H), 7.78 (dd, J = 3.8, 1.3 Hz, 1H), 7.76 – 7.73 (m, 1H), 7.58 (dd, J = 5.0, 1.3 Hz, 1H), 7.52 (s, 1H), 7.50 – 7.40 (m, 5H), 7.32 – 7.28 (m, 1H), 7.20 (s, 1H), 7.04 (dd, J = 5.0, 3.9 Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.2, 137.0, 135.1, 134.9, 133.9, 133.5, 131.6, 130.4, 130.3, 129.7, 128.8, 127.9, 127.8, 125.4, 125.1, 124.1, 122.5, 120.7, 114.1, 91.7; **IR** (NaCl, neat):

3104, 1447, 1377, 1229, 1177, 1130, 1022, 934, 858, 746, 721, 673 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{13}^{79}\text{Br}_2\text{FNO}_2\text{S}_2\text{Na}$: 543.8646; Found. 543.8626.

3-(2-(2,2-Dibromovinyl)phenyl)-1-(diphenylphosphoryl)-1*H*-indole (**2.1p**)

Following general procedure D, aldehyde **2.7p** (0.711 g, 2 mmol) and CBr_4 (0.995 g, 3 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.48 mL, 6 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1p** as an orange syrup. The syrup was cooled in a liquid N_2 bath for ~1 minute until complete solidification occurred. After warming to room temperature, hexanes (20 mL) was added and the suspension sonicated until the solid mass was completely pulverized. This was kept at -20 °C overnight, and then the solids were successively triturated with hexanes (20 mL), 10% EtOAc in hexanes (10 mL), and 20% EtOAc in hexanes (10 mL) to afford the title compound as an off-white solid (1.039 g, 90% yield).. R_f = 0.44 (hexanes:EtOAc 1:1). **MP** 137-138 °C; **^1H NMR** (400 MHz, CDCl_3) δ 7.76 (ddd, J = 9.4, 7.6, 2.3 Hz, 5H), 7.66 – 7.59 (m, 4H), 7.58 – 7.51 (m, 5H), 7.43 (td, J = 7.5, 1.2 Hz, 1H), 7.35 (td, J = 7.6, 1.3 Hz, 1H), 7.25 – 7.19 (m, 3H), 6.70 (d, J = 3.3 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ 138.9 (d, J = 3.0 Hz), 137.8, 134.7, 133.4 (d, J = 2.9 Hz), 132.7, 132.3 (d, J = 10.7 Hz), 130.3 (2C), 130.1, 129.6, 129.2 (d, J = 13.4 Hz), 129.1, 128.9 (d, J = 5.9 Hz), 128.7, 127.1, 124.1, 123.4 (d, J = 141.7 Hz), 122.7, 120.1, 119.4 (d, J = 6.7 Hz), 115.2 (d, J = 1.1 Hz), 90.8; **^{31}P NMR** (162 MHz, CDCl_3) δ 25.2; **IR** (NaCl, neat): 3059, 1603, 1449, 1437, 1225, 1171, 1142, 1125, 1113, 1017, 936, 770, 746, 729, 718, 694 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{28}\text{H}_{21}^{79}\text{Br}_2\text{NOP}$: 575.97275; Found. 575.97310.

(3-(2-(2,2-Dibromovinyl)phenyl)-1*H*-indol-1-yl)(phenyl)methanone (2.1q)

Following general procedure D, aldehyde **2.7q** (0.586 g, 1.8 mmol) and CBr₄ (0.895 g, 2.7 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.25 mL, 5.4 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1q** as an orange solid. Crude **2.1q** was suspended in EtOAc (~3 mL) and pentane (~15 mL) and kept at -20 °C overnight. The supernatant was carefully decanted, and the solids triturated with hexanes (10 mL) to afford **2.1q** as a white solid (0.478 g, 55% yield). *R*_f = 0.47 (pentane:EtOAc 10:1). *MP* 158-160 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, *J* = 8.3 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.73 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.64 – 7.54 (m, 5H), 7.48 – 7.37 (m, 5H), 7.32 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 137.4, 136.4, 134.8, 134.4, 132.3, 132.1, 130.2, 130.0, 129.7, 129.5, 129.0, 128.8, 127.6, 127.3, 125.7, 124.5, 120.8, 120.1, 116.9, 91.2; IR (NaCl, neat): 3062, 1684, 1601, 1564, 1451, 1363, 1233, 1189, 1073, 955, 912, 873, 771, 749, 715, 696 cm⁻¹; HRMS (ESI) [M+H]⁺ Calcd for C₂₃H₁₆⁷⁹Br₂NO: 479.95986; Found. 479.96017.

3-(2-(2,2-Dibromovinyl)phenyl)-*N,N*-diphenyl-1*H*-indole-1-carboxamide (2.1r)

Following general procedure D, aldehyde **2.7r** (0.833 g, 2 mmol) and CBr₄ (0.995 g, 3 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.48 mL, 6 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 15:1)

afforded the title compound as a light yellow solid (0.891 g, 78% yield). **R_f** = 0.32 (pentane:EtOAc 13:1). **MP** 142-143 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.40 – 7.34 (m, 8H), 7.28 – 7.15 (m, 8H), 7.11 (s, 1H), 7.03 (s, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 153.4, 143.6, 137.3, 136.3, 134.9, 132.5, 130.3, 129.8, 129.3, 128.9, 128.6, 127.4, 126.7, 126.3, 125.4, 124.8, 123.2, 120.0, 119.8, 115.3, 91.1; **IR** (NaCl, neat): 3064, 1695, 1593, 1490, 1451, 1363, 1280, 1201, 1181, 1145, 909, 860, 828, 750, 735, 698, 693, 649 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₉H₂₁⁷⁹Br₂N₂O: 571.00206; Found. 571.00254.

***N,N*-dibenzyl-3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole-1-carboxamide (2.1s)**

Following general procedure D, aldehyde **2.7s** (1.112 g, 2.5 mmol) and CBr₄ (1.244 g, 3.75 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of P(*Oi*-Pr)₃ (1.85 mL, 7.5 mmol) in DCM (2.5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (7.5% EtOAc in hexanes) afforded the title compound as a white solid (1.388 g, 92% yield). **R_f** = 0.51 (hexanes:EtOAc 4:1). **MP** 54-56 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.48 – 7.22 (m, 16H), 4.63 (s, 4H); **¹³C NMR** (100 MHz, CDCl₃) δ 155.2, 137.6, 136.4, 136.1, 134.7, 132.6, 130.3, 129.7, 129.2, 128.8, 128.6, 128.1, 127.2, 125.6, 124.6, 122.7, 120.2, 118.8, 114.0, 91.0, 51.1; **IR** (NaCl, neat): 3063, 3030, 2930, 1682, 1603, 1495, 1452, 1412, 1350, 1223, 978, 908, 860, 735, 698 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₃₁H₂₅⁷⁹Br₂N₂O: 599.03336; Found. 599.03462.

Phenyl 3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole-1-carboxylate (2.1t**)**

Following general procedure D, aldehyde **2.7t** (0.888 g, 2.6 mmol) and CBr₄ (1.293 g, 3.9 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.93 mL, 7.8 mmol) in DCM (3 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1t** as an orange syrup. The syrup was kept at -20 °C overnight, and seed crystals of **2.1t** were seen the following morning. Complete crystallization was induced by gentle scratching of the flask with a Pasteur pipette. Crude **2.1t** was successively triturated with hexanes (10 mL) and 10% EtOAc in hexanes until the washings were colourless. This afforded **2.1t** as a cream-coloured solid (0.73 g, 57% yield). *R*_f = 0.44 (hexanes:EtOAc 9:1). *MP* 114-116 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, *J* = 8.2 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.77 (s, 1H), 7.58 – 7.42 (m, 7H), 7.37 – 7.32 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 150.4, 137.2, 135.0, 132.2, 130.4, 130.1, 129.9, 129.6, 128.8, 127.8, 126.7, 125.5, 124.6, 124.0, 121.7 (2C), 120.5, 115.7, 91.5; *IR* (NaCl, neat): 3061, 1751, 1568, 1493, 1456, 1375, 1308, 1254, 1229, 1198, 1163, 1146, 1018, 1003, 752, 687 cm⁻¹; *HRMS* (ESI) [M+H]⁺ Calcd for C₂₃H₁₆⁷⁹Br₂NO₂: 495.95478; Found. 495.95415.

