Leibniz-Institut für Katalyse e. V. an der Universität Rostock

SYNTHESIS AND CATALYTIC FUNCTIONALIZATION OF BIOLOGICALLY ACTIVE INDOLES

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Abstract

Universität Rostock

SYNTHESIS AND CATALYTIC FUNCTIONALIZATION
OF BIOLOGICALLY ACTIVE INDOLES

by Nicolle Schwarz

Leibniz-Institut für Katalyse e. V. an der Universität Rostock

The indole ring system constitutes one of the most important heterocycles in nature. This thesis presents the synthesis of new indole derivatives and their further functionalization to potential $5HT_6$-receptor ligands. Based on our prior synthesis to tryptamines and tryptopholes we investigated a novel synthetic strategy to innovative indole scaffolds via Ti- or Zn-catalyzed hydroamination and hydrohydrazination of terminal alkynes. Thereby we developed the pharmaceutically interesting class of 3-silyloxyindoles and their application in several palladium-catalyzed reactions. Both Buchwald-Hartwig amination, C-O cross-coupling, nucleophilic substitution and sulfonylation were utilized and optimized. All pharmaceutical relevant final products and their intermediates were tested to be biologically active. Additional achievements in the field of indole synthesis are included.

Table of Contents

List of Abbreviations

Ac	Acetyl
aq	Aqueous
Ar	Aryl
BINAP	2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
*n*Bu	*normal*-Butyl
*t*Bu	*tert*-Butyl
*t*BuOH	*tert*-Butanol
(tBu_2*)* BP-phos	2-(Di-*tert*-butylphosphino)bi-phenyl
Bz	Benzoyl
Cat.	Catalyst
Conv.	Conversion
Cy	Cyclohexyl
dba	Dibenzylidene acetone
DBU	1,8-Diazobicyclo [5.4.0]-undec-7-ene
DCM	Dichlormethane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPEphos	Bis(2-diphenylphosphinophenyl)ether
dppf	Bis(diphenylphosphino)ferrocen
dppm	Bis(diphenylphosphino)methane
EOM	Ethoxymethyl
EWG	Electron-withdrawing group
equiv	Equivalent
Et	Ethyl
et al.	et alii, et aliae or et alia
etc.	et cetera
EtOH	Ethanol
EP	Receptor for E series ofPprostaglandins
GC	Gas chromtography
h	Hour
L	Ligand
LiHMDS	Lithium hexamethyldisilazide
m	Meta

M	Molar
Me	Methyl
MeOH	Methanol
min	Minute
MOM	Methoxymethyl ether
Nf	Nonaflate
NMR	Nuclear Magnetic Resonance
OAc	Acetate
OMe	Methoxy
o	Ortho
p	Para
Ph	Phenyl
PhH	Benzene
PhMe	Toluene
pin	Pinacol
Piv	Pivaloyl
*i*Pr	*i*so-Propyl
R	Organic rest
rt	Room temperature
SEM	(Trimethylsily)ethoxymethyl
Sphos	Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Tf	Triflate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TON	Turnover number
Tos	Tosyl
TPABr	Tetrapropylammonium bromide
X	Halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Y	Halide

Preface

The search for drugs is an old human dream and constitutes still a real challenge for scientists. Already alchemists sought for the one drug, the *Elixir* healing all human ailments. Today, the growing knowledge in pharmacy and biology makes the search for novel drugs complex and difficult. Therefore it is not surprising that organic chemists are interested in the development of easy accessible synthesis to new potential drugs.

An interesting target for drug design is the serotonin (5-hydroxytryptamine 5-HT) receptor ligand. It is one of the oldest known neurotransmitter in the central nervous system and responsible for controlling our body temperature, mood, sexual drive and sleep rhythm. This hormone is implicated in many diseases like schizophrenia, anxiety, obesity and Alzheimer's disease. Based on the indole skeleton it is an interesting building block which is of importance to the pharmaceutical industry. The application of new 5-HT receptor ligands against these diseases demanded an easy access to indole derivatives and wide scope of functionalization.

Metal-catalyzed cross-coupling reactions have profoundly changed the protocols for the construction of natural products, building blocks of supermolecular chemistry and lead compounds in medicinal chemistry from simpler entities. The development of efficient new carbon-carbon bond forming reactions by metal-catalyzed cross-coupling has continued to progress dramatically and some of the reactions are finding industrial application on the multipleton scale. Furthermore new protocols for C-N and C-O couplings have been introduced and find particular use in the synthesis of biologically active compounds for pharmaceutical application.

Cross-coupling reactions play an important role in the development of new 5-HT-receptor ligands as well. Finding the optimized conditions in C-N- or C-O- bond forming processes is one of the key steps in the synthesis of new indole derivatives.

1 Palladium-catalyzed Coupling Reactions of Indoles

1.1 Introduction

Indoles represent an essential class of heterocyclic compounds in nature. Based on the various biological actions, this ring system has become a privileged building block for the pharmaceutical industry. Nowadays, a variety of drugs with significant structural diversity and different biologically activity belong to the indole family.[1] In Figure 1 few selected examples of known pharmaceutical agents based on the indole scaffold are shown. The corresponding medical indications are listed in Table 1.

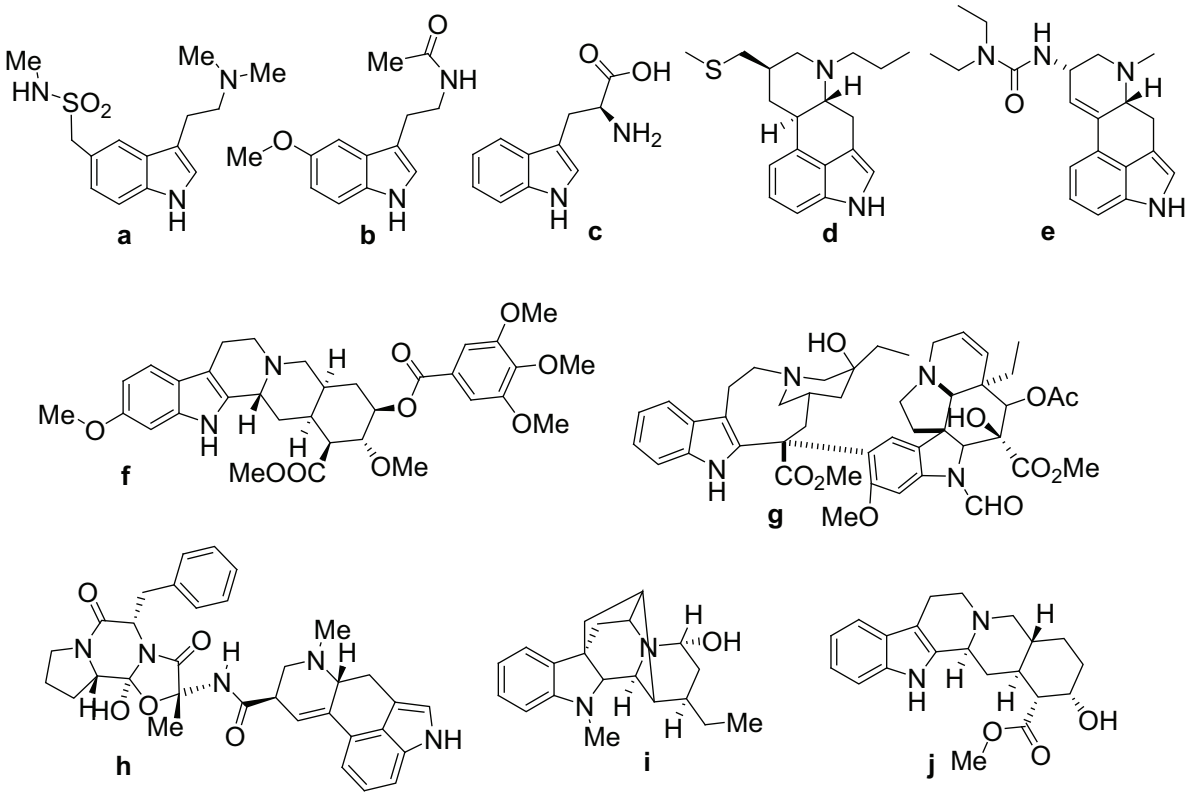


Figure 1. Selected biologically active compounds with indole skeleton.

In general, indole derivatives are used for diseases related to the central nervous systems (CNS), e.g. against migraine headaches like sumatriptan **a**, lisurid **e**, and ergrotamin **h**, or vincristine **g** against Parkinson's disease.

Clearly, the development of novel methods for the synthesis of indoles is stimulated by their widespread utility in life science.[2] Over the last century the preparation and functionalization of indoles continued to be an important object of research. Today, a range of well-established “classical” methods are available. Typical examples include the Fischer indole synthesis, the Gassman synthesis, the Madelung cyclization, the Bischler indole synthesis and the Batcho-Leimgruber synthesis.[3]

Table 1. Selected indole drugs and their medical indication.

	Name	Domain	Drug
a	Sumatriptan	migraine headaches, hypertonia	Imigran®
b	Melatonin	hormone, primary insomnia	Circadin®
c	Tryptophan	epilepsy, depression	L-Tryptophan-ratiopharm®, Ardeydorm®
d	Pergolid	Parkinson’s disease	Parkotil®
e	Lisurid	Parkinson’s disease, migraine headaches	Dopergin®
f	Reserpin	hypertension	Briserin®
g	Vincristine	cancer chemotherapy	Oncovin®
h	Ergotamin	migraine headaches	Ergo-Kranit®
I	Ajmalin	cardiac arrhythmia	Gilurytmal®
j	Yohimbin	hypertension, aphrodisiac	Yocon-Glenwood® Yocon®, Yohimbin Spiegel®

In addition, a variety of more modern transition metal-based syntheses and domino reactions have been developed. In general, the availability of starting materials and the functional group tolerance defines the suitability of the respective indole synthesis.[4]

In the last two decades transition metal-catalyzed coupling reactions have dramatically improved the synthesis of biologically active molecules.[5]

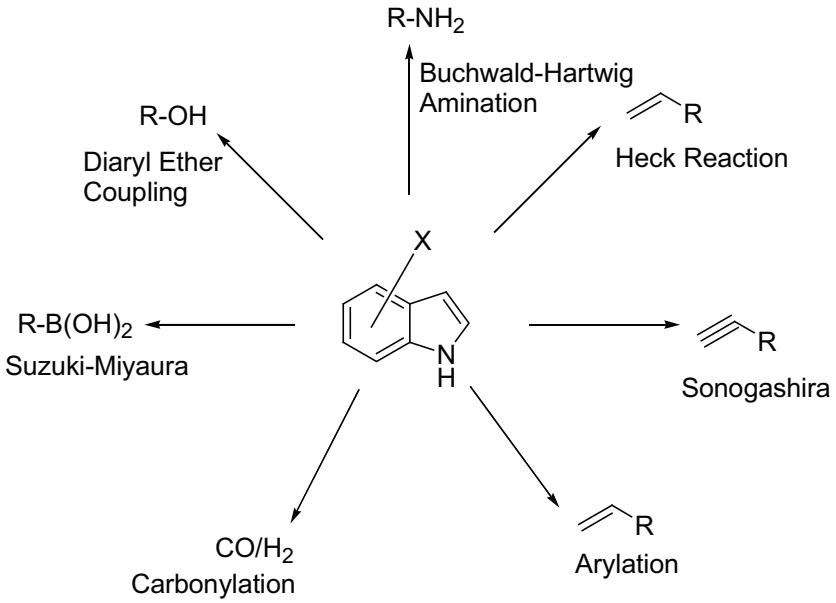
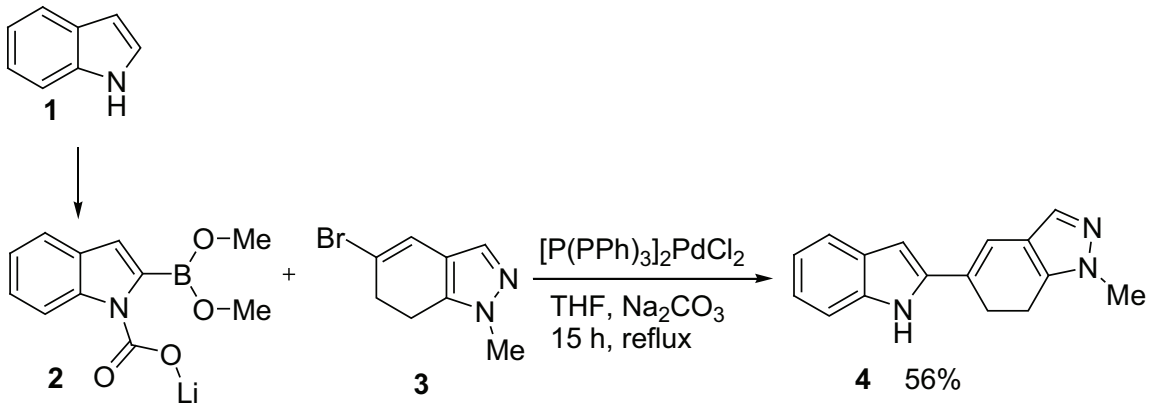


Figure 2. Catalytic functionalizations of indoles (X = I, Br, Cl, OTs, OTf, etc.).

Especially palladium-catalyzed carbon-carbon, carbon-nitrogen, and carbon-oxygen bond forming reactions have become powerful tools for their synthesis.[6,7] Striking features of these methods are their tolerance towards a wide range of functional groups on both coupling partners and their ability to construct efficiently complex organic building blocks in few steps. In Figure 2 several palladium-catalyzed coupling reactions of indoles are illustrated. In this review the more recent developments from 2003 to 2008 in palladium-catalyzed coupling reactions of indoles are highlighted and summarized. Emphasis is given on those reactions leading to new substituted indole derivatives and less on coupling reactions of azaindoles, carbazoles, and oxindoles.

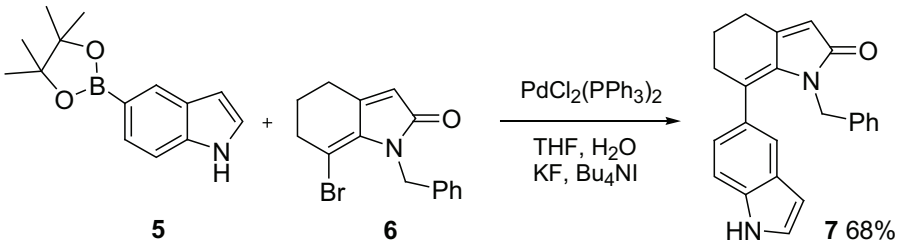
1.2 Suzuki-Miyaura Coupling Reaction

The cross-coupling reaction of organoboron reagents with aryl or vinyl halides in the presence of base and palladium catalysts is commonly known as the Suzuki-Miyaura reaction.[8] After the first application in natural product synthesis in 1981 by Rossi and co-workers[9e] it has been extensively applied over the past 20 years.[9,10] As a key step in the mechanism the coupling reaction of organoboron compounds involves transmetallation from boron to the corresponding arylpalladium(II) halides. In the presence of (aqueous) base the reaction proceed smoothly and offers a wide range of selective C-C bond formations. Organoboron compounds are convenient reagents, generally thermally stable and inert to water and oxygen. Typically, these transformations can be performed without special precautions. Thus, it is not surprising that Suzuki-Miyaura coupling reactions of indolyl-based boronic acids and indolylboronates have found widespread application in the functionalization of the indole ring. Using different *N*-protecting groups, all positions of the indole skeleton can be functionalized applying this cross-coupling protocol. For example, a large-scale preparation of *N*-methyldihydro-indazoledien **4** is reported by Hudkins and co-workers.[11] As outlined in Scheme 1 the synthesis of indazole **4** is realized in 56% yield via palladium-catalyzed Suzuki-Miyaura coupling using 5-bromo-1-methyl-6,7-dihydro1*H*-indazol **3** and indole-2-boronate **2**. Conveniently, the 1-carboxy-protected indole-2-boranate **2** is produced in situ by sequential reaction of indole **1** with carbon dioxide and trimethylborate.[12]



Scheme 1. Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of indole-2-boranate.

Kumar and co-workers developed an attractive method for the substitution of indoles with novel 7-bromo-5,6-dihydroindole-2-ones.[13] This type of coupling partner is isosteric to indoles and is believed to possess similar biological activity.[14]

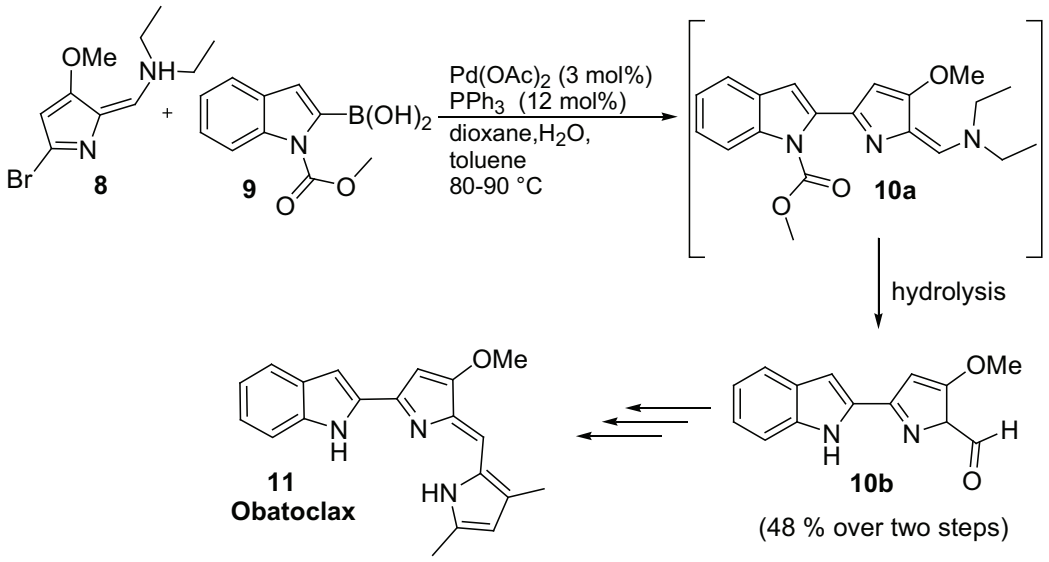


Scheme 2. Suzuki-Miyaura cross-coupling reation of 5-pinacol-indole with 7-bromo dihydroindole-2-one.

Scheme 2 shows an example of the coupling of the non-protected indole pinacol ester **5** by using a dual-solvent system, KF as base, and Bu_4NI as phase-transfer catalyst. Here, the desired product **7** is obtained in good yield (68%).

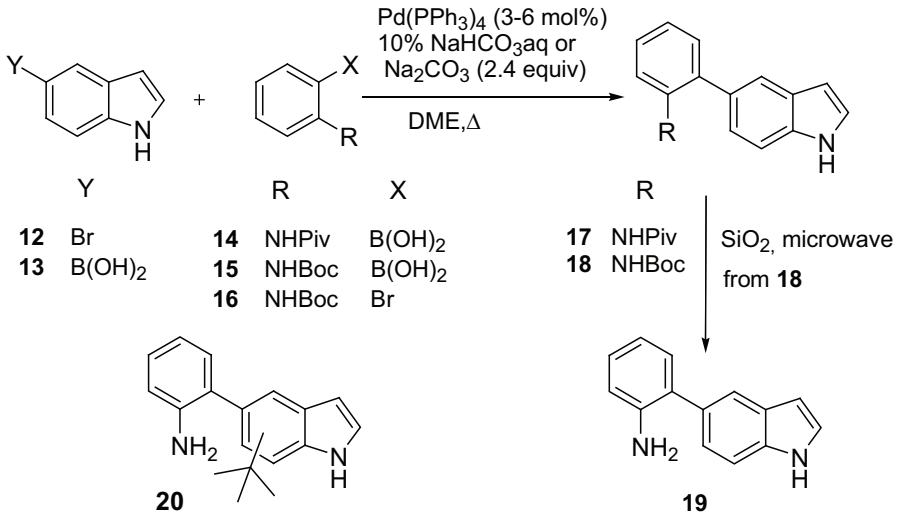
Obatoclax **11** is known to be biological active and shows potent anticancer activity in several animal tumor models. This novel indolylprodigiosin derivative has the ability to antagonize multiple members of the B-cell lymphoma family of anti-apoptotic proteins.[15] The three-step synthesis involves a haloformylation reaction[16,] followed by a Suzuki cross-coupling reaction with an indole-2-boronic acid **9** to give compound **10a** (Scheme 3). The Suzuki reaction proceeded rapidly in the presence of 3 mol% $Pd(OAc)_2$ and 12 mol% PPh_3. However, an excess of boronic acid is required for an acceptable yield. The mixture of different solvents slowed down the decomposition of indole-2-boronic acid **9** and raised the yield additionally. Subsequent hydrolysis of both the enamine and the *N*-methoxy carbonyl group afforded the indolylpyrrole aldehyde **10b**. The final step includes the acid mediated condensation of **10b** with 2,4-dimethyl-1*H*-pyrrole to provide the HCl-salt of Obatoclax **11**. Notably, this three-step synthesis was recently applied to the production of Obatoclax on kg-scale to support clinical studies.

Sapi and co-workers described a short synthesis of fused indole heterocycles via palladium-catalyzed cross-coupling.[17]



Scheme 3. Suzuki-Miyaura coupling key step in the synthesis of Obatoclax.

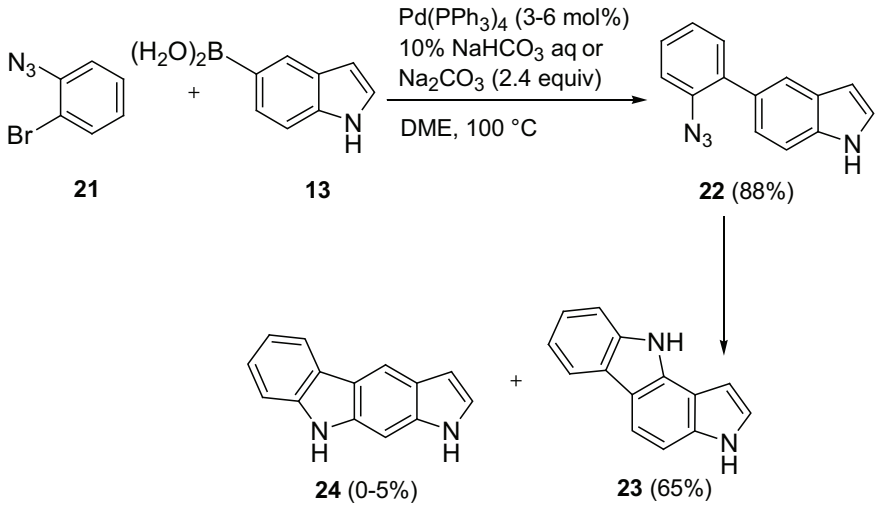
Therefore the authors investigated the reaction of 5-bromoindole **12** and 2-(2,2-dimethylpropionylamino)phenyl boronic acid[18] **14** (Scheme 4). Using $Pd(PPh_3)_4$ as catalyst system and 10% aqueous $NaHCO_3$ solution or Na_2CO_3 as base in DME, the corresponding diaryl compound **17** is formed in 66% yield. Because of problems in the deprotection of the pivaloyl- protecting group, the authors also performed the cross coupling of **12** with the *N*-Boc-protected 2-aniline boronic acid **15** under the same conditions with a yield of 55%. They got higher yields of the same coupling product, using 1*H*-indole boronic acid **13** with *N*-Boc-protected 2-bromoaniline **16** (66%).



Scheme 4. Palladium-catalyzed Suzuki-Miyaura reaction to indole derivatives.

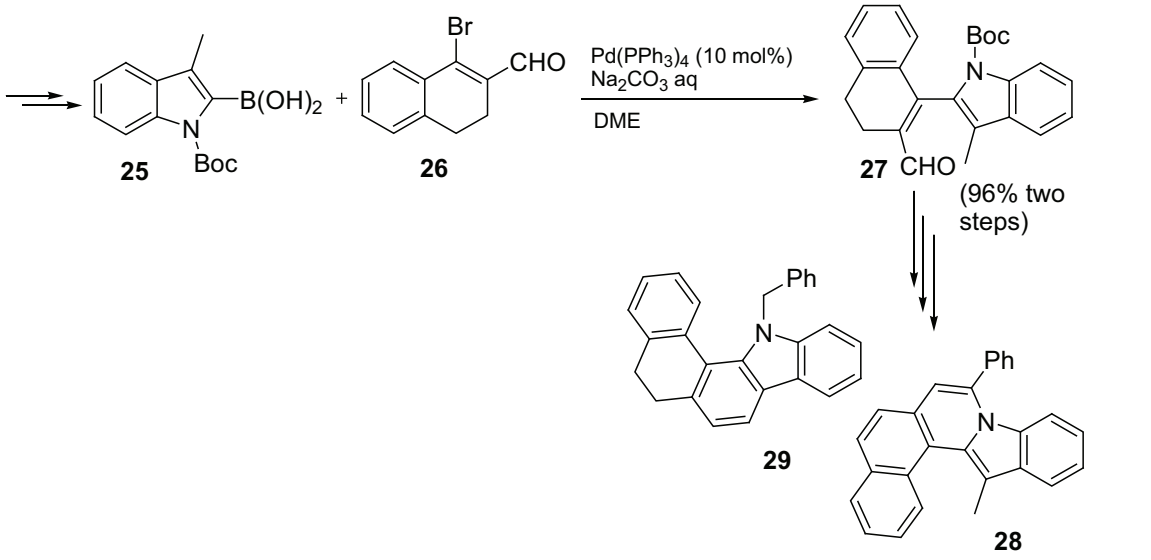
After deprotection the desired compound **19** is obtained with a varying amount of the *tert*-butyl-substituted derivative **20**. This type of side product is well known in peptide synthesis using Boc-strategies.

Furthermore, the same group reported Suzuki-type coupling reactions with azide-substituted arenes.[17] Among the different coupling reactions also 1-azido-2-bromobenzene[19] **21** reacted with 1*H*-indole-5-boronic acid **13** to the desired azido-diaryl compound **22** in 88% yield (Scheme 5). Decomposition of **22** by heating gave the annulated aromatic polycycles **23** and **24**.



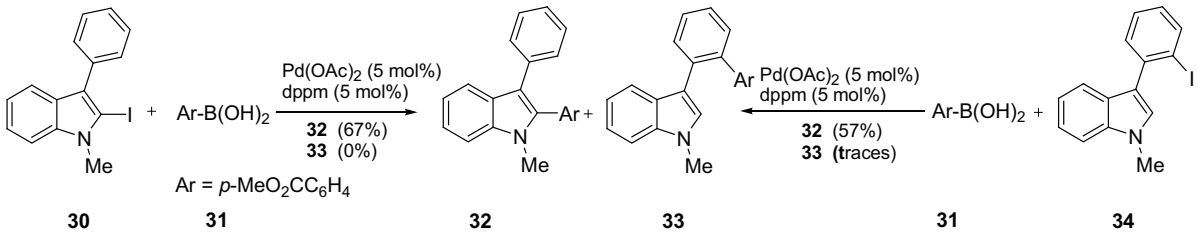
Scheme 5. Suzuki-Miyaura coupling reaction of 1-azido-2-bromobenzene with 1*H*-indole-5-boronic acid.

Different strategies for the synthesis of annulated indoles such as cryptaustoline and cryttowolin[20] were performed by de Koning and co-workers.[21] These alkaloides have been reported to possess anti-leukemic and anti-tumor activities. Thus, indole-2-yl boronic acid **25**, typically prepared with butyl lithium and borate, was dissolved in ethanol and reacted with naphthalene **26** in the presence of $Pd(PPh_3)_4$ (10 mol%) and Na_2CO_3 as base (Scheme 6).[22] The coupling intermediate **27** is obtained in a yield of 96% over two steps. Noteworthy, deprotection of the Boc-group and formation of the aromatic ring[23] gave instead of the expected naphtho[*a*]carbazole **29** the isoquinoline **28**. In addition, other syntheses towards the cryptaustoline nucleus involving Suzuki-Miyaura couplings of indoles as key step have been mentioned.[21]



Scheme 6. Suzuki-Miyaura coupling reaction of indole-2-yl boronic acid and dihydro-naphthalene.

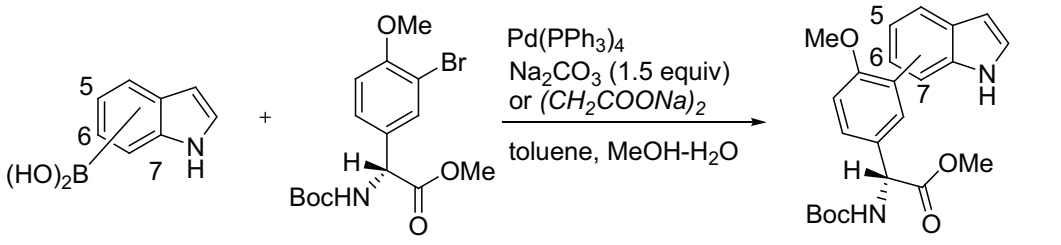
When using indoles in Suzuki-Miyaura reactions this chemistry involves in general the utilization of indolyl halides. In this respect, Larock and co-workers analyzed novel 1,4-palladium migrations.[24] More specifically, they observed 1,4-palladium-migration in organopalladium intermediates derived from *o*-halobiaryls. As an example they examined the reaction of 2-iodo-1-methyl-3-phenylindole **30** and boronic acid **31** (Scheme 7). To avoid that the base activates the aryl boronic acid prior to palladium migration, the system was buffered using a combination of cesium pivalate and pivalic acid. Hence, components **30** and **31** were stirred at 100 °C in the presence of 5 mol% $Pd(OAc)_2$, 5 mol% $(PPh_2)_2CH_2$ (dppm), 2 equiv of cesium pivalate and 2 equiv of pivalic acid in DMF containing 20 equiv of water. After 3 h product **32** is obtained selectively in 67% yield. Interestingly when 3-(2-iodophenyl)-1-methylindole **34** is allowed to react with **31** under the same conditions, product **32** is produced in a yield of 57% along some traces of isomer **33**.



Scheme 7. 1,4-Palladium-migration of an *o*-halobiaryl with an arylboronic acid.

This indicated a clear preference for palladium-migration from the phenyl ring to the indole ring.[25] Under non-migration conditions[26] adduct **33** is obtained exclusively in 79% yield when **34** is allowed to react with boronic acid **31**. Apparently, palladium migration could be activated or suppressed by manipulation of the reaction conditions.

Systematic investigations of potential racemizations in aryl-aryl Suzuki couplings were disclosed by Williams, Giralt and co-workers.[27] The authors focused on a model reaction where the aryl halide coupling partner was a racemizeable probe molecule **37** and a simple arylboronic acid (**13**, **35**, **36**) as its counterpart (Scheme 8).[28,29] The authors were interested in employing the indolyl boronic acids in particular because the indolylphenylglycines **38-40** produced are models of the biaryl bisamino acids found in the chloropeptins.[30] In the presence of $Pd(PPh_3)_4$ as catalyst, all couplings were carried out in a mixture of toluene-MeOH-H_2O. Using Na_2CO_3 (1.5 equiv) as base in couplings between **13**, **35**, **36** and hydroxyphenylglycine **37**, the corresponding biaryls **38-40** are produced in 85%, 68%, and 77% yield, respectively. In the case of compound **38** they indicated that 29% of the enantiomer had been produced, analyzed by HPLC. Changing the base to $(CH_2COONa)_2$ the yields dropped to 52%, 46%, and 42% but led to optically pure compounds. As a non-typical base for Suzuki-Miyaura coupling reactions, $(CH_2COONa)_2$ could be an excellent test case in screening reactions for racemisation of sensitive substrates.



13 indol-5-yl boronic acid
35 indol-6-yl boronic acid
36 indol-7-yl boronic acid

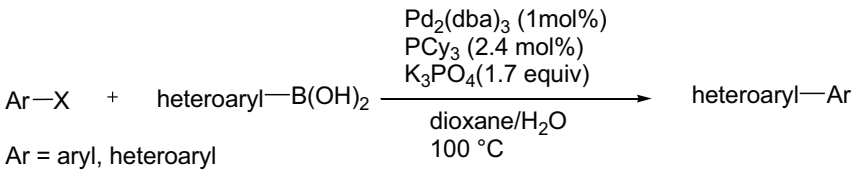
37

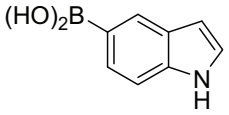
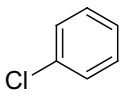
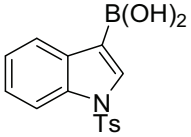
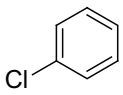
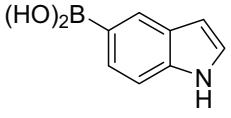
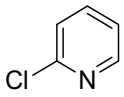
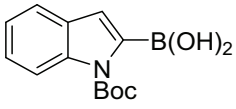
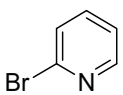
38 indol-5-yl (85%, *52%*)
39 indol-6-yl (68%, *46%*)
40 indol-7-yl (77%, *42%*)

Scheme 8. Suzuki-Miyaura coupling reaction of a racemic molecule and indole-5 (6 or 7)-yl boronic acid.

A wide-ranging study for Suzuki reaction of nitrogen-containing cross-coupling partners has been performed by Fu and co-workers.[31] The authors reported on a new catalyst system that achieved Suzuki-Miyaura cross-couplings of an array of nitrogen-containing boronic acids and aryl halides. The presence of amino groups and nitrogen heterocycles, which are pervasive in medicinal chemistry, led often to lower reactivity in coupling reactions. For that reason the development of a general method for substrates including nitrogen heterocycles[32] continues to be an important issue. Table 2 shows the general method with one single procedure for all indole examples. In all cases under an argon atmosphere the heteroarylboronic acid, $Pd_2(dba)_3$ and PCy_3 were added to a Schlenk flask and dissolved in dioxane. Finally the (hetero)aryl halide and aqueous K_3PO_4 were added. After 18 h at 100 °C the coupling products were isolated in good yields. Thereby the indole was always posed as the boronic acid and led to interesting new indole structures, even with unprotected nitrogen.[33] This seems to be an efficient method and was used with inactivated aryl chlorides as well.

Table 2. Suzuki-Miyaura cross-couplings of heteroarylboronic acids with inactivated aryl halides.

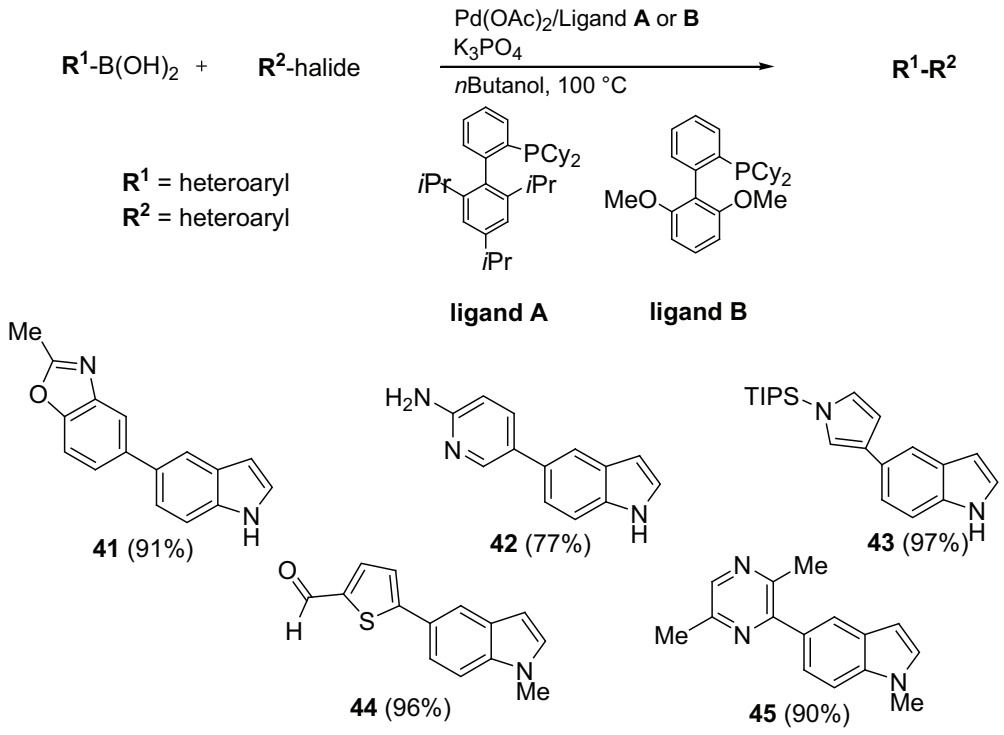


Entry	Heteroaryl boronic acid	Ar-X	Yield [%][a]
1			78
2			85
3			89
4			30[b]

[a] Isolated yield. [b] Boc-protecting group was removed during the Suzuki reaction.

Buchwald and co-workers developed a similar access to heteroaryl compounds via Suzuki-Miyaura reaction.[34] They reported on active catalysts composed of palladium and dialkylbiphenylphosphino ligands **A** or **B** as a general system for the Suzuki reaction of challenging heterocyclic substrates.

As shown in Scheme 9 an excess of indole boronic acid in the case of **41**, **42**, **44** and **45** reacted with various heteroaryl halide in the presence of $Pd(OAc)_2$ and K_3PO_4 in *n*-butanol (*s*-butanol for **45**) at 100 °C (**43**, **44**) or at 120 °C (**41**, **42**, **45**) to give the coupling products in high yields. In the case of **43** the indole was used as the heteroaryl halide component and $Pd_2(dba)_3$ instead of $Pd(OAc)_2$. Unprotected amino groups are traditionally problematical in cross-coupling reactions. The free NH_2-group retards the catalytical cycle by binding to the metal center. Therefore the basicity of the aminoheteroaryl moiety should directly associate to the efficacy of the palladium-catalyzed process.[33a, 35] For the success of the transformation previous article reported that it is essential to protect the NH_2-group in one hand or the need of chelating ligands to prevent competitive binding of the substrate on the other hand.[36] This protocol presented a highly stable and active palladium-catalyst system for the Suzuki-Miyaura coupling of pyridine, pyrrole, and indole boronic acids/esters with non chelating ligands.

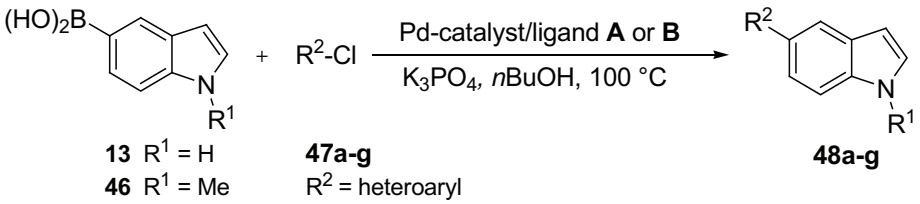


Scheme 9. Suzuki-Miyaura coupling of indoles.

Further work applying the same catalytic system to a wider array of heteroaryl substrates was published one year later by the same workers.[37]
Buchwald and co-workers used the same reaction conditions for various indole coupling products. Indole-derived boronic acids were investigated by several groups,[38] but only a few protocols considered the cross coupling of heteroaryl chlorides with these substrates.[31,34]

A wide variety of heterobiaryls in good to excellent yields were developed by the authors (Table 3). Activated heteroaryl chlorides were successfully coupled with indol-5-yl boronic acids by utilization of the palladium-catalyst system. *N*-Methyl-5-indolyl boronic acid **46** smoothly reacted with 3-chloro-2,5-dimethylpyrazine, 3-chloropyridine and 5-chloro-2-thiophenecarb-aldehyde in 90%, 77% and, 96% yield, respectively (Table 3, entries 1-3) in the presence of $Pd(OAc)_2$ (2 mol%, 0.25 mol% for entry 3) and ligand **A** (see Scheme 9). The reaction mixture was solved in *s*-butanol and heated up to 100 °C for 10-18 h. Indol-5-yl boronic acid **13** was converted with inactivated heteroaryl chlorides **47d-g** (Table 3, entries 4-7) and led to desired biaryls **48d-g** in 71-91% yield. However, for reaction completion it was necessary to increase the reaction temperature to 120 °C in the presence of 2 mol% $Pd_2(dba)_3$ and ligand **B** (see Scheme 9) in *n*-butanol. This method presented an efficient Suzuki-Miyaura reaction of indole boronic acids with heteroaryl chlorides.

Table 3. Suzuki-Miyaura reaction of indole boronic acids.



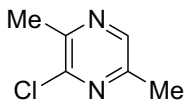
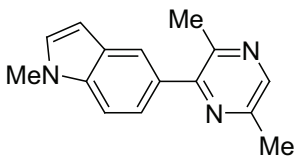
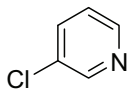
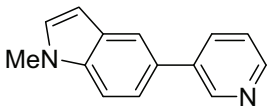
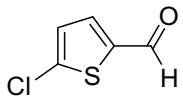
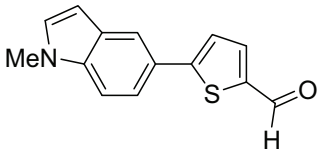
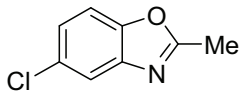
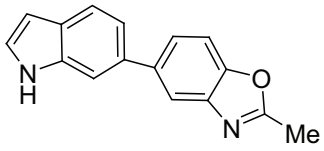
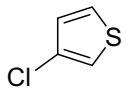
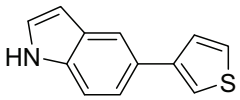
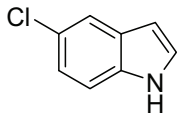
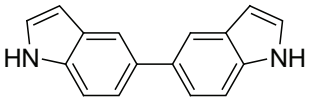
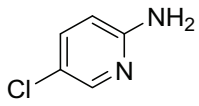
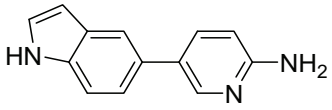
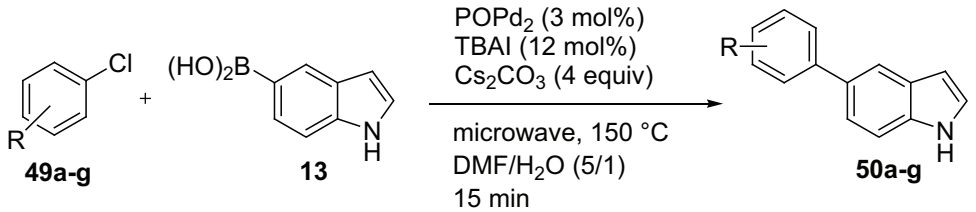
Entry	Ar-Cl **47**	Ligand	Product **48**	Yield[%]
1	**a** 	**A**		90

Table 3. Suzuki-Miyaura reaction of indole boronic acids, continued.

Entry		Ar-Cl **47**	Ligand	Product **48**	Yield[%]
2	**b**		**A**		77
3	**c**		**A**		96
4	**d**		**B**		91
5	**e**		**B**		90
6	**f**		**B**		71
7	**g**		**B**		77

Another catalyst system for palladium cross-coupling was published by Yu and colleagues.[39] The authors developed a microwave promoted Suzuki coupling reaction of aryl chlorides and boronic acids in an aqueous media in the presence of $POPd_2$[40] shown in Scheme 10. Microwave irradiation has been reported to promote metal-mediated reactions like Suzuki-Miyaura cross-coupling.[41] They chose an aqueous solvent system (DMF/H_2O, 5:1) based on Leadbeater's work.[42] The use of TBAI as an additive was beneficial in this mixed solvent system, similar to previous reports employing neat water as the solvent.[43] After optimization of the initial reaction conditions by varying temperature, ratio of reactants, and percentage of catalysts the method was applied to the synthesis of 5-arylindoles **50a-g** (Scheme 10). Different aryl chlorides **49a-g** were converted with indol-5-yl boronic acid **13** via palladium-catalyzed cross-coupling under special conditions, mentioned before, and resulted the desired compounds in good yields (61-76%).

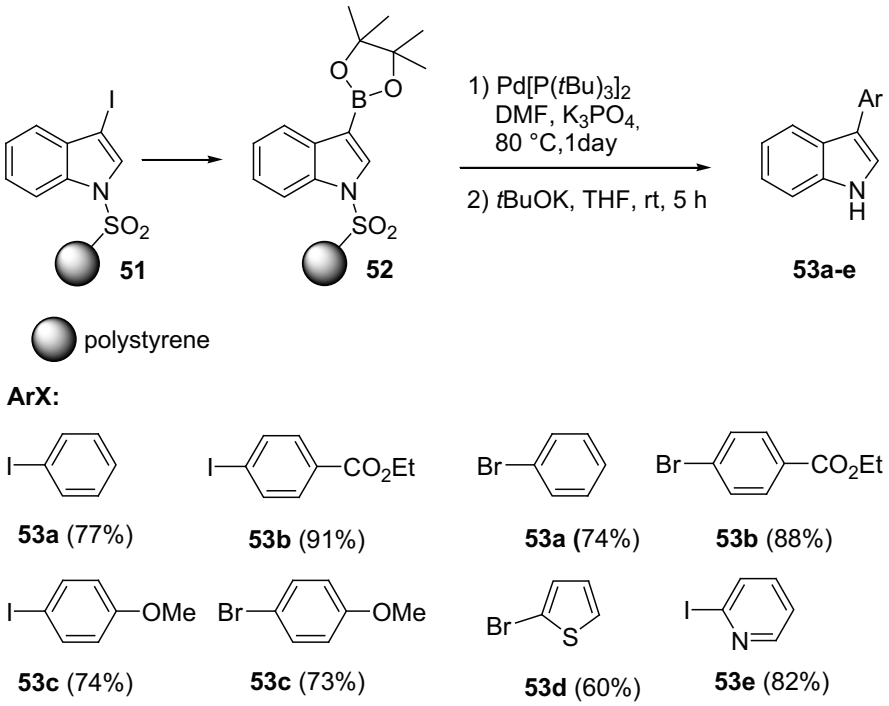


50	a	b	c	d	e	f	g
R:	H	4-OMe	4-F	4-Me	2-Me	4-CF_3	4-CN
Yield [%]	61	72	76	71	68	64	75

Scheme 10. Palladium-catalyzed Suzuki-Miyaura reaction of indol-5-yl boronic acid.

The next example investigated the synthesis of indoles via palladium-catalyzed Suzuki-Miyaura reaction on a polystyrene solid phase. Combining solid phase synthesis with high throughput screening has made a significant contribution for lead discoveries and optimization in pharmaceutical research. For producing combinatorial libraries, solid phase synthesis is regarded as a very efficient method.[44] Suzuki reactions have been already applied to solid phase synthesis but a limited number of examples were reported for the coupling reaction of immobilized arylmetals with free aryl halides in solution.[45] T. Kasahara and Y. Kondo found a method where immobilized 3-pinacol-substituted indole reacted with different aryl halides under Suzuki standard conditions.[46] The paper describes the preparation of immobilized indolylboron and the subsequent arylation using palladium-catalyst (Scheme 11). The immobilized 3-iodoindole **51** was easily prepared from indole via iodonation followed by immobilization using chlorosulfonylated polystyrene.

Continued along palladium-catalyzed borylation[47] via Murata's protocol[48] the indolylboron **52** was investigated. Palladium-catalyzed cross-coupling was examined subsequently with $Pd[P(tert\text{-}Bu)_3]_2$ [49] as catalyst and led to the according coupled products **53a-e** in good to very good yields.

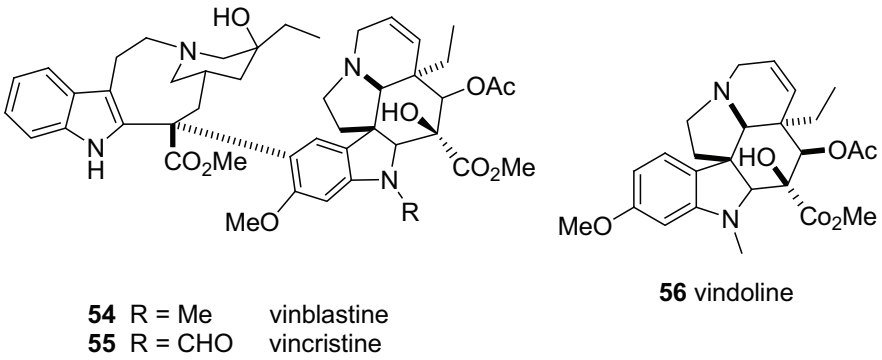


Scheme 11. Palladium-catalyzed Suzuki-Miyaura reaction of immobilized indole.

Because it was difficult to estimate the exact loading value (mmol/g) of the immobilized indolylboron, the three-step yield from **51** was used to evaluate the performance of the coupling reaction with various aryl halides. For the reaction of the heteroaryl halides **53d** and **53e,** better results were obtained by using $Pd(PPh_3)_4$ as catalyst. In general the reaction proceeded smoothly for both electron-rich and -poor aryl halides. Additionally they reported a synthesis with dibromomaleimide under the same conditions.

The bisindolylmaleimide subunit is present in numerous biologically active metabolites including staurosporine and rebeccamycin.[50] Vinblastine **54** and vincristine **55** are two bisindole alkaloid natural products as well. Both possesses considerable amitotic carcinomas and thus have found use in the treatment for various carcinomas, particularly childhood leukemia and Hodgkin's disease.[51] The following study led to the preparation of a number of structurally novel vindolin analogues **58a-j** and opened also the door to new strategies for the synthesis of vinblastine, vincristine, and related anti-cancer agents.[52]

The authors described a general protocol for the rapid construction of C-15-substituted analogues of vindoline **56** using palladium cross-coupling reactions (Figure 3, Table 4).



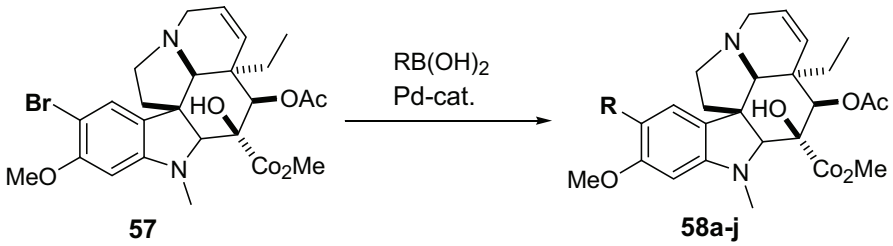
54 R = Me vinblastine
55 R = CHO vincristine

56 vindoline

Figure 3. Vinblastine, vincristine and vindoline.

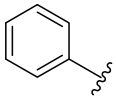
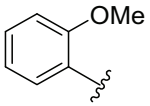
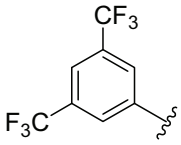
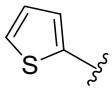
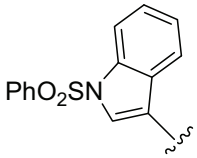
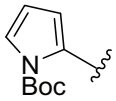
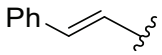
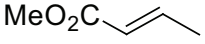
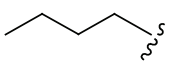
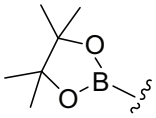
The conversion of vindoline **56** (Figure 3) to 15-bromovindoline **57** (Table 4) was proved eventfully and gave nearly quantitative yield. The cross-coupling afterwards of bromovindoline **57** with a broad range of boronic acids (Table 4) led to biaryl products **58a-j** in good yields (Table 4, entries 1-6). The ability to use heteroaryl boronic acids allowed the access to a wide range of arylated vindoline analogues. The introduction of functionality on these partners, which mimic the "upper" portion of vinoblastine, permitted also the identification of new bioactive analogues of this important drug. Vinylboronic acids were less effective coupling partners, giving the corresponding products in moderate to low yields. The commercially available Xphos-ligand was highly effective[53] and accepted also couplings with an alkylboronic acid (Table 4, entry 13).

Table 4. Suzuki-Miyaura couplings of bromovindoline.



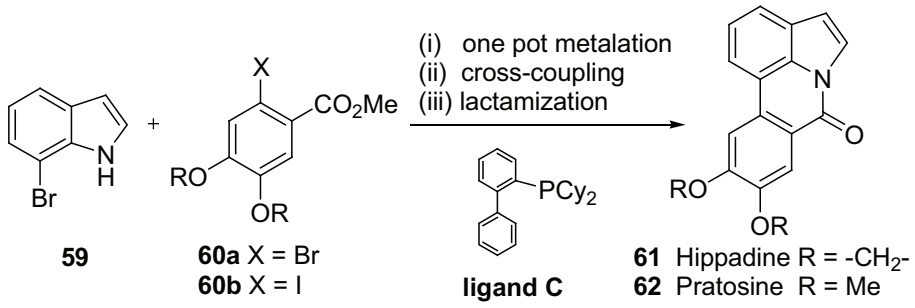
57 **58a-j**

Table 4. Suzuki-Miyaura couplings of bromovindoline, continued.

Entry	Conditions	R	**58**	Yield [%]
1	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 1 h		**a**	75
2	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 2 h		**b**	59
3	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 14 h		**c**	77
4	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 20 h		**d**	38
5	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 20 h		**e**	35
6	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 19 h		**f**	45
7	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 18 h			49
8	$Pd(OAc)_2$, K_2CO_3, DPEphos, $PhCH_3$, 16 h		**g**	0
9	$Pd(OAc)_2$, K_2CO_3, DPEphos, $PhCH_3$, 16 h			10
10	$Pd(OAc)_2$, K_2CO_3, X-Phos, $PhCH_3$, 16 h			75
11	$Pd(PPh_3)_4$, K_2CO_3, DME-H_2O, 16 h		**h**	30
12	$Pd(OAc)_2$, K_2CO_3, X-Phos, $PhCH_3$, 18 h			67
13	$Pd(OAc)_2$, K_2CO_3, X-Phos, $PhCH_3$, 18 h		**i**	52
14	$Pd(dppf)Cl_2$, KOAc, DMF, 16 h		**j**	64

The conversion of bromovindoline **57** with pinacol boronate (Table 4, entry 14) is particularly interesting. With the availability of vindoline boronate, it should be possible to use a vast array of commercially available aryl and vinyl halides to prepare innumerable analogues of vindoline.

Indole alkaloids containing a pyrrolophenanthridinone core have been the subject of many synthetic studies due to their interesting biological activities.[54] This family of alkaloids is exemplified by hippadine **61** and pratosine **62** (Scheme 12).



Scheme 12. General reaction sequence to indole alkaloids.

Previous synthesis of hippadine **61** required a series of additional synthetic transformation either before or after the construction of the ring system. The total synthesis of hippadine by a tandem metalation/cross-coupling/lactamization strategy starting from 7-bromoindole **59** was investigated by Tønder and colleagues.[55] As shown in Scheme 12, the pyrrolophenanthridinone ring system was formed by a series of steps, (i) metalation, of either two coupling partners **59** or **60a**, **60b**, followed by (ii) a transition-metal-catalyzed cross-coupling, and finally a base-mediated lactamization. Inspired by an elegant intermolecular tandem palladium-catalyzed Suzuki-Miyaura coupling[56] and the corresponding intramolecular Stille variant[57], the metalation of 7-bromoindole **59** was investigated. It was not possible to introduce zinc, magnesium or tin into the indole 7-position. They assumed that the unprotected indole nitrogen was responsible for the problems so the magnesiation and stannylation were tested with benzyl-protected 7-bromoindole without success again.

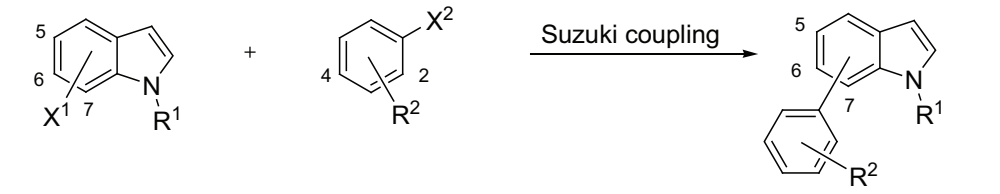
Table 5. Tandem Metalation/Cross-Coupling/Lactamization.

Entry	Component I/II	Reaction Conditions	Yield [%]
1	**59**/**60a**	1. $Pd(OAc)_2$ (5%), **C** (20%), Et_3N (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min 2. H_2O, **60a**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 4 h	67
2	**59**/**60a**	1. $Pd(OAc)_2$ (5%), **C** (20%), Et_3N (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min 2. H_2O, **60a**, CsF (3 equiv), 80 °C, 4 h	64
3	**60a**/**59**	1. $Pd(OAc)_2$ (5%), **C** (20%), Et_3N (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min 2. H_2O, **59**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 4 h	15
4	**59**/**60b**	1. $Pd(OAc)_2$ (5%), **C** (20%), Et_3N (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min 2. H_2O, **60b**, CsF (3 equiv), 80 °C, 4 h	74

In earlier reports[29a,58] boron was inserted in the 7-position of the indole-ring system reflecting that the palladium-catalyzed borylation is the only metalation strategy that prefers electron-rich substrates.[48a,56a] Thus, a maximum of 93% borylation of compound **59** was achieved in 15 min using 1.5 equiv of triethylamine, 2-(dicyclohexylphosphin-(biphenyl)[59] ligand **C** and $Pd(OAc)_2$ at 80 °C. After borylation as the best metalation procedure they went on to see if the one-pot borylation/Suzuki reaction/lactamization would work in the hippadine system. The formation of the hippadine **61** was observed. It was found that under optimized conditions (Table 5, entry 1) hippadine obtained in a yield of 67%. Because of the hydrolysis of the piperonate ester it was suspected that the yield could increase by changing the base to CsF. However, this did not lead to an improvement when aryl bromide was employed (Table 5, entry 2). Comparing the aryl bromide **60a** with the aryl iodide **60b** led to the expected increase in yield for the iodide. CsF as base led to the highest observed yield of hippadine when **60b** was used as component II (Table 5, entry 4). The use of **59** as component I also gave product but in lower yield (Table 5, entry 3).

Yields of Suzuki couplings involving indoles were dependent on upon whether arylboronic acids or arylpinacolboronate esters were used, whether the heterocycle was the aryl halide or the arylboron coupling partner, and whether the heterocycle was protected or not.

Lloyd-Williams, Giralt and co-workers investigated a systematic comparative study of aryl boronic acids and arylboronate esters and their performance (Scheme 13).[60]



X^1 = Br, $B(OH)_2$, Bpin
R^1 = H, Boc, Tos

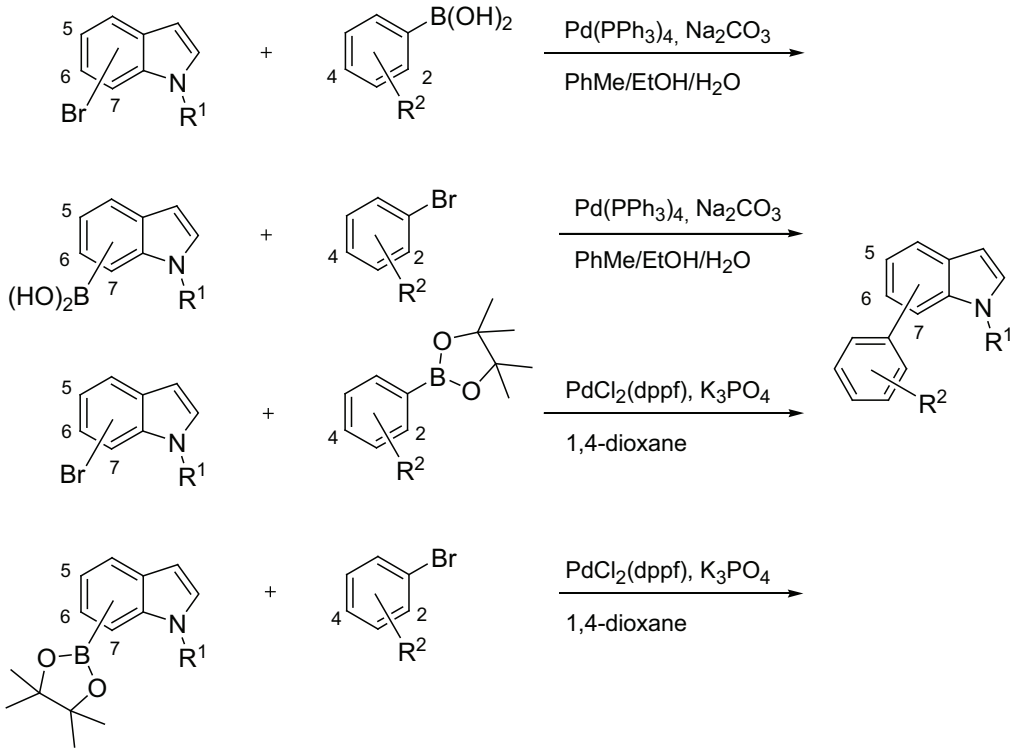
X^2 = Br, $B(OH)_2$, Bpin
R^2 = 4-Me, 4-OMe, 2-Me, 2-OMe

R^1 = H, Boc, Tos
R^2 = 4-Me, 4-OMe, 2-Me, 2-OMe

Scheme 13. General overview about the different coupling partners of the comparative study.

The mechanism by which it proceeded is known to be complex in its details[61], and the oxidative addition,[8c,10b,62] transmetalation,[63] and reductive elimination[64] steps have all been reported to be rate-determining in certain cases. Nevertheless the reaction is not fully understood and much remains to be clarified. All Suzuki chemistry was carried out using aryl bromides under similar reaction conditions in regard to stoichiometry, catalyst batch, solvent composition, concentration, reaction time and temperature. $Pd(PPh_3)_4$ was used as catalyst, Na_2CO_3 as base and a mixture of toluene-EtOH-H_2O as solvent for the series employing arylboronic acids. For the series employing arylboronate esters, $PdCl_2$(dppf) was used as the Pd(0) source, K_3PO_4 as base and 1,4 dioxane as solvent (Scheme 14). These reaction conditions reflect typical current practice for this chemistry. We just summarize this report, because there are numerous of results that would go beyond the scope of this review. In conclusion the authors found out that the yields in Suzuki couplings involving 5-, 6-, or 7- substituted indoles dependent on different factors. Whether arylboronic acids or arylpinacol-boranate esters were used as coupling partners. The arylboronic acids were more reactive and almost furnished biaryls in higher yields, except for Tos-protected indolyl boronic acids, which performed poorly. On the other hand arylpinacolboronate esters were

considerable less reactive. They gave generally lower yields of biaryls, especially in couplings involving unprotected indoles.



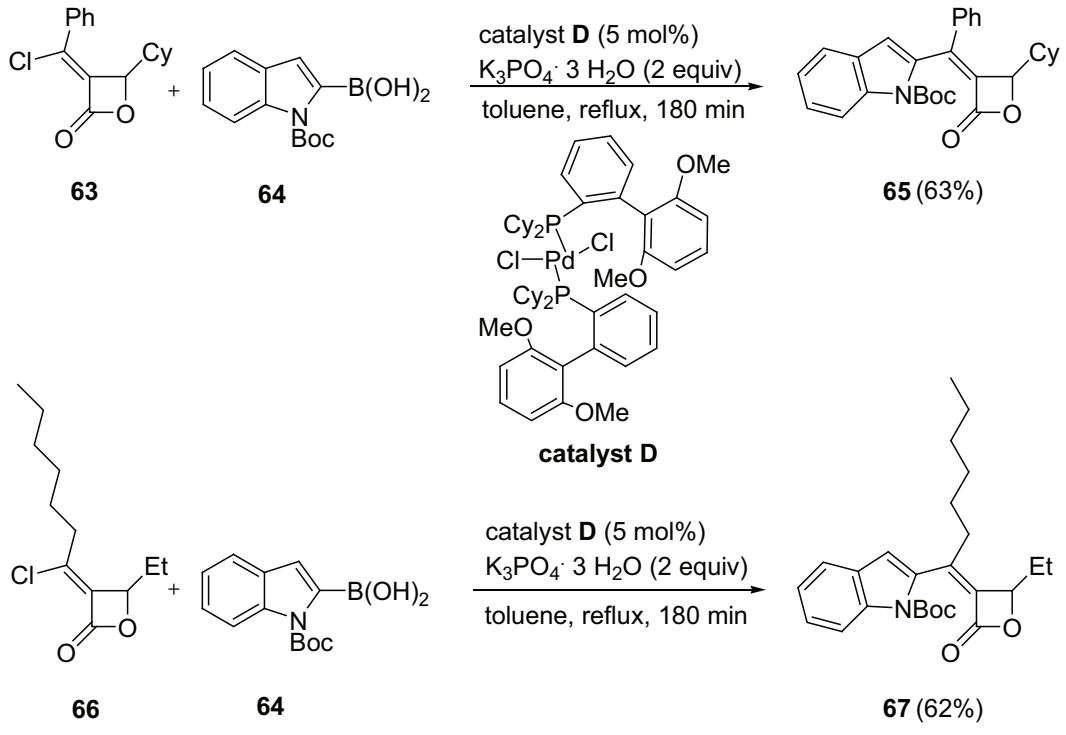
Scheme 14. Suzuki-coupling reaction of different indole boronic acids and -esters.

Only traces of the desired biaryl product were found. Another role played the assignment of the partner. Reactions employing arylboronic acids gave different results when partner roles were swapped. The formation of the biaryl proceeded most efficiently when the heterocycle was the bromoaryl partner. When indolyl boronic acids were coupled with phenylbromides, yield was generally lower. In the case of the arylpinacolboronates the partner role swapping had a limited impact. Similar results were obtained whether the heterocycle was the aryl bromide or the arylboronate ester. The last influence was whether the indole was protected or not. In couplings between phenylbromides and indolyl boronic acids, the influence of the substituent at nitrogen was unimportant. However, it was substantial in couplings between phenyl bromides and indolyl boronic acids where the yields diminished as the electron-withdrawing capacity of the substituent increased. Suzuki couplings employing either phenyl or indole-derived arylpinacolboronate esters gave only traces of biaryl with unprotected indoles. Only the strongly electron-withdrawing Tos-group gave acceptable yields. To ensure optimum

results in Suzuki coupling reactions it seems clear that careful selection of protecting groups and of the arylboron reagent together with a judicious assignment of the component roles are crucial.

A highly efficient Suzuki-Miyaura coupling reaction of α-chloroalkylidene-β-lactones and β-lactams with organoboronic acids was developed by a Hou *et al*..[65]

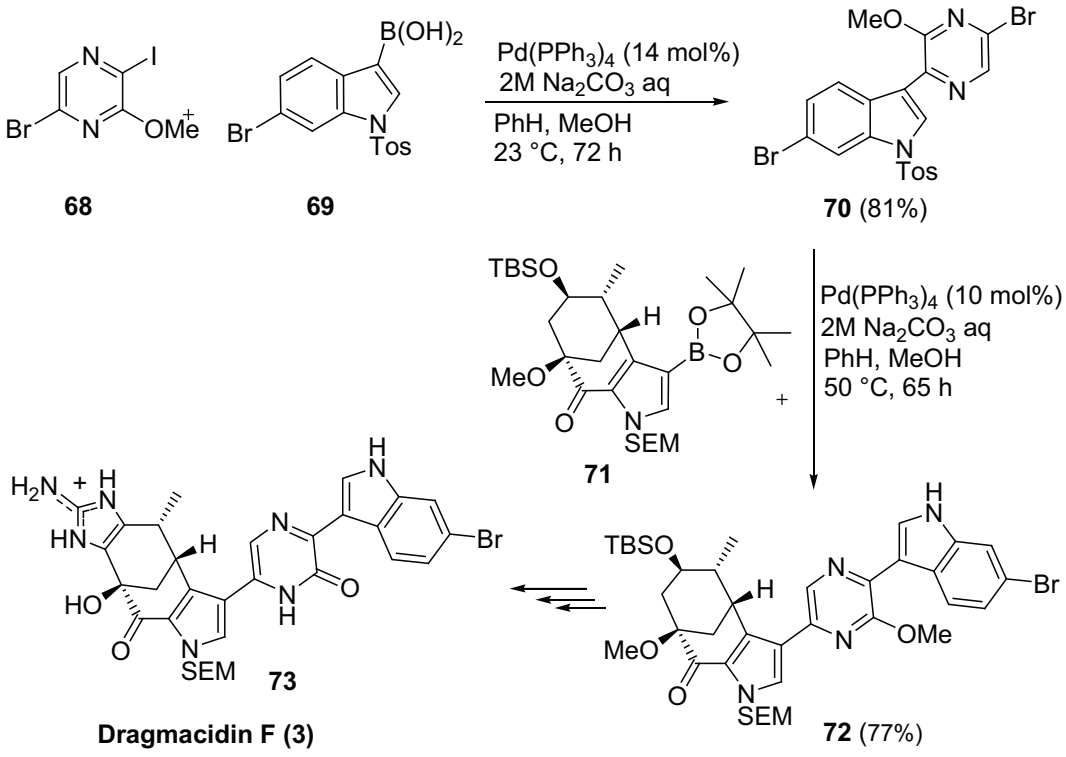
β-Lactones[66] and *β*-lactams[67] are structural units in biologically active natural products. Different boronic acids were coupled with (Z)-*α*-chloroalkylidene-*β*-lactones **63** and **66** to gave products in excellent yields. It was observed that electron-withdrawing groups on the phenyl ring of aromatic boronic acids were more efficient than those bearing a electron-donating group.[68] 2-Indolyl-groups were easily introduced via coupling protocol (Scheme 15). Different effects of base and solvents in these Suzuki-Miyaura reactions were tested but did not mention here. Scheme 15 just shows the coupling reactions with indol-2-yl boronic acid **64** to the corresponding indole lacton products **65** (63%) and **67** (62%) in good yield, in the presence of catalst **D**, $K_3PO_4 \cdot 3H_2O$ as base in toluene under reflux. The catalyst **D** was prepared in advance by stirring 2 equiv of Sphos with $PdCl_2(PhCN)_2$ in benzene for 1 day at room temperature.[32a,69]



Scheme 15. Palladium-catalyzed Suzuki-Miyaura reaction with lacton derivatives.

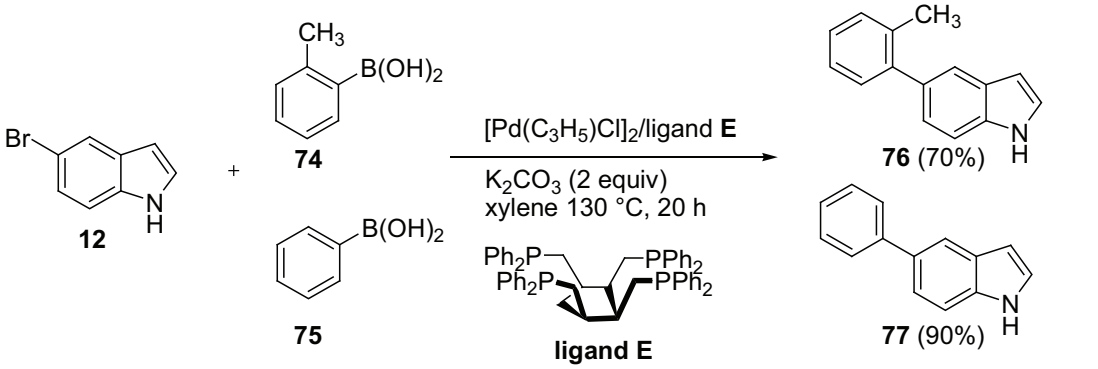
Like indol-2-yl boronic acids also indol-3-yl boronic acids can be very interesting units for organic synthesis. They were successfully used in the total synthesis of the marine alkaloids nortopsentins A-D,[70] in the synthesis of mono- and bis(indolyl)-4-trifluoromethylpyridines,[71] in the construction of the skeleton of dragmacidine D by stepwise cross-coupling reactions,[72] in the synthesis of bisindole alkaloids,[73] and in the preparation of some analogues of camalexin.[74] Dragmacedins belongs to the family of marine alkoloids that possess a variety of interesting structural biological features.[75]

Stoltz and co-workers described a total synthesis of dragmacidine F including two Suzuki-Miyaura coupling key steps.[76] *N*-Tosyl-3-indolyl boronic acid **69**, *N*-SEM-3-indolylboronate **71** were involved in key steps and are shown in Scheme 16. The first coupling step was already investigated in the synthesis of dragmacidin D.[77] The pyrazine derivative **68** was converted with indol-3-yl boronic acid **69** under Suzuki-Miyaura coupling conditions to the desired product **70** in 81% yield. In the critical halogen-selective Suzuki fragment-coupling reaction, pyrroloboronic ester **71** and dibromide **70** reacted under Pd(0) catalysis. Coupling intermediate **72** was obtained under nearly the same conditions in a yield of 77%. Further steps like selective deprotection of silylether and oxidation with Dess-Martin gave finally compound **73**.