Benzyl 3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole-1-carboxylate (2.1u**)**

Following general procedure D, aldehyde **2.7u** (0.711 g, 2 mmol) and CBr₄ (0.995 g, 3 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.48 mL, 6 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred

at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1u** as an orange syrup. The syrup was kept at -20 °C for 30 minutes, and seed crystals of **2.1u** started to form. Complete crystallization was induced by gentle scratching of the flask with a Pasteur pipette. The crude product was triturated with hexanes (20 mL) to afford pure **2.1u** as a white solid (0.458 g, 45% yield). $R_f = 0.43$ (hexanes:EtOAc 9:1). **MP** 85-86 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.28 (d, $J = 7.2$ Hz, 1H), 7.77 (dd, $J = 6.7, 2.4$ Hz, 1H), 7.64 (s, 1H), 7.54 – 7.48 (m, 4H), 7.47 – 7.36 (m, 6H), 7.32 – 7.27 (m, 2H), 5.50 (s, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 137.3, 134.9, 132.3, 130.4, 129.8, 129.6, 129.0, 128.9, 128.8, 128.6, 127.6, 125.2, 124.7, 123.6, 120.9, 120.3, 115.5, 91.3, 69.0; **IR** (NaCl, neat): 3065, 3032, 1740, 1452, 1395, 1358, 1306, 1260, 1231, 1099, 1053, 762, 748 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{18}^{79}\text{Br}_2\text{NO}_2$: 509.97043; Found. 509.96933.

3-(2-(2,2-Dibromovinyl)phenyl)-1-phenyl-1H-indole (2.1v)

Following general procedure D, aldehyde **2.7v** (0.595 g, 2 mmol) and CBr_4 (0.995 g, 3 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.48 mL, 6 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (10% DCM in hexanes) afforded the title compound as a light orange solid in quantitative yield. $R_f = 0.45$ (hexanes:EtOAc 19:1). **MP** 104-105 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.80 (dd, $J = 7.8, 0.5$ Hz, 1H), 7.73 (dd, $J = 7.3, 0.8$ Hz, 1H), 7.69 (dd, $J = 7.7, 1.2$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.62 – 7.55 (m, 4H), 7.49 (td, $J = 7.6, 1.3$ Hz, 1H), 7.46 (s, 1H), 7.44 – 7.39 (m, 2H), 7.38 (s, 1H), 7.33 – 7.29 (m, 1H), 7.27 – 7.23 (m, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 139.5, 138.3, 136.3, 134.4, 133.9, 130.3, 129.9, 129.6, 128.8, 128.3, 128.1, 127.0, 126.5, 124.6, 123.1, 121.2, 120.3, 116.6, 110.9, 90.3; **IR** (NaCl, neat): 3059, 1597, 1549, 1501, 1456, 1379, 1221, 887, 860, 789, 765, 745, 696 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{16}^{79}\text{Br}_2\text{N}$: 451.96495; Found. 451.96620.

1-Benzyl-3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole (2.1w)

Following general procedure D, aldehyde **2.7w** (0.311 g, 1 mmol) and CBr_4 (0.5 g, 1.5 mmol) were dissolved in dry DCM (4 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (0.69 mL, 3 mmol) in DCM (1 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 19:1) afforded the title compound which co-eluted with a yellow impurity. The chromatographed material was triturated with hexanes (~3 mL) to wash away the impurity. This afforded **2.1w** as a white solid (0.354 g, 76% yield). R_f = 0.49 (hexanes:EtOAc 9:1). **MP** 96-97 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.42 (td, J = 7.5, 0.9 Hz, 1H), 7.36 – 7.30 (m, 5H), 7.28 – 7.24 (m, 1H), 7.22 – 7.20 (m, 3H), 7.16 (t, J = 7.5 Hz, 1H), 7.13 (s, 1H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 137.1, 136.6, 134.3, 134.2, 130.2, 129.5, 129.0, 128.9, 128.7, 127.9, 127.4, 127.2, 126.1, 122.5, 120.4, 120.1, 114.7, 110.1, 90.0, 50.4; **IR** (NaCl, neat): 3059, 3028, 1598, 1474 1465, 1178, 942, 859, 770, 743, 695 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{18}^{79}\text{Br}_2\text{FN}$: 465.98060; Found. 465.98035.

.3-(2-(2,2-Dibromovinyl)phenyl)-1-phenethyl-1*H*-indole (2.1x)

Following general procedure D, aldehyde **2.7x** (0.39 g, 1.2 mmol) and CBr_4 (0.6 g, 1.8 mmol) were dissolved in dry DCM (8 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (0.93 mL, 3.6 mmol) in DCM (2 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 19:1)

afforded the title compound as a thick orange syrup (0.515 g, 89% yield). R_f = 0.44 (hexanes:EtOAc 9:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.75 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 7.7, 1.2 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.35 – 7.20 (m, 6H), 7.19 – 7.11 (m, 3H), 6.98 (s, 1H), 4.41 (t, J = 7.6 Hz, 2H), 3.18 (t, J = 7.6 Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.4, 138.3, 136.2, 134.4, 134.2, 130.2, 129.4, 128.9, 128.8, 128.6, 128.2, 127.4, 127.0, 126.1, 122.2, 120.2 (2C), 114.4, 109.7, 89.9, 48.3, 36.9; **IR** (NaCl, neat): 3059, 3026, 2931, 1541, 1466, 1454, 1391, 1373, 1360, 1165, 912, 887, 860, 791, 766, 741, 698 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{20}^{79}\text{Br}_2\text{N}$: 479.99625; Found. 479.99509.

(3-(2-(2,2-Dibromovinyl)phenyl)-1*H*-indol-1-yl)(1*H*-indol-1-yl)methanone (2.1y)

Following general procedure D, aldehyde **2.7y** (0.911 g, 2.5 mmol) and CBr_4 (1.244 g, 3.75 mmol) were dissolved in dry DCM (10 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (1.85 mL, 7.5 mmol) in DCM (2.5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup yielded crude **2.1y** as an orange solid. The crude product was suspended in hexanes (~10 mL) and kept at -20 °C for 30 minutes, then triturated with hexanes (10 mL x 2) until the washings were colourless to afford **2.1y** as an off-white solid (0.983 g, 76% yield). R_f = 0.53 (hexanes:EtOAc 4:1). **MP** 145-147 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.13 (dtd, J = 8.3, 1.7, 0.9 Hz, 2H), 7.76 (ddd, J = 6.4, 1.6, 0.7 Hz, 1H), 7.67 (ddd, J = 7.7, 1.2, 0.7 Hz, 1H), 7.63 – 7.56 (m, 3H), 7.51 – 7.32 (m, 8H), 6.81 (dd, J = 3.7, 0.7 Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 148.6, 137.3, 136.6, 136.5, 134.9, 131.8, 130.5, 130.4, 129.8, 129.6, 128.9, 127.8, 126.9, 126.0, 125.5, 125.1, 124.2, 124.0, 121.5, 121.2, 120.5, 115.3, 115.2, 109.4, 91.6; **IR** (NaCl, neat): 3053, 1713, 1605, 1564, 1533, 1447, 1383, 1362, 1327, 1229, 1209, 1194, 1138, 1017, 947, 883, 837, 766, 746 735, 718, 623 cm^{-1}

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1*H*-pyrrole (2.13)

Following general procedure D, aldehyde **2.19** (1.3 g, 4 mmol) and CBr_4 (1.99 g, 6 mmol) were dissolved in dry DCM (16 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (2.8 mL, 12 mmol) in DCM (4 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 10:1) afforded the title compound as a thick, clear yellow syrup (1.547 g, 80% yield). R_f = 0.26 (hexanes:EtOAc 9:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.84 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 7.7 Hz, 1H), 7.39 – 7.28 (m, 6H), 7.22 (ddd, J = 5.4, 3.5, 2.2 Hz, 2H), 6.45 (dd, J = 3.2, 1.7 Hz, 1H), 2.42 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 145.3, 137.8, 136.0, 133.6, 132.9, 130.3, 129.5, 128.9 (2C), 127.8, 127.2, 127.1, 121.2, 119.4, 114.6, 91.4, 21.8; IR (NaCl, neat): 3139, 2923, 1596, 1492, 1373, 1188, 1173, 1137, 1099, 1065, 914, 888, 858, 812, 794, 755, 676 cm^{-1} ; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{16}^{79}\text{Br}_2\text{NO}_2\text{S}$: 479.9262; Found. 479.9262.