Scheme 16. Suzuki-Miyaura coupling key steps in the synthesis of dragmacidin F.

A new system using heteroaryl halides with a range of arylboronic acids with very high substrate/catalyst ratio, was investigated by Santelli and co-workers.[78] Supported by a tetraphosphine/palladium catalyst, several heteroaromatic substrates were coupled with a variety of arylboronic acids. Substrates like pyridines, quinolines, thiophenes, pyrimidines, furane and indole have been applied. Phosphine ligands on complexes have an important influence on the stability of the catalyst and on the rate of catalyst reactions.[79] The authors prepared a new tetrapodal[80] phosphine ligand, Tedicyp 1 (Scheme 17, ligand **E**)[81] binding four diphenylphosphinoalkyl groups stereo-specifically to the same face of the cyclopentane. Based on previous results, xylene was chosen as solvent and potassium carbonate as base. All reactions were generally performed under argon in the presence of a 1/2 ratio of $[Pd(C_3H_5)Cl]_2$/**E** as catalyst. In order to obtain high ratio between substrate and catalyst, the reactions were performed at 130 °C.



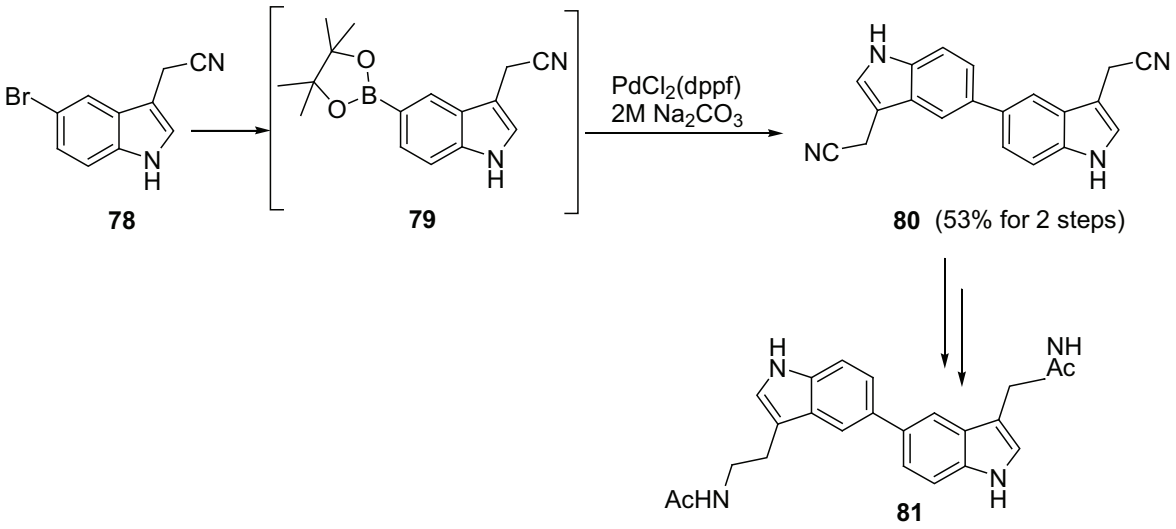
	76	**77**
ratio substrate/catalyst	100 000	100 000
TON	70 000	90 000

Scheme 17. Suzuki-Miyaura-coupling of 5-bromoindole.

Halo-substituted indoles that could potentially bind palladium through nitrogen or sulfur were suitable substrates for Suzuki-Miyaura reactions. Ton's of 90 000 were obtained for Suzuki-Miyaura coupling of 5-bromoindole **12** with phenyl boronic acids **74** and **75**. With some substrates only 0.00001% catalyst was necessary for the reaction. Only traces of (<1) of homocoupling products were observed with this catalyst. It is an economically attractive procedure and because of the low catalyst loading increasingly important for industrial processes.

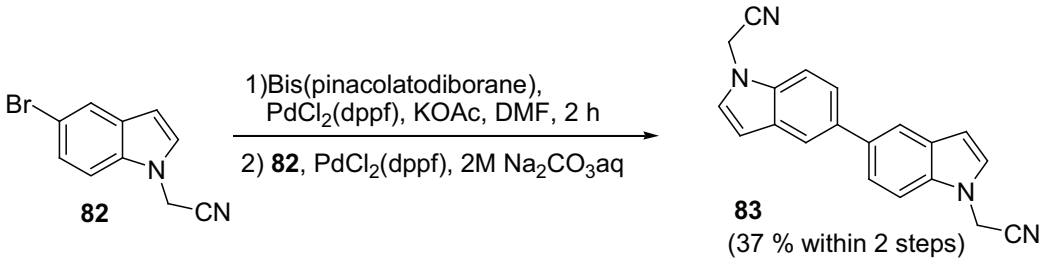
Indeed, industrially interesting as well is the synthesis of new melatonin analogues via Suzuki homocoupling. Melatonin plays a major role in the regulation of seasonal cycles and the control of circadian rhythms[82] and has been the focus of clinical interests. The selective melatonin synthesis is still a challenge.

Viaud-Massuard and co-workers concentrated thereby on developing a catalytic approach to dimers of indoles.[83] The homocoupling of (5-bromo-1*H*-indol-3-yl)acetonitrile **78** using borane **79** generated in situ, gave the corresponding dimer **80** in 53% yield. Compound **80** was finally converted to the final, compound **81** after hydrogenation over Raney nickel and concomitant N-acetylation (Scheme 18).



Scheme 18. Palladium-catalyzed homocoupling of (5-bromo-1*H*-indol-3-yl)acetonitrile.

In a similar way described below, (5-bromoindo-1-yl)acetonitrile **82** was coupled with the according borane to the dimer **83** within a 2-step yield of 37% in the presence of $PdCl_2$(dppf) (Scheme 19). The use of organoboron compounds is valued because the inorganic by-products of the reactions are nontoxic and can be readily removed by simple workup procedures. Many parameters as shown above in several examples can be change to success in the Suzuki-Miyaura reaction. The metal/ligand systems that facilitate the cross-coupling with different electrophiles have been the most extensively studied.

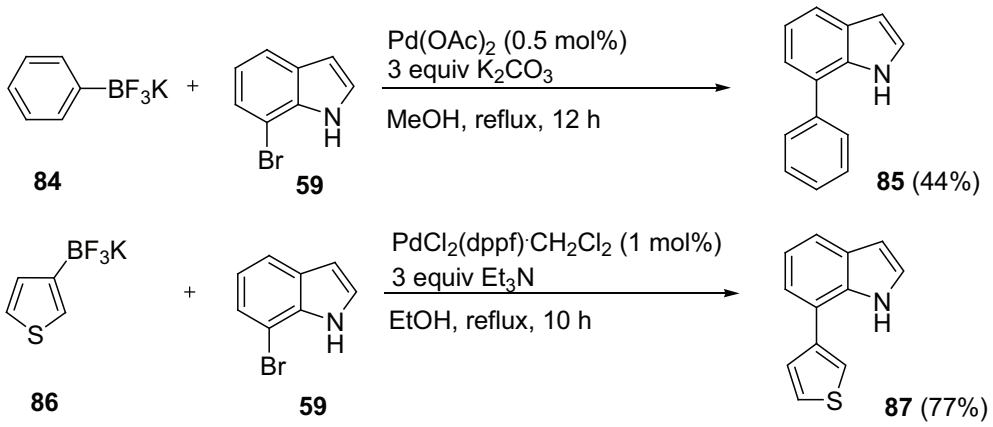


Scheme 19. Palladium-catalyzed homocoupling of (5-bromoindo-1-yl)acetonitrile.

Different palladium sources in the absence of ligands[84] to very elaborate catalyst/ligand systems[85] have been applied. The development of several air-stable catalysts has been reported to improve the catalyst turnover, to achieve the coupling of less reactive electrophiles or to permit coupling with hindered substrates.[86] The use of alternative organoborone coupling partners is an underdeveloped area. The boronic acids are subject to cyclic trimerization and the resulting uncertainties in stoichiometry require an excess of these compounds in coupling reactions. The use of boronic esters can solve that problem. Then again, there is a lack of atom economy and additional purification steps, especially when catechol and pinacol are used as the alcohol moiety. One alternative to boron reagents are potassium trifluoroborate derivatives. These are monomeric solids, easily prepared from organoboronic acids or esters by treatment with an aqueous solution of KHF_2.[87] They are in general air stable and environmentally friendly. No protecting groups are necessary bearing ketones, alcohols, aldehyds, or carboxylic acids. Finally the trifluoroborate system appeared less subject to protodeboronation than other boron derivatives.

Molander and Biolatto investigated palladium-catalyzed Suzuki-Miyaura coupling reactions of potassium aryl- and heteroaryltrifluoroborates.[88] The authors described that generally the trifluoroborate coupling system proved to be more reactive than the corresponding boronic acids or esters under Suzuki standard reaction conditions. They demonstrated many successful ligandless couplings of reagents bearing a variety of functional groups. All reactions were carried out in air with no lost in yield. In general a lower catalyst loading, lower temperatures and shorter reaction times were utilized. Another advantage was the ability to use electron-deficient arylborons routinely. Following Scheme 20 shows the cross-

coupling reactions of potassium phenyltrifluoroborate **84** and potassium 3-thiophenetrifluoroborate **86** with 7-bromoindole **59** as the heteroaryl halide.

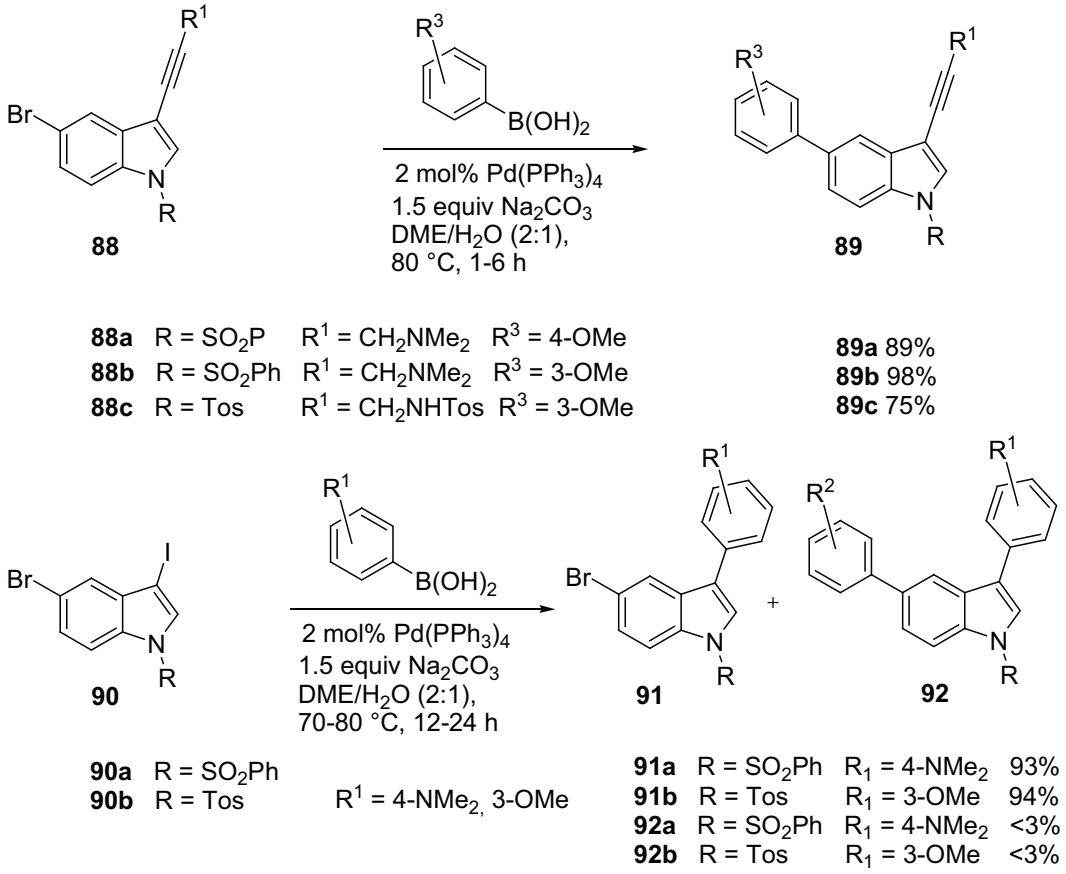


Scheme 20. Cross-coupling reactions of potassium phenyl-trifluoroborate and potassium 3-thiophenetrifluoro-borate with 7-bromoindole.

The reaction with the unprotected 7-bromoindole **59** under ligandless conditions produced partial conversion of the heteroaryl bromide and led to an isolated product yield of 44%. They assumed that under the basic conditions may form the nitrogen anion. This did not only increase the electron density of the indole, but also may increase the complexation to the catalyst. The complexation reduced its activity in the catalytic cycle.[89] Interestingly the reaction of 3-thiophenetrifluoroborate **86** with the unprotected 7-bromoindole **59** produced the corresponding coupling product **87** in a high yield. Under this basic conditions the unprotected nitrogen atom did not compete with the dppf-ligand for complexation of the catalyst.

Biaryls are found in many compounds and are of pharmaceutical interests. Many recently reported drug candidates and analogues have been synthesized via Suzuki-Miyaura coupling reactions. The next example deals with potential 5-HT receptor ligands. The function of many 5-HT receptors can be unequivocally associated with specific physiological responses, ranging from modulation of neuronal activities, transmitter releases to behavioural changes. The neurotransmitter serotonin (5-hydroxytryptamine) mediates a wide range of physiological functions by interacting with multiple receptors.[90] The design of selective ligands for receptors shall offer much promise for future drug design. As part of a program on synthesis of functionalized indoles and carbazoles via

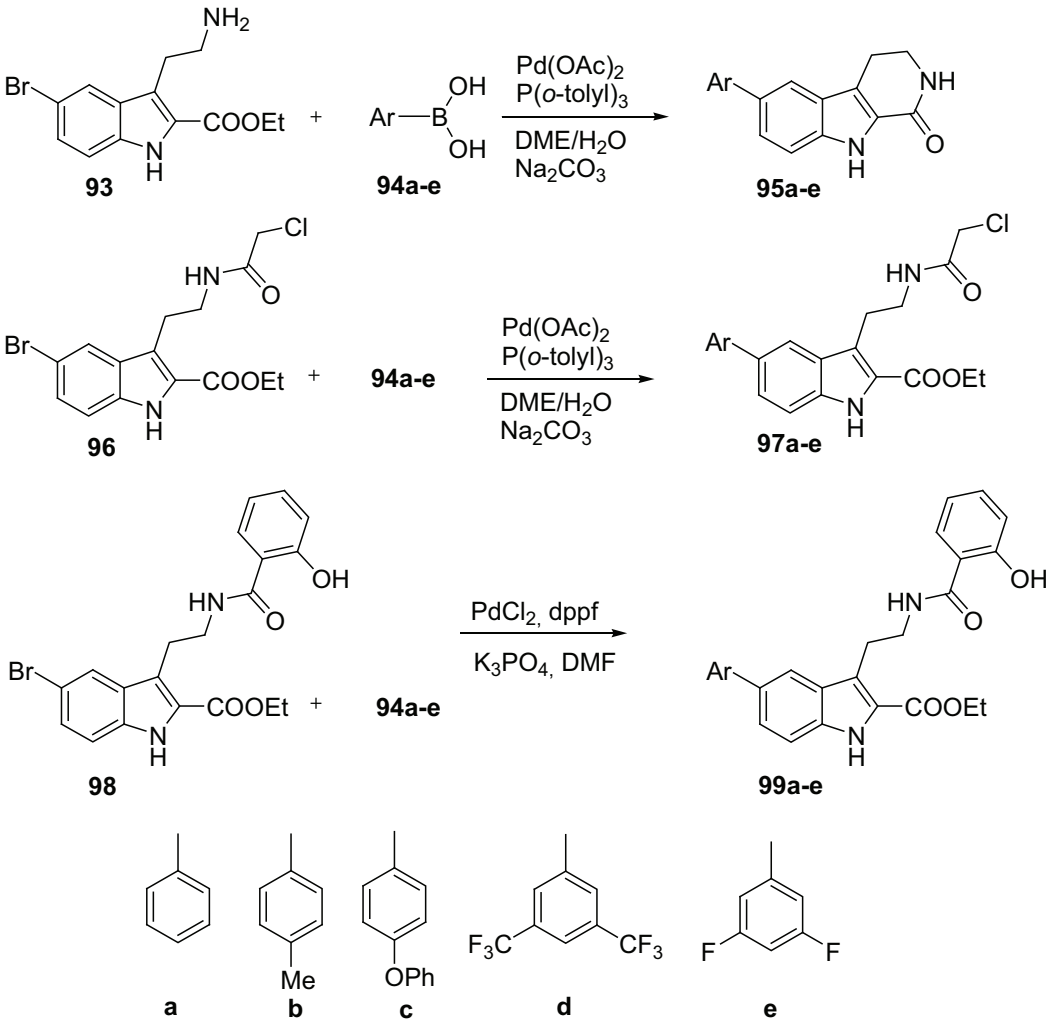
transition-metal-catalyzed cross-coupling reactions Witulski and co-workers reported about Suzuki-Miyaura reactions to obtain a large range of new functionalized indoles which are potential 5-HT receptor ligands (Scheme 21).[91] 3,5-Bis-halogenated indoles **88** and **90** as molecular scaffolds were investigated via palladium-catalyzed cross-coupling reactions. For this purpose the 3-alkynyl-5-bromoindoles **88a-c**, achieved with Sonogashira coupling, were subjected to Suzuki-Miyaura coupling reactions with 3- or 4-methoxybenzeneboronic acids and led to new substituted indoles **89a-c** in excellent yields (Scheme 21). The Suzuki reaction between 5-bromo-3-iodoindole **90a,b** and 3-methoxy-benzeneboronic acid or 4-dimethylaminobenzeneboronic acid after 24 h of heating gave the according new indole derivatives **91a,b** in brilliant yields. The reaction seems to be less selective since some bis-coupling product **92a,b** (3%) was also isolated. They developed a flexible strategy for the design of a new indole library closely related to the structural motif of serotonin. Sequential Sonogashira-Sonogashira, Sonogashira-Suzuki, as well as Suzuki-Sonogashira couplings starting from 5-bromo-3-iodo-indoles and indazoles led to interesting potentially new drugs.



Scheme 21. Suzuki-reaction of functionalized indoles.

Serotonin is the major neurotransmitter in the central nervous system (CNS) which regulates our mood, appetite, sleep, and self control.[92] Thereby tryptamine is the fundamental building block. Due to their remarkable chemical and biological importance, novel tryptamine derivatives are desired products.

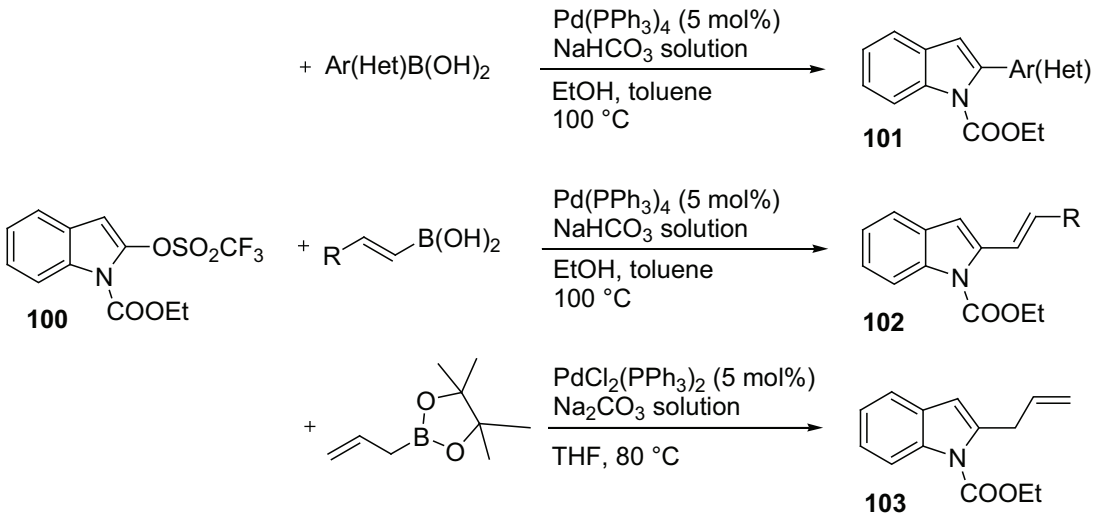
For the preparation of such desired tryptamine derivatives, Novák and co-workers reported on the synthesis of novel tryptamines and β-carboline derivatives via palladium-catalyzed reaction of bromotryptamine with organic boronic acid.[93] Scheme 22 displays the treatment of bromotryptamine **93** and different phenylboronic acids **94a-e** with catalytic amounts of palladium complex $[Pd(OAc)_2[P(o\text{-tolyl})_3]_2]$ (0.05 equiv) and aqueous Na_2CO_3 (2 equiv). Unexpectedly the first examples afforded a tetrahydro-β-carboline structure **95a-e**.



Scheme 22. Palladium-catalyzed reactions of bromotryptamines with organoboronic acids.

The formation of **95a-e** was imagined via two steps: the expected cross coupling reaction, followed by simultaneous intramolecular cyclization. The efficiency of these reactions was dependent on the substituents of the boronic acid. With increasing electron-withdrawing character of the substituent the yields increased substantially (19-42%). In the next two afterimages in Scheme 22, the authors protected the free amino-group of the tryptamine with acylation to avoid the cyclization reaction. The *N*-chloroacetyl derivative **96** was subjected to Suzuki-Miyaura coupling and yielded the tryptamine derivatives **97a-e** in acceptable yields (20-62%). Likewise the 2-hydroxybenzoyl-acylated tryptamine **98** resulted, under Suzuki coupling reaction conditions, new tryptamines derivatives **99a-e** in moderate yields (28-52%). Suzuki-Miyaura reactions are not only possible with indole halides.

Rossi *et al*. developed a method for Suzuki-Miyaura coupling reactions with 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester **100**.[94] In particular, 2-aryl, 2-heteroaryl, 2-allyl, and 2-vinyl indoles **101-103** were prepared in good to excellent yield by palladium-catalyzed reactions of **100** with commercially available boronic acids or boronic ester. Following Scheme 23 shows the different coupling possibilities.



Scheme 23. Suzuki-Miyaura coupling of 2-trifluoromethanesulfonyl-oxyindole-1-carboxylic acid ethyl ester.

Various reactions of indol-2-yl triflate **100** have been reported and account for their effectiveness and synthetic application in palladium-catalyzed Suzuki-Miyaura reaction. Indol-2-yl triflate **100** was synthesized in multigram quantities starting from an inexpensive intermediate. The Indole **100** is a reactive and stable precursor for 2-carbosubstituted indoles thus providing a valuable alternative to previously reported synthetic strategies.

1.3 Heck Coupling Reaction

The Heck reaction has become one of the most fundamental metal-catalyzed C-C bond forming process for the synthesis of complex molecules.[95] The carbopalladation of an alkene by an organopalladium halide is an essential step in organic synthesis. Richard Heck and his group transferred this reaction into a catalytically reaction and started to demonstrate its usefulness as well as its rather broad scope. Therefore the applications range from the preparation of hydrocarbons, novel polymers and dyes to new advanced enantioselective synthesis of natural products and biologically active non-natural compounds. The Heck reaction is one true “power tool” in contemporary organic synthesis and a continuous annual growth in publications of 15% per year, competing favorably with the Diels-Alder reactions (25000 references), olefin metathesis (1500 references), Wittig reaction (15000 references) or Claisen rearrangement (15000 references).[7]

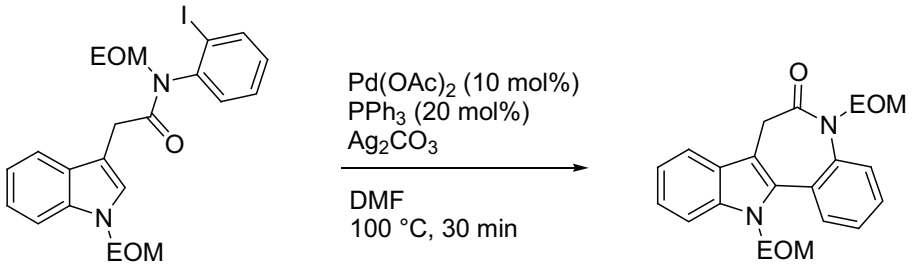
The first step of the mechanism starts with the oxidative addition of a haloalkene or haloarene to the unsaturated palladium(0)complex, generating a σ-alkenyl- or σ-aryl-palladium(II)complex.[96] The complex accepts an alkene molecule in its coordination sphere. If the alkenyl residue and alkene ligand on palladium are in *cis*-orientation, rotation of the alkene can lead to its in plane coordination, and subsequent syn-insertion of the σ-alkenyl- or σ-aryl-palladium bond into the C=C double bond occurs to yield a σ-(β-alkenyl) or σ-(β-aryl)alkylpalladium complex. In the next step β-hydride elimination takes place. The subsequent *syn*-elimination yielding an alkene and a hydridopalladium halide is reversible. Therefore more stable (E)-alkene is generally obtained when the coupling reaction is performed with a terminal alkene. Reductive elimination of HX from the hydridopalladium halide aided by the added base regenerates the active catalyst and completes the catalytic cycle.

This review discusses only the palladium-catalyzed Heck reaction and the intramolecular Heck reaction of indoles.[97]

An application of the intramolecular Heck reaction via palladium coupling is the access to paullone analogues. Paullones[98] are a series of structures from 7,12-

dihydroindolo[3,2-*d*]benzazepin-6(5*H*)-ones, which constitute a class of CDK inhibitors.[99] These cyclin-dependent kinases are a family of serine-threonine kinases that plays a major role in cell cycle division.

Joseph and co-workers developed a new way in synthesis of paullones with palladium-catalyzed intramolecular Heck reaction.[100] The key step via Heck reaction is shown in Scheme 24.

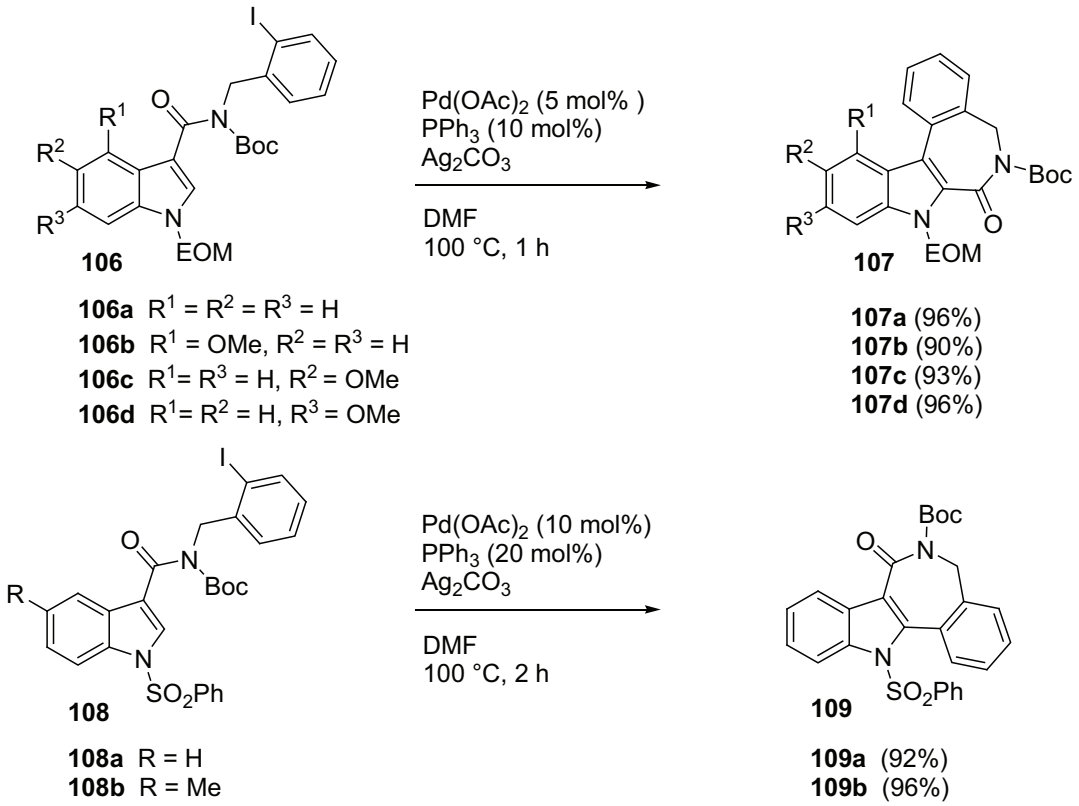


104 **105** (92%)

Scheme 24. Palladium-catalyzed intramolecular Heck reaction as a key step in the synthesis of paullones.

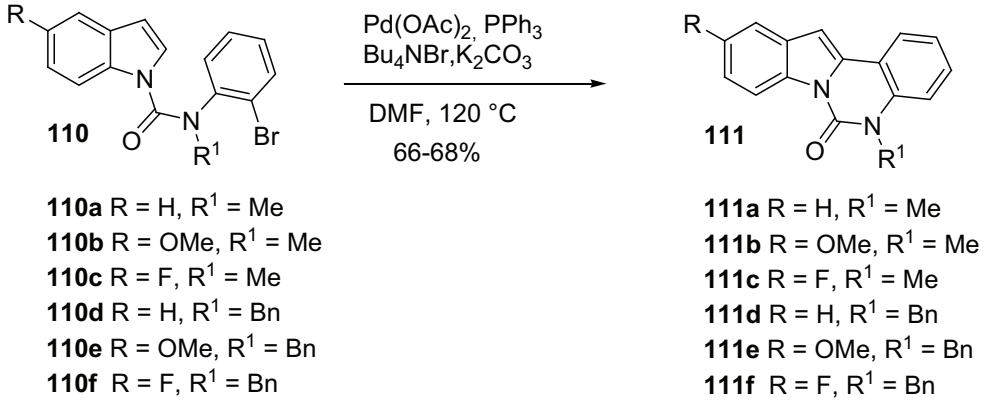
The EOM-protected indole **104** was converted under coupling conditions with $Pd(OAc)_2$ and the bulky phosphane PPh_3 in DMF. The according coupling product **105** was obtained in a yield of 92% in 30 min. Romero-Ortega and co-workers used the same method for the methyl-protected paullone analogue.[101]

Based on the skeleton, Joseph and colleagues investigated the synthesis of latonduine derivatives with the same reaction conditions.[102] They were found inactive in cytotoxicity assays against a panel of human cancer lines and for enzyme inhibition against a panel of protein kinases.[103] The authors developed an efficient synthesis for a new heterocyclic ring-fused benzazepinone scaffold via intramolecular Heck coupling reaction. The coupling reaction was a major step in the total synthesis of paullones and latonduines and led to the coupling products **107a-d** and **109a-b** in excellent yields (Scheme 25).



Scheme 25. Intramolecular Heck coupling reaction to benzazepinone scaffold.

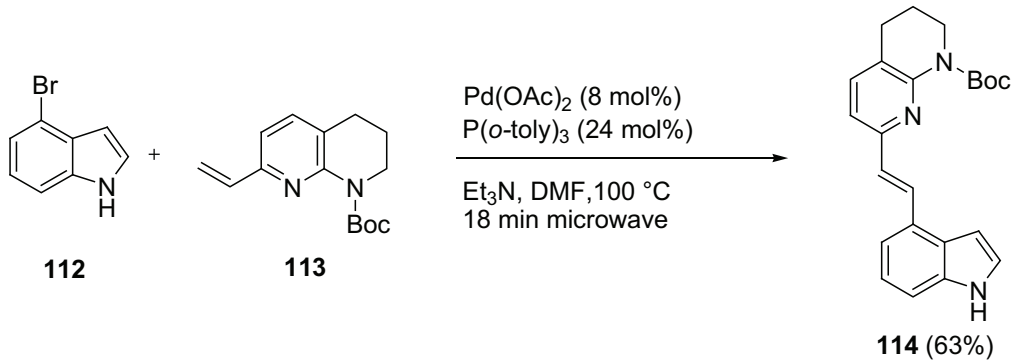
Another system for the synthesis of paullones was described by Bremner and Sengpracha.[104] In a similar way like before, different indole derivatives **110a-f** were converted to the corresponding products **111a-f** in the presence of $Pd(OAc)_2$ and PPh_3 to new paullone analogues (Scheme 26).



Scheme 26. New paullone derivatives via palladium-catalyzed Heck reaction.

Another interesting class of compounds is the short chain 4-substituted class of indoles. The structure is found in many attractive targets like the $\alpha_v\beta_3$ antagonist that belongs to the heterodimeric integrin superfamily. It is known that the transmembrane vitronectin receptor, $\alpha_v\beta_3$ integrin, has recognized as emerging potential therapeutic treatment for various diseases like osteoporosis, arthritis and metastatic cancer.

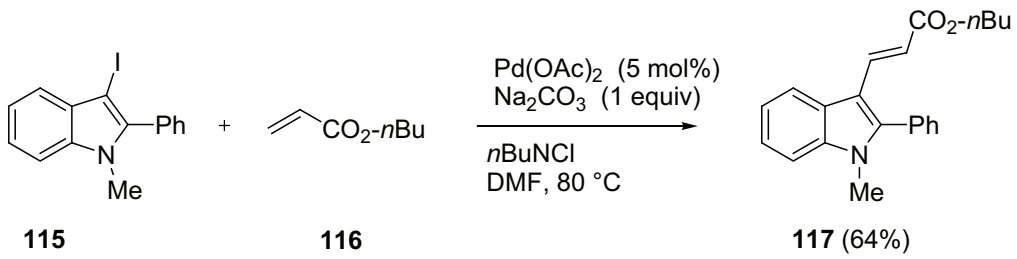
Raboisson and co-workers performed the identification of a novel class of less flexible 1,4-disubstituted indoles with single digit nanomolar binding affinity for $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptors.[105] The key intermediate **114**, exhibit in Scheme 27, was obtained by Heck coupling reaction between the commercially available 4-bromoindole **112** and the Boc-protected 7-vinyl-1,2,3,4-tetrahydronaphthyridine **113**. In the presence of $Pd(OAc)_2$ and tri-(*o*-tolyl)phosphine as ligand, Et_3N as base in DMF, the coupling product resulted in a yield of 63% after purification by column chromatography.



112 **113** **114** (63%)

Scheme 27. Heck coupling reaction between 4-bromoindole and the Boc-protected 7-vinyl-1,2,3,4-tetrahydronaphthyridine.

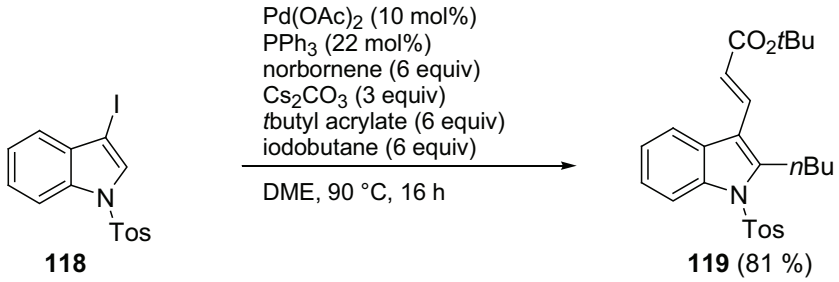
Larock and colleagues investigated the synthesis of 3-iodoindoles via Pd/Cu-catalyzed coupling of *N,N*-dialkyl-2-iodoanilines and terminal alkynes, followed by electrophilic cyclization.[106] The 3-iodoindoles, produced by this chemistry are useful for the synthesis of a wide variety of substituted indoles. They were further functionalized by applying palladium-catalyzed coupling reactions. They found *n*-butyl *E*-3-(1-methyl-2-phenylindole-3-yl)propenoate **117** with an overall yield of 64% (Scheme 28), respectively from *N,N*-dimethyl-*o*-iodoaniline and phenyl acetylene by the two-step coupling/cyclization process, followed by the palladium-catalyzed cross-coupling.



115 **116** **117** (64%)

Scheme 28. Palladium-catalyzed Heck reaction of 3-iodoindole.

Similarly the group around Lautens gave an account of a tandem palladium-catalyzed multicomponent reaction of thiophenes and indoles.[107] The authors constructed tri-substituted thiophenes in good yield by palladium-catalyzed tandem alkylation/alkenylation reaction of 3-iodothiophene. Finally they described one indole example based on their method (Scheme 29). They proposed that Pd(0) inserts into the C-I bond of 3-iodoindole **118** followed by carbopalladation of norbornene. Activation of C-H in 2-position formed the according intermediate. Oxidative addition of the alkyl iodide led to the Pd(IV) species and reductive elimination generated the alkylated indole product. Heck reaction with *tert*-butylacrylate yielded the product **119** in 81%. They assumed that an excess of norbornene is needed to compete with the direct Heck pathway. During their research they observed that the protecting group at the nitrogen is crucial to the efficiency of the reaction. The use of the Me-protected indole resulted only in the direct Heck product.

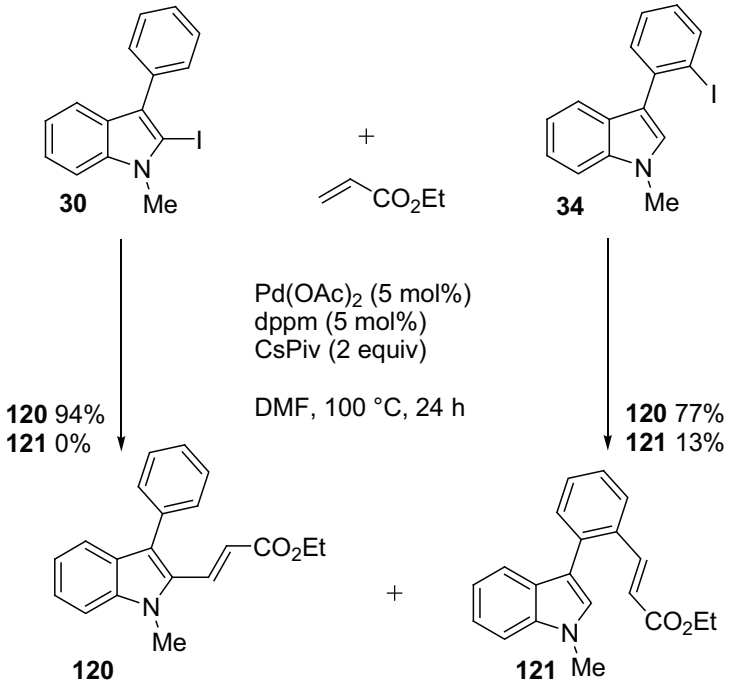


118 **119** (81 %)

Scheme 29. Palladium-catalyzed tandem alkylation/alkenylation reaction of Tos-protected 3-iodoindole.

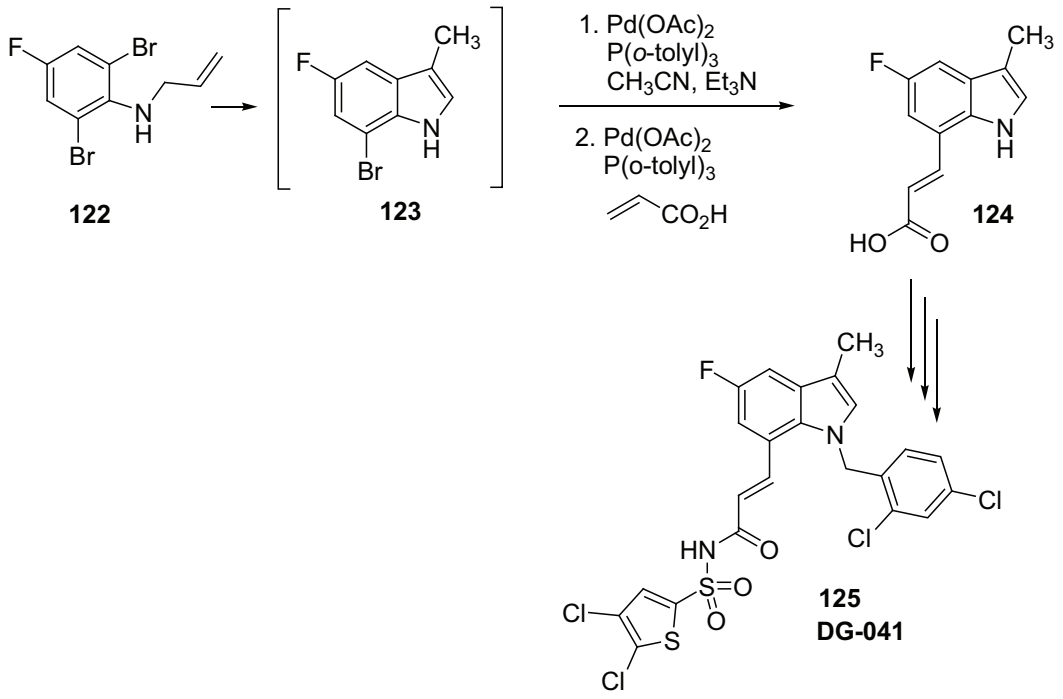
About an aryl-aryl palladium-migration via Heck coupling of *o*-halobiaryls reported Campo *et al.*.[24] They found that, upon carrying out Heck reactions and Suzuki cross-couplings with *o*-halobiaryls under various conditions led to mixtures of the

expected *o*- as well as to the unexpected *o´*-derived Heck and Suzuki products (Scheme 30). Their observations suggested the presence of a 1,4 rearrangement of the palladium moiety between *o*- and *o´*-positions of these biaryls. For a more general understanding of the scope and geniality of the palladium-migration several biaryls have been investigated and illustrated. One example is shown in Scheme 30. Therefore *N*-methylindole analogues **30** and **34** reacted with ethyl acrylate in the presence of $Pd(OAc)_2$. Using the migration conditions compound **30** in attendance of $Pd(OAc)_2$, dppm and CsPiv in DMF at 100 °C produced exclusively *E*-3-(1-methyl-3-phenylindole-2-yl)acrylate **120** in 94% yield in 24 h. By using migration conditions again indole acrylate **120** generated from **34** gave 77% yield. They reported that the 13% yield of indole acrylate **121** resulted of slow palladium equilibration. It might be due to unfavorable steric interactions imposed on the palladium when migrating to the relatively more hindered 2-position of the *N*-methylindole. They postulated that steric hindrance was a significant factor in this palladium-migration chemistry disfavoring sterically congested arylpalladium intermediates.



Scheme 30. Aryl-aryl palladium-migration in Heck coupling of *o*-halobiaryls.

Following Heck reaction is engaged in the development of a scalable process for DG-041 **125**, a potent EP_3 receptor antagonist, via tandem reaction (Scheme 31).[108]

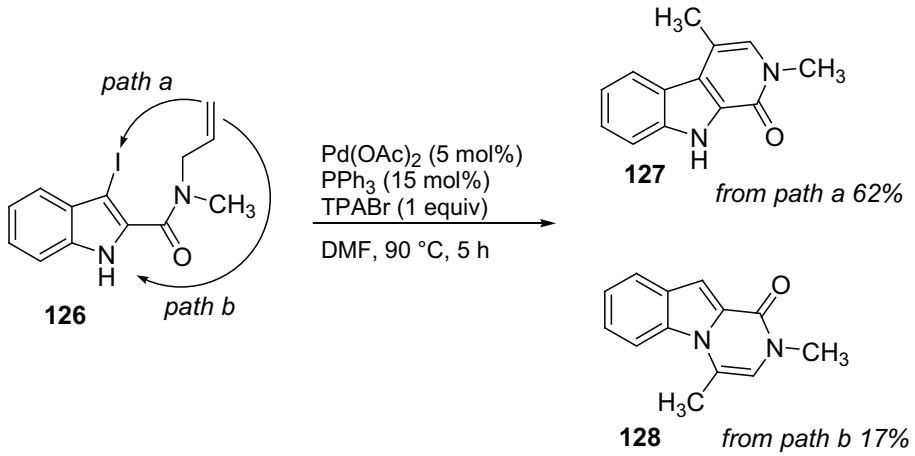


Scheme 31. Synthesis of DG-041, a potent EP_3 receptor antagonist, via tandem Heck reaction.

DG-041 **125** is a small molecule antagonist of the EP_3 receptor for prostaglandin E_2 that is in the clinical development of treatment of peripheral artery disease. The key step in the reaction sequence contains of two sequential Heck reactions. The optimized process led to the development of a four-step sequence involving an intramolecular Heck cyclization followed by an intermolecular Heck coupling. It was performed in one pot and produced the highly substituted indole core **124**. The conversion of compound **122** to the key intermediate **123** in one pot minimized the processing time and the number of unit operations. Treatment of **122** with the palladium/P(*o*-tolyl)$_3$ system in acetonitrile in the presence of Et_3N, catalyzed the transformation to intermediate **123** within 3 h under reflux. Upon completion of conversion, the reaction mixture was recharged with additional palladium/P(*o*-tolyl)$_3$ followed by acrylic acid. The isolation of product **124** was facilitated by the discovery that it crystallized readily from the reaction mixture upon dilution with methyl-*tert*-butyl ether as its Et_3N-salt with quantities of Et_3N-

hydobromide (salt mixture 87% yield). The salt mixture was dissolved in water and acidification induced precipitation of **124** in excellent purity (67%).

Studies on reactivity of indole derivatives in the intramolecular Heck reaction were planned by the group of Beccalli.[109] The authors reported about a synthetic route to β- and γ- carbolinones, starting from 3-iodo-1*H*-indole-2-carboxylic acid allylamide **126**. The cross-coupling afforded Heck products **127** and **128** in good yield. Scheme 32 pictured the attempt to obtain β-carbolinones by intramolecular Heck reaction. The authors observed besides the expected product **127** the formation of the pyrazinol[1,2-*a*]indole derivative **128** arisen from an intramolecular amination reaction between the indole nitrogen atom and the double bond of the allylic chain and leaking of the iodine atom in position 3. This unexpected product was explained by the instability of 3-iodoindoles. Due to its therapeutically use as serotonin antagonist, the interests in the pyrazinol[1,2-*a*]indole system **128** rises.

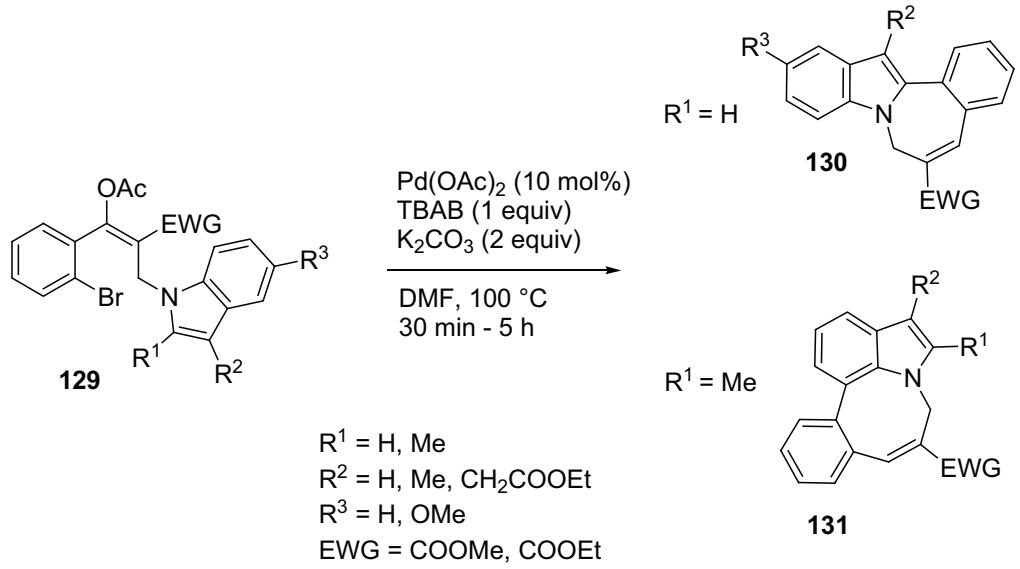


Scheme 32. Synthetic route to β- and γ- carbolinones by intramolecular Heck reaction.

Medium-sized heterocyclic compounds like the examples before are found in natural products, drugs, and preclinical leads. Because of that, it is not surprising that the synthesis of these compounds by intramolecular Heck reaction has received much attention. Palladium-mediated synthesis of medium-sized heterocycles has been investigated, but studies involving the Baylis-Hillman adducts have not been reported much.

Kim and co-workers examined the intramolecular Heck reaction with indole-containing Baylis-Hillman adducts demonstrated in Scheme 33.[110] All tries afforded the desired product **130** in variable yields (24-65%) by using

$Pd(OAc)_2$/TBAB and K_2CO_3 in DMF. The 2-methyl-group (R^1) in compound **129** rendered the formation of seven-membered ring impossible, and aryl-aryl bond-formation occurred to form the eight-membered compound **131** in moderate yield (53-60%). However, they synthesized tetracyclic indole derivatives via palladium-catalyzed intramolecular Heck reaction from indole containing Baylis-Hillman adducts.



Scheme 33. Heck reaction with indole-containing Baylis-Hillman adducts.

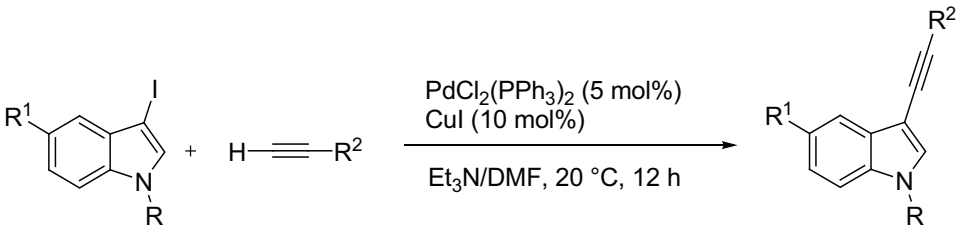
1.4 Sonogashira Coupling Reaction

The Sonogashira reaction is the most frequently used method to affect the alkynylation of an aryl halide. The traditionally accepted mechanistic pathway of the Sonogashira reaction is similar to that originally proposed by Sonogashira and Hagihara in 1975.[111] Typically palladium is used along with generally twice this amount of CuI as co-catalyst. Alkynes undergo the cross-coupling reaction with aryl- and heteroaryl halides in the presence of $PdCl_2(PPh_3)_2$ as catalyst, CuI as co-catalyst and amine as solvent. The reaction is normally conducted at room temperature. It is believed that copper assists the reaction through formation of an acetylide and then this group is transferred to palladium by a transmetalation step. Nevertheless, modifications of the conditions have continued to be investigated because copper acetylides can also lead to homocoupling products. Although

many researchers have established some flexibility in the conditions, no general method is yet available for all substrates for this reaction.[112,113]

One application of the Sonogahsira cross coupling of indoles was described by Witulski and co-workers.[91] The authors developed a strategy for the synthesis of functionalized indoles via transition metal-catalyzed reactions. Sonogashira as well as Suzuki reactions with 3,5-bis-halogenated indoles or their 2-azabioisosteres and indazoles led to the preparation of conjugated serotonin derivatives. In order to test the feasibility of the Sonogashira reaction in sequential palladium-catalyzed reactions in the indole series, they attempted to synthesize a variety of 3-alkynyl indoles structurally related to serotonin (Table 6). The direct iodination followed by N-protection of the indole nitrogen resulted 3-iodoindole derivatives **132a-h**. These coupling reactions of iodoindoles with a set of terminal alkynes proceeded under mild conditions and gave the according coupling products **133a-m**.

Table 6. Sonogashira coupling reactions starting from 3-iodoindole derivatives.



132a-h **133a-m**

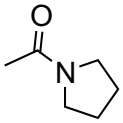
Entry	**132**	R	R^1	R^2	**133**	Yield [%]
1	**a**	Boc	H	CH_2NMe_2	**a**	69
2	**a**	Boc	H	CH_2NHTos	**b**	81
3	**b**	Tos	H	CH_2NHTos	**c**	84
4	**c**	Boc	OMe	CH_2NMe_2	**d**	97
5	**c**	Boc	OMe		**e**	93
6	**d**	SO_2Ph	OMe	CH_2NMe_2	**f**	94
7	**d**	SO_2Ph	OMe	CH_2NHTos	**g**	96
8	**d**	SO_2Ph	OMe	CH_2OH	**h**	91
9	**e**	Tos	OMe	Ph	**I**	76
10	**f**	Boc	Br	CH_2NHTos	**j**	91

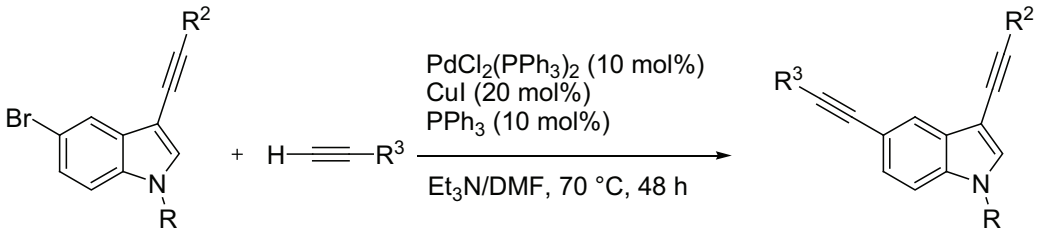
Table 6. Sonogashira coupling reactions starting from 3-iodoindole derivatives, continued.

Entry	**132**	R	R^1	R^2	**133**	Yield [%]
11	**g**	SO_2Ph	Br	CH_2NMe_2	**k**	88
12	**h**	Tos	Br	CH_2NHTos	**l**	90
13	**h**	Tos	Br	CH_2OH	**m**	79

All reactions were carried out at room temperature in the presence of 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI as catalysts. The corresponding new 3-alkynyl indoles **133a-m** were obtained in good to excellent yields after purification by column chromatography. To avoid any couplings at the N-1-position it was necessary to protect the nitrogen atom in all cases. Thereby the choice of the protecting group played no significant role. As well as the substituent R^1 on the benzene moiety of the indole showed no significant influence on the course of the coupling reaction. Interestingly for the derivatives, which had an iodine, atom in 3-position and a bromine atom at the 5-position were exclusively functionalized at the 3-position when the reactions ran at room temperature (Table 6, entries 10-13).

In the next step they examined Sonogashira-Sonogashira sequential cross-couplings in the indole series. Arylbromides were less reactive than the parent iodides in palladium cross-coupling reactions. The conversion of 5-bromoindole into its bis-alkynylated derivative did not proceed at room temperature but required heating at 70 °C. In these cases an additional amount of PPh_3 was necessary to stabilize the active catalyst in one hand and to keep the overall efficiency catalysis on the other hand. Table 7 shows the coupling reaction of 3-alkynyl-5-bromoindoles **133j-l** with different terminal alkynes to bisalkynylated indole derivatives **134a-d**. In comparison with the first Sonogashira coupling reaction, ran this coupling reaction with up to 3 days relatively slow. Therefore they used a higher catalyst loading of $PdCl_2(PPh_3)_2$ and 2-3 equiv of monoalkynes. Under this optimized conditions the reaction advanced two days to give the according indole products **134a-d**. All Sonogashira reactions proceeded smoothly affording a large range of new alkynylated indoles, which are analogues of serotonin especially $5HT_4$-$5HT_7$ receptors.

Table 7. Sonogashira cross-coupling reactions with 3-alkynyl-5-bromoindoles.

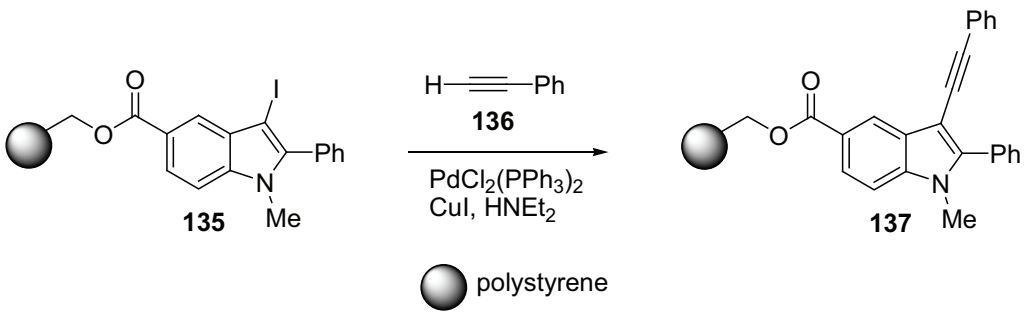


133j-l **134a-d**

Entry	**133**	R	R^2	R^3	**134**	Yield [%]
1	**j**	Boc	CH_2NHTos	CH_2NHTos	**a**	55
2	**k**	SO_2Ph	CH_2NMe_2	CH_2NHTos	**b**	83
3	**k**	SO_2Ph	CH_2NMe_2	CH_2OH	**c**	74
4	**l**	Tos	CH_2NHTos	CH_2NMe_2	**d**	77

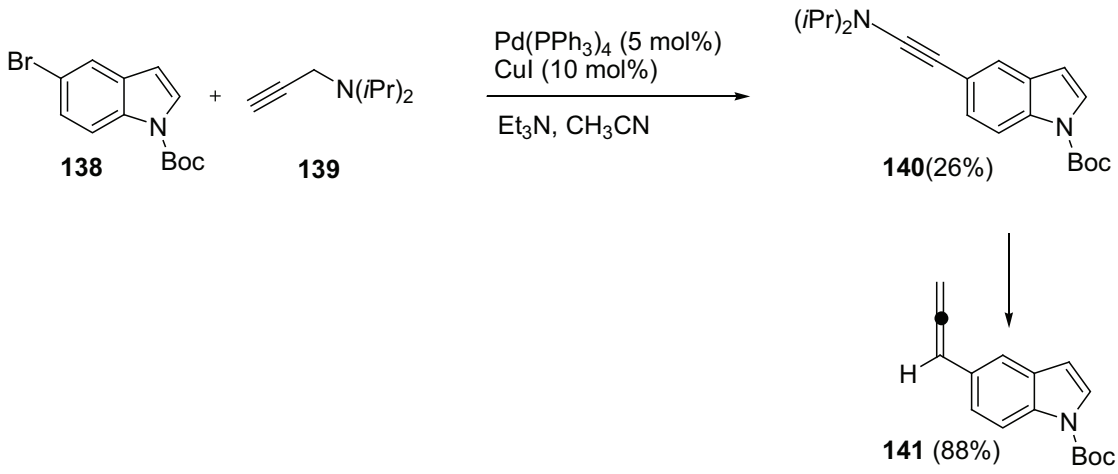
Indoles are known to exhibit a broad range of biological activity. There is always a great demand for their evaluation as potential drug candidates.

Larock *et al*. reported about a solid-phase synthesis of trisubstituted indoles and their further elaboration through palladium-mediated coupling reactions.[114] The authors developed an iodocyclization process that presented iodo-containing products supported by solid phase. Such an iodo-containing compound is shown in Scheme 34. The immobilized 3-iodoindole **135** was converted with phenylacetylen **136** under standard Sonogashira reaction conditions to the corresponding coupled product **137**. The authors were obtained the final solid phase-free compound by tranesterification and isolation of the methyl ester in a yield of 91% with a purity of 93%.



Scheme 34. Solid phase Sonogashira coupling with trisubtituted indole.

The group around Nakamura described heterocycles containing propargylic diisopropylamines.[115] These propargyl-diisopropylamines were easily prepared from heterocyclic bromides by Sonogashira coupling reaction. Followed by allene transformation reaction the corresponding heterocyclic allenes were produced in good to high yields. Allenes are very important building blocks for organic synthesis.[116] The heterocyclic allenes precursors were synthesized using Sonogashira coupling reaction of *N,N*-diisopropylprop-2-ynylamine **139** with different heterocyclic bromides. Scheme 35 shows the coupling reaction of the indole example **138**. The reaction was carried out in the presence of $Pd(PPh_3)_4$, CuI and Et_3N in CH_3CN at 60 °C.

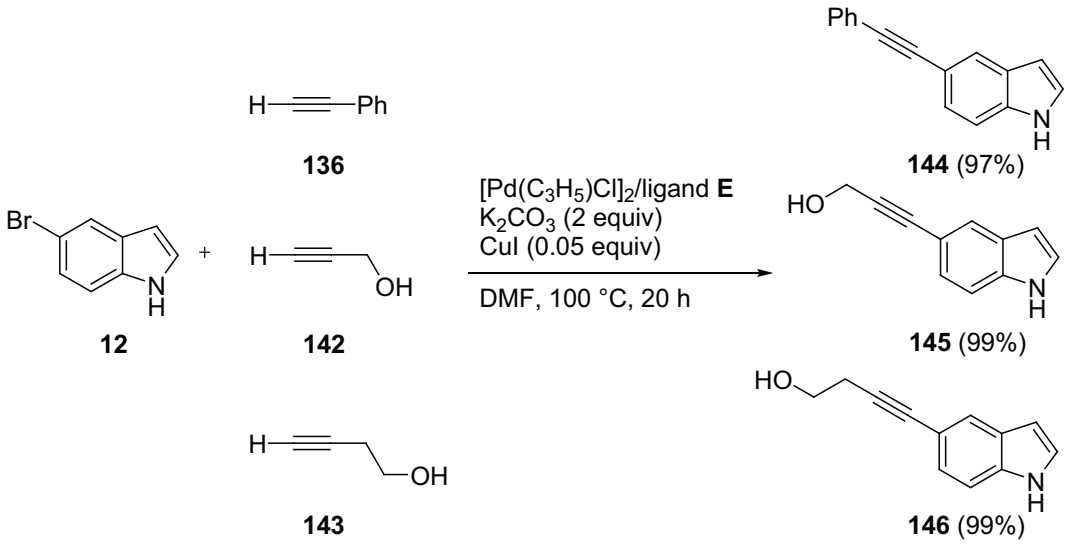


Scheme 35. Sonogashira coupling reaction of Boc-protected 5-bromoindole with *N,N*-diisopropylprop-2-ynylamine.

The authors reported that the reaction with N-unprotected 5-bromoindole did not undergo the Sonogashira coupling however, the reaction with *N*-Boc-5-bromoindole **138** gave desired product **140** in a yield of 26%. For the palladium-catalyzed allene transformation, compound **140** was converted in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%) as catalyst, and 1,2-bis[bis(pentafluorophenyl)-phosphino]ethan (10 mol%) at 100 °C in $CHCl_3$. The indole allene **141** resulted in a yield of 88%.

Santelli and colleagues described the Sonogahira reaction of heteroaryl halides with alkynes catalyzed by a palladium-tetraphosphine-complex.[117] They used the same catalytic system described already in the Suzuki part in Scheme 17. The Tedicyp/$PdCl(C_3H_5)]_2$ catalytic system catalyzed the Sonogashira reaction of

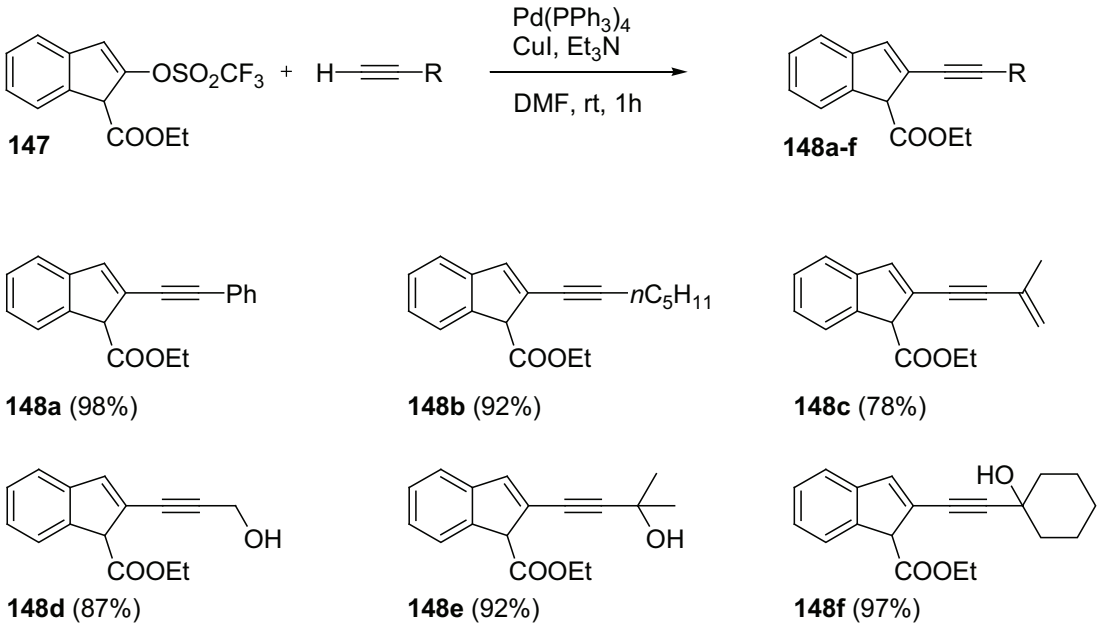
different heteroaryl halides with a range of alkynes in good yields. The ratios between substrate and catalyst were nearby moderate to high in the process. Various heteroaryl halides like indoles, thiophenes, pyridines and quinolines were employed successfully. The examples of Sonogashira reaction of 5-bromoindole with different alkynes are shown in Scheme 36. The bromo-substituted indole was a suitable substrate for Sonogashira coupling. TON's of 6000-8000 were obtained for the coupling of 5-bromoindole **12** with phenylacetylene **136**. Lower TON's were observed by the coupling with propargyl alcohol **142** and but-3-yn-1-ol **143**. The coupling products **144-146** were obtained in excellent yields up to 99%. The results represent economically attractive procedures.



Scheme 36. Sonogashira coupling reaction with 5-bromoindole.

Because of the high price of palladium, their low catalyst loading is a practical advantage and become increasingly important for industrial processes.

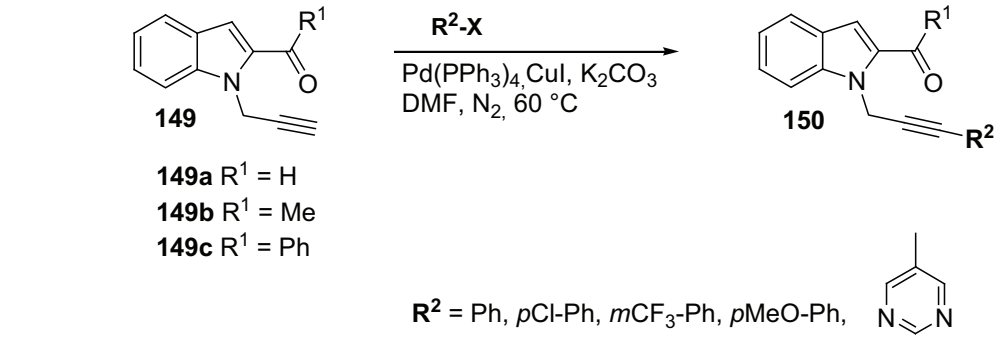
Sonogashira coupling reactions are not only possible with aryl halides especially indole halides, but also with other substrates like 2-trifluoromethanesulfonyloxy-indoles.[118] Rossi and co-workers developed palladium-catalyzed reactions with 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester and different partners.[94] Compound **147** was synthesized first and its reactivity was tested afterwards. The authors prepared 2-aryl, 2-heteroaryl, 2-allyl, and 2-vinyl indoles **148a-f** in good to excellent yields by palladium-catalyzed coupling of **147** with commercially available alkynes. Scheme 37 gives an account of the reaction with different alkynes following the Sonogashira protocol.



Scheme 37. Palladium-catalyzed reaction with 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester.

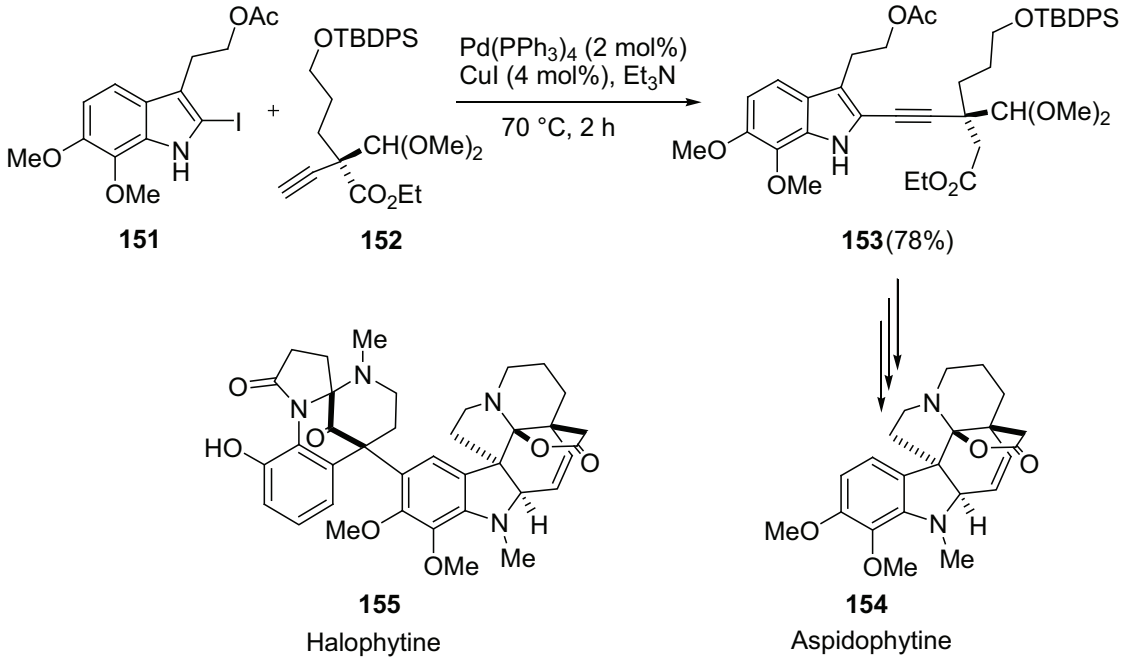
2-Alkynyl indole derivatives **148a-f** were synthesized in the presence of $Pd(PPh_3)_4$/CuI, Et_3N in DMF. Starting from commercially available and inexpensive intermediate 1,3-dihydroindol-2-one, they obtained the reactive and stable precursor **147** for 2-carbosubstituted indoles, thus providing a valuable alternative to until that time reported synthetic strategies.

In the upper examples the indole part was normally used as the heteroaryl halide unit that was coupled with several alkynes. The group around Abbiati reported about the synthesis of pyrazino[1,2-*a*]indole achieving by intramolecular cyclization of several 2-carbonyl-1-propargylindoles in the presence of ammonia (Scheme 38).[119] Therefore the authors used the Sonogashira coupling as key step by using the indole as the alkyne source and several aryl halides as coupling partners. The 1-propargyl-1-*H*-indole-2-carbaldehyd **149a**, the 2-acetyl-1-propargyl-1-*H*-indole **149b**, and the 2-benzo-yl-1-propargyl-1-*H*-indole **149c** were synthesized by standard conditions, starting from readily accessible 1-*H*-indole-2-carbaldehyd, 2-acetyl-1-*H*-indole and 2-benzoyl-1-*H*-indole. The following standard palladium-catalyzed Sonogashira reaction of **149** with different aryl halides (R^2-X) gave the resultant products **150** in 61-91% yield. Thermal cyclization of the intermediates **150** led to pyrazino[1,2-*a*]indoles in good yields.



Scheme 38. Sonogashira reaction of 1-alkynyl-indole derivatives.

The Sonogashira reaction as key step was applied in the enantioselective total synthesis of aspidophytine **154** as well (Scheme 39).[120] Aspidophytine is the right-half of haplophytine **155**, a dimeric indole alkaloid isolated from the dried leaves of the plant *Haplophyton cimicidum*. That is the reason why it is a precursor for biosynthesis and also a possible synthetic intermediate to **155**.

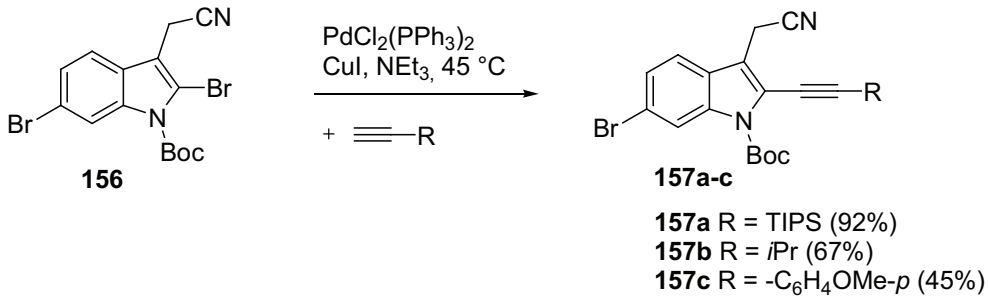


Scheme 39. Coupling key-step in the synthesis of aspidophytine.