4-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1*H*-pyrazole (2.14)

Following general procedure D, aldehyde **2.23** (0.424 g, 1.3 mmol) and CBr_4 (0.65 g, 1.95 mmol) were dissolved in dry DCM (8.5 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (0.9 mL, 3.9 mmol) in DCM (1.5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (16% EtOAc in hexanes) afforded the title compound as a thick yellow syrup (0.172 g, 27% yield). R_f = 0.35 (hexanes:EtOAc 4:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.16 (d, J = 0.5 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 0.5 Hz, 1H), 7.57 – 7.55 (m, 1H), 7.40 – 7.30 (m, 5H), 7.30 (s, 1H),

2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.3, 144.9, 136.9, 134.2, 134.0, 130.3, 129.8, 129.4 (2C), 129.1, 129.0, 128.4, 128.0, 123.9, 93.0, 21.9; IR (NaCl, neat): 3123, 3064, 1595, 1383, 1325, 1193, 1175, 1096, 1050, 1039, 949, 890, 812, 790, 759, 677 cm^{-1} ; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{15}^{79}\text{Br}_2\text{N}_2\text{O}_2\text{S}$: 480.92210; Found. 480.92331.

2-(2,2-Dibromovinyl)-3'-(phenylsulfonyl)biphenyl (2.34)

Following general procedure D, aldehyde **2.38** (1.29 g, 4 mmol) and CBr_4 (1.99 g, 6 mmol) were dissolved in dry DCM (16 mL) and cooled to 0 °C. A solution of $\text{P}(\text{O}i\text{-Pr})_3$ (2.8 mL, 12 mmol) in DCM (4 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) afforded **2.34** which was contaminated with phosphorus containing byproducts. The chromatographed material was dissolved in acetic acid (4.5 mL) and concentrated HCl (4.5 mL), and refluxed at 110 °C under an N_2 atmosphere for 14 hours. After cooling to room temperature, distilled water (20 mL) was added, and solid Na_2CO_3 was carefully added portionwise until the pH was slightly basic. The aqueous layer was extracted with Et_2O (30 mL x 2), successively washed with distilled water and brine, dried over MgSO_4 , and the solvent removed *in vacuo* to afford **2.34** as a thick orange syrup (1.531 g, 80% yield). R_f = 0.39 (hexanes:EtOAc 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.03 – 8.00 (m, 2H), 7.96 (ddd, J = 9.1, 5.4, 1.6 Hz, 2H), 7.63 – 7.51 (m, 6H), 7.45 – 7.42 (m, 2H), 7.35 – 7.33 (m, 1H), 7.14 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.0, 141.7, 141.5, 139.0, 136.8, 134.2 (2C), 133.4, 130.0, 129.6, 129.6, 129.4, 129.1, 128.5, 128.3, 128.0, 126.8, 92.4; IR (NaCl, neat): 3062, 3021, 1447, 1321, 1306, 1154, 1102, 913, 861, 757, 721, 689 cm^{-1} ; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{15}^{79}\text{Br}_2\text{O}_2\text{S}$: 476.9154; Found. 476.9154.

3.3 Palladium-Catalyzed Domino Reactions

General Procedure

An oven-dried Biotage microwave vial, capped with a septum, was cooled under Ar. To the vial was sequentially added the *gem*-dibromoolefin substrate, **Pd-1** (10 mol %), K_2CO_3 (2 equiv.), and CsOPiv (50 mol %), all under an Ar atmosphere. The vial was purged with Ar for 5 minutes, toluene was added via syringe, the vial sealed under Ar with a Teflon cap, put into an oil bath pre-heated to 100 °C, and stirred overnight. After cooling to room temperature, the crude mixture was filtered over a short plug of Celite, washing liberally with DCM. The solvent was removed *in vacuo*, and the residue purified by column chromatography.

Benzo[*c*]carbazole 2.3a

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1a** (106.3 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) afforded **2.3a** as a cream coloured solid (40 mg, 54% yield). R_f = 0.38 (hexanes:EtOAc 4:1). **MP** 210-211 °C; 1H NMR (400

MHz, CDCl₃) δ 8.62 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 7.7 Hz, 1H), 8.40 – 8.36 (m, 2H), 8.14 (d, J = 8.1 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.63 – 7.51 (m, 3H), 7.42 (d, J = 8.1 Hz, 1H), 2.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.3, 137.4, 134.3, 132.3, 131.5, 131.1, 130.2, 129.9, 129.3, 128.4, 127.3, 126.8, 125.3, 125.2, 124.9, 124.2, 123.6, 122.7 (2C), 120.0, 117.4, 115.5, 22.1; **IR** (NaCl, neat): 3055, 2954, 2923, 2869, 1609, 1448, 1357, 1330, 1228, 1180, 1169, 1079, 947, 751, 748, 734 cm⁻¹; **HRMS** (ESI) [M+NH₄]⁺ Calcd for C₂₃H₁₉N₂O₂S: 387.11672; Found. 387.11698.

Benzo[*c*]carbazole **2.3b**

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1b** (109.1 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 4:1) afforded **2.3b** as a light-brown solid (39.6 mg, 52% yield). R_f = 0.27 (hexanes:EtOAc 4:1). **MP** 228-230 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.63 (d, J = 8.4 Hz, 1H), 8.37 (s, 1H), 8.24 (d, J = 8.6 Hz, 2H), 8.14 (d, J = 8.1 Hz, 1H), 8.04 – 8.02 (m, 2H), 7.72 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 6.9 Hz, 2H), 2.63 (s, 3H), 2.57 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.2, 135.5, 134.6, 132.3, 131.6, 131.1, 130.2, 129.8, 129.4, 128.3, 128.1, 127.6, 125.2 (2C), 124.2, 123.6, 122.9, 122.5, 120.0, 117.5, 115.1, 22.1, 22.0; **IR** (NaCl, neat): 3055, 2920, 1603, 1485, 1331, 1233, 1188, 1169, 1150, 1132, 1078, 912, 876, 808, 741, 685, 677, 640, 633 cm⁻¹; **HRMS** (ESI) [M+NH₄]⁺ Calcd for C₂₄H₂₁N₂O₂S: 401.13237; Found. 401.13314.

Benzo[*c*]carbazole 2.3c

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1c** (109.1 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) afforded **2.3c** as a beige solid (31.9 mg, 42% yield). *R_f* = 0.31 (hexanes:EtOAc 4:1). **MP** 257 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.80 (d, *J* = 7.9 Hz, 1H), 8.48 – 8.46 (m, 2H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.12 – 8.10 (m, 2H), 7.76 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.48 (ddd, *J* = 8.2, 1.5, 0.7 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 1H), 3.05 (s, 3H), 2.61 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 144.4, 137.6, 135.5, 132.8, 131.6, 131.2, 130.5, 130.1 (2C), 129.2, 128.4, 127.2, 125.5, 125.4, 125.1, 124.6, 123.7, 122.9, 120.6, 120.2, 118.1, 23.3, 22.1; **IR** (NaCl, neat): 2975, 2932, 1357, 1323, 1297, 1283, 1270, 1258, 1190, 1164, 1143, 1089, 913, 882, 792, 744, 732 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₄H₁₈NO₂S: 384.10582; Found. 384.10547.

Benzo[*c*]carbazole 2.3d

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1d** (112.3 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 4:1) afforded **2.3d** as a light orange solid (27 mg, 34% yield). *R_f* = 0.37 (hexanes:EtOAc 7:3). **MP** 263-265 °C; **¹H NMR** (400 MHz,

CDCl₃) δ 8.67 (d, J = 8.3 Hz, 1H), 8.52 (s, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.14 (t, J = 3.8 Hz, 2H), 8.00 (d, J = 2.3 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.23 (dd, J = 9.0, 2.4 Hz, 1H), 4.03 (s, 3H), 2.62 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 144.3, 135.4, 132.4, 131.9, 131.7, 131.2, 130.3, 130.0, 129.5, 128.6, 128.5, 125.4, 125.3, 124.3, 123.5, 122.9, 120.2, 117.9, 116.2, 114.5, 107.0, 56.24, 22.2; IR (NaCl, neat): 2938, 2833, 1581, 1482, 1429, 1326, 1256, 1167, 1076, 1034, 913, 878, 851, 747, 744 cm⁻¹; HRMS (ESI) [M+H]⁺ Calcd for C₂₄H₁₈NO₃S: 400.10047; Found. 400.10154.