The authors prepared the indole unit **151** commenced with a known benzaldehyde and the desired acetylene unit. The two synthesized fragments were joined to form the 11-membered secondary amine. Sonogashira coupling of **151** and **152** gave

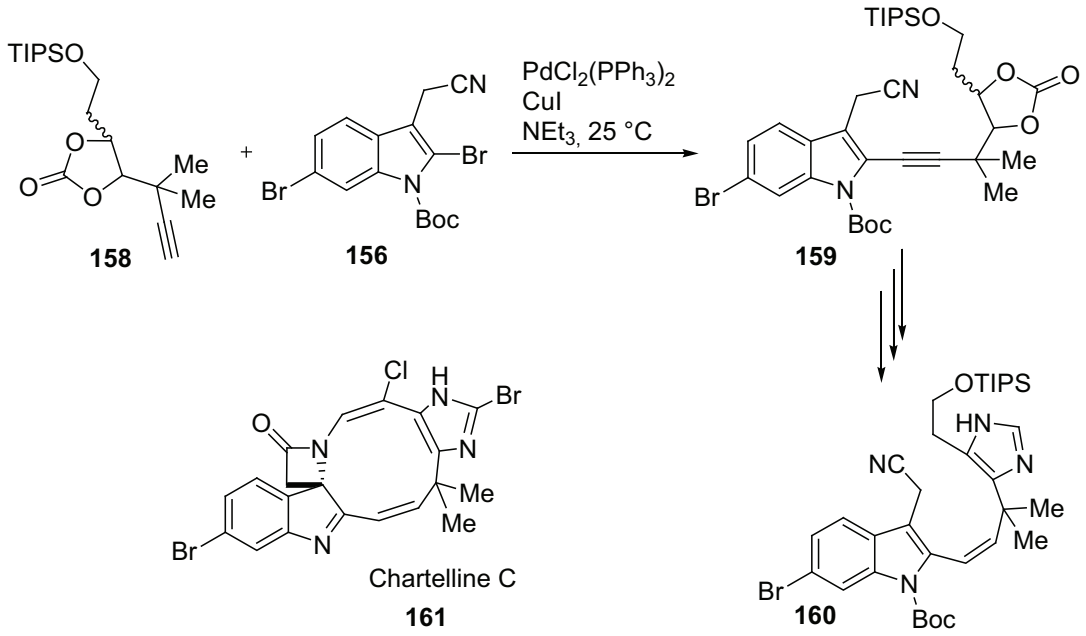
the 2-alkynylindole derivative **153** in a yield of 78%. Under Sonogashira standard conditions with $Pd(PPh_3)_4$, CuI and Et_3N they got the key intermediate **153** for the construction of the aspidosperma skeleton.

A further application in synthesis of natural structures is the study towards the marine alkaloid chartelline C **161** by Magnus *et al.*.[121] The authors developed a regioselective Sonogashira coupling of 2,6-dibromoindole at the 2-position with simple acetylenic partners (Scheme 40). The authors were interested to see if a 2,6-dibromoindole **156** exhibited any selectivity in Songashira coupling reaction. Scheme 40 shows the conversion of the dibrominated indole **156** with different alkynes with complete regioselectivity to the 2-coupled indoles **157a-c** in good yields under standard Sonogashira coupling reaction conditions. Therefore the choice of the protecting group on the indole nitrogen atom was essential for achieving regioselectivity in Sonogashira coupling reaction.



Scheme 40. Sonogashira coupling of 2,6-dibromoindole derivative.

The authors applied their findings in the synthesis of chartelline C analogue **160** subsequently. Scheme 41 outlined the development to the desired compound **160** in the presence of the dibrominated indole **156** and the complex alkyne **158**. The desired compound **159** was obtained in a yield of 67%. The regioselective Sonogashira coupling reaction was used to synthesize the 2-isoprene-imidazole chain whereas the imidazol was constructed after coupling reaction.



Scheme 41. Synthesis of indole-imidazole with Sonogashira key step.

1.5 Buchwald-Hartwig Amination

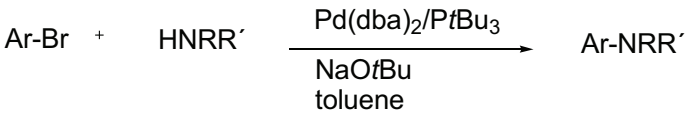
Functionalized aromatic and heteroaromatic amines are important building blocks for the synthesis of pharmaceuticals. In many areas in organic synthesis arylamines play an important role. They are not only parts in natural compounds but also in conductive polymers and photographic materials.[122] So it is not very amazing that an easy synthetic access becomes very interesting for the chemical industry. The classical exposure to these compounds is carried out by nitration-/reduction sequences or by reductive amination of aniline derivatives. These methods requires often many synthetic steps and expensive reagents. Additionally the scope for a range of functional moieties is limited because of the reaction conditions. Buchwald and Hartwig developed an effective synthesis for arylamines. Aryl halides and -triflates were coupled with amines in the presence of a palladium catalyst. The palladium-catalyzed Buchwald-Hartwig amination has matured from a synthetic laboratory procedure to a technique that is widely used in natural synthesis as well as in other fields of academic interests. Furthermore due to the versatility and reliability of this reaction, researchers in industrial environments have included this methodology in their toolbox as a standard procedure for the synthesis of amine derivatives. The process is in many points similar to palladium-catalyzed Suzuki-, Heck-, or Stille reaction. The crucial influence for the reaction success is dependent on the catalytically active Pd(0) binding ligand. Extensive synthesis of new amino-substituted indoles is restrained due to the lack of a general regioselective method for introduction of amino-groups into this heterocycle. In recent years palladium-catalyzed arylation of amines was successfully used for building new C-N bonds. Nevertheless, this reaction still remains rare in the series of indoles and its derivatives. In all conscience there are only three publication until 2002 containing palladium-catalyzed amination of indoles.[123]

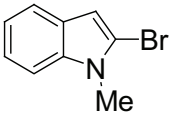
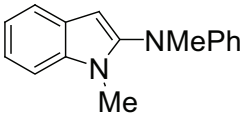
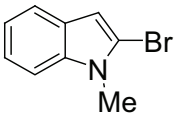
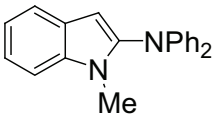
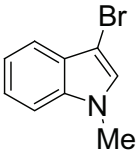
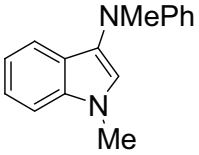
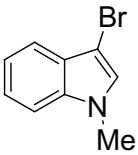
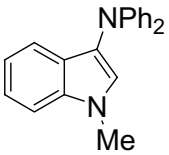
Hooper *et al*. reported about palladium-catalyzed intermolecular amination of 2- and 3-bromoindoles in 2003.[124] They studied the activity of palladium catalysts for the amination of five-membered heterocyclic halides and determined the factors that control the scope of this reaction. Table 8 represents the amination reaction of

2- and 3-bromo-*N*-methylindoles catalyzed by P(*tert*-Bu)$_3$ and Pd(dba)$_2$. To prevent competition between the reacting amine and indole N-H, *N*-methylindoles were used instead of the parent indoles. The reactions of 2- and 3-bromo-*N*-methylindoles with *N*-methylaniline (Table 8, entries 1 and 3) occurred at room temperature whereas reactions of 2- and 3-bromo-*N*-methylindoles with diphenylamine (Table 8, entries 2 and 4) occurred at 100 °C. Non reaction of these bromoindoles were observed with primary or secondary alkylamines and with primary arylamines.

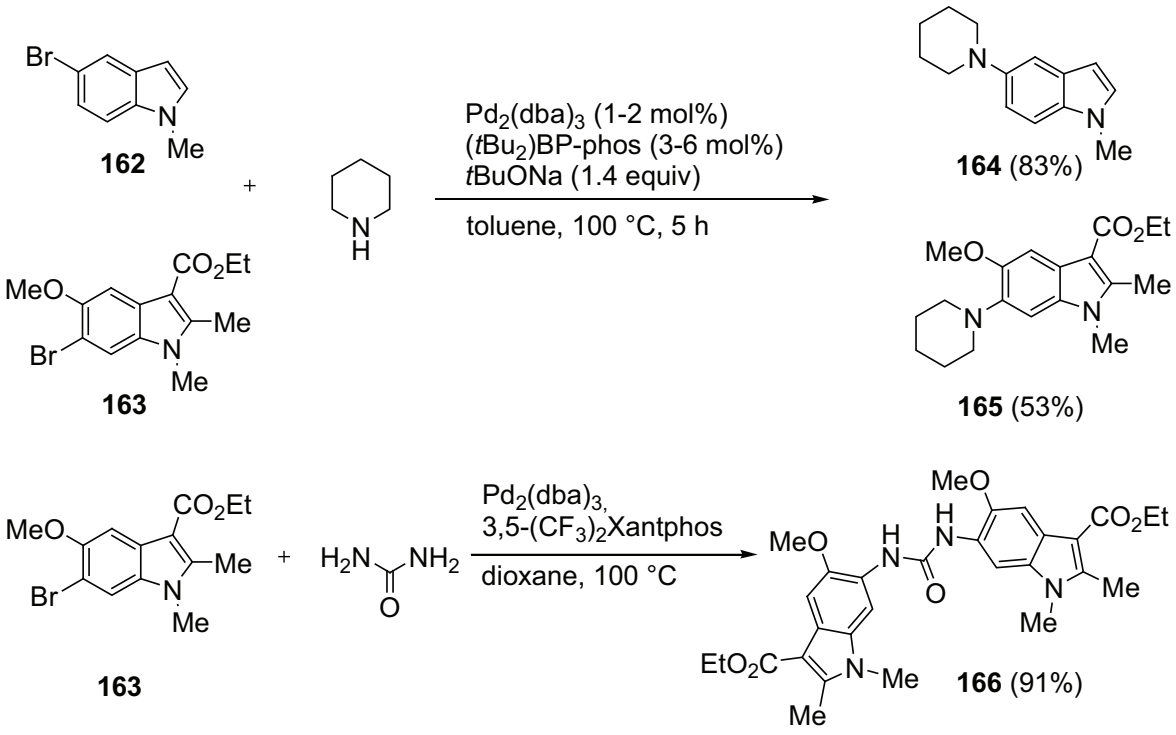
Further palladium-catalyzed aminations were listed in this publication and proceeded with a range of electron-rich heteroaromatic bromides and chlorides with certain classes of amines.

Table 8. Amination of indole bromides with Pd(dba)$_2$/P*t*Bu$_3$.



Entry	Ar-Br	Amine	Product	Cond.	Yield [%]
1		HNMePh		rt, 16 h	83
2		$HNPh_2$		100 °C, 16 h	86
3		HNMePh		rt, 16 h	70
4		$HNPh_2$		100 °C, 16 h	71

Beletskaya and co-workers examined the possibility of applying nitrogen-containing groups (amino, amido, ureido) into halogen-substituted indoles, benzofurans and tetrahydro-carbazoles.[125] Following Scheme 42 demonstrates selective examples of the palladium-catalyzed amination of bromoindoles with amines.



Scheme 42. Palladium-catalyzed amination of 5- and 6-bromo-indole.

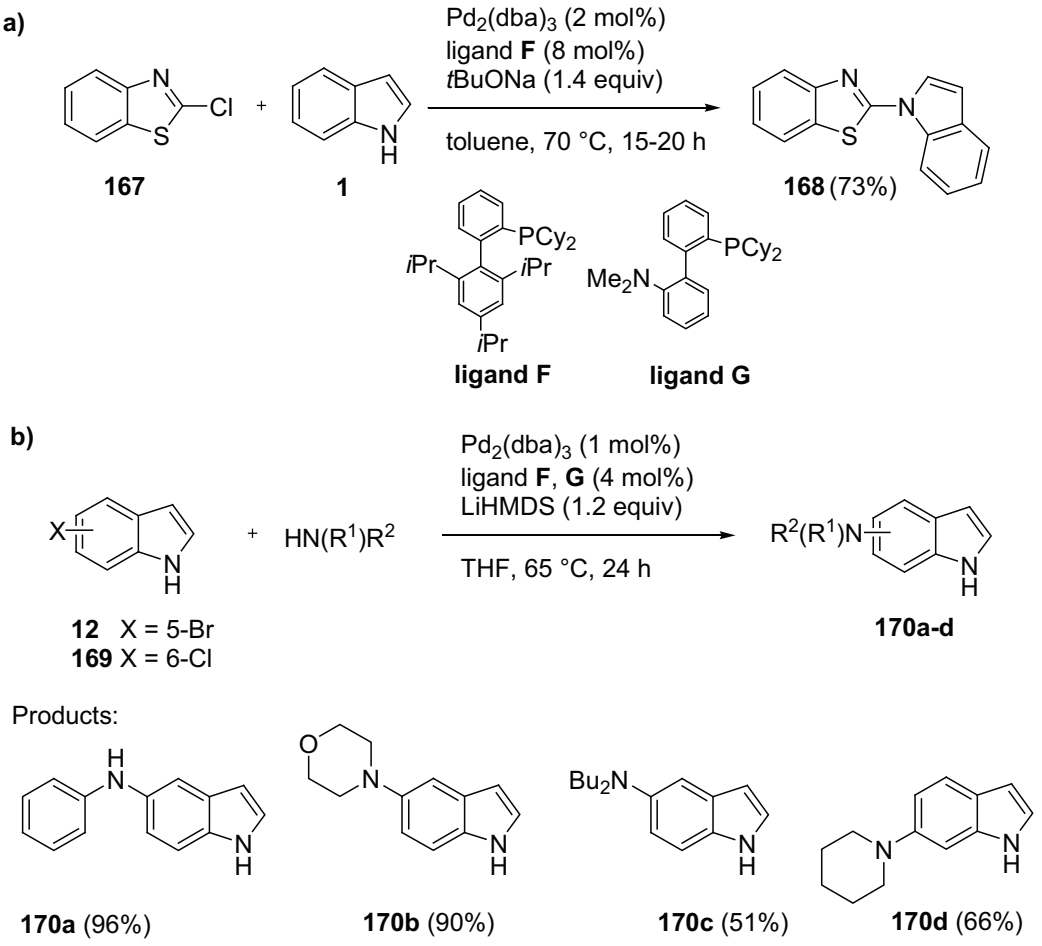
Bromoindoles having no substituent on the nitrogen atom did not undergo the palladium-catalyzed amination reaction. Additionally they observed quantitative removal of acetyl and phenylsulfonyl protecting groups so that these substrates could not be used in amination reaction as well.

The authors succeeded in obtaining the target product **164** in 83% yield by coupling indole **162** with piperidine using $Pd_2(dba)_3$ (1 mol%) as catalyst, (*tert*-Bu_2BP-phos) (3 mol%) as ligand and *tert*-BuONa as base in toluene at 100 °C in 5 h. The amount of palladium catalyst was increased to 2 mol% (*tert*-BuONa, 6 mol%) to attain moderate yield of amination product **165** (53%) in 10 h in the less smooth reaction with bromomindole **163**.

The reaction was accompanied by formation of the dehydro-brominated by-product with a yield of 30%. The last example shows the palladium-catalyzed amidation of indole **163** with urea. Unlike amination, the amidation of 6-bromoindole **163** was characterized by high yield of product **166**. The yield of the corresponding *N,N*-diethylhetarylurea in the presence of 3,5-$(CF_3)_2$Xantphos was optimized to 91%.

While in cases above amination with bromoindoles bearing a free NH did not succeed, the next examples will demonstrate the first coupling of amines with chloro- and bromoindoles bearing a free NH-group.

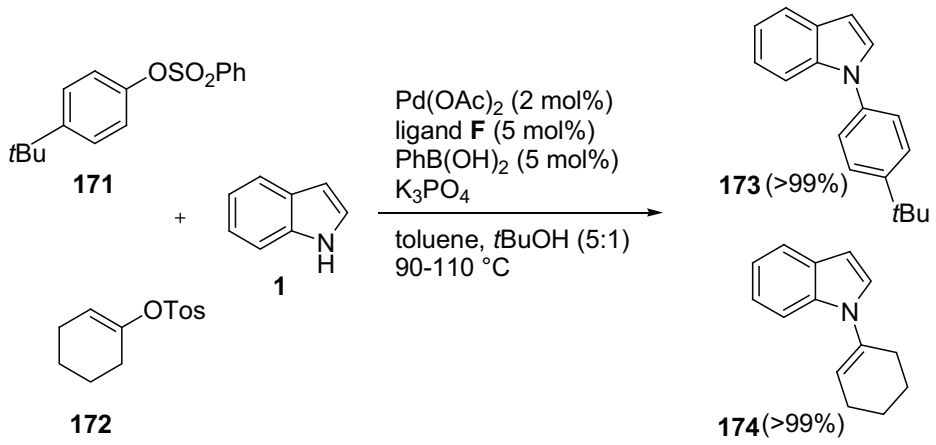
Buchwald and co-workers reported about the palladium-catalyzed amination of different heteroaryl halides by utilizing bulky electron-rich biaryl phosphine ligands.[126]



Scheme 43. a) Palladium-catalyzed amination of benzothiazole with indole. b) Palladium-catalyzed amination of halo-indoles.

Scheme 43 imaged on one hand the palladium-catalyzed amination of 2-chlorobenzothiazole **167** and indole **1** as the coupling partner (a) and on the other hand the amination of 5-bromoindole **12** and 6-chloroindole **169** as the halide component with different amines to the desired coupling products **168** and **170a-d** (b). Bulky electron-rich biaryl ligands **F** and **G** were employed for these reactions. The product **168** from the coupling of 2-chlorobenzothiazole **167**, in the presence of $Pd_2(dba)_3$/ligand **F** (1:4) as catalyst system, *tert*-BuONa as base in toluene at 100 °C, was isolated in a yield of 73%. Finally, 5-bromoindole **12** and 6-chloroindole **169**, possessing a free NH, were viable coupling partners with anilines and acyclic and cyclic secondary alkylamines. Using the procedure in Scheme 43 (b) with $Pd_2(dba)_3$/ligand **F** or **G** as catalyst system and 2.2 equiv LiHMDS as base in THF at 65 °C for 24 h gave the according products **170a-d** in excellent to good yields, respectively. The more difficult reaction with *n*-$BuNH_2$ afforded 51% of the desired product **170c**. An acceptable yield for the coupling of 6-chloroindole **169** with piperidine to structure **170d** was only obtained with ligand **F** in a yield of 66%.

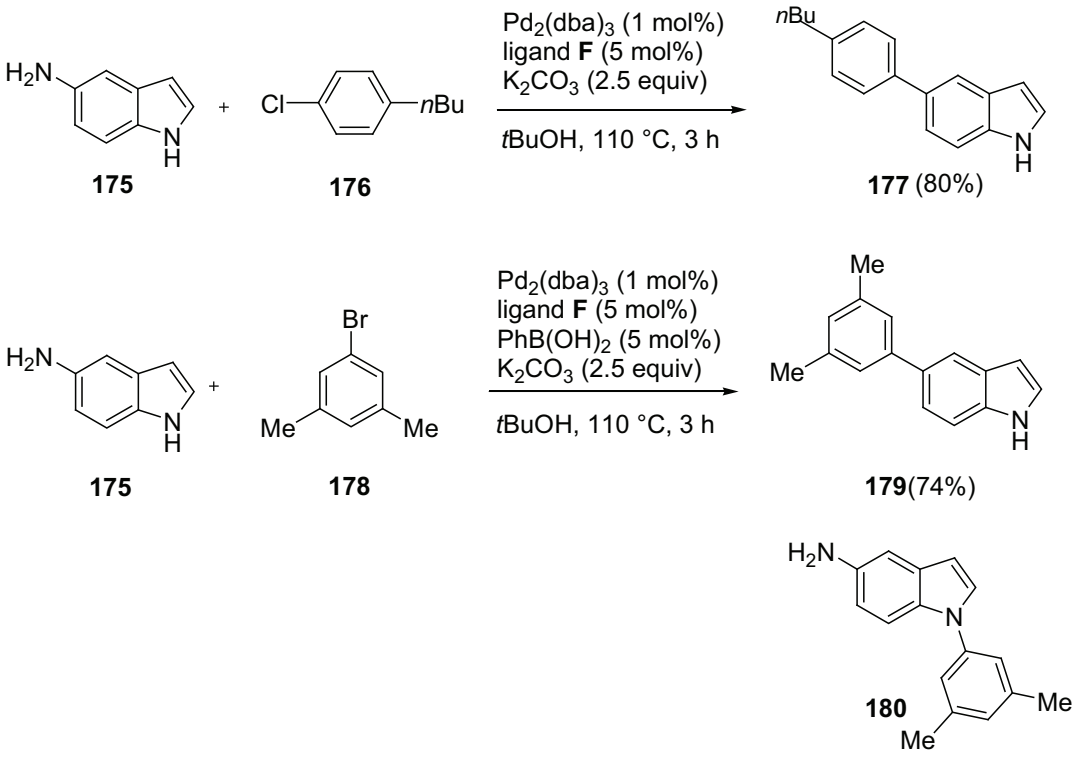
Ligand **F** was also used in the palladium-catalyzed amination of aryl benzenesulfonates, reported by the same group.[127] The use of benzenesulfonates typically provided higher yields and shorter reaction times as tosylates. As can be seen in Scheme 44, the reaction of a benzenesulfonate **171** and an aryl tosylate **172** with indole **1** led to the wanted products **173** and **174** in excellent yields. In both cases it was necessary to add a catalytic quantity of phenyl boronic acid to ensure complete conversion of the Pd(II) precatalyst to Pd(0).



Scheme 44. Palladium-catalyzed amination of aryl benzene-sulfonate and aryl tosylate with indole.

Under this reaction condition the indole coupling products **173** and **174** were isolated in 99% yield in the presence of $Pd(OAc)_2$ as catalyst, K_3PO_4 as base in toluene/*tert*-BuOH as solvent.

Additionally to that, they investigated the palladium-catalyzed amination of 5-aminoindole **175**. Scheme 45 shows the nearly selective palladium-catalyzed amination of 5-aminoindole **175** with two different amines **176** and **178** to product **177** and **179** in very good yields. It is surprising, that a simple arylbromide and arylchloride gave arylation of the 5-amino group at the indole in moderate to high selectivity in attendance of $Pd_2(dba)_3$, ligand **F** (Scheme 43) and K_2CO_3.

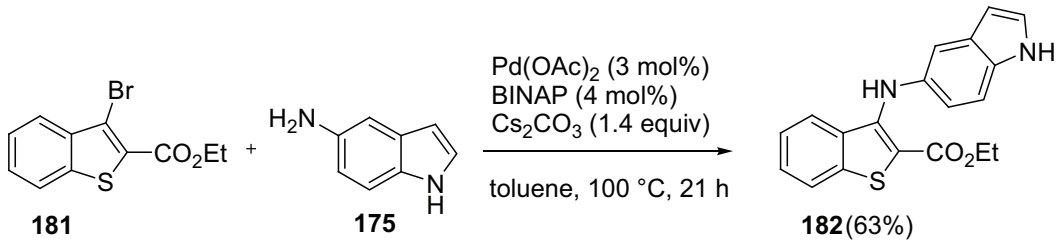


Scheme 45. Complementary C-N couplings using Pd-catalyst.

Using copper as catalyst the selectivity switched exclusively to the coupling product **180** (98%). However, it was possible to influence the selectivity by different metal-catalysts to complementary products.

In a similar way Queiroz *et al.* reported about the palladium-catalyzed amination of ethyl-3-bromobenzo[*b*]thiophene-2-carboxylate **181** with 5-aminoindole **175** (Scheme 46).[128] The precursor **181** was prepared from the corresponding 3-amino compound. The 5-aminoindole was used as coupling component and gave

the coupling product **182** after 5 h heating in a yield of 40%, while on leaving the reaction overnight the yield was increased to 63%.



Scheme 46. Palladium-catalyzed amination of ethyl-3-bromo-benzo[*b*]thiophene-2-carboxylate with 5-aminoindole.

In attendance of 3 mol% $Pd(OAc)_2$ as palladium source, 4 mol% BINAP and 1.4 equiv Cs_2CO_3 as base in toluene at 100 °C resulted the diarylamine benzo[*b*]thiophene **182** in good yield. Benzo[*b*]thiophenes are important heterocycles, either in biologically active molecules or as luminescent components used in organic materials.[129]

Pujol and co-workers were also interested in obtaining new compounds with biological activity. Therefore they required an easy source of N-aryl derivatives to serve as precursors. Aryl bromides were coupled with N-compounds to give the corresponding arylamines in the presence of palladium catalyst, suitable ligand, and weak base.[130] They prepared arylamines from interesting substrates by using $Pd[P(o\text{-tolyl})_3]_2Cl_2$ (0.12 mol%) as catalyst, BINAP (0.0075 mol%) or PPh_3 as chelating ligands, and Cs_2CO_3 as base (1 mmol) without solvent or a few drops of toluene when the starting material was a solid compound. Table 9 shows the coupled products from the synthesis of indoles with different substrates. When 5-bromoindole (Table 9, entries 6-9) was treated with 3-fluoroaniline, the arylation took place exclusively at the 1-position over the N-atom.

The corresponding *N*-arylindole was obtained as a single isomeric product at a temperature near 150 °C (Table 9, entries 7 and 8). and the expected 5-(3-fluorophenylamimo)indole was not detected under these conditions.

Table 9. Palladium-catalyzed N-arylation of indole.

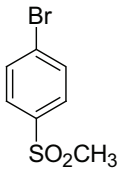
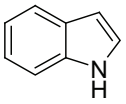
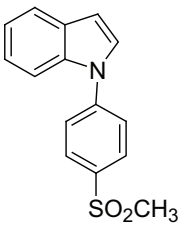
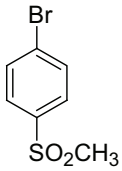
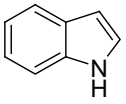
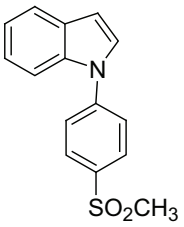
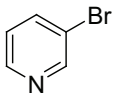
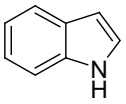
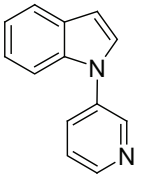
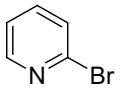
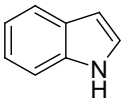
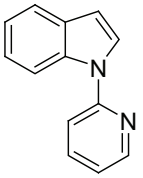
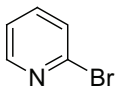
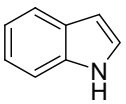
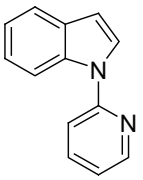
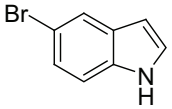
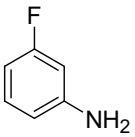
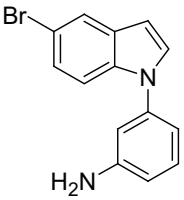
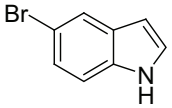
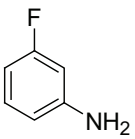
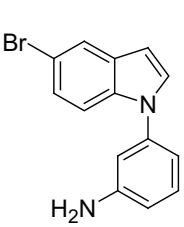
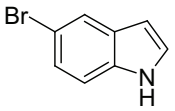
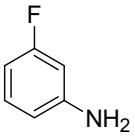
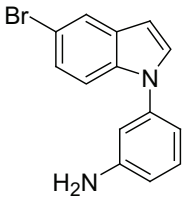
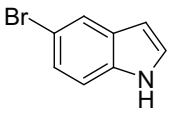
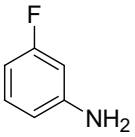
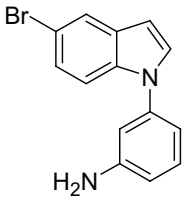
Entry	Ar-Br	R^1R^2NH	Product	Yield [%]	Cond.
1[a]				87	2 h, 120 °C
2[b]				90	2 h, 120 °C
3[a]				48	2 h, 120 °C
4[a]				86	2 h, 120 °C
5[b]				88	2 h,120 °C
6[a]				0	24 h,130 °C
7[a]				30	6 h,150 °C

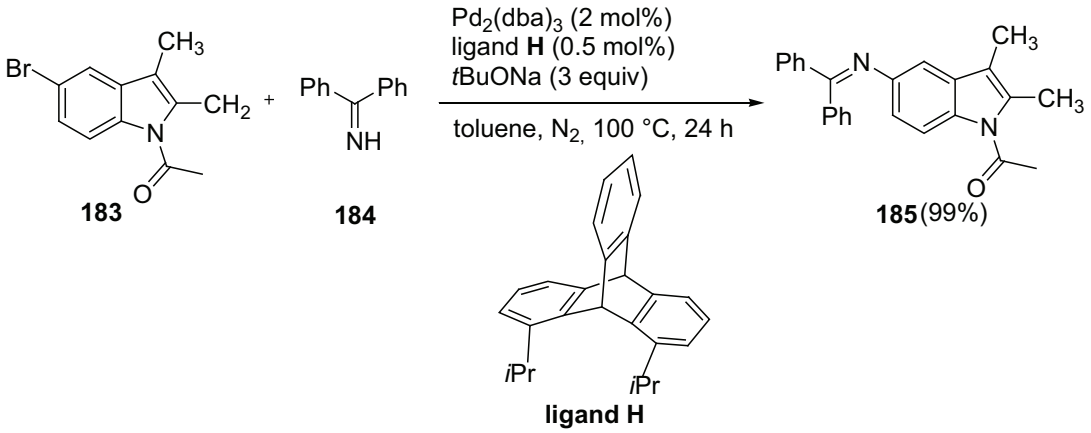
Table 9. Palladium-catalyzed N-arylation of indole, continued.

Entry	Ar-Br	R^1R^2NH	Product	Yield [%]	Cond.
8[a]				65	24 h,150 °C
9[c]				0	24 h,180 °C

Reaction conditions: [a] $Pd[P(o\text{-tolyl})_3]_2Cl_2$, (+)-BINAP, Cs_2CO_3. [b] $Pd[P(o\text{-tolyl})_3]_2Cl_2$, PPh_3, Cs_2CO_3. [c] (+)-BINAP, Cs_2CO_3, without catalyst.

In contrast the reaction was completely unsuccessful at 130 °C after more than 24 h (Table 9, entry 6). The displacement of 3-fluoroaniline instead of 5-bromoindole is not clear. Aryl fluorides have long been considered inert to palladium-catalyzed coupling reactions.[131] Only aryl fluorides with strong electron-withdrawing substituents give coupling reactions.[132] Just the high temperature can explain this behavior. The attempts to couple these substrates without catalyst failed (Table 9, entry 9). The pyridinylation of indole was also conducted in the same manner as described above. In the reaction with 3-bromopyridine and indole the coupling product resulted in a low yield (Table 9, entry 3). Nevertheless 2-bromopyridine gave under the same conditions an excellent yield (Table 9, entry 4). In general, this coupling reaction was found to be temperature dependent, higher temperature increases the yield. By raising the temperature to 180 °C, the ratio of side products was increased. However, this method allowed the synthesis of *N*-(3-aminophenyl)-5-bromoindole.

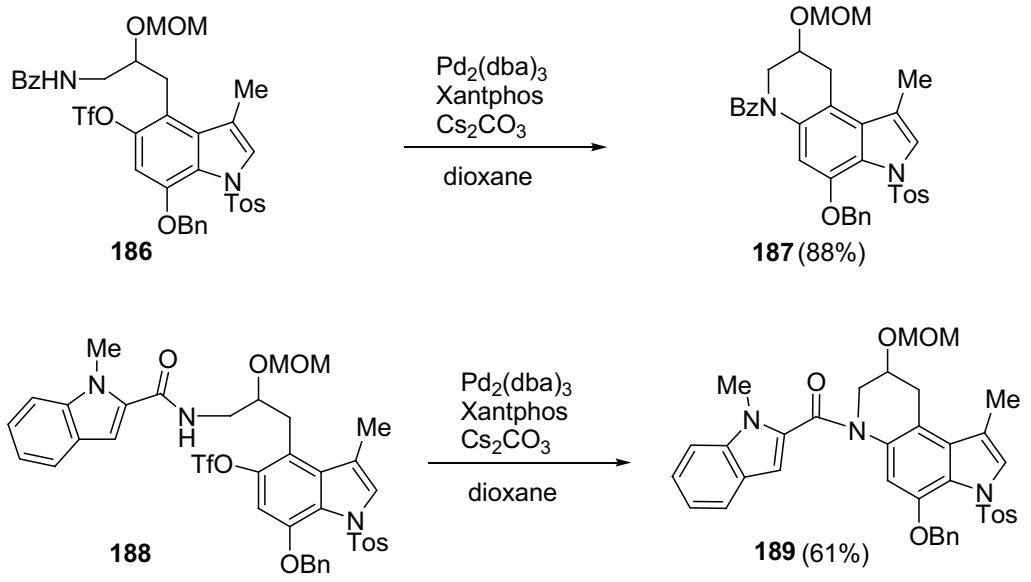
Grossman *et al.* described a new protocol for palladium-catalyzed Buchwald-Hartwig amination of aryl chlorides and -bromides with benzophenone imine as ammonia surrogate.[133] Their suggested reaction conditions are mild and were applied to numerous sensitive starting materials. Following Scheme 47 illustrates one indole-containing example.



Scheme 47. Palladium-catalyzed amination of a 5-bromoindole derivative with benzophenone imine.

Under optimized reaction conditions in the presence of 2 mol% $Pd_2(dba)_3$ and 1,8-bisdiisopropylphosphinotriptycene **H** as catalytic system, *tert*-BuONa as base, the according product **185** was isolated in a yield of 99%. Fascinating compounds like **183** were effectively aminated by benzophenone imine **184** and led to interesting new structures that represent important building blocks for construction of sensors (anthracene-1,8-diamine)[134] and molecular switches (indole derivatives)[135].

A further application of Buchwald-Hartwig coupling reaction was described by Ganton and Kerr in total synthesis of the (±)-CC-1065 CPI subunit.[136] CC-1065 and the related compounds like duocarmycins are members of a structurally unique family of naturally occurring molecules and remain some of the most rigorously studied antitumor compounds to date. Their derivatives remain as some of the strongest candidates for new exceptionally potent and highly selective therapeutic agents against tumorigenic cells. Structurally CC-1065 consists of two identical central and eastern pyrrolo[3,2-*e*] indole-4-one subunits linked together to the western subunit by amide bonds through pyrrolidine nitrogen. The key steps of the synthesis were a Diels-Alder reaction and a palladium-catalyzed intramolecular aryl triflate amidation. Scheme 48 pictured two selected examples of the intramolecular amidation.

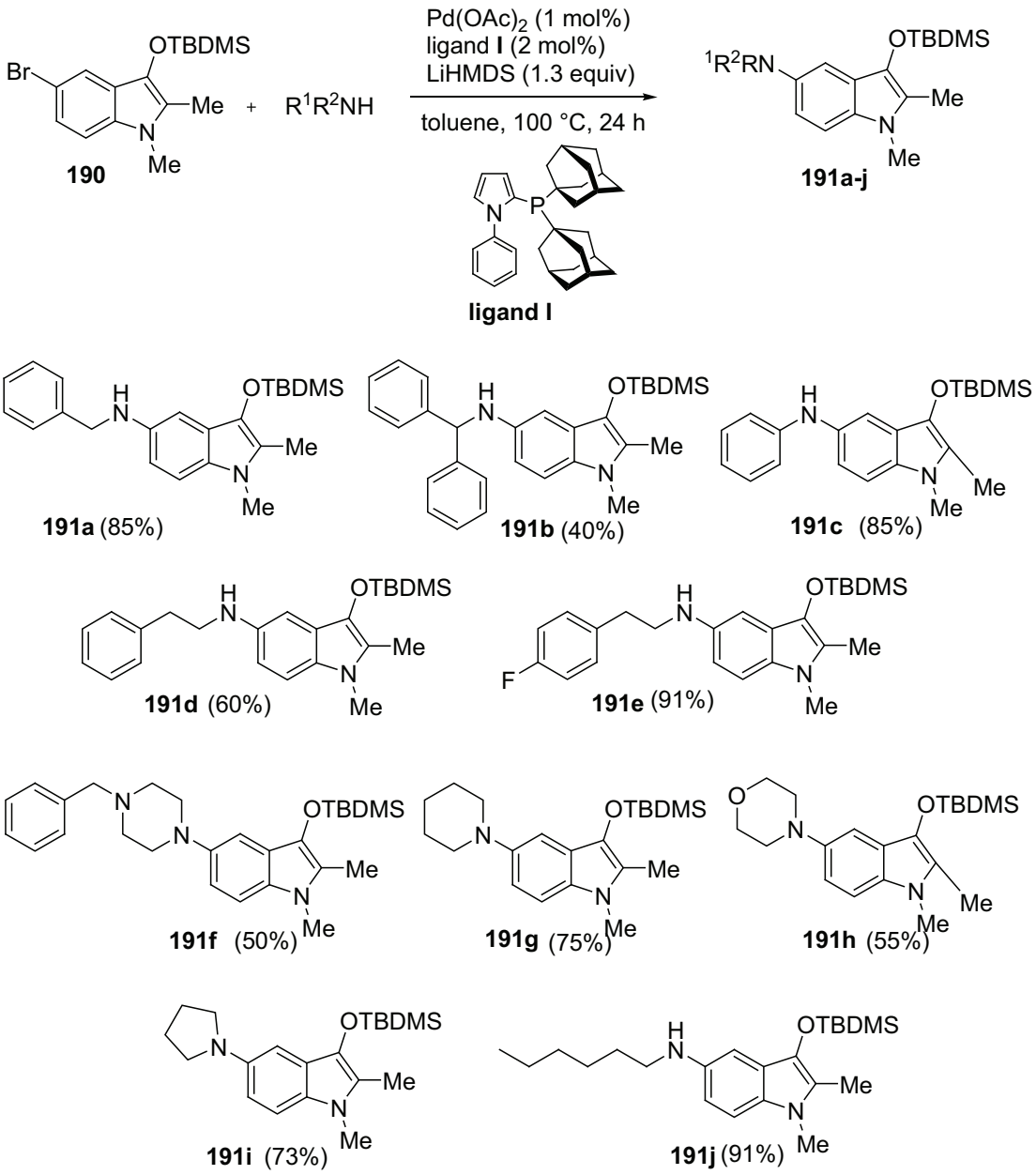


Scheme 48. Intramolecular aryl amidation with complex cross-coupling partners.

The amidation reactions of **186** and **188** were done in a Schlenk tube in attendance of $Pd_2(dba)_3$ (7 mol%), Xantphos (23 mol%) and Cs_2CO_3 (1.5 equiv) in dioxane for 22 h. The complex coupling products **187** and **189** were isolated in 88% and 61%, respectively. The intramolecular aryl amidation formed the key intermediate precursor for the CC-1065 subunit.

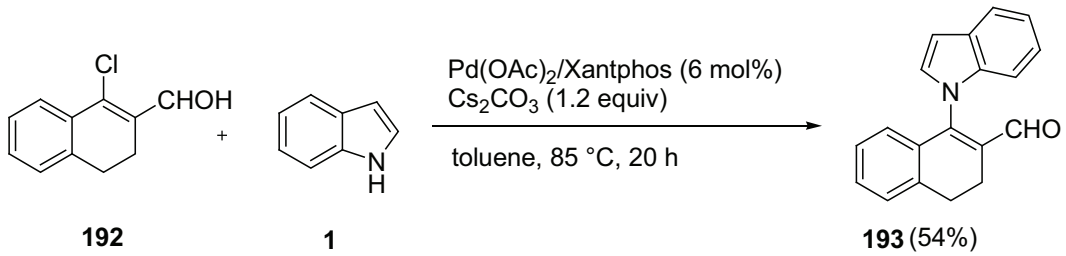
Numerous known indoles, especially amino-functionalized derivatives represent key structures for various biologically active compounds. The amination of 3-silyloxy-5-bromoindole **190** with several primary and secondary amines led to new potentially bioactive amino-functionalized indole derivatives.[137]

A novel palladium catalyst for Buchwald-Hartwig amination was developed by Beller and co-workers and opened new ways to interesting tryptamine derivatives. In Scheme 49 the general reaction sequence and the resulted coupling products **191a-j** can be seen in good to excellent yields. They studied different effects of base, and ligands on the reaction and optimized the reaction conditions to 1 mol% $Pd(OAc)_2$, 2 mol% *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole **I** as catalytic system, LiHMDS as base in toluene for 24 h at 100 °C. The corresponding indole products **191a-j** obtained in 40-91% yield. This catalytic system works well with different primary and secondary amines and gave a novel class of electron-rich indoles.



Scheme 49. Palladium-catalyzed amination of 3-silyloxy-5-bromo-2-methylindole.

Very active catalysts for Buchwald-Hartwig amination have been devised not only for aryl bromides but also for the less reactive aryl chlorides or sulfonates.[138] In addition, the reaction has been extended to many NH-containing species other than amines such as amides, lactams, ureas, and hydrazines etc.. Hess and Kirsch examined Buchwald-Hartwig amination of β-chloroacrolein by lactams and heteroarylamines.[139] Vinyl chlorides[140] were scarcely studied and to investigate their reactivity in cross-coupling amination is an interesting application. Following Scheme 50 pictured the palladium-catalyzed Buchwald-Hartwig amination of β-chloroacrolein with indole.

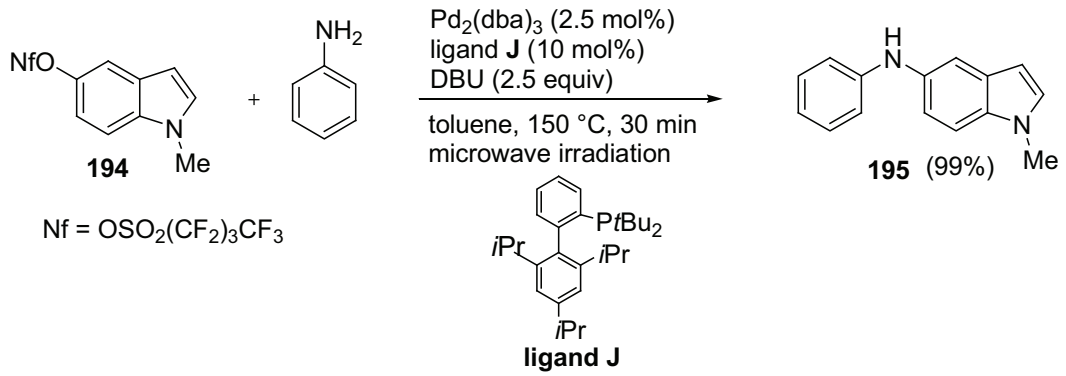


192 **1** **193** (54%)

Scheme 50. Amination of β-chloroacrolein by indole.

Reacting indole **1** with β-chloroacrolein **192** in the presence of $Pd(OAc)_2$/Xantphos and Cs_2CO_3 gave **193** in 54% yield. Several NH-containing species were studied in the C-N coupling in this paper and led to the desired coupling products. There is still a continuing interest in the improvement of new catalyst systems for aryl chlorides as well as for sulfonates. Recent efforts in this area have focused on the development of more active catalysts that operate at lower catalyst loadings and with shorter reaction times.

Buchwald and co-workers developed an expedited palladium-catalyzed amination of aryl nonaflates through the use of microwave-irradiation and soluble organic amine bases.[141] C-N Bond forming reactions using microwave irradiation mostly employed highly polar solvents and strong bases.[142] Consequently, base sensitive functional groups were not tolerated and limited the use and application. Soluble organic amine should improve the functional group tolerance and provided more efficient heating and stirring in microwave-assisted palladium-catalyzed amination reaction with aryl nonaflates. Scheme 51 pictured one selective example of indole nonaflate with aniline.



194 **195** (99%)

Nf = $OSO_2(CF_2)_3CF_3$

ligand J

Scheme 51. Palladium-catalyzed amination of indole nonaflates.

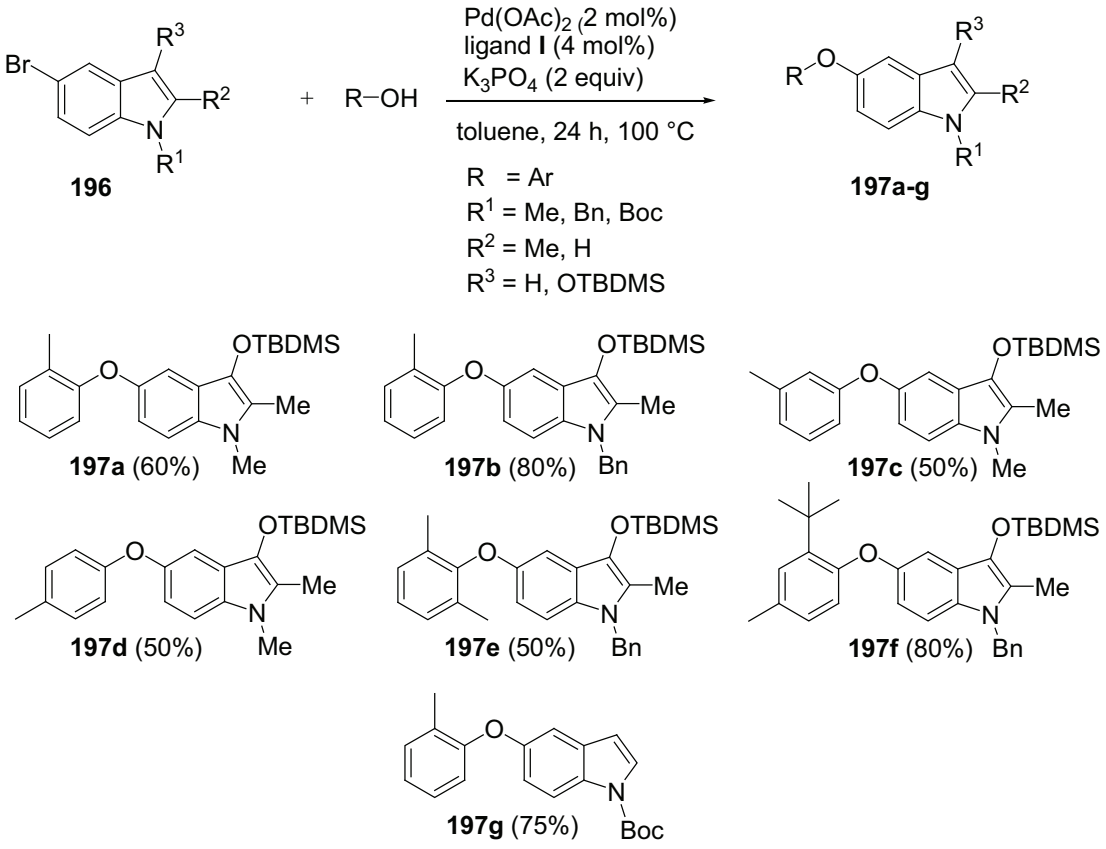
In the presence of $Pd_2(dba)_3$ and ligand **J**, together with the weak organic base DBU, *N*-methyl-5-nonaflate-indole **194** was converted with aniline to the aminated product **195** in excellent yield (99%). In only 30 min at 150 °C the indole derivative was fully converted and isolated. Several substrates (amines and aryl nonaflates) with a broad scope of functional groups were utilized in the microwave supported C-N bond forming process and led to new interesting compounds in very good to excellent yields.

1.6 Diaryl Ether Coupling Reaction

An important class in organic chemistry are diaryl ethers throughout in life science and polymer industry.[143] A number of diaryl ethers have been reported to possess significant biological activity, like natural products of the isodityrosine family, the antibiotic vancomycin,[144] angiotensin-converting enzyme inhibitor K-13,[145] (+)-piperazinomycin,[146] the antitumor compounds bouvardin and bastadin, [147] some new neuropeptide Y5 antagonists, [148] and numerous weed-killing chemicals.[149] Fritz Ullmann and Irma Goldberg started their pioneering work on copper-mediated and copper-catalyzed coupling reactions a hundred years ago. For the first time they coupled inactivated aryl halides with various nucleophiles like amines, phenols and carboxyamides. The classic arylation of phenols with aryl halides under standard Ullmann reaction conditions usually requires harsh reaction conditions and needs stoichiometric amounts of copper, large excess of phenols and high temperatures.[150] Buchwald and Hartwig introduced palladium-catalyzed approaches to overcome these synthetic problems. Even 100 years after the discovery of Ullmann diaryl ether synthesis, copper-mediated aryl-couplings still remain the reaction of choice for large- and industrial-scale formation of the diaryl ether bond in pharmaceutical, agrochemical, fine and polymer chemistries.[151]

Nevertheless and with the best of our knowledge we just found one publication that investigated the palladium-catalyzed diaryl ether coupling reaction of indoles. Beller and co-workers described C-O coupling reactions of electron-rich indole derivatives pictures in Scheme 52.[152] They presented a general palladium-catalyzed diaryl ether formation of electron-rich indoles to 3,5-dioxyindole

derivatives, which constituted a novel class of electron-rich indoles. Different alkylated phenols reacted in the presence of $Pd(OAc)_2$, ligand **I** (see Scheme 49) to give potentially bioactive indole derivatives.



Scheme 52. Palladium-catalyzed C-O coupling of indole derivatives.

1.7 Summary

The palladium-catalyzed coupling reaction is one of the most important instruments for organic chemists forming new C-C, C-N, and C-O bonds. As amply demonstrated above, palladium catalyzed coupling reactions of indoles has benefited a lot in the last few decades. The marvelous tools allow chemists to play with different parameters in chemical synthesis. It is often a helpful key step in total synthesis of natural compounds including an indole skeleton but also a useful method for further functionalization and investigations of indoles. This review has shown several of different possibilities to come to novel indole derivatives and their applications.

1.8 References

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2 Objectives of this Work

This thesis is presented as a cumulative collection of publications that have been submitted to or are already published in a range of international journals. The purpose of this summary is to depict the underlying reasons and ideas behind the journal articles and to clarify the relationship among them.

The major aim of this work was the development of novel indole derivatives and their catalytic functionalization via palladium catalysis to biologically active 5-HT receptor ligands. Based on our experience in indole synthesis, our main focus was the titanium- and zinc-mediated synthesis to substituted indoles and their further functionalization. We presented for the first time the synthesis of electron-rich silyloxyindoles via titanium-catalyzed hydrohydrazination of propargyl alcohol derivatives in *Synlett* **2007** and the zinc-promoted hydrohydrazination of terminal alkynes to new indole derivatives in *Angew. Chem. Int. Ed* **2008**.
Furthermore we concentrated on their functionalization via palladium–catalyzed Buchwald-Hartwig amination reported in *Tetrahedron Lett.* **2007** and C-O cross-coupling reaction published in *Synthesis* **2007**.
We investigated a multitude of new complex targets based on the indole skeleton via cross-coupling reactions, sulfonylation and nucleophilic substitution to new 5-HT receptor ligands published in *Org. Biomol. Chem.* **2008** and in *Eur. J. Org. Chem.* **2008**. Additionally, most of the synthesized compounds have been tested for it's biologically activity.

Additional achievements in catalytic hydroaminations which have been investigated during the synthesis of potential biologically active compounds are reported in *Eur. J. Org. Chem.* **2007**, *Tetrahedron* **2008**, *ChemSusChem* **2008**, *Org. Lett.* **2008** and *Tetrahedron Lett.* **2008**. They include improvements and explorations of methodologies for the synthesis and functionalization of indoles.

3 Publications

3.1 Titanium-Catalyzed Hydroamination of Propargyl Alcohol Derivatives: Synthesis of 3-Silyloxy-2-methylindoles via Hydrohydrazination

Nicolle Schwarz, Karolin Alex, Iliyas Ali Sayyed, Vivek Khedkar, Annegret Tillack, Matthias Beller, *Synlett* **2007**, *7*, 1091-1095.

Contributions: In this paper, I contributed to a significant amount of the argumentation and the synthetic work. I performed all catalytic investigations in Table 1 and the synthesis of compounds **4a**, **4b**, **4c** and **4d**. My contribution as co-author of this paper is approximately 50%.

Titanium-Catalyzed Hydroamination of Propargyl Alcohol Derivatives: Synthesis of 3-Silyloxy-2-methylindoles via Hydrohydrazination

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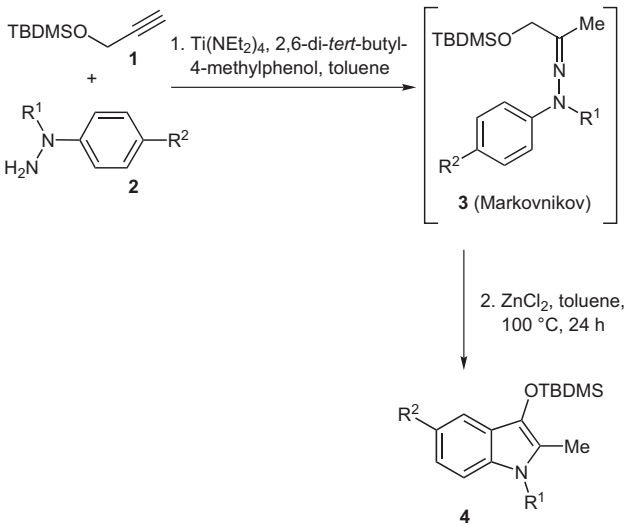
Abstract: A general method for the one-pot synthesis of substituted 3-(*tert*-butyldimethylsilyloxy)indoles via hydrohydrazination of alkynes and subsequent Fischer indole synthesis has been developed. For the first time titanium-catalyzed hydroaminations of propargyl alcohol derivatives are shown.

Key words: alkyne, hydrazine, hydroamination, indole, titanium

The addition of nitrogen compounds across carbon–carbon triple bonds continues to be an important subject for organic synthesis and catalysis.[1] Such addition reactions are perfectly suited to fulfill today's needs of green chemistry because atom economy or atom efficiency is in principle 100%. In recent years a variety of catalysts based on both early as well as late-transition-metal complexes has been developed. Based on the pioneering work of Bergman et al.[2] especially metallocenes have become popular catalysts in these reactions. More recently, Doye,[3] Odom,[4] Schafer[5] and other[6] made significant contributions to the further development of titanium catalysts with respect to intermolecular hydroaminations. However, in most reactions nonfunctionalized aromatic or simple aliphatic alkynes were reacted with primary amines as substrates. Thus, the hydroamination of more functionalized alkynes is still a challenging task. During our studies on the hydroamination of olefins and alkynes,[7] we became interested in the selective hydroamination of propargylic alcohols and their derivatives, which constitute probably the most prominent class of functionalized aliphatic alkynes. Here, we report the first examples of such reactions in the presence of titanium catalysts.

In addition to being environmentally benign, the hydroamination of alkynes opens up interesting possibilities for novel domino and one-pot reactions based on the resulting imines, enamines, or hydrazones. Recent examples include the combination of hydroamination coupled with direct nucleophilic addition of organometallic reagents[8] and electrocyclic rearrangements such as the Fischer indole synthesis.[9] For some time our group has been interested in the application of catalytic domino sequences such as hydrohydrazinomethylation of olefins,[10] carbonylations,[11] and hydrohydrazination of alkynes[12] for the synthesis and refinement of indoles.[13] Recently, we developed a one-pot synthesis of functionalized tryptamines and tryptophols starting from commercially available aryl hydrazines and chloroalkynes or 3- and 4-silyloxyalkynes.[12a,b] Based on this work, we studied the reaction of aniline, isobutylamine and *N*-methyl-*N*-phenylhydrazine with *tert*-butyldimethylsilyl-protected propargyl alcohol in the presence of a catalytic amount of tetrakis(diethylamino)titan [$Ti(NEt_2)_4$] and different phenols as ligands. While the former two model reactions gave only low yields (<5%) of the corresponding internal imine, the catalytic hydrohydrazination proceeded with significant conversion (>80%) in the presence of 2,6-di-*tert*-butyl-4-methylphenol as ligand! Interestingly, the resulting hydrazone is easily further converted in the presence of stoichiometric amounts of $ZnCl_2$ to give the corresponding siloxyindole in respectable yield (Scheme 1).



Scheme 1 Hydrohydrazination of silyl-protected propargyl alcohol to 3-silyloxy-2-methylindoles

To our delight the catalytic hydrohydrazination proceeded smoothly with high regioselectivity to the Markovnikov isomer **3**,[14] which underwent a selective Fischer indole synthesis to yield exclusively the 2,3-disubstituted indole **4**. To the best of our knowledge there is only a characterization of 3-phenoxy- and 3-methoxyindoles established and one different preparation of a special 2-substituted 3-silyloxyindole known in literature.[15] Noteworthy, a similar structural motif is found in furo[3,2-*b*]indoles, which are known to have potent analgesic and anti-inflammatory

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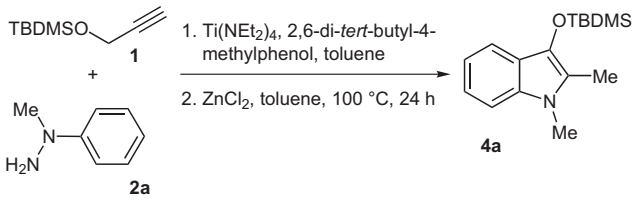
Table 1 Reaction of *tert*-Butyldimethylsiloxy-2-propyne (**1**) with *N*-Methyl-*N*-phenylhydrazine (**2a**)[a]



Entry	$Ti(NEt_2)_4$ (mol%)	Ligand (mol%)	Temp (°C)	Ratio hydrazine/alkyne	Time (h)	Yield (%)[b]
1	5	–	100	1.3:1	24	42
2	10	20	100	1.3:1	24	51
3	5	10	80	1.3:1	24	60
4	5	10	100	1.3:1	24	65
5	5	10	120	1.3:1	24	42
6	5	10	100	1:1.3	24	50
7	5	10	100	1.3:1	4	53

[a] *Reaction conditions*: hydrohydrazination: see Table 1; Fischer indole cyclization: $ZnCl_2$ (3.0 equiv), 100 °C, 24 h.
[b] Isolated yield based on *tert*-butyldimethylsiloxy-2-propyne.

activity[16] and act as potent BK_{Ca} channel openers for the treatment of neuronal damages or to treat cardiovascular diseases.[17]

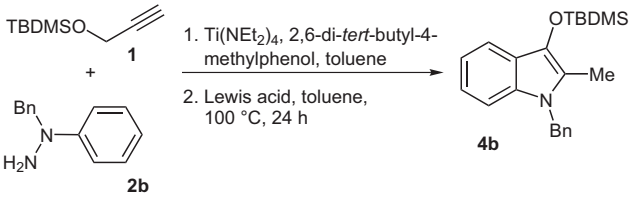
Selected results of the model reaction of *tert*-butyldimethylsiloxy-2-propyne (**1**)[18] with *N*-methyl-*N*-phenylhydrazine (**2a**) are shown in Table 1. The best yield of indole **4** (65%) is achieved applying 5 mol% $Ti(NEt_2)_4$ and 10 mol% 2,6-*tert*-butyl-4-methyl-phenol at 100 °C in the presence of a slight excess of hydrazine (Table 1, entry 4). Next, the effect of different Lewis acids on the Fischer indole cyclization was investigated. Therefore the hydrohydrazination of *tert*-butyldimethylsiloxy-2-propyne (**1**) and *N*-benzyl-*N*-phenylhydrazine (**2b**) was performed in the presence of different Lewis and Brønsted acids like *p*-toluenesulfonic acid (PTSA),[19] polyphosphoric acid (PPA),[20] and iron(III)chloride[21] instead of zinc chloride (Table 2).

However, none of the tested acids gave a better result compared to $ZnCl_2$ (50%).

Finally, we applied the optimized hydrohydrazination–cyclization protocol to ten different indole products (Table 3).[22] Commercially available aryl hydrazines with different substituents in the *para* position such as Me, OMe, F, Cl, Br, and SO_2Me were alkylated with methyl iodide or benzyl bromide in the presence of base and reacted with the in situ titanium catalyst and $ZnCl_2$ to give the desired 3-siloxyindole derivatives in good to moderate yields.

In general, the *N*-methyl-protected indoles gave a higher yield compared to the *N*-benzyl-protected indoles. Noteworthy, the reaction sequence can be performed easily up to a 10 g scale without loss in yield.

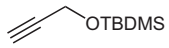
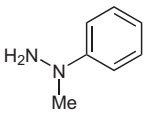
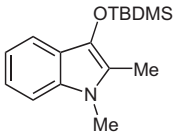
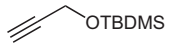
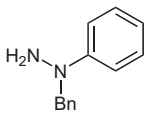
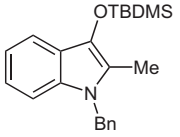
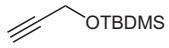
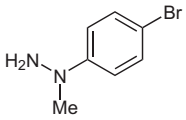
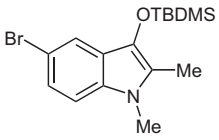
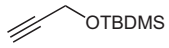
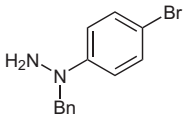
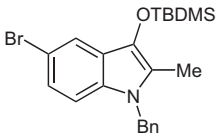
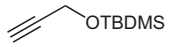
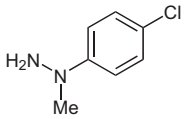
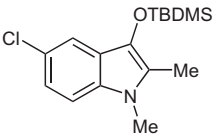
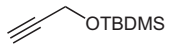
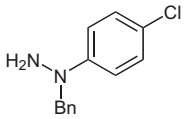
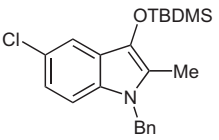
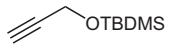
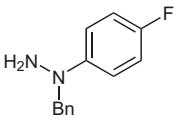
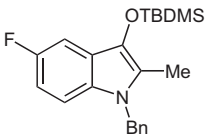
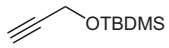
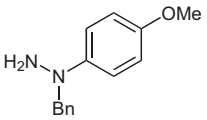
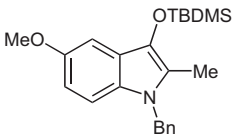
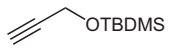
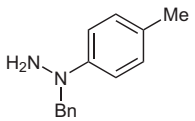
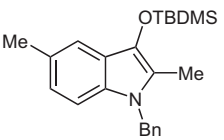
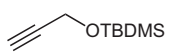
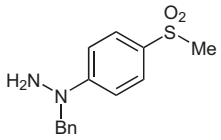
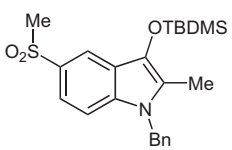
Table 2 Reaction of *tert*-butyldimethylsiloxy-2-propyne (**1**) with *N*-Benzyl-*N*-phenylhydrazine (**2b**)[a]



Entry	Lewis acid	Yield (%)[b]
1	$FeCl_3$	<1
2	NH_4Cl	<10
3	SO_2Cl_2	<1
4	AcOH	<1
5	PPA	<1
6	PTSA	<1
7	$Y(OTf)_3$	<10
8	$Zn(OTf)_2$	28
9	$ZnCl_2$	50

[a] *Reaction conditions*: hydrohydrazination: *tert*-butyl-dimethylsiloxy-2-propyne (1.0 mmol), *N*-benzyl-*N*-phenylhydrazine (1.3 mmol), $Ti(NEt_2)_4$ (5 mol%), 2,6-di-*tert*-butyl-4-methylphenol (10 mol%), toluene (2 mL), 100 °C, 24 h; Fischer indole cyclization: Lewis acid (3.0 mmol), 100 °C, 24 h.
[b] Isolated yield based on *tert*-butyldimethylsiloxy-2-propyne.

Table 3 Reaction of *tert*-Butyldimethylsiloxy-2-propyne (**1**) with Various Substituted Hydrazines (**2a**–**j**)[a]

Entry	Alkyne **1**	Hydrazine **2**		Product **4**		Yield (%)[b]
1			**2a**		**4a**	65
2			**2b**		**4b**	50
3			**2c**		**4c**	45
4			**2d**		**4d**	40
5			**2e**		**4e**	40
6			**2f**		**4f**	40
7			**2g**		**4g**	35
8			**2h**		**4h**	60
9			**2i**		**4i**	40
10			**2j**		**4j**	20

[a] *Reaction conditions*: hydrohydrazination: *tert*-butyldimethylsiloxy-2-propyne (1.0 mmol), arylhydrazine (1.3 mmol), $Ti(NEt_2)_4$ (5 mol%), 2,6-di-*tert*-butyl-4-methyl-phenol (10 mol%), toluene (2 mL), 100 °C, 24 h; Fischer indole cyclization: $ZnCl_2$ (3.0 mmol), 100 °C, 24 h.
[b] Isolated yield based on *tert*-butyldimethylsiloxy-2-propyne.

In conclusion, a new efficient method for the synthesis of functionalized 3-silyloxy-2-methylindoles has been developed. As key step the first titanium-catalyzed hydroamination of a propargylic alcohol derivative is applied. Starting from commercially available aryl hydrazines and silyl-protected propargyl alcohol a variety of new electron-rich indole derivatives are accessible with high regioselectivity in the presence of $Ti(NEt_2)_4$ and

2,6-di-*tert*-butyl-4-methylphenol. Further use of these 3-silyl-oxyindoles as intermediates for potential pharmaceuticals is currently under way in our laboratory.

Acknowledgment

This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213 and Leibniz prize), and the Fonds der Chemischen Industrie (FCI). We thank Dr. J. Holenz and Dr. J. L. Díaz Fernández (both Esteve, Spain) for general discussions. We also thank Dr. W. Baumann, Dr. D. Michalik, Dr. C. Fischer, S. Buchholz, and A. Lehmann for their excellent technical and analytical support.

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(22) **Representative Procedure: Synthesis of 1-Benzyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl-1*H*-indole (4b)**

In an ACE pressure tube under an argon atmosphere the ligand 2,6-di-*tert*-butyl-4-methylphenol (22.0 mg, 0.1 mmol) is dissolved in 3 mL dry toluene. To this solution *N*-benzyl-*N*-phenylhydrazine (257.7 mg, 1.3 mmol), *tert*-butyldimethylsiloxy-2-propyne (209.0 mL, 1.0 mmol) and $Ti(NEt_2)_4$ (18 μL, 0.05 mmol) were added. The reaction mixture was heated at 100 °C for 24 h. Then the pressure tube was opened under argon to add $ZnCl_2$ (410.0 mg, 3.0 mmol). The reaction mixture was heated at 100 °C for further 24 h. After cooling to r.t. the solution was decanted and the dark residue was washed with toluene and EtOAc. After removal of the combined solvents in vacuo and purification by column chromatography (eluent: hexane–EtOAc = 10:1) yielded 1-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl-1*H*-indole (175.8 mg, 50%) as light yellow solid (mp 69 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 1 H), 7.27–7.21 (m, 3 H, *m*-, *p*-Ph), 7.10 (m, 1 H), 6.93 (m, 2 H), 6.86–6.87 (m, 2 H, *o*-Ph), 5.22 (s, 2 H, CH_2Ph), 2.20 (s, 3 H), 0.83 (s, 12 H), 0.15 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4 (*i*-Ph), 135.6, 133.6, 128.9 (*m*-Ph), 128.4, 127.8 (*p*-Ph), 125.8 (*o*-Ph), 121.7, 120.6, 120.8, 120.7, 108.7, 46.9, 25.8, 18.2, 9.1, –5.3 ppm. MS (EI, 70 eV): *m/z* (relative intensity) = 351 (100) [M^+], 294 (27), 260 (13), 221 (25), 204 (12), 177 (8), 115 (15), 91 (90), 73 (71), 65 (8), 43 (6). HRMS (EI): *m/z* calcd for $C_{22}H_{29}NOSi$: 351.2013; found: 351.1999.

3.2 Zinc-Promoted Hydrohydrazination of Terminal Alkynes: An Efficient Domino Synthesis of Indoles

Karolin Alex, Annegret Tillack, Nicolle Schwarz, Matthias Beller, *Angew. Chem. Int. Ed*. **2008**, *47*, 2304-2307; *Angew. Chem*. **2008**, *20*, 2337-2340.

Contributions: In this paper, I was involved in experimental planning, as well as discussion and argumentation of the results. I contributed significantly to the draft of the manuscript and supported the synthetic work. My contribution as co-author of this paper is approximately 10%.

Indole Synthesis

DOI: 10.1002/anie.200703823

Zinc-Promoted Hydrohydrazination of Terminal Alkynes: An Efficient Domino Synthesis of Indoles**

*Karolin Alex, Annegret Tillack, Nicolle Schwarz, and Matthias Beller**

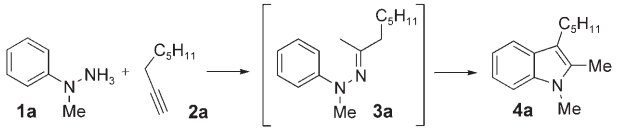
There is continuing interest in the development of improved methods for the synthesis of indoles owing to their importance as one of the most represented building block in natural bioactive products and marketed drugs.[1,2] Thus, indole and its derivatives have been termed "privileged pharmacological structures" as they bind to many biological receptors with high affinity.[3]

In recent years, domino sequences in particular have provided efficient complementary access to various indoles.[4] Such sequences start in general from easily available substrates. A reactive intermediate is generated with the aid of a catalyst, which is subsequently transformed to the desired indole. For example, the domino hydroformylation–Fischer indole sequence has evolved into a direct method for the one-pot construction of complex indoles from olefins.[5,6] More recently, Ackermann and Born reported the use of a combination of $TiCl_4$ and $tBuNH_2$ as catalyst for the domino hydroamination–Fischer indole cyclization.[7] In 1991, Bergman et al. reported the first zirconium-mediated synthesis of indoles by trapping a hydrazidozirconocene complex with alkynes and subsequent addition of hydrochloric acid.[8] Then, Odom and co-workers described the first titanium-catalyzed intermolecular hydroamination of arylhydrazines with alkynes.[9,10] The arylhydrazones obtained have been used further in the Fischer indole reaction to provide *N*-alkyl and *N*-aryl indoles in high yield. Based on this elegant approach, we have developed the titanium-catalyzed synthesis of functionalized tryptamines and tryptamine homologues, and tryptophol and tryptophol derivatives, starting from commercially available arylhydrazines and alkynes.[11] A problem which prevents widespread use of this reaction is the sensitivity of the titanium complexes towards functional groups, and the necessity for hydrazine protection and indole deprotection steps.

Our continuing interest in indole syntheses led us to look for alternative catalysts for the intermolecular hydrohydrazination. Herein we report the intermolecular zinc-mediated and -catalyzed hydroamination reactions of alkynes which provide a general synthesis of indoles.[12,13]

Our initial investigations involved studying the effect of different metal complexes on the model reaction of *N*-methyl-*N*-phenylhydrazine **1a** with 1-octyne **2a** (Table 1). The

Table 1: Variation of different metal salts for the indole synthesis.[a]



Entry	Metal salt	Equiv	Conversion[b] [%]	Yield[b] [%]
1[c]	$Ti(NEt_2)_4$/L/$ZnCl_2$	0.05/0.1/3	100	85
2	$Zn(OTf)_2$	1	100	>99
3	$ZnCl_2$	1	78	66
4	$FeCl_3 \cdot 6H_2O$	1	8	0
5	$HAuCl_4$	1	97	0
6	$H_2PtCl_6 \cdot 6H_2O$	1	100	<5
7	$IrCl_3$	1	100	0
8	$Sc(OTf)_3$	1	<5	<5
9	$Yb(OTf)_3$	1	10	<5
10	$Zn(OTf)_2$	0.5	96	94
11	$Zn(OTf)_2$	0.25	72	70
12	$Zn(OTf)_2$	0.1	36	30
13	$ZnCl_2$	3	100	97
14	$ZnBr_2$	1	79	55
15	$Zn(OAc)_2$	1	<5	0

[a] Reaction conditions: 1 mmol octyne, 1.3 mmol *N*-methyl-*N*-phenylhydrazine, 2 mL THF, 100°C, 24 h. [b] Determined by GC with hexadecane as internal standard. [c] For hydroamination: 5 mol% $Ti(NEt_2)_4$, 10 mol% 2,6-di-*tert*-butyl-4-methyl-phenol (L), 2 mL toluene, 100°C, 24 h. For Fischer indole cyclization: 3 mmol $ZnCl_2$, 100°C, 24 h.

amination reaction proceeds smoothly in the presence of 5 mol% of known titanium catalysts. Subsequent addition of 3 equivalents of $ZnCl_2$ to promote the Fischer indole cyclization furnished the desired indole in good yield (85%; Table 1, entry 1). Surprisingly, the overall reaction sequence also proceeds in good to excellent yield without any titanium catalyst. Only in the presence of $Zn(OTf)_2$ and $ZnCl_2$ (Table 1) is **4a** obtained in >99 and 66% yields, respectively (Table 1, entries 2 and 3). Thus, simple zinc salts promote both the intermolecular hydroamination of the arylhydrazine **1** with the terminal alkyne **2** to the corresponding arylhydrazone **3** and subsequently initialize the [3,3]-sigmatropic cyclization to the corresponding indole **4**.