Benzo[*c*]carbazole **2.3e**

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1e** (117.9 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 2:1) afforded **2.3e** as a light orange solid (26.5 mg, 31% yield). R_f = 0.28 (hexanes:EtOAc 7:3). MP 277-278 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.05 (s, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.59 – 8.57 (m, 2H), 8.30 (dd, J = 8.4, 1.4 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.16 – 8.15 (m, 2H), 7.82 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 4.04 (s, 3H), 2.63 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 144.6, 137.0, 136.2, 132.3, 131.4, 131.2, 130.9, 130.5, 130.2, 129.5, 129.0, 128.4, 126.2, 125.9, 125.3, 124.4, 124.2, 123.7, 122.4, 119.4, 117.6, 116.9, 52.6, 22.2; IR (NaCl, neat): 2952, 1714, 1432, 1334, 1300, 1292, 1273, 1250, 1168, 1096, 980, 913, 847, 748, 743, 668 cm⁻¹; HRMS (ESI) [M+H]⁺ Calcd for C₂₅H₁₈NO₄S: 428.09565; Found. 428.09666.

Benzo[*c*]carbazole 2.3j

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1j** (109.5 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 4:1) afforded **2.3j** as a light brown solid (10.2 mg, 13% yield). *R*_f = 0.23 (hexanes:EtOAc 4:1). **MP** 228-230 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.75 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 7.4 Hz, 1H), 8.49 (s, 1H), 8.41 (d, *J* = 7.2 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.68 – 7.58 (m, 3H), 7.18 (d, *J* = 8.5 Hz, 1H), 4.04 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 163.5, 137.5, 134.0, 131.2, 130.3, 129.6, 128.6, 127.5, 127.4, 127.0, 126.5, 125.5, 125.0, 123.8, 122.9, 122.8, 120.2, 117.6, 115.6, 114.9, 113.7, 109.8, 56.1;

Benzo[*c*]carbazole 2.3l

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1l** (112.3 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 7:3) afforded **2.3l** as a light orange solid (34.9 mg, 44% yield). *R*_f = 0.31 (hexanes:EtOAc 7:3). **MP** 240-242 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.58 (d, *J* = 9.0 Hz, 1H), 8.48 (d, *J* = 7.3 Hz, 1H), 8.39 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.37

(s, 1H), 8.18 (d, $J = 8.1$ Hz, 1H), 8.07 (s, 1H), 7.64 – 7.56 (m, 2H), 7.47 (d, $J = 8.1$ Hz, 1H), 7.43 – 7.38 (m, 2H), 3.97 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.0, 144.2, 137.5, 133.2, 132.5, 132.4, 131.7, 129.8, 127.4, 126.8, 125.2, 124.9, 124.8, 124.5, 124.2, 122.6, 121.5, 120.8, 120.3, 117.8, 115.6, 108.4, 55.5, 22.1; IR (NaCl, neat): 1600, 1372, 1316, 1243, 1232, 1168, 1144, 1117, 1032, 938, 891, 878, 810, 754, 740, 717, 692 cm^{-1} ; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{18}\text{NO}_3\text{S}$: 400.10047; Found. 400.10145.

Benzo[*c*]carbazole **2.3m**

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1m** (117 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 $^\circ\text{C}$ for 18 hours. Subsequent workup and column chromatography (40% DCM in hexanes) afforded **2.3m** as a golden yellow solid (44.8 mg, 53% yield). $R_f = 0.37$ (hexanes:DCM 1:1). MP 250-252 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.70 (d, $J = 8.4$ Hz, 1H), 8.59 – 8.50 (m, 3H), 8.43 (d, $J = 8.3$ Hz, 1H), 8.37 (d, $J = 7.1$ Hz, 1H), 8.15 (d, $J = 8.2$ Hz, 1H), 7.93 (d, $J = 8.2$ Hz, 1H), 7.81 (t, $J = 7.2$ Hz, 1H), 7.68 – 7.57 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.6 (q, $J = 1.2$ Hz), 137.3, 135.4 (q, $J = 33.2$ Hz), 134.0, 132.9, 131.2, 130.5, 129.8, 129.2, 127.4, 127.3, 125.9, 125.6 (q, $J = 3.5$ Hz), 125.4, 125.3, 123.8, 123.5, 123.3 (q, $J = 273.6$ Hz), 122.9, 122.2 (q, $J = 3.9$ Hz), 120.6, 116.4, 115.6; ^{19}F NMR (377 MHz, CDCl_3) δ -64.1; IR (NaCl, neat): 3073, 1476, 1416, 1341, 1283, 1221, 1175, 1134, 1088, 1069, 947, 912, 887, 808, 787, 748, 741 cm^{-1} ; HRMS (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{13}\text{F}_3\text{NO}_2\text{S}$: 424.06191; Found. 424.06097.

Benzo[c]carbazole 2.3n

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1n** (107 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 15 hours. Subsequent workup and column chromatography (hexanes:DCM 1:1) afforded **2.3n** which co-eluted with an orange impurity. The chromatographed material was triturated with hexanes (0.5 mL x 3) to wash away the impurity and afford **2.3n** as an off-white solid (30.3 mg, 41% yield). **R_f** = 0.22 (hexanes:DCM 1:1). **MP** 220-223 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.50 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.41 – 8.34 (m, 2H), 8.30 (dd, *J* = 8.8, 5.2 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.92 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.77 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.36 (ddd, *J* = 8.8, 7.7, 2.4 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 165.5 (d, *J* = 255.4 Hz), 137.3, 135.0 (d, *J* = 9.2 Hz), 134.2, 131.1 (d, *J* = 3.1 Hz), 131.0, 130.4, 129.7, 129.0, 127.3, 127.2 (d, *J* = 9.9 Hz), 127.1, 125.7, 125.2, 123.7, 123.3, 122.8, 120.4, 116.7 (d, *J* = 2.6 Hz), 116.6 (d, *J* = 23.3 Hz), 115.5, 111.8 (d, *J* = 24.2 Hz); **¹⁹F NMR** (377 MHz, CDCl₃) δ -104.13 (td, *J* = 8.2, 6.0 Hz); **IR** (NaCl, neat): 3075, 1605, 1586, 1481, 1447, 1337, 1287, 1225, 1173, 1119, 1078, 922, 824, 787, 752, 635 cm⁻¹; **HRMS** (ESI) [M+NH₄]⁺ Calcd for C₂₂H₁₆FN₂O₂S: 391.09195; Found. 391.09119.

Benzo[c]carbazole 2.3o

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1o** (104.7 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 3:1) afforded **2.3o** as a red-brown solid (30 mg, 42% yield). *R*_f = 0.31 (hexanes:EtOAc 7:3). **MP** 206-208 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.70 (d, *J* = 8.4 Hz, 1H), 8.53 (d, *J* = 7.5 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 5.1 Hz, 1H), 7.78 – 7.75 (m, 2H), 7.65 – 7.56 (m, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 140.6, 136.5, 134.2, 131.8, 131.4, 130.7, 130.0, 129.2, 128.5, 126.8, 126.7, 125.3, 124.6, 123.7, 123.2, 123.1, 122.8, 118.6, 115.0, 114.8; **IR** (NaCl, neat): 1319, 1308, 1281, 1229, 1169, 1123, 932, 908, 880, 843, 781, 745, 729, 702 cm⁻¹; **HRMS** (ESI) [M+NH₄]⁺ Calcd for C₂₀H₁₅N₂O₂S₂: 379.05749; Found. 379.05777.

Benzo[*c*]carbazole **2.3r**

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1r** (114.5 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:DCM:EtOAc 85:10:5) afforded **2.3r** as a yellow-orange solid (49.1 mg, 60% yield). *R*_f = 0.25 (hexanes:DCM:EtOAc 85:10:5). **MP** 237-238 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.75 (d, *J* = 8.4 Hz, 1H), 8.46 (d, *J* = 7.0 Hz, 1H), 8.26 – 8.22 (m, 2H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.53 – 7.45 (m, 4H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.29 – 7.25 (m, 3H), 7.11 – 7.09 (m, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 156.3, 143.4, 142.1, 141.2, 140.1, 133.2, 131.9, 130.5, 129.5, 129.2, 129.0 (2C), 128.6, 128.1, 127.7, 127.5, 127.2, 126.5, 125.9, 125.7, 125.3, 124.6, 124.4, 123.8, 121.8, 121.0, 120.3; **IR** (NaCl, neat): 3060, 1692, 1490, 1471, 1447, 1362, 1340, 1323, 1311, 1261, 908, 790, 779, 764, 743, 731, 668 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₉H₁₉N₂O: 411.14974; Found. 411.14776.

10H-Benzo[*b*]indolo[3,2,1-de]phenanthridine (2.3w)

Following the general procedure, a mixture of *gem*-dibromoolefin **2.1w** (93.4 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 20:1) afforded **2.3w** which co-eluted with an impurity. The chromatographed material was triturated with a minimal amount of hexanes to wash away the impurity and afford **2.3w** as a yellow solid (33.6 mg, 55% yield). *R*_f = 0.28 (hexanes:EtOAc 15:1). **MP** 247-249 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.57 (d, *J* = 8.2 Hz, 1H), 8.48 (d, *J* = 7.9 Hz, 1H), 8.11 (dd, *J* = 7.7, 0.7 Hz, 1H), 8.06 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.62 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.51 (dd, *J* = 4.5, 0.8 Hz, 2H), 7.44 – 7.42 (m, 3H), 7.36 (td, *J* = 7.4, 1.3 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 5.55 (s, 2H); **¹³C NMR** (100 MHz, CDCl₃) δ 138.8, 134.8, 130.4, 130.3, 130.1, 129.9, 129.4, 128.5, 128.0, 127.7, 126.9, 124.1, 124.0, 123.3, 123.1, 123.0, 122.2, 120.4, 119.2, 118.6, 113.3, 109.3, 45.4; **IR** (NaCl, neat): 3047, 1620, 1593, 1588, 1531, 1498, 1489, 1471, 1442, 1410, 1386, 1377, 1313, 1226, 1016, 913, 876, 785, 744, 719 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₆N: 306.12827; Found. 306.12936.

Benzo[*e*]indole 2.30

Following the general procedure, a mixture of *gem*-dibromoolefin **2.13** (96.3 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4

mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:DCM 35:65) afforded **2.30** as a dark yellow solid (33.7 mg, 53% yield). R_f = 0.28 (hexanes:EtOAc 4:1). **MP** 248-250 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.38 (s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.16 – 8.14 (m, 2H), 8.07 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 3.4 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 3.4 Hz, 1H), 2.59 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 144.2, 132.1, 131.8, 131.0, 130.8, 129.9, 129.8, 128.4, 127.9, 125.6, 125.4, 125.1, 124.6, 123.6, 121.0, 120.1, 116.8, 109.6, 22.1; **IR** (NaCl, neat): 3130, 3054, 2918, 1604, 1362, 1331, 1200, 1171, 1139, 913, 878, 812, 798, 748, 743, 684 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{14}\text{NO}_2\text{S}$: 320.0739; Found. 320.0727.

3.4 Synthesis of Compounds Used in Mechanistic Studies

3-(2-(Bromoethynyl)phenyl)-1-tosyl-1*H*-indole (**2.41**)

To a flame-dried flask cooled under N₂ was added **2.1a** (1.063 g, 2 mmol) and dry THF (10 mL). To the stirred solution was added TBAF (10 mL of 1M solution in THF, 10 mmol, 5 equiv.) in one portion, and the reaction was heated to 60 °C for 3 hours under N₂. THF was removed *in vacuo*, the residue redissolved in EtOAc, successively washed with saturated NH₄Cl and brine, dried over MgSO₄, and the solvent removed *in vacuo*. Purification via column chromatography (hexanes:EtOAc 12:1) afforded **2.41** which co-eluted with a brown impurity. The chromatographed material was triturated with hexanes until the washings were colourless to afford **2.41** as an off-white solid (0.268 g, 30% yield). *R*_f = 0.46 (hexanes:EtOAc 4:1). *MP* 118–120 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.60 (t, *J* = 8.9 Hz, 2H), 7.53 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.27 – 7.22 (m, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 145.1, 135.6, 135.2, 135.1, 134.2, 130.1, 129.9, 129.8, 129.0, 127.4, 127.1, 125.5, 124.9, 123.5, 121.7, 121.2, 120.6, 113.8, 79.8, 53.0, 21.7; IR (NaCl, neat): 3065, 2195, 1597, 1560, 1487, 1447, 1371, 1188, 11777, 1134, 1111, 1090, 1020, 1011, 934, 908, 812, 766, 746, 723, 669 cm⁻¹; HRMS (ESI) [M+H]⁺ Calcd for C₂₃H₁₇⁷⁹Br₂NO₂S: 450.0157; Found. 450.0136.

2-Bromobenzaldehyde-α-d (**2.42**)

WARNING: KCN IS EXTREMELY TOXIC, ALL OPERATIONS INVOLVING KCN MUST BE CONFINED TO A WELL-VENTILATED HOOD; ALL SURFACES THAT HAVE COME INTO CONTACT WITH KCN MUST BE RIGOROUSLY DECONTAMINATED WITH BASIC PEROXIDE OR BLEACH.

To a stirred solution of 2-bromobenzaldehyde (3.5 mL, 30 mmol) in dry Et₂O (15 mL) and D₂O (15 mL, 99.8% D) was added KCN (3.91 g, 60 mmol, 2 equiv.) in one portion. The biphasic mixture was vigorously stirred for 68 hours at room temperature. The layers were separated, the aqueous layer extracted with Et₂O (30 mL x 3), dried over MgSO₄, and removed *in vacuo*. Purification by column chromatography (hexanes:EtOAc 20 :1) afforded the title compound as a light yellow oil (3.324 g, 60% yield, 95% D). The analytical data was consistent with literature.⁹⁶ ¹H NMR (400 MHz, CDCl₃) δ 10.37 (d, J = 0.42, 0.05 H), 7.95 – 7.89 (m, 1H), 7.68 – 7.62 (m, 1H), 7.48 – 7.40 (m, 2H).

Deuterated pinacol ester **2.43**

An oven-dried heavy wall pressure vessel was cooled under Ar. PdCl₂(MeCN)₂ (83 mg, 0.32 mmol, 2 mol %) and SPhos (526 mg, 1.28 mmol, 8 mol %) were weighed under Ar, and the vessel purged with Ar for another 5 minutes. Still under an Ar atmosphere, dioxane (10 mL), **2.42** (1.9 mL, 16 mmol), triethylamine (6.7 mL, 48 mmol, 3 equiv.) and pinacol borane (3.5 mL, 24 mmol, 1.5 equiv.) were sequentially added via a syringe. The vessel was sealed under Ar and heated to 110 °C for 5 hours. After cooling to room temperature, the mixture was filtered over a pad of Celite, the solvent removed *in vacuo*, and the residue chromatographed (hexanes:EtOAc 11:1) to afford **2.43** as an unstable red-orange oil (0.772 g, 21% yield, 95% D). ¹H NMR showed that the material was ~70% pure; due to its instability, the impure material was used immediately in the next step without further purification or characterization. ¹H NMR (400

⁹⁶ Jagdale, A. R.; Youn, S. W. *Eur. J. Org. Chem.* **2011**, 3904-3910.

MHz, CDCl₃) δ 10.54 (d, J = 0.5 Hz, 0.05H), 7.98 – 7.94 (m, 1H), 7.88 – 7.84 (m, 1H), 7.59 – 7.53 (m, 2H), 1.39 (s, 12H).