Owing to the highly selective Markovnikov reaction[14] of the alkyne with the hydrazine, only the 2,3-disubstituted

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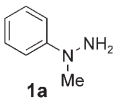
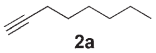
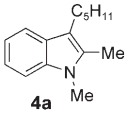
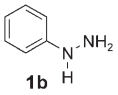
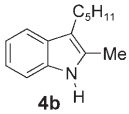
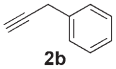
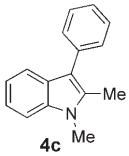
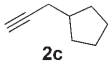
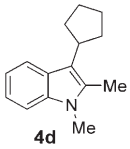
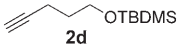
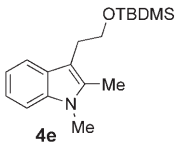
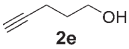
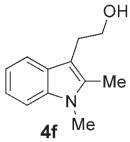
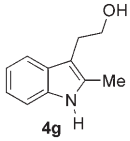
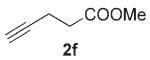
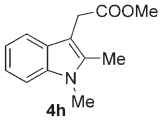
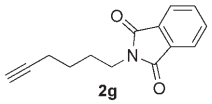
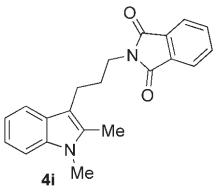
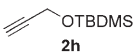
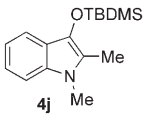
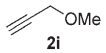
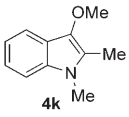
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2: Reaction of *N*-methyl-*N*-phenylhydrazine or *N*-phenylhydrazine with various substituted alkynes.[a]

Entry	Lewis acid	Arylhydrazine **1**	Alkyne **2**	Indole **4**	Yield[b] [%]
1	$ZnCl_2$	 **1a**	 **2a**	 **4a**	94
2	$ZnCl_2$	 **1b**	**2a**	 **4b**	91
3	$ZnCl_2$ $Zn(OTf)_2$	**1a**	 **2b**	 **4c**	81 96
4	$ZnCl_2$ $Zn(OTf)_2$	**1a**	 **2c**	 **4d**	95 94
5	$ZnCl_2$	**1a**	 **2d**	 **4e**	82
6	$ZnCl_2$	**1a**	 **2e**	 **4f**	97
7	$ZnCl_2$	**1b**	**2e**	 **4g**	97
8	$Zn(OTf)_2$	**1a**	 **2f**	 **4h**	58
9	$ZnCl_2$	**1a**	 **2g**	 **4i**	50
10	$ZnCl_2$	**1a**	 **2h**	 **4j**	60
11	$Zn(OTf)_2$	**1a**	 **2i**	 **4k**	53

[a] Reaction conditions: 1.5 mmol alkyne, 1.95 mmol *N*-methyl-*N*-phenylhydrazine or *N*-phenylhydrazine, 3 equiv $ZnCl_2$ or 1 equiv $Zn(OTf)_2$, 4 mL THF, 100 °C, 24 h. TBDMS = *tert*-butyldimethylsilyl. [b] Yield of isolated product.

indole is produced in excellent yield. Other typical Lewis acids, such as $FeCl_3$ and rare earth triflates, are not active in this reaction (Table 1, entries 4, 8, and 9). Furthermore, $HAuCl_4$, H_2PtCl_6, and $IrCl_3$, which are active in electrophilic aromatic substitutions, gave no desired product (Table 1, entries 5, 6, and 7).[15] Instead, oligomers of the alkyne are mainly formed as side products.

We investigated whether the reaction also proceeds in the presence of catalytic amounts of $Zn(OTf)_2$. Indeed, with 0.5 and 0.25 equivalents of Lewis acid, the indole is obtained in 94 and 70% yield, respectively (Table 1, entries 10 and 11). However, a further decrease to 0.1 equivalents led to lower yields (Table 1, entry 12).

Variation of the reaction conditions demonstrated that the model reaction of *N*-methyl-*N*-phenylhydrazine with 1-octyne proceeds in high yield in polar solvents, such as tetrahydrofuran, dioxane, and dimethylformamide. Notably, toluene, which is the commonly used solvent in titanium-catalyzed hydrohydrazinations, gave only a low yield of 21% (24 h, 100 °C, 3 equiv $ZnCl_2$). To achieve full conversion and high yield, a slight excess of *N*-methyl-*N*-phenylhydrazine is advantageous.

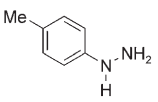
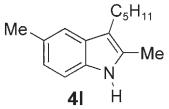
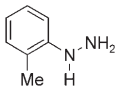
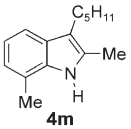
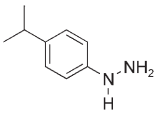
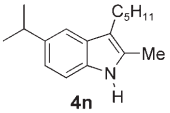
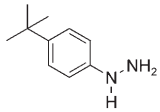
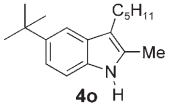
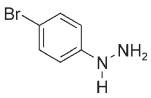
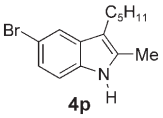
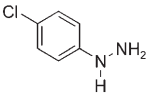
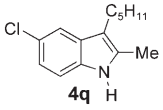
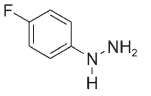
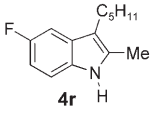
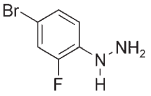
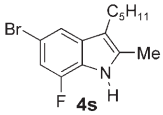
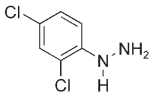
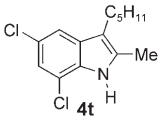
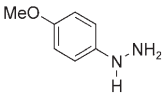
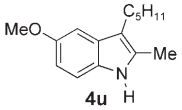
We were interested in the scope and limitations of the procedure with different alkynes (Table 2). For this purpose, we studied the reaction of *N*-methyl-*N*-phenylhydrazine and *N*-phenylhydrazine with various alkynes in the presence of $Zn(OTf)_2$ and $ZnCl_2$. Notably, applying the unprotected hydrazine together with 1-octyne, the free indole **4b** is formed in high yield (91%; Table 2, entry 2). This is the first example of free indole formation by hydrohydrazination of alkynes. Apart from 1-octyne other alkynes, for example 3-phenyl-1-propyne and 3-cyclopentyl-1-propyne, also gave the corresponding indoles **4c** and **4d** in up to 96% yield (Table 2, entries 3 and 4). We developed a synthesis for pharmaceutically relevant tryptophol

homologues by reaction of silyl-protected (2- and 3-hydroxyalkyl)alkynes with *N*,*N*-disubstituted arylhydrazines.[11b] The yield of this reaction using simply $ZnCl_2$ is 82% (Table 2, entry 5). The particular advantage of this reaction is that by using $ZnCl_2$, there is no need for protecting groups at the alkyne or the hydrazine unit. Thus, the tryptophol homologue **4g** is obtained in excellent yield (97%) by reacting *N*-phenylhydrazine with pentyn-1-ol in the presence of $ZnCl_2$ (Table 2, entry 7). Moreover, the reaction of *N*-methyl-*N*-phenylhydrazine with methyl pent-4-ynoate gave the indomethacin analogue **4h** (Table 2, entry 8). Similarly, the phthalimide-protected 6-aminohexyne afforded the tryptamine homologue **4i** (Table 2, entry 9). Even sensitive electron-rich 3-silyloxyindoles **4j**[16] and 3-methoxyindole **4k** were obtained, although only in moderate yields because of decomposition. To our knowledge, the latter reaction is the first example of a hydroamination of a propargylalkylether. In addition, we carried out some initial trials with internal alkynes, for example 1-phenyl-1-propyne and diphenylacetylene. However, these substrates resulted only in traces of the respective indoles under the optimized conditions, and in these cases, further work is necessary.

We explored the reaction of 1-octyne with various substituted arylhydrazines **2** in the presence of $Zn(OTf)_2$. Again, a protection of the arylhydrazine is not necessary, and the free indole is obtained in good to excellent yields (Table 3). Comparing *ortho*-and *para*-methylphenylhydrazine, the former is less reactive. Arylhydrazines substituted with electron-withdrawing groups required higher temperatures and more $Zn(OTf)_2$ for complete conversion (Table 3, entries 5–9), which is in agreement with the Fischer indole cyclization of aldehydes. Applying these conditions, all monohalophenylhydrazines gave product yields of $>95\%$. In the case of dihalosubstituted arylhydrazines, somewhat lower yields were observed (Table 3, entries 8 and 9).

In conclusion, we have developed a convenient one-pot method for the synthesis of various substituted indoles. Starting from commercially available arylhydrazines and terminal alkynes, a range of pharmaceutically relevant indole building blocks are obtained selectively in the presence of either $Zn(OTf)_2$ or $ZnCl_2$. No expensive catalyst is required for this novel environmentally friendly reaction, and for the first time free indoles, for example, tryptophol derivatives, are directly available from alkynes.

Table 3: Reaction of 1-octyne with various substituted arylhydrazines.[a]

Entry	Hydrazine **1**	Indole **4**	Yield[b] [%]
1		 **4l**	97
2		 **4m**	82
3		 **4n**	95
4		 **4o**	67
5[c]		 **4p**	97
6[c]		 **4q**	97
7[c]		 **4r**	96
8[c]		 **4s**	80
9[c]		 **4t**	52
10		 **4u**	97

[a] Reaction conditions: 1.5 mmol 1-octyne, 1.95 mmol arylhydrazine, 1 equiv $Zn(OTf)_2$, 4 mL THF, 100°C, 24 h. [b] Yield of isolated product. [c] 2 equiv $Zn(OTf)_2$, 4 mL THF, 120°C, 24 h.

Experimental Section

General procedure: $ZnCl_2$ (4.5 mmol, 545.3 mg) or $Zn(OTf)_2$ (1.5 mmol, 613.3 mg) were dissolved in THF in an ACE pressure tube under an argon atmosphere. Arylhydrazine (1.95 mmol) and alkyne (1.5 mmol) were then added to this solution. The pressure tube was sealed and the reaction mixture was heated at 100°C for 24 h. After removal of the solvent in vacuo, the indole product was purified by column chromatography (hexane/ethyl acetate).

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3.3 A Novel Palladium Catalyst for the Amination of Electron-Rich Indole Derivatives

Nicolle Schwarz, Annegret Tillack, Karolin Alex, Iliyas Ali Sayyed, Ralf Jackstell, Matthias Beller, *Tetrahedron Lett.* **2007**, *48*, 2897-2900.

Contributions: In this paper I contributed to a significant amount of the argumentation and the synthetic work. I performed all catalytic investigation. My contribution as co-author of this paper is approximately 80%.

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A novel palladium catalyst for the amination of electron-rich indole derivatives

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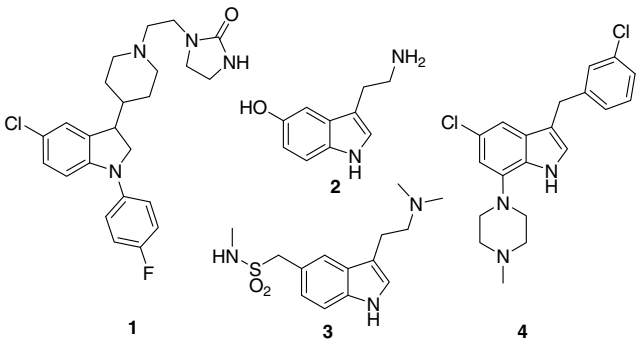
Abstract—The palladium-catalyzed amination of a 3-silyloxy-substituted bromo-indole with primary and secondary amines is described for the first time. In the presence of the novel catalyst system of $Pd(OAc)_2$/*N*-phenyl-2-(di-1-adamantylphosphino)pyrrole potentially bioactive amino-functionalized indole derivatives are obtained in a general manner in high yield.

The indole ring system constitutes one of the most important heterocycles in nature and substituted indoles have been referred to as 'privileged pharmaceutical structures' since they are capable of binding to many biological receptors with high affinity.[1] Due to their importance as building blocks for pharmaceuticals and natural products the preparation of new indole derivatives is an actual topic in organic chemistry. Owing to the great structural diversity of biologically active indoles, there is also a continuing interest in the development of improved methods for the synthesis of indoles.[2]

Among the numerous known indoles, especially amino-functionalized derivatives represent key structures for various biologically active compounds (Scheme 1). In particular tryptamine derivatives are involved in several biological processes, for example, melatonin in the control of the circadian rhythm and serotonin **2** in neurological processes. Thus, amino-functionalized indoles are used for the medical treatment of diverse diseases like migraine (Sumatriptan **3**), schizophrenia (Sertindole **1**), and many others. Due to the pharmaceutical relevance of amino-substituted tryptamine and its analogues, numerous syntheses have been reported and the development of new methods is still a subject of intensive research.[3]



Scheme 1. Examples of amino-substituted indole derivatives.

Based on our long standing interest in indole syntheses[4] as well as in palladium-catalyzed coupling reactions,[5] we became interested in the preparation of new functionalized indole derivatives via Buchwald–Hartwig aminations.

Clearly, palladium-catalyzed C–N-bond formation (Buchwald–Hartwig reaction) of aryl halides with amines has been extensively studied in the past few years.[6] In general, these processes have excellent functional group tolerance and wide substrate scope, which make them ideally suited for applications in the pharmaceutical area. However, there is relatively little known on the coupling reactions of electron-rich indoles.

Clearly, the palladium-catalyzed activation is more difficult here compared to electron-poor substrates.

Keywords: Amination; C–N coupling; Palladium; Indoles.
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0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
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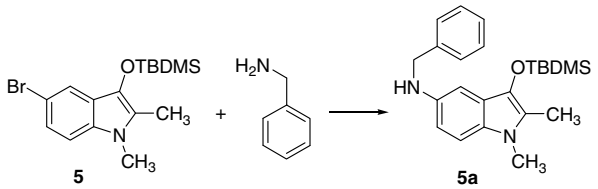
Table 1. Reaction of 3-*tert*-butyldimethylsilyloxy-5-bromo-indole with benzylamine in the presence of different ligands and bases[a]



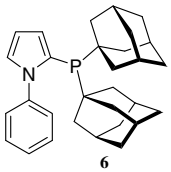
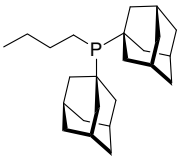
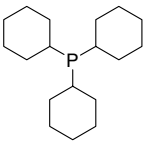
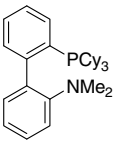
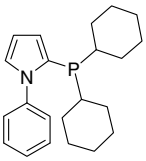
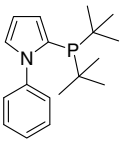
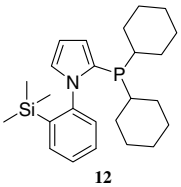
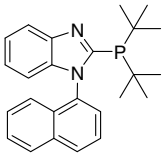
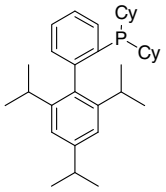
Entry	Ligand	Base	Yield[b] (%)
1		LiHMDS[c]	85
2		K_3PO_4	5
3		Cs_2CO_3	70
4		NaO^{t}Bu	40
5		Without	0
	6		
6		LiHMDS	<10
	7		
7		LiHMDS	<10
	8		
8		LiHMDS	51
	9		
9		LiHMDS	25
	10		
10		LiHMDS	75
	11		
11		LiHMDS	95
	12		

Table 1 (*continued*)

Entry	Ligand	Base	Yield[b] (%)
12		LiHMDS	40
	13		
13		LiHMDS	85
	14		

[a] Reaction conditions: 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole (0.56 mmol), benzylamine (0.67 mmol), solvent: toluene (3 mL), 1 mol % $Pd(OAc)_2$, 2 mol % ligand, base (0.73 mmol), 24 h, 100 °C.

[b] Isolated yield based on 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole.

[c] 1 M solution of lithium-bis(trimethylsilyl)amide in toluene.

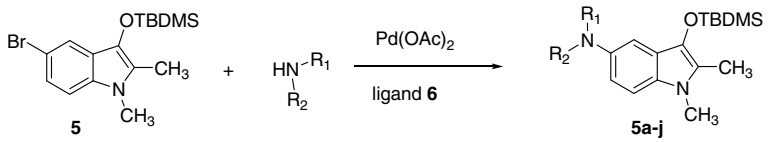
In the present Letter we describe for the first time the palladium-catalyzed amination of 3-silyloxy-5-bromo-indole with primary and secondary amines in the presence of $Pd(OAc)_2$ and *N*-phenyl-2-(di-1-adamantylphosphino)-pyrrole as ligand to give new indole derivatives.

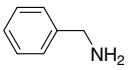
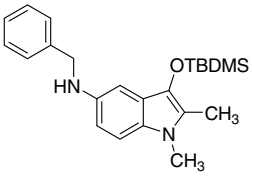
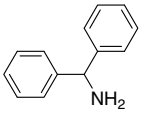
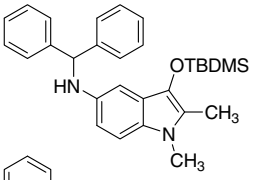
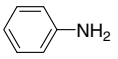
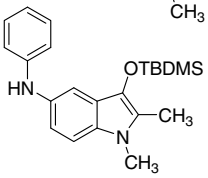
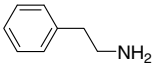
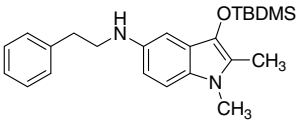
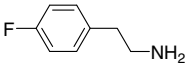
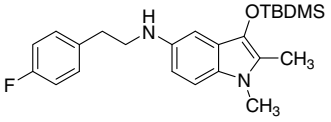
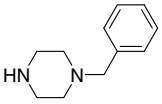
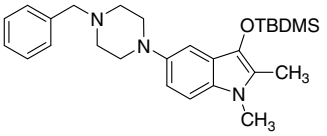
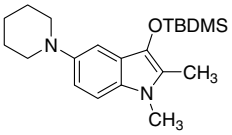
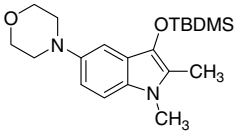
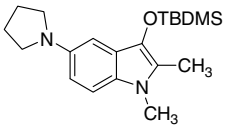
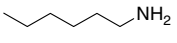
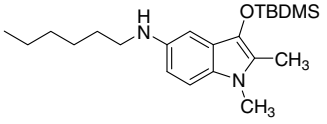
In exploratory experiments, we studied the effect of base and ligands on the reaction of 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole **5** and benzylamine to the corresponding indole **5a**. As shown in Table 1 the best yield of indole **5a** (85%) is achieved with 1.3 equiv of 1 M solution of LiHMDS in toluene. Further variation of the base revealed only lower yields (5–70%) of the corresponding indole (Table 1, entries 2–5). As expected the reaction without any base was not successful (Table 1, entry 5). Next, we were interested in the influence of different sterically demanding ligands on our model reaction. All reactions were performed at 100 °C for 24 h in toluene in the presence of 1 mol % $Pd(OAc)_2$ and 1.3 equiv of LiHMDS (Table 1, entries 6–13). In general, sterically hindered biaryl-type ligands gave the best yields. Thus, using ligands **11**, **12**, and **14** gave 75–95% yield of the corresponding indole. Employing di-1-adamantyl-*n*-butylphosphine **7** or tricyclohexylphosphine **8** the isolated yield decreased to <10%. Here, we observed mainly reductive dehalogenation via β-hydride-elimination as competing reaction pathway.

After testing different ligands and bases, we were interested in the scope and limitations of the catalyst system for different amines. For this purpose we used the silyl-protected 3-oxy-5-bromo-2-methylindole **5** and diverse primary and secondary amines.

Although ligands **12** and **14** gave comparable or even improved results in the model coupling reaction, nevertheless, we used **6** for the further synthesis of

Table 2. Reaction of different amines with the silyl-protected 3-oxy-5-bromo-2-methylindole[a]



Entry	Amine	Product		Yield[b] (%)
1			**5a**	85
2			**5b**	40
3			**5c**	85
4			**5d**	60
5			**5e**	91
6			**5f**	50
7			**5g**[8]	75
8			**5h**	55
9			**5i**	73
10			**5j**	91

[a] Reaction conditions: 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole (0.56 mmol), amine (0.67 mmol), solvent: toluene (3 mL), 1 mol % $Pd(OAc)_2$, 2 mol % ligand **6**, 1 M solution of lithium-bis(trimethylsilyl)amide in toluene (0.73 mmol), 24 h, 100 °C.

[b] Isolated yield based on 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole.

amino-functionalized indoles, because of the easier availability of this in-house developed ligand.[7] As shown in Table 2 the corresponding indole products are obtained in 40–91% yield. The novel catalyst system works well with different primary and secondary amines which are all commercially available. With respect to the yield there is no clear trend on the electronic or steric factors of the amine.

In conclusion, we presented the first palladium-catalyzed amination of silyl-protected 3-oxyhaloindoles, a novel class of electron-rich indoles. Different amines reacted smoothly in the presence of $Pd(OAc)_2$, *N*-phenyl-2-(diadamantyl-phosphino)pyrrole **6** to give potentially bioactive amino-functionalized indoles.

Acknowledgments

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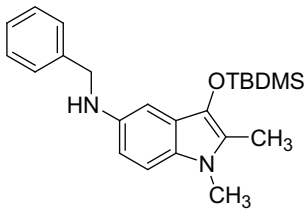
8. Preparative procedure for the Pd-catalyzed amination reaction (**5g**): In an Ace-pressure tube under an argon atmosphere 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole (0.56 mmol), $Pd(OAc)_2$ (1 mol %) and ligand **6** (2 mol %) were dissolved in toluene (3 mL). To this solution LiHMDS (0.73 mmol) and piperidine (0.67 mmol) were added. The pressure tube was fitted with a Teflon cap and heated at 100 °C for 24 h. After removal of the solvent in vacuo, the desired indole product was isolated by column chromatography in hexane/ethyl acetate. Isolated yield: 150 mg (75%), (mp: 85–88 °C). ^{1}H NMR (300.13, $CDCl_3$) $\delta = -0.17$ (s, 6H, H-12a,b); 1.09 (s, 9H, H-13a,b,c); 1.5–1.9 (m, 7H, H-16a,b; H-17); 2.28 (s, 3H, H-11); 3.08 (t, 4H, $^3J_{15,16} = 5.4$ Hz, H-15a,b); 3.57 (s, 3H, H-10); 6.92 (dd, 1H, $^4J_{4,6} = 2.2$ Hz, $^3J_{6,7} = 8.8$ Hz, H-6); 7.01 (d, 1H, $^4J_{4,6} = 2.2$ Hz, H-4); 7.11 (d, 1H, $^3J_{6,7} = 8.8$ Hz, H-7) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz,) $\delta = -3.9$ (C-12); 9.4 (C-11); 18.4 (C-14); 24.6 (C-17); 26.1 (C-13); 26.6 (C-16a,b); 29.7 (C-10); 53.8 (C-15a,b); 105.1 (C-4); 108.9 (C-6); 115.2 (C-7); 121.8, 122.9, 129.8, 130.4, 146.1 (C-9, C-8, C-5, C-3, C-2) ppm. MS (EI, 70 eV) *m*/*z* (rel. intensity): 358 (100) [M^+], 343 (3), 301 (6), 228 (12). HRMS calcd for $C_{21}H_{34}N_2OSi$: 358.24349. Found: 358.242665.

Experimental Data

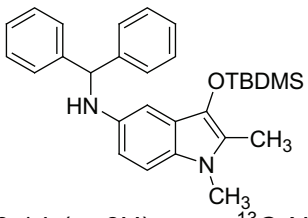
All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros and Strem and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 300, AV 400 and AV 500 spectrometers. The ^{1}H and ^{13}C NMR chemical shifts are referenced to TMS (δ TMS = 0 (^{1}H)), and to the solvent resonance (δ CDCl3 = 77.0 (^{13}C)). EI mass spectra were recorded on an AMD 402 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded on a FT-IR Nicolet 6700 (Thermo ELECTRON CORPORATION).

[3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-benzyl-amine (5a)



Yield 85%. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.39-7.22 (m, 5H); 7.00 (d, 1H, J = 8.4 Hz); 6.63 (d, 1H, J = 2.1 Hz), 6.56 (dd, 1H, J = 8.4 Hz, J = 2.1 Hz), 4.34 (s, 2H); 3.51 (s, 3H); 2.23 (s, 3H); 1.03 (s, 9H); 0.06 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 141.1 (q); 140.2 (q); 129.7 (q); 128.6 (q); 128.5; 127.5; 126.9; 122.8 (q); 122.0 (q);110.4; 109.0; 99.6; 49.8 (CH_2); 29.4; 25.9; 18.1 (q); 9.2; -4.3 ppm. MS (EI, 70 eV) m/z (rel. intensity): 381 (37), 380 (M^+, 100), 323 (6), 290 (13), 289 (63), 232 (7), 91 (5), 73 (9). HRMS Calcd. for $C_{23}H_{32}N_2OSi$: 380.22784. Found: 380.227528. FTIR (ATR): 3413, 3388, 3084, 3027, 2955, 2927, 2856, 1627, 1584, 1480, 1452, 1379, 1309, 1247, 1165, 929, 895, 834, 777, 736, 693 cm^{-1}.

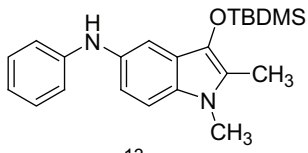
Benzhydryl-[3-(*tert*-butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-amine (5b)



Yield: 40%. Mp.: 88-95 °C. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.67-7.62 (m, 4H); 7.57-7.42 (m, 6H); 7.22 (d, 1H, *J* = 8.6 Hz); 6.77 (dd, 1H, *J* = 8.6 Hz, *J* = 2.3 Hz); 6.68 (d, 1H, *J* = 2.3 Hz); 5.71 (s, 1H); 3.74 (s, 3H); 2.45 (s, 3H); 1.81 (bs, 1H, NH); 1.19 (s, 9H); 0.14 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 143.7 (q); 140.4 (q); 132.5 (q); 129.8 (q); 128.7 (4x CH); 128.5 (q); 127.5 (4x CH); 127.1 (2x CH); 122.8 (q); 121.9 (q); 110.9; 108.9; 100.2; 64.5; 29.5; 25.9; 18.1 (q); 9.2; -4.4 ppm. MS (EI, 70 eV) m/z (rel. intensity): 457 (M^{+1}, 23), 456 (M^+, 72), 291 (20), 290 (97), 289 (100), 234 (8), 233 (21), 218 (7), 168 (33), 167 (50), 165 (20), 75 (11). HRMS Calcd. for $C_{29}H_{36}N_2OSi$: 456.25914. Found:

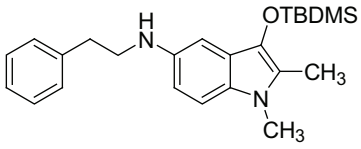
456.258767. FTIR (Nujol): 3379, 2925, 2854, 1668, 1626, 1565, 1461, 1378, 1263, 1168, 1074, 948, 891, 839, 787, 701cm^{-1}.

[3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-phenyl-amine (5c)



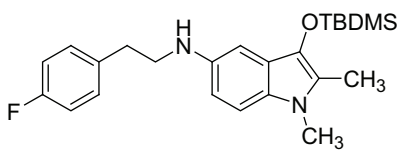
Yield: 85%. Mp: 135-140 °C. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.24 (d, 1H, *J* = 1.9 Hz); 7.21-7.11 (m, 3H); 6.95-6.87 (m, 3H); 6.78 (m, 1H); 3.59 (s, 3H); 2.29 (s, 3H); 1.58 (bs, 1H, NH); 1.05 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 146.9 (q); 133.7 (q); 131.2 (q); 130.4 (q); 129.4 (2xCH); 123.7 (q); 122.2 (q); 118.8; 117.2; 115.0 (2xCH); 110.7; 109.2; 29.8; 26.1; 18.4 (q); 9.5; -4.0 ppm. MS (EI, 70 eV) m/z (rel. intensity): 367 (M^{+1}, 30), 366 (M^{+}, 100), 310 (6), 309 (9), 236 (9), 235 (7), 167 (4), 73 (11). HRMS Calcd. for $C_{22}H_{39}N_2OSi$: 366.21219. Found: 366.211482. FTIR (Nujol): 3384, 2925, 2854, 1600, 1511, 1462, 1376, 1321, 1250, 1156, 1072, 938, 895, 842, 801, 782, 741, 690 cm^{-1}.

[3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-phenethyl-amine (5d)



Yield: 60%. Mp: 77-80 °C. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.31 (m, 2H); 7.22 (m, 3H); 7.01 (d, 1H, *J* = 8.6 Hz); 6.71 (d, 1H, *J* = 2.2 Hz); 6.52 (dd, 1H, *J* = 8.6 Hz, *J* = 2.2 Hz); 3.53 (s, 3H); 3.43 (t, 2H, *J* = 6.8 Hz); 2.94 (t, 2H, *J* = 6.8 Hz); 2.25 (s, 3H); 1.07 (s, 9H); 0.15 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 140.9 (q); 140.0 (q); 129.9 (q); 129.1 (2x CH); 129.0 (q); 128.8 (2x CH); 126.5; 123.1 (q); 122.4 (q); 111.1; 109.3; 100.3; 46.9 (CH_2); 35.8 (CH_2); 29.8; 26.2; 18.5 (q); 9.5; -3.9 ppm. MS (EI, 70 eV) m/z (rel. intensity): 395 (M^{+1}, 16), 394 (M^{+}, 60), 303 (100), 302 (6), 264 (4), 263 (1), 174 (3), 173 (17), 142 (11), 141 (11), 73 (7). HRMS Calcd. for $C_{24}H_{34}N_2OSi$: 394.24349. Found: 394.243114. FTIR (Nujol): 3348, 2927, 2855, 1620, 1581, 1493, 1467, 1377, 1286, 1250, 1163, 941, 891, 874, 840, 778, 741, 700,cm^{-1}.

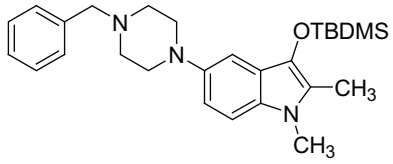
[3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-[2-(4-fluoro-phenyl)-ethyl]-amine (5e)



Yield: 91%. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.22-7.18 (m, 2H); 7.06-6.98 (m, 3H); 6.72 (d, 1H, *J* = 2.1 Hz); 6.53 (dd, 1H, *J* = 8.7 Hz, *J* = 2.1 Hz); 3.56 (s, 3H); 3.43 (t, 2H, *J* = 6.9 Hz); 2.93 (t, 2H, *J* = 6.9 Hz); 2.28 (s, 3H); 1.09 (s, 9H); 0.18 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 161.6 (d, *J* = 244 Hz, q); 140.6 (q); 135.4 (d, *J* = 3.2 Hz, q); 130.3 (d, J = 7.8 Hz); 129.7 (q); 128.8 (q); 123.1 (q); 122.2

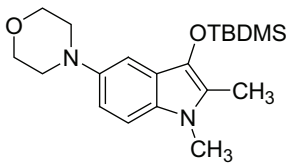
(q); 115.3 (d, J = 21.2 Hz); 110.8; 109.2; 100.0; 46.8 (CH_2); 34.7 (CH_2); 29.5; 26.0; 18.2 (q); 9.3; -4.1 ppm. MS (EI, 70 eV) m/z (rel. intensity): 413 (9), 412 (M^+, 29), 305 (5), 304 (21), 303 (100), 274 (2), 217 (3), 188 (2), 187 (3), 150 (1), 149 (8). HRMS Calcd. for $C_{24}H_{33}FN_2OSi$: 412.23407. Found: 412.234775. FTIR (Nujol): 3377, 2928, 2856, 1624, 1588, 1567, 1512, 1489, 1475, 1379, 1281, 1255, 1171, 944, 892, 862, 840, 779 cm^{-1}.

5-(4-Benzyl-piperazin-1-yl)-3-(*tert*-butyl-dimethyl-silanyl-oxy)-1,2-dimethyl-1*H*-indole (5f)



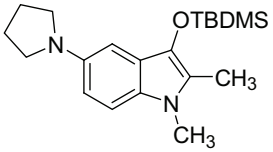
Yield: 50%. ^1H NMR (300.13, $CDCl_3$): δ = 7.40-7.24 (m, 5H); 7.10 (d, 1H, *J* = 8.8 Hz); 6.97 (d, 1H, *J* = 2.2 Hz); 6.88 (dd, 1H, *J* = 8.8 Hz, *J* = 2.2 Hz); 3.59 (s, 2H); 3.55 (s, 3H); 3.15 (t, 4H, *J* = 4.9 Hz); 2.67 (t, 4H, *J* = 4.9 Hz); 2.26 (s, 3H); 1.07 (s, 9H); 0.14 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 144.7 (q); 138.0 (q); 130.1 (q); 129.7 (q); 129.3 (2x CH); 128.2 (2x CH); 127.1; 122.9 (q); 121.6 (q); 114.2; 108.8; 104.5; 63.2 (CH_2); 53.5 (2x CH_2); 51.9 (2x CH_2); 29.5; 25.9; 18.2 (q); 9.2; -4.2 ppm. MS (EI, 70 eV) m/z (rel. intensity): 450 (M^{+1}, 33), 449 (M^+, 100), 435 (7), 434 (19), 358 (15), 304 (16), 303 (67), 302 (16), 245 (9), 217 (8), 92 (6), 91 (29), 77 (10). HRMS Calcd. for $C_{27}H_{39}N_3OSi$: 449.28569. Found: 449.287064. FTIR (KBr): 3460, 3089, 3023, 2954, 2933, 2860, 2819, 2692, 2214, 1842, 1489, 1464, 1452, 1371, 1296, 1250, 1225, 1175, 1146, 1077, 1005, 953, 889, 839, 808, 788, 779, 739, 700 cm^{-1}.

[3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-morpholin-4-yl-amine (5h)



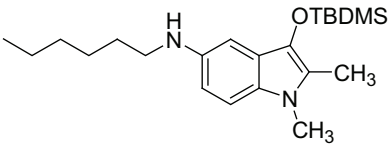
Yield: 55%. Mp.: 110-117 °C. ^1H NMR (300.13, $CDCl_3$): δ = 7.12 (d, 1H, *J* = 8.8 Hz); 6.97 (d, 1H, *J* = 2.3 Hz); 6.86 (dd, 1H, *J* = 8.8 Hz, *J* = 2.3 Hz); 3.90 (t, 4H, *J* = 4.7 Hz); 3.56 (s, 3H); 3.11 (t, 4H, *J* = 4.7 Hz); 2.27 (s, 3H); 1.08 (s, 9H); 0.15 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 144.8 (q); 130.3 (q); 130.0 (q); 123.3 (q); 121.9 (q); 113.8; 109.1; 104.5; 67.5 (CH_2); 52.3 (CH_2); 29.7; 26.1; 18.4 (q); 9.4; -3.9 ppm. MS (EI, 70 eV) *m/z* (rel. intensity): 361 (M^{+1}, 29), 360 (M^+, 100), 303 (7), 302 (8), 245 (5), 86 (2). HRMS Calcd. for $C_{20}H_{32}N_2O_2Si$: 360.22276. Found: 360.222092. FTIR (KBr): 3450, 2957, 2927, 2892, 2851, 2812, 1489, 1459, 1372, 1306, 1292, 1257, 1223, 1164, 1119, 951, 895, 838, 810, 776 cm^{-1}.