Synthesis of Deuterated *gem*-dibromoolefin **2.45**

Deuterated aldehyde **2.44**

An oven-dried heavy wall pressure vessel was cooled under Ar. To it was added indole **2.6a** (0.795 g, 2 mmol), Pd(dba)₂ (57.5 mg, 0.1 mmol, 5 mol %), PPh₃ (52.5 mg, 0.2 mmol, 10 mol %), and CsF (0.608 g, 4 mmol, 2 equiv.). Under an Ar purge, pinacol ester **2.43** (0.723 g, assumed 2.17 mmol based on 70% purity, 1.085 equiv.) was dissolved in DME (2 mL), and transferred to the pressure vessel via syringe. The vial containing **2.43** was rinsed with DME (2 x 2 mL) and the rinsings were added to the vessel. Finally, additional DME (4 mL) was added to the pressure vessel, and then it was sealed under Ar and heated to 90 °C for 16 hours. After cooling to room temperature, the mixture was diluted with Et₂O, washed with 1M NaOH and brine, dried over MgSO₄, and the solvent removed *in vacuo*. Purification by column chromatography (15% EtOAc in hexanes) gave the title compound as a red-orange syrup (0.629 g, 83% yield, 95% D). R_f = 0.34 (hexanes:EtOAc 4:1). ¹H NMR (400 MHz, CDCl₃) δ 9.90 (d, J = 0.7 Hz, 0.05H), 8.08 (dd, J = 8.4, 1.5 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.67 (td, J = 7.5, 1.4 Hz, 1H), 7.63 (s, 1H), 7.55 – 7.50 (m, 2H), 7.42 – 7.37 (m, 2H), 7.29 – 7.24 (m, 3H), 2.36 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.51 (t, J = 27.2 Hz), 145.5, 136.2, 135.1, 135.0, 134.6 (t, J = 3.6 Hz), 134.2, 131.5, 130.9, 130.2, 128.5, 128.0, 127.0, 125.7, 125.6, 124.2, 120.1, 119.8, 114.0, 21.7; IR (NaCl, neat): 3127, 3065, 2118 (C-D stretch), 1670, 1599, 1447, 1371, 1188, 1177, 1132, 1090, 1020, 1011, 934, 910, 812, 772, 748, 735, 669 cm⁻¹; HRMS (ESI) [M+H]⁺ Calcd for C₂₂H₁₇DNO₃S: 377.1064; Found. 377.1058.

Deuterated *gem*-dibromoolefin **2.45**

Following general procedure D, aldehyde **2.44** (0.56 g, 1.5 mmol) and CBr₄ (0.746 g, 2.25 mmol) were dissolved in dry DCM (8.5 mL) and cooled to 0 °C. A solution of P(O*i*-Pr)₃ (1.11 mL, 4.5 mmol) in DCM (1.5 mL) was then added dropwise over several minutes. The reaction was stirred at 0 °C for 30 minutes. Subsequent workup and column chromatography (hexanes:EtOAc 11:1) afforded the title compound as a white solid (0.725 g, 91% yield, 95% D). *R*_f = 0.46 (hexanes:EtOAc 4:1). **MP** 119-120 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.76 – 7.73 (m, 1H), 7.56 (s, 1H), 7.51 – 7.34 (m, 5H), 7.28 – 7.23 (m, 3H), 7.19 (s, 0.05H), 2.35 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.2, 136.8 (t, *J* = 24 Hz), 135.2, 135.1, 134.7, 131.8, 130.3, 130.2, 130.1, 129.7, 128.8, 127.7, 127.1, 125.5, 125.2, 123.7, 121.5, 120.6, 113.9, 91.5, 21.8; **IR** (NaCl, neat): 3131, 3063, 2241 (C-D stretch), 1597, 1447, 1371, 1188, 1177, 1132, 1090, 1020, 1011, 934, 908, 768, 747, 719, 667 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₇D⁷⁹Br₂NO₂S: 540.9482; Found. 530.9499.

Deuterated benzo[*c*]carbazole **2.46**

Following the general procedure for the palladium-catalyzed domino reaction, a mixture of deuterated *gem*-dibromoolefin **2.45** (106.5 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:EtOAc 9:1) afforded **2.46** as a light brown solid (34.6 mg, 47% yield, 94% D). *R*_f = 0.31 (hexanes:EtOAc 4:1). **MP** 215 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 7.3 Hz, 1H), 8.37 (d, *J* = 7.5 Hz, 1H), 8.31 (s, 0.06H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.99 – 7.95 (m, 2H), 7.68 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.52 – 7.48 (m, 1H), 7.40 (dd, *J* = 8.1, 0.6 Hz, 1H), 2.53 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 144.2, 137.3, 134.2, 132.2, 131.5, 131.0, 130.1, 129.8, 129.3, 128.4, 127.3, 126.8, 125.3, 125.2,

124.8, 124.1, 123.5, 122.7, 122.4 (t, $J = 23.4$ Hz), 119.9, 117.2, 115.4, 22.1; **IR** (NaCl, neat): 3057, 2922, 2872, 1601, 1485, 1333, 1227, 1179, 1169, 910, 885, 814, 772, 739, 694, 667, 648 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{15}\text{DNO}_2\text{S}$: 371.0959; Found. 371.0966.

(Z)-3-(2-(2-bromovinyl)phenyl)-1-tosyl-1H-indole (2.47)

To a flame-dried flask cooled to -78°C in a dry ice/acetone bath and under N_2 was added (bromomethyl)triphenylphosphonium bromide (2.006 g, 4.6 mmol, 1.15 equiv.) and dry THF (12 mL). KOt-Bu (0.516 g, 4.6 mmol, 1.15 equiv.) was added at -78°C , and the flask washed down with additional THF (2 mL). The mixture was stirred at -78°C for 1 hour to complete ylid formation, then a solution of **2.7a** (1.502 g, 4 mmol) in THF (4 mL) was added dropwise over several minutes. The vial containing **2.7a** was rinsed with additional THF (2 mL), and the rinsings were added to the reaction. The mixture was stirred at -78°C for 2.5 hours, then let warm to room temperature over 2 hours. Pentane (40 mL) was added to precipitate triphenylphosphine oxide, and the suspension filtered over a pad of silica on a coarse frit, eluting with Et_2O until no more product was detected. The solvent was removed *in vacuo*, and the residue purified by column chromatography (hexanes:EtOAc 12:1) to afford **2.47** as a yellow gum (1.048 g, 58% yield). Crystallization was induced by cooling to -78°C in a dry ice/acetone bath for several minutes until **2.47** solidified completely into light yellow crystals. $R_f = 0.44$ (hexanes:EtOAc 4:1). **MP** $46\text{--}48^\circ\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ 8.05 (dt, $J = 8.3, 0.8$ Hz, 1H), 7.93 – 7.91 (m, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 7.54 (s, 1H), 7.46 – 7.38 (m, 4H), 7.35 (ddd, $J = 8.4, 7.3, 1.1$ Hz, 1H), 7.26 – 7.20 (m, 3H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.34 (d, $J = 8.0$ Hz, 1H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 145.2, 135.3, 135.0, 134.3, 132.4, 132.1, 130.5, 130.4, 130.0, 129.7, 128.4, 127.6, 127.1, 125.2, 125.1, 123.6, 122.2, 120.9, 113.9, 108.5, 21.7; **IR** (NaCl, neat): 3065, 1597, 1559, 1447, 1371, 1188, 1177, 1130, 1111, 1088, 1020, 1011, 934, 835, 812, 770, 746, 704, 682, 667, 635 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{19}^{79}\text{Br}_2\text{NO}_2\text{S}$: 452.0314; Found. 452.0302.

Synthesis of *E*-bromide 2.50

(2-(1-Tosyl-1*H*-indol-3-yl)phenyl)methanol (**2.48**)

To a suspension of **2.7a** (3.754 g, 10 mmol) in methanol (70 mL) cooled to 0 °C was added NaBH₄ (0.757 g, 20 mmol) in small portions over several minutes. After complete addition of NaBH₄, the reaction was stirred at 0 °C for 10 minutes, then let warm to room temperature. The reaction was re-cooled to 0 °C, and concentrated HCl was carefully added dropwise until pH was around 6. Methanol was removed *in vacuo*, and saturated NH₄Cl added to the residue. The aqueous layer was extracted with DCM (30 mL x 2), the extracts were washed with brine, dried over MgSO₄, and the solvent removed *in vacuo*. Purification by column chromatography (hexanes:EtOAc 7:3) afforded **2.48** as a clear, viscous syrup (3.558 g, 94% yield). *R*_f = 0.29 (hexanes:EtOAc 7:3). ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.73 (s, 1H), 7.59 (d, *J* = 7.1 Hz, 1H), 7.45 – 7.33 (m, 5H), 7.26 – 7.20 (m, 3H), 4.54 (d, *J* = 5.3 Hz, 2H), 2.35 (s, 3H), 1.69 (t, *J* = 5.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 145.2, 139.3, 135.3, 135.1, 131.6, 130.8 (2C), 130.1, 129.1, 128.3, 128.0, 127.0, 125.1, 124.8, 123.7, 121.8, 120.4, 113.9, 63.4, 21.7; IR (NaCl, neat): 3555 (br), 3370 (br), 3134, 3065, 2924, 1597, 1445, 1371, 1188, 1175, 1130, 1090, 1013, 932, 908, 812, 772, 748, 731, 718, 669 cm⁻¹; HRMS (ESI) [M+Na]⁺ Calcd for C₂₂H₁₉NO₃SNa: 400.0977; Found. 400.0981.

3-(2-(Bromomethyl)phenyl)-1-tosyl-1*H*-indole (**2.49**)

To a flame-dried flask cooled under N₂ was added **2.48** (3.4 g, 9 mmol) and dry DCM (45 mL). The mixture was cooled to 0 °C, and PBr₃ (0.85 mL, 9 mmol) was added dropwise over 20 minutes via syringe pump. The reaction was stirred for 30 minutes at 0 °C, and carefully quenched with saturated NaHCO₃ at 0 °C until pH reached 7, whereupon an emulsion formed. The mixture was re-acidified with concentrated HCl until the emulsion disappeared. The layers were separated, the aqueous layer was extracted with DCM (50 mL), the combined extracts

were washed with distilled water, dried over MgSO_4 , and the solvent removed *in vacuo*. Purification by column chromatography (40% DCM in hexanes) afforded **2.49** as a white foam (1.924 g, 49% yield). $R_f = 0.47$ (hexanes:EtOAc 4:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.08 (d, $J = 8.3$ Hz, 1H), 7.88 – 7.83 (m, 3H), 7.58 – 7.54 (m, 1H), 7.42 – 7.32 (m, 5H), 7.26 – 7.21 (m, 3H), 4.36 (s, 2H), 2.35 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 145.2, 136.6, 135.3, 135.1, 132.4, 131.3, 131.2, 130.9, 130.1, 128.9, 128.7, 127.1, 125.2, 124.6, 123.7, 121.4, 120.3, 114.0, 32.2, 21.7; **IR** (NaCl, neat): 3065, 2924, 1597, 1493, 1445, 1371, 1188, 1177, 1128, 1109, 1092, 1020, 1013, 936, 908, 812, 746, 718, 669 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{19}^{79}\text{Br}_2\text{NO}_2\text{S}$: 440.0314; Found. 440.0305.

(*E*)-3-(2-(2-bromovinyl)phenyl)-1-tosyl-1*H*-indole (**2.50**)

To a flame-dried flask cooled to -78°C in a dry ice/acetone bath and under N_2 was added dry Et_2O (12 mL) and NaHMDS (12 mL of 1M solution in THF, 12 mmol, 3 equiv.). The flask was then wrapped in aluminum foil to exclude light for the remainder of the reaction. In the dark, CH_2Br_2 (1.12 mL, 16 mmol, 4 equiv.) was added over 5 minutes via syringe pump, and stirred at -78°C for 20 minutes. Then, a solution of **2.49** (1.762 g, 4 mmol) in dry THF (5 mL) was added dropwise over 15 minutes via syringe pump at -78°C . The reaction was stirred at -78°C for 3 hours, then let warm to room temperature over 16 hours. Et_2O (50 mL) was added, and the mixture was filtered over a coarse frit containing silica topped with Celite. The Et_2O addition and filtration sequence was repeated a total of 4 times. The organics were combined, removed *in vacuo*, and purified by careful column chromatography (hexanes:EtOAc 13:1) to afford **2.50** as a light orange solid (0.654 g, 36% yield). $R_f = 0.28$ (hexanes:EtOAc 9:1). **MP** 115–116 $^\circ\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.12 (dt, $J = 8.4, 0.9$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 2H), 7.57 (s, 1H), 7.56 – 7.52 (m, 1H), 7.47 – 7.37 (m, 5H), 7.33 – 7.25 (m, 3H), 7.02 (d, $J = 13.9$ Hz, 1H), 6.73 (d, $J = 13.9$ Hz, 1H), 2.39 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 145.3, 136.2, 135.3, 135.2 (2C), 131.0, 130.9, 130.4, 130.2, 128.5, 128.3, 127.0, 126.6, 125.5, 125.2, 123.8, 121.9, 120.7, 114.0, 107.6, 21.8; **IR** (NaCl, neat): 3067, 1597, 1445, 1371, 1188, 1177, 1130, 1109, 1088, 1020, 1011, 934, 908, 812, 768, 746, 714, 669 cm^{-1} ; **HRMS** (ESI) $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{19}^{79}\text{Br}_2\text{NO}_2\text{S}$: 452.0314; Found. 452.0298.

7-Tosyl-7H-benzo[c]carbazole (2.51)

Following the general procedure for the palladium-catalyzed domino reaction, a mixture of *Z*-bromide **2.47** (90.5 mg, 0.2 mmol), **Pd-1** (13.5 mg, 0.02 mmol, 10 mol %), K₂CO₃ (55.3 mg, 0.4 mmol, 2 equiv.), and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 hours. Subsequent workup and column chromatography (hexanes:DCM 3:1) afforded **2.51** as a white solid (59.1 mg, 80% yield). *R*_f = 0.44 (hexanes:EtOAc 4:1). **MP** 148-150 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.61 (d, *J* = 9.1 Hz, 1H), 8.52 (d, *J* = 8.2 Hz, 1H), 8.47 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.72 – 7.66 (m, 3H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 2.22 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.1, 138.3, 136.7, 135.2, 131.2, 129.8, 129.3, 128.9, 128.7, 127.4, 127.3, 126.5, 126.3, 125.0, 124.4, 123.7, 122.3, 120.0, 115.6, 115.1, 21.6; **IR** (NaCl, neat): 3090, 3053, 2922, 1597, 1586, 1518, 1464, 1447, 1435, 1368, 1267, 1242, 1188, 1177, 1161, 1119, 1090, 1059, 1030, 1020, 928, 908, 810, 789, 743, 706, 673, 656 cm⁻¹; **HRMS** (ESI) [M+H]⁺ Calcd for C₂₃H₁₈NO₂S: 372.10582; Found. 372.10559.

Appendix 1: Selected ^1H and ^{13}C NMR Spectra

3-Iodo-1-tosyl-1H-indole (2.6a)

3-Iodo-5-methyl-1-tosyl-1H-indole (2.6b)

3-Iodo-7-methyl-1-tosyl-1H-indole (2.6c)

3-Iodo-5-methoxy-1-tosyl-1H-indole (2.6d)

Methyl 3-iodo-1-tosyl-1*H*-indole-6-carboxylate (2.6e)

3-Iodo-1-tosyl-1H-indole-5-carbonitrile (2.6f)

3-Iodo-5-nitro-1-tosyl-1H-indole (2.6g)

3-Iodo-1-tosyl-7-azaindole (2.6h)

1-(Benzylsulfonyl)-3-iodo-1*H*-indole (2.6i)

3-Iodo-1-(4-methoxyphenylsulfonyl)-1*H*-indole (2.6j)

3-Iodo-1-(4-nitrophenylsulfonyl)-1H-indole (2.6k)

4-Iodo-1-tosyl-1H-pyrazole (2.22)

(3-Iodo-1*H*-indol-1-yl)(phenyl)methanone (3.2)

2-(1*H*-Indol-3-yl)benzaldehyde (2.10)

2-(1-Tosyl-1*H*-indol-3-yl)benzaldehyde (2.7a)

2-(5-Methyl-1-tosyl-1H-indol-3-yl)benzaldehyde (2.7b)

2-(7-Methyl-1-tosyl-1*H*-indol-3-yl)benzaldehyde (2.7c)

2-(5-Methoxy-1-tosyl-1H-indol-3-yl)benzaldehyde (2.7d)

Methyl 3-(2-formylphenyl)-1-tosyl-1H-indole-6-carboxylate (2.7e)

3-(2-Formylphenyl)-1-tosyl-1*H*-indole-5-carbonitrile (2.7f)

2-(5-Nitro-1-tosyl-1*H*-indol-3-yl)benzaldehyde (2.7g)

2-(1-Tosyl-1*H*-7-azaindol-3-yl)benzaldehyde (2.7h)

2-(1-(Benzylsulfonyl)-1H-indol-3-yl)benzaldehyde (2.7i)

2-(1-(4-Methoxyphenylsulfonyl)-1H-indol-3-yl)benzaldehyde (2.7j)

2-(1-(4-Nitrophenylsulfonyl)-1H-indol-3-yl)benzaldehyde (2.7k)

5-Methoxy-2-(1-tosyl-1H-indol-3-yl)benzaldehyde (2.7l)

2-(1-(4-(Trifluoromethyl)phenylsulfonyl)-1H-indol-3-yl)benzaldehyde (2.7m)

2-(1-(4-Fluorophenylsulfonyl)-1H-indol-3-yl)benzaldehyde (2.7n)

2-(1-(Thiophen-2-ylsulfonyl)-1H-indol-3-yl)benzaldehyde (2.7o)

2-(1-(Diphenylphosphoryl)-1H-indol-3-yl)benzaldehyde (2.7p)

2-(1-Benzoyl-1H-indol-3-yl)benzaldehyde (2.7q)

3-(2-Formylphenyl)-*N,N*-diphenyl-1*H*-indole-1-carboxamide (2.7r)

***N,N*-Dibenzyl-3-(2-formylphenyl)-1*H*-indole-1-carboxamide (2.7s)**

Phenyl 3-(2-formylphenyl)-1H-indole-1-carboxylate (2.7t)

Benzyl 3-(2-formylphenyl)-1H-indole-1-carboxylate (2.7u)

2-(1-Phenyl-1H-indol-3-yl)benzaldehyde (2.7v)

2-(1-Benzyl-1H-indol-3-yl)benzaldehyde (2.7w)

2-(1-Phenethyl-1*H*-indol-3-yl)benzaldehyde (2.7x)

2-(1-(1H-Indole-1-carbonyl)-1H-indol-3-yl)benzaldehyde (2.7y)

2-(1-Tosyl-1H-pyrrol-3-yl)benzaldehyde (2.19)

2-(1-Tosyl-1H-pyrazol-4-yl)benzaldehyde (2.23)

2-((Trimethylsilyl)ethynyl)benzaldehyde (2.27)

2-Ethynylbenzaldehyde (2.28)

2-(1-Tosyl-1*H*-1,2,3-triazol-4-yl)benzaldehyde (2.29)

3-Bromobenzene-1-sulfonyl fluoride (2.36)

1-Bromo-3-(phenylsulfonyl)benzene (2.37)

3'-(Phenylsulfonyl)biphenyl-2-carbaldehyde (2.38)

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1H-indole (2.1a)

3-(2-(2,2-Dibromovinyl)phenyl)-5-methyl-1-tosyl-1H-indole (2.1b)

3-(2-(2,2-Dibromovinyl)phenyl)-7-methyl-1-tosyl-1H-indole (2.1c)

3-(2-(2,2-Dibromovinyl)phenyl)-5-methoxy-1-tosyl-1H-indole (2.1d)

Methyl 3-(2-(2,2-dibromovinyl)phenyl)-1-tosyl-1H-indole-6-carboxylate (2.1e)

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1H-indole-5-carbonitrile (2.1f)

3-(2-(2,2-Dibromovinyl)phenyl)-5-nitro-1-tosyl-1H-indole (2.1g)

1-(Benzylsulfonyl)-3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole (2.1i)

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-methoxyphenylsulfonyl)-1*H*-indole (2.1j)

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-nitrophenylsulfonyl)-1*H*-indole (2.1k)

3-(2-(2,2-Dibromovinyl)-4-methoxyphenyl)-1-tosyl-1H-indole (2.11)

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-indole (2.1m)

3-(2-(2,2-Dibromovinyl)phenyl)-1-(4-fluorophenylsulfonyl)-1H-indole (2.1n)

3-(2-(2,2-Dibromovinyl)phenyl)-1-(thiophen-2-ylsulfonyl)-1H-indole (2.1o)

3-(2-(2,2-Dibromovinyl)phenyl)-1-(diphenylphosphoryl)-1H-indole (2.1p)

(3-(2-(2,2-Dibromovinyl)phenyl)-1*H*-indol-1-yl)(phenyl)methanone (2.1q)

3-(2-(2,2-Dibromovinyl)phenyl)-*N,N*-diphenyl-1*H*-indole-1-carboxamide (2.1r)

***N,N*-dibenzyl-3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole-1-carboxamide (2.1s)**

Phenyl 3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole-1-carboxylate (2.1t)

Benzyl 3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole-1-carboxylate (2.1u)

3-(2-(2,2-Dibromovinyl)phenyl)-1-phenyl-1H-indole (2.1v)

1-Benzyl-3-(2-(2,2-dibromovinyl)phenyl)-1*H*-indole (2.1w)

3-(2-(2,2-Dibromovinyl)phenyl)-1-phenethyl-1H-indole (2.1x)

(3-(2-(2,2-Dibromovinyl)phenyl)-1*H*-indol-1-yl)(1*H*-indol-1-yl)methanone (2.1y)

3-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1H-pyrrole (2.13)

4-(2-(2,2-Dibromovinyl)phenyl)-1-tosyl-1H-pyrazole (2.14)

2-(2,2-Dibromovinyl)-3'-(phenylsulfonyl)biphenyl (2.34)

Benzo[*c*]carbazole 2.3a

Benzo[c]carbazole 2.3b

Benzo[c]carbazole 2.3c

Benzo[*c*]carbazole 2.3d

Benzo[*c*]carbazole 2.3e

Benzo[c]carbazole 2.3j

Benzo[c]carbazole 2.31

Benzo[c]carbazole 2.3m

Benzo[c]carbazole 2.3n

Benzo[c]carbazole 2.3o

Benzo[c]carbazole 2.3r

10H-Benzo[*b*]indolo[3,2,1-de]phenanthridine (2.3w)

Benzo[e]indole 2.30

3-(2-(Bromoethynyl)phenyl)-1-tosyl-1*H*-indole (2.41)

2-Bromobenzaldehyde- α -d (2.42)

Deuterated aldehyde 2.44

Deuterated *gem*-dibromoolefin 2.45

Deuterated benzo[*c*]carbazole 2.46

(Z)-3-(2-(2-bromovinyl)phenyl)-1-tosyl-1H-indole (2.47)

(2-(1-Tosyl-1*H*-indol-3-yl)phenyl)methanol (2.48)

3-(2-(Bromomethyl)phenyl)-1-tosyl-1H-indole (2.49)

(E)-3-(2-(2-bromovinyl)phenyl)-1-tosyl-1H-indole (2.50)

7-Tosyl-7H-benzo[c]carbazole (2.51)

Appendix 2: X-Ray Crystal Data

Table A2.1 Crystal data and structure refinement for **2.3a**

Identification code	k11179	
Empirical formula	C ₂₃ H ₁₅ N O ₂ S	
Formula weight	369.42	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2 ₁ /n	
Unit cell dimensions	a = 12.1432(6) Å	a = 90°.
	b = 7.8399(3) Å	b = 105.211(2)°.
	c = 18.1247(9) Å	g = 90°.
Volume	1665.05(13) Å ³	
Z	4	
Density (calculated)	1.474 Mg/m ³	
Absorption coefficient	0.214 mm ⁻¹	
F(000)	768	
Crystal size	0.28 x 0.26 x 0.14 mm ³	
Theta range for data collection	3.13 to 27.52°.	
Index ranges	-15 ≤ h ≤ 15, -9 ≤ k ≤ 10, -17 ≤ l ≤ 23	
Reflections collected	10644	
Independent reflections	3782 [R(int) = 0.0533]	
Completeness to theta = 25.24°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.972 and 0.883	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3782 / 0 / 245	
Goodness-of-fit on F ²	1.056	
Final R indices [I > 2σ(I)]	R1 = 0.0561, wR2 = 0.1366	
R indices (all data)	R1 = 0.1021, wR2 = 0.1665	
Largest diff. peak and hole	0.348 and -0.494 e.Å ⁻³	