3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-5-pyrrolidin-1-yl-1*H*-indole (5i)



Yield: 73%. Mp: 150-155 °C. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.23 (d, 1H, *J* = 8.6 Hz); 6.70-6.50 (m, 2H); 3.55 (s, 3H); 3.31 (t, 4H, *J* = 6.2 Hz); 2.27 (s, 3H); 2.03 (t, 4H, *J* = 6.2 Hz); 1.09 (s, 9H); 0.17 (s, 6H)ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): 144.8 (q); 130.3 (q); 130.0 (q); 123.3 (q); 121.9 (q); 113.8; 109.1; 104.5; 48.9 $(CH_2)_2$; 29.8; 26.1; 25.5 $(CH_2)_2$; 18.4 (q); 9.5; -3.9 ppm. MS (EI, 70 eV) *m/z* (rel. intensity): 344 (M^+, 100), 287 (8), 229 (5), 73 (9). HRMS Calcd. for $C_{20}H_{32}N_2OSi$: 344.22784. Found: 344.227392. FTIR (KBr): 3433, 3078, 2954, 2927, 2893, 2856, 1806, 1626, 1498, 1480, 1376, 1356, 1314, 1302, 1286, 1250, 1175, 906, 897, 838, 777 cm^{-1}.

[3-(*tert*-Butyl-dimethyl-silanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]-hexyl-amine (5j)



Yield: 95%. Mp.: 83-90°C. ^{1}H NMR (300.13, $CDCl_3$): δ = 7.01 (d, 1H, *J* = 8.4 Hz); 6.67 (d, 1H, *J* = 2.2 Hz); 6.54 (dd, 1H, *J* = 2.2 Hz, *J* = 8.4 Hz); 3.53 (s, 3H); 3.13 (t, 2H, *J* = 7.1 Hz); 2.25 (s, 3H); 1.70-1.58 (m, 2H); 1.50-1.20 (m, 6H); 1.1 (s, 9H); 0.92 (t, 3H, *J* = 6.7 Hz); 0.17 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 141.6 (q); 129.9 (q); 128.9 (q); 123.0 (q); 122.4 (q); 110.9; 109.2; 99.8; 46.0 (CH_2); 32.0 (CH_2); 29.9 (CH_2); 29.7; 27.2 (CH_2); 26.1; 22.9 (CH_2); 18.4 (q); 14.3; 9.4; -3.9 ppm. MS (EI, 70 eV) *m/z* (rel. intensity): 375 (M^{+1}, 28), 374 (M^+, 100), 304 (13), 303 (57), 245 (3), 244 (8), 173 (18), 142 (7), 84 (10). HRMS Calcd. for $C_{22}H_{38}N_2OSi$: 374.27479. Found: 374.274037. FTIR (Nujol): 3395, 2927, 2856, 1624, 1568, 1463, 1378, 1282, 1246, 1168, 1069, 1006, 939, 895, 841, 778, 728 cm^{-1}.

3.4 Palladium-Catalyzed C-O and C-C Coupling Reactions of Electron-Rich Indoles

Nicolle Schwarz, Anahit Pews-Davtyan, Karolin Alex, Annegret Tillack, Matthias Beller, *Synthesis* **2007**, *23*, 3722-3730.

Contributions: In this paper I contributed to a significant amount of the argumentation and the synthetic work. I performed all catalytic investigation. My contribution as co-author of this paper is approximately 80%.

Palladium-Catalyzed C–O and C–C Coupling Reactions of Electron-Rich Indoles

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Abstract: A novel palladium-catalyzed formation of indole aryl ethers is described. In general, the corresponding indole ethers are obtained in the presence of $Pd(OAc)_2$ combined with *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole in high yields.

Key words: indoles, diaryl ethers, palladium, cross-coupling

Diaryl ethers form an important class of organic compounds throughout the life science and polymer industries.[1] Aryl ethers, including oxygen heterocycles, have been reported to possess significant biological activity; for example, natural products of the isodityrosin family, vancomycin,[2] angiotensin-converting enzyme inhibitor K-13,[3] (+)-piperazinomycin,[4] and antitumor compounds such as bouvardin and bastadin.[5] Until recently, the most general synthesis for the preparation of diaryl ethers was the classic Ullmann ether synthesis, but it is often limited by harsh reaction conditions, use of stoichiometric amounts of copper and the necessity of a large excess of the phenolic substrate.[6] In the last decade a number of interesting and improved methods for diaryl ether formation have been reported.[7] For instance, the palladium-catalyzed coupling of phenols and aryl halides is an important extension of other reported carbon–heteroatom bond-forming reactions.[8] In this regard intermolecular palladium-catalyzed C–O bond formation in the presence of electron-rich bulky aryldialkylphosphines by Buchwald and co-workers is also noteworthy.[9]

Based on our continuing interest in the synthesis and derivatization of indoles[10] as well as in Pd-catalyzed coupling reactions,[11] very recently we developed a convenient protocol for electron-rich 3-siloxy- and 3-alkoxyindoles.[10d] In the present paper we describe for the first time the Pd-catalyzed aryl ether synthesis of different 5-bromoindoles.

In exploratory experiments, we investigated the influence of different electron-rich sterically demanding ligands on the coupling of 5-bromo-3-(*tert*-butyldimethylsiloxy)-1,2-dimethyl-1*H*-indole (**13**) with *o*-cresol, which served as our model reaction. As shown in Table 1, most of the ligands gave only traces of the desired product. The best yield of the corresponding indole **16** (34%) was achieved with the in-house-developed ligand *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole (**7**) (Table 1, entry 7).[12]

Apparently, a subtle balance of steric and electronic factors of the ligand is important to activate the Pd center. Hence, the replacement of the dicyclohexyl substituents of ligand **10** by di-*tert*-butyl and, more importantly, by di-1-adamantyl substituents (ligand **11** and **7**, respectively) led to a significant increase of the product yield. Further variation of different bulky ligands showed no appreciable improvements. Apart from **7** only the Buchwald ligand **12** (Table 1, entry 12) gave the corresponding indole in noticeable yield (15%). Apparently, our model reaction was challenging and further modification of the reaction parameters was necessary.

Therefore, we examined the influence of different bases, metal precursors, temperatures (100–160 °C), and the catalyst concentration (0.5–6 mol% Pd). The results of this optimization study are shown in Table 2. Neither the change of base nor the variation of the palladium source raised the product yield. However, applying 2 mol% $Pd(OAc)_2$ at 120 °C enhanced the yield of **16** from 34% (Table 2, entry 2) to 83% (Table 2, entry 5). Doubling the catalyst concentration gave a similar yield at 100 °C (Table 2, entry 13). Also ligand **12** gave an improved yield, however, somewhat lower compared to **7** (Table 2, entry 4 vs entry 3). As expected the reaction did not work without any ligand, base, or catalyst.

Next, we were interested in the scope and limitation of the catalyst system for different phenols and indoles. All reactions in Table 3 were performed at 120 °C for 24 hours in toluene in the presence of 2 mol% $Pd(OAc)_2$, 4 mol% *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole (**7**) and 2 equivalents of K_3PO_4.

As shown in Table 3, the corresponding indole products **16–23** were obtained in moderate to good yields (52–85%). The Pd catalyst system works well with various alkylated phenols and different N-protected indole derivatives. There is no significant difference in reactivity between 2-, 3-, and 4-methylphenol and 2,6-dimethylphenol (Table 3, entries 1,4,5,6). The *N*-benzyl- and *N*-Boc-protected indoles gave an improved yield of the coupling product (Table 3, entries 2,3). Unfortunately, under the same reaction conditions 5-bromoindole and 6-bromoindole with a free NH-group gave either no ether products or only traces (<2%). In none of these reactions we have observed reductive dehalogenation of the bromoindoles. Noteworthy, the C–O coupling reaction of the simple *N*-Boc-indole proceeded smoothly in 85% yield (Table 3, entry 8).

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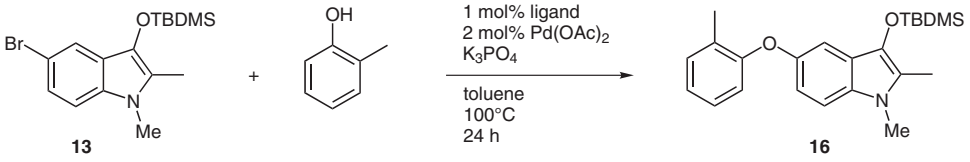
Table 1 Model Reaction of Indole **13** with *o*-Cresol[a]



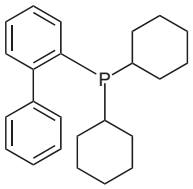
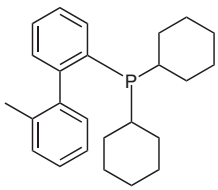
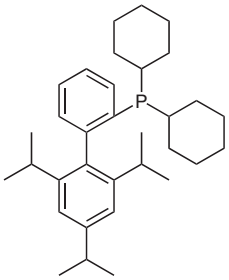
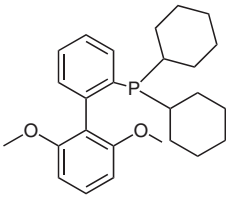
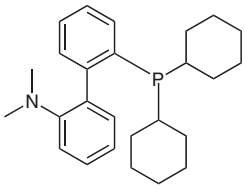
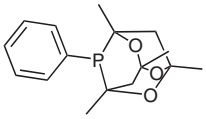
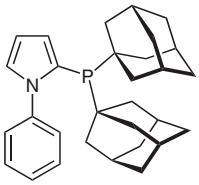
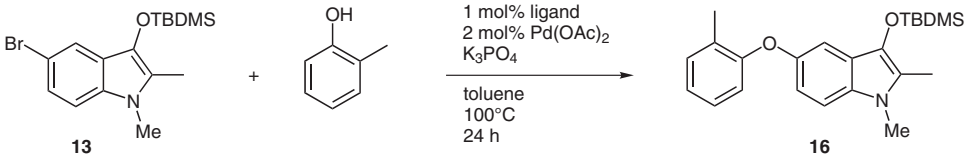
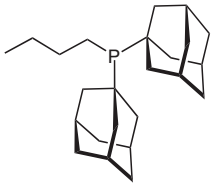
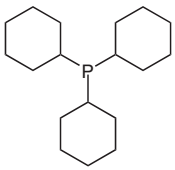
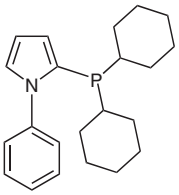
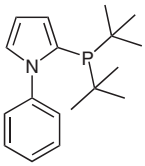
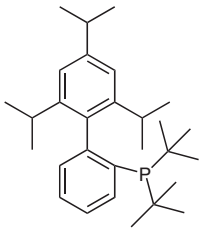
Entry	Ligand		Yield (%)[b]
1		**1**	<1
2		**2**	<1
3		**3**	1
4		**4**	<1
5		**5**	<1
6		**6**	<1
7		**7**	34

Table 1 Model Reaction of Indole **13** with *o*-Cresol[a] (continued)



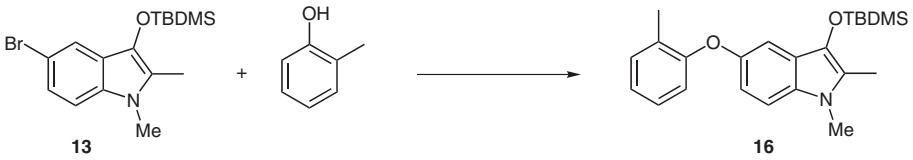
Entry	Ligand		Yield (%)[b]
8		**8**	<1
9		**9**	<1
10		**10**	<1
11		**11**	2
12		**12**	15

[a] Reaction conditions: indole **13** (0.14 mmol), *o*-cresol (0.17 mmol), $Pd(OAc)_2$ (1 mol%), ligand (2 mol%), K_3PO_4 (0.28 mmol), solvent: toluene (3 mL), 24 h, 100 °C.
[b] GC yield based on **13** with hexadecane as internal standard.

Interestingly, in the case of the coupling reaction with α-naphthol we could not isolate the desired ether compounds. To our surprise instead of the indole ethers, we obtained 5-(4-hydroxynaphthyl)indoles by selective C–C coupling reaction (Table 4). It should be noted that the resulting 5-arylindole motif is reported to be present in potent agonists of the CNS neurotransmitter serotonin.[13] For example Yang reported the first preparation of this class of compounds via the Suzuki cross-coupling of indolylboronic acids with aryl bromides.[14] Although probably not generally applicable, our reaction presented here allows for a much easier access of such compounds.

In conclusion, we have presented a general palladium-catalyzed diaryl ether formation of electron-rich indoles to 3,5-dioxyindole derivatives, which constitute a novel class of electron-rich indoles. Different alkylated phenols reacted in the presence of $Pd(OAc)_2$ and *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole (**7**) to give potentially bioactive indole derivatives.

Table 2 Optimization of the Model Reaction of Indole **13** with *o*-Cresol[a]



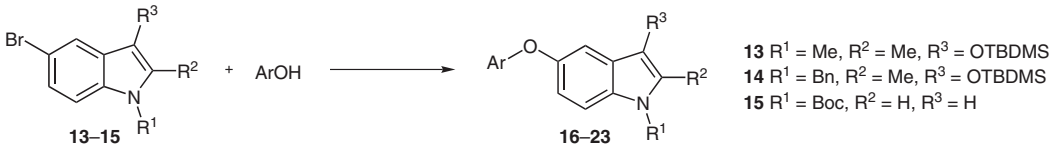
13 **16**

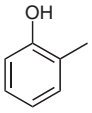
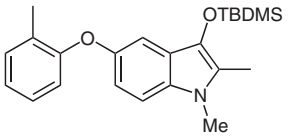
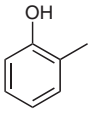
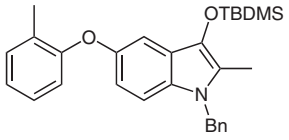
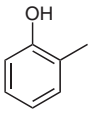
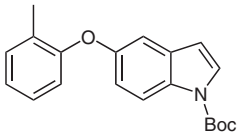
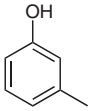
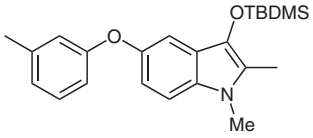
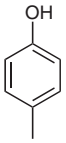
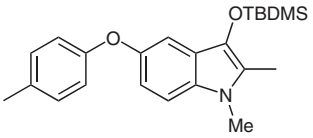
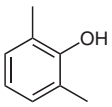
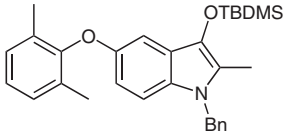
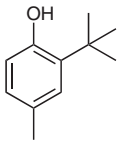
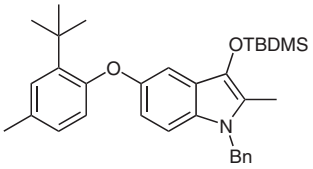
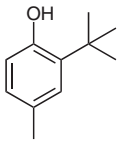
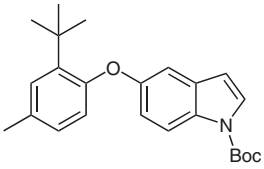
Entry	Pd source	Catalyst (mol%)	Ligand **7** (mol%)	Solvent	Base	Temperature (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	0.5	1	toluene	K_3PO_4	100	25
2	$Pd(OAc)_2$	1	2	toluene	K_3PO_4	100	34
3	$Pd(OAc)_2$	2	4	toluene	K_3PO_4	100	75
4	$Pd(OAc)_2$	2	4[c]	toluene	K_3PO_4	100	60
5	$Pd(OAc)_2$	2	4	toluene	K_3PO_4	120	83
6	$Pd(OAc)_2$	2	4	toluene	K_3PO_4	140	75
7	$Pd(OAc)_2$	2	4	toluene	K_3PO_4	160	71
8	Pd_2dba_3	2	4	toluene	K_3PO_4	100	44
9	Pd_2dba_3	2	4	toluene	K_3PO_4	120	38
10	$PdCl_2$	2	4	toluene	K_3PO_4	100	<1
11	$PdCl_2$	2	4	toluene	K_3PO_4	120	1
12	$Pd(OAc)_2$	3	6	toluene	K_3PO_4	100	76
13	$Pd(OAc)_2$	4	8	toluene	K_3PO_4	100	77
14	$Pd(OAc)_2$	4	8	THF	K_3PO_4	100	25
15	$Pd(OAc)_2$	4	8	toluene	LiHMDS	100	1
16	$Pd(OAc)_2$	4	8	THF	LiHMDS	100	<1
17	$Pd(OAc)_2$	4	8	toluene	*t*-BuONa	100	2
18	$Pd(OAc)_2$	4	8	THF	*t*-BuONa	100	<1
19	$Pd(OAc)_2$	4	8	toluene	Cs_2CO_3	100	15
20	$Pd(OAc)_2$	4	8	THF	Cs_2CO_3	100	3
21	$Pd(OAc)_2$	4	8	toluene	*t*-BuOK	100	10
22	$Pd(OAc)_2$	4	8	THF	*t*-BuOK	100	<1
23	$Pd(OAc)_2$	4	8	toluene	–	100	<1
24	$Pd(OAc)_2$	6	12	toluene	K_3PO_4	100	70

[a] Reaction conditions: indole **13** (0.14 mmol), *o*-cresol (0.17 mmol), Pd complex (0.5–6 mol%) and ligand **7** (1–12 mol%), base (0.28 mmol), solvent: (3 mL), 24 h.
[b] GC yield based on **13** with hexadecane as internal standard.
[c] Reaction with ligand **12** (Table 1, entry 12).

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros, and Strem, and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS, and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 300, AV 400, and AV 500 spectrometer. The ^{1}H and ^{13}C NMR chemical shifts are reported relative to the center of solvent resonance [$CDCl_3$: 7.25 ppm(^{1}H), 77.0 ppm (^{13}C)]. Mass spectra were recorded on a MAT 95XP spectrometer (Thermo Electron Corporation). IR spectra were recorded on a FTIR Nicolet 6700 (Thermo Electron Corporation). GC was performed on a Hewlett Packard HP 6890 chromatograph with a 30 m HP5 column. All yields reported in Tables 1 and 2 refer to GC yields using hexadecane as an internal standard. The spectral data of compounds **13** and **14** prepared by literature procedure[10d] are reported below.

Table 3 Reaction of Indole Derivatives with Different Phenols[a]



Entry	ArOH	Product		Yield (%)[b]
1			**16**	60
2			**17**	80
3			**18**	75
4			**19**	52
5			**20**	50
6			**21**	50
7			**22**	80
8			**23**	85

[a] Reaction conditions: indole derivative (0.35 mmol), substituted phenol (0.42 mmol), $Pd(OAc)_2$ (2 mol%), **7** (4 mol%), K_3PO_4 (0.7 mmol), solvent: toluene (3 mL), 24 h, 120 °C.
[b] Isolated yield based on the starting indole.

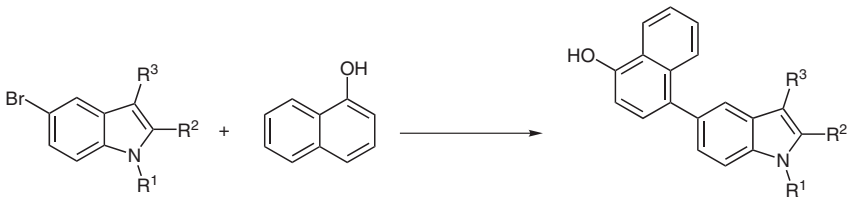
5-Bromo-3-(*tert*-butyldimethylsiloxy)-1,2-dimethyl-1*H*-indole (13)[10d]

FTIR (KBr): 3072, 2955, 2933, 2896, 2858, 1479, 1377, 1286, 1245, 891, 839, 806, 780 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 1.9 Hz, 1 H), 7.15 (dd, *J* = 1.9, 8.5 Hz, 1 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 3.56 (s, 3 H), 2.27 (s, 3 H), 1.07 (s, 9 H), 0.14 (s, 6 H).

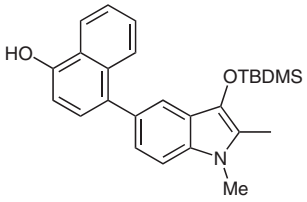
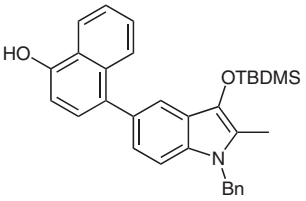
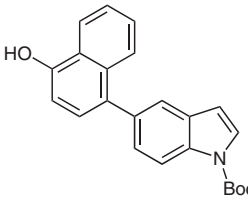
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 132.5 (q), 129.9 (q), 124.2 (q), 123.4, 123.3 (q), 119.7, 111.8 (q), 110.1, 29.8, 26.1, 18.3 (q), 9.5, –3.8.

Table 4 Reaction of Indole Derivatives with α-Naphthol[a]



13–15

24 R^1 = Me, R^2 = Me, R^3 = OTBDMS
25 R^1 = Bn, R^2 = Me, R^3 = OTBDMS
26 R^1 = Boc, R^2 = H, R^3 = H

Entry	Product		Yield (%)[b]
1		**24**	60
2		**25**	65
3		**26**	85

[a] Reaction conditions: indole derivative (0.35 mmol), α-naphthol (0.42 mmol), $Pd(OAc)_2$ (2 mol%), **7** (4 mol%), K_3PO_4 (0.7 mol), solvent: toluene (3 mL), 24 h, 120 °C.
[b] Isolated yield based on the starting indole.

MS (EI, 70 eV): *m*/*z* (%) = 353 (69), 299 (12), 239 (13), 225 (21), 217 (100), 202 (18), 158 (42), 143 (14), 131 (13), 115 (11), 75 (19), 57 (22).

HRMS: *m*/*z* calcd for $C_{16}H_{24}BrNOSi$: 353.0805; found: 353.0807.

1-Benzyl-5-bromo-3-(*tert*-butyldimethylsiloxy)-2-methyl-1*H*-indole (14)[10d]

FTIR (KBr): 3065, 2950, 2925, 2856, 1578, 1471, 1454, 1372, 1289, 1253, 1182, 1087, 896, 873, 839, 824, 807, 790, 782, 732, 699 cm^{-1}.

^1H NMR (300.13 Hz, $CDCl_3$): δ = 7.39 (d, *J* = 1.8 Hz, 1 H), 7.04 (m, 3 H), 6.93 (dd, *J* = 1.8, 8.6 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 1 H), 6.68 (m, 2 H), 5.02 (s, 2 H), 2.02 (s, 3 H), 0.87 (s, 9 H), –0.03 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 137.9 (q), 132.5 (q), 130.4 (q), 129.0, 127.5, 125.9, 124.0 (q), 123.8, 123.7 (q), 119.9, 112.1 (q), 110.6, 46.7, 26.1, 18.3 (q), 9.5, –3.9.

MS (EI, 70 eV): *m*/*z* (%) = 431 (100), 429 (95), 293 (30), 234 (4), 202 (31), 115 (10), 91 (63), 73 (98), 59 (11), 57 (3).

HRMS: *m*/*z* calcd for $C_{22}H_{28}BrNOSi$: 429.11181; found: 429.111561.

5-Aryloxyindole Derivatives 16–26; General Procedure

In an Ace pressure tube under argon, N-protected 5-bromoindole derivative (0.35 mmol), phenol derivative (0.42 mmol), $Pd(OAc)_2$ (2 mol%), *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole (**7**; 4 mol%), and K_3PO_4 (0.7 mmol) were dissolved in toluene (3 mL). The pressure tube was fitted with a Teflon cap and heated at 120 °C for 24 h. After removal of the solvent in vacuo, the corresponding indole product is isolated by column chromatography in hexane–EtOAc.

3-(*tert*-Butyldimethylsiloxy)-1,2-dimethyl-5-(2-methylphenoxy)-1*H*-indole (16)

FTIR (KBr): 3052, 2941, 1481, 1437, 1375, 1282, 1244, 1223, 1211, 1186, 1141, 1130, 1069, 932, 892, 872, 843, 828, 782, 756 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.22 (m, 1 H), 7.13 (d, *J* = 8.7 Hz, 1 H), 7.06 (m, 1 H), 6.97 (m, 2 H), 6.80 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.75 (dd, *J* = 1.1, 8.0 Hz, 1 H), 3.59 (s, 3 H), 2.33 (s, 3 H), 2.28 (s, 3 H), 1.01 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.1 (q), 150.2 (q), 131.3, 130.7 (q), 130.5 (q), 128.8 (q), 127.0, 124.0 (q), 122.5, 122.0 (q), 177.7, 113.4, 109.4, 106.7, 29.8, 26.1, 18.3 (q), 16.5, 9.5, –4.0.

MS (EI, 70 eV): *m*/*z* (%) = 381 (41), 276 (19), 275 (100), 218 (59), 177 (14), 163 (7), 144 (26), 112 (7), 75 (6), 57 (7).

HRMS: *m*/*z* calcd for $C_{23}H_{31}NO_2Si$: 381.21186; found: 381.211376.

1-Benzyl-3-(*tert*-butyldimethylsiloxy)-2-methyl-5-(2-methylphenoxy)-1*H*-indole (17)

FTIR (KBr): 3064, 3031, 2958, 2929, 2852, 1586, 1570, 1477, 1373, 1358, 1298, 1256, 1235, 1212, 1185, 1143, 935, 867, 838, 781, 728 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.23 (m, 4 H), 7.07 (m, 2 H), 7.00 (d, *J* = 2.3 Hz, 1 H), 6.97 (dd, *J* = 1.4, 7.4 Hz, 1 H), 6.92 (m, 2 H), 6.77 (m, 2 H), 5.23 (s, 2 H), 2.32 (s, 3 H), 2.22 (s, 3 H), 1.01 (s, 9 H), 0.11 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.9 (q), 150.5 (q), 138.4 (q), 131.3, 131.0 (q), 130.5 (q), 129.0 (q), 129.1, 127.4, 127.0, 126.0, 123.8 (q), 122.6, 122.4 (q), 117.9, 113.6, 109.9, 106.6, 46.8, 26.1, 18.3 (q), 9.5, –4.0.

MS (CI, isobutane): *m*/*z* (%) = 458 (34), 457 (63), 351 (100), 295 (6), 91 (12), 73 (30).

HRMS: *m*/*z* calcd for $C_{29}H_{35}NO_2Si$: 457.24316; found: 457.242447.

***tert*-Butyl 5-(2-Methylphenoxy)indole-1-carboxylate (18)**

FTIR (KBr): 3151, 3120, 3058, 2974, 2921, 1733, 1490, 1462, 1372, 1350, 1278, 1258, 1231, 1213, 1186, 1160, 1118, 1082, 1024 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 1 H), 7.59 (d, *J* = 3.7 Hz, 1 H), 7.25 (m, 1 H), 7.13 (m, 1 H), 7.04 (m, 2 H), 6.99 (dd, *J* = 1.3, 7.9 Hz,1 H), 6.46 (dd, *J* = 0.6, 3.7 Hz, 1 H), 2.29 (s, 3 H), 1.67 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.8 (q), 153.6 (q), 149.9 (q), 131.7 (q), 131.6, 131.4 (q), 129.7 (q), 127.2, 127.1, 123.5, 119.0, 116.2, 115.8, 109.4, 107.3, 83.9 (q), 28.5, 16.6.

MS (EI, 70 eV): *m*/*z* (%) = 323 (45), 268 (32), 267 (100), 223 (73), 222 (19), 207 (11), 161 (17), 117 (86), 104 (8), 91 (12), 85 (5), 69 (11), 57 (66).

HRMS: *m*/*z* calcd for $C_{20}H_{21}NO_3$: 323.15160; found: 323.150899.

3-(*tert*-Butyldimethylsiloxy)-1,2-dimethyl-5-(3-methylphenoxy)-1*H*-indole (19)

FTIR (KBr): 3054, 3036, 2950, 2929, 2860, 1481, 1376, 1283, 1254, 1212, 1157, 837, 778 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.09 (m, 2 H), 7.05 (d, *J* = 2.1 Hz, 1 H), 6.76 (m, 2 H), 6.67 (m, 2 H), 3.54 (s, 3 H), 2.22 (s, 3 H), 2.21 (s, 3 H), 0.96 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.8 (q), 149.0 (q), 139.7 (q), 131.1 (q), 130.5 (q), 129.3, 124.1 (q), 122.7, 122.0 (q), 117.8, 144.4, 114.3, 109.4, 108.4, 29.8, 26.0, 21.6, 18.3 (q), 9.5, –4.0.

MS (EI, 70 eV): *m*/*z* (%) = 381 (100), 324 (9), 267 (4), 251 (9), 218 (4), 217 (22), 73 (12), 56 (2).

HRMS: *m*/*z* calcd for $C_{23}H_{31}NO_2Si$: 381.21186; found: 381.211345.

3-(*tert*-Butyldimethylsiloxy)-1,2-dimethyl-5-(4-methylphenoxy)-1*H*-indole (20)

FTIR (KBr): 3027, 2954, 2925, 2852, 1579, 1507, 1483, 1463, 1377, 1289, 1243, 1228, 1205, 1133, 932, 892, 871, 858, 837, 800, 785 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.8 Hz, 1 H), 7.13 (d, *J* = 2.1 Hz, 1 H), 7.09 (m, 2 H), 6.85 (m, 3 H), 3.62 (s, 3 H), 2.32 (s, 3 H), 2.31 (s, 3 H), 1.05 (s, 9 H), 0.14 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.5 (q), 149.4 (q), 131.3 (q), 131.0 (q), 130.5 (q), 130.1, 124.1 (q), 122.1 (q), 117.3, 114.1, 109.4, 108.1, 29.8, 26.1, 20.8, 18.4 (q), 9.6, –4.0.

MS (EI, 70 eV): *m*/*z* (%) = 381 (100), 325 (7), 266 (9), 251 (8), 217 (26), 73 (12), 56 (2).

HRMS: *m*/*z* calcd for $C_{23}H_{31}NO_2Si$: 381.21186; found: 381.211563.

1-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-(2,6-dimethylphenoxy)-2-methyl-1*H*-indole (21)

FTIR (KBr): 3027, 2954, 2925, 2856, 1588, 1571, 1495, 1472, 1374, 1359, 1299, 1266, 12221, 1191, 1143, 1082, 935, 858, 837, 781 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.24 (m, 3 H), 7.06 (m, 4 H), 6.92 (m, 2 H), 6.74 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.59 (d, *J* = 2.3 Hz, 1 H), 5.20 (s, 2 H), 2.19 (s, 3 H), 2.15 (s, 3 H), 0.96 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 152.2 (q), 151.9 (q), 138.5 (q), 132.0 (q), 130.8 (q), 129.5 (q), 129.0, 128.9, 127.4, 126.1, 124.8, 123.6 (q), 122.2 (q), 110.6, 109.8, 101.0, 46.8, 25.9, 18.3 (q), 16.6, 9.4, –4.2.

MS (EI, 70 eV): *m*/*z* (%) = 472 (37), 471 (100), 297 (3), 202 (5), 91 (21), 73 (43).

HRMS: *m*/*z* calcd for $C_{30}H_{37}NO_2Si$: 471.25881; found: 471.258729.

1-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-(2-*tert*-butyl-4-methylphenoxy)-2-methyl-1*H*-indole (22)

FTIR (KBr): 3060, 3027, 2925, 2856, 1588, 1570, 1456, 1373, 1360, 1300, 1254, 1228, 1145, 1089, 936, 839, 815, 780 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 7.25 (m, 3 H), 7.16 (d, *J* = 2.0 Hz, 1 H), 7.07 (m, 2 H), 6.93 (m, 2 H), 6.86 (m, 1 H), 6.76 (dd, *J* = 2.5, 8.7 Hz, 1 H), 6.66 (d, *J* = 8.3 Hz, 1 H), 5.23 (s, 2 H), 2.30 (s, 3 H), 2.22 (s, 3 H), 1.45 (s, 9 H), 1.02 (s, 9 H), 0.12 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.7 (q), 150.7 (q), 139.7 (q), 138.4 (q), 131.2 (q), 130.9 (q), 130.5 (q), 128.9, 127.7, 127.5, 127.4, 126.1, 123.8 (q), 122.5 (q), 119.0, 114.2, 109.8, 107.3, 46.8, 34.9 (q), 30.9, 26.1, 21.2, 18.4 (q), 9.5, –4.0.

MS (EI, 70 eV): *m*/*z* (%) = 514 (62), 513 (100), 293 (4), 223 (3), 202 (5), 149 (4), 117 (4), 91 (18), 73 (43), 57 (11).

HRMS: *m*/*z* calcd for $C_{33}H_{43}NO_2Si$: 513.30576; found: 513.305329.

***tert*-Butyl 5-(2-*tert*-Butyl-4-methylphenoxy)indole-1-carboxylate (23)**

FTIR (KBr): 3452, 3153, 2954, 2864, 1731, 1494, 1463, 1372, 1350, 1332, 1258, 1210, 1161, 1116, 1082, 1024, 955, 844, 826, 811, 763, 722 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 3.6 Hz, 1 H), 7.19 (d, *J* = 2.1 Hz, 1 H), 7.10 (d, *J* = 2.4 Hz, 1 H), 6.98 (dd, *J* = 2.4, 9.0 Hz, 1 H), 6.92 (ddd, *J* = 0.6, 2.2, 8.2 Hz, 1 H), 6.70 (d, *J* = 8.2 Hz, 1 H), 6.47 (dd, *J* = 0.5, 3.8 Hz, 1 H), 2.33 (s, 3 H), 1.66 (s, 9 H), 1.43 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.4 (q), 153.8 (q), 149.7 (q), 140.4 (q), 132.1 (q), 131.6 (q), 131.1 (q), 127.8, 127.5, 126.8, 119.8, 116.2, 116.0, 109.9, 107.2, 83.7 (q), 34.7 (q), 30.2, 28.2, 21.1.

MS (EI, 70 eV): *m*/*z* (%) = 379 (37), 323 (100), 308 (85), 279 (65), 264 (65), 248 (16), 147 (28), 117 (15), 57 (73), 41 (26).

HRMS: *m*/*z* calcd for $C_{24}H_{29}NO_3$: 379.21420; found: 379.214105.

4-[3-(*tert*-Butyldimethylsiloxy)-1,2-dimethyl-1*H*-indol-5-yl]naphthalen-1-ol (24)

FTIR (KBr): 3058, 3044, 2953, 2925, 2852, 1588, 1472, 1375, 1345, 1272, 1252, 870, 840, 825, 803, 781, 762 cm^{-1}.

^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 1.3 Hz, 1 H), 7.35 (m, 1 H), 7.26 (m, 1 H), 7.11 (m, 3 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 5.14 (s, 1 H, OH), 3.53 (s, 3 H), 2.20 (s, 3 H), 0.89 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.5 (q), 135.0 (q), 133.5 (q), 133.2 (q), 131.0 (q), 130.6 (q), 127.2, 126.9, 126.3, 125.5 (q), 125.2, 124.6 (q), 123.5, 123.4 (q), 121.8, 118.9, 108.5, 108.2, 29.8, 26.1, 18.4 (q), 9.5, –4.0.

MS (EI, 70 eV): *m*/*z* (%) = 417 (100), 360 (11), 287 (5), 167 (4), 149 (13), 97 (9), 83 (11), 73 (7), 57 (18), 43 (17).

HRMS: *m*/*z* calcd for $C_{26}H_{31}NO_2Si$: 417.21186; found: 417.211468.

4-[1-Benzyl-3-(*tert*-butyldimethylsiloxy)-2-methyl-1*H*-indol-5-yl]naphthalen-1-ol (25)

FTIR (KBr): 3023, 2929, 2864, 1471, 1452, 1376, 1347, 1278, 1253, 1231, 1212, 1048, 862, 842, 822, 803, 783, 764, 732 cm^{-1}.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.3 Hz, 1 H), 7.99 (d, *J* = 8.3 Hz, 1 H), 7.57 (d, *J* = 1.1 Hz, 1 H), 7.48 (m, 1 H), 7.41 (m, 1 H), 7.27 (m, 5 H), 7.16 (dd, *J* = 1.1, 6.3 Hz, 1 H), 7.00 (m, 2 H), 6.87 (d, *J* = 7.7 Hz, 1 H), 5.31 (s, 2 H), 5.28 (s, 1 H, OH), 2.27 (s, 3 H), 1.04 (s, 9 H), 0.18 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.4 (q), 138.3 (q), 134.8 (q), 133.3 (q), 133.0 (q), 131.2 (q), 131.0 (q), 128.8, 127.3, 127.0, 126.8, 126.2, 126.0, 125.0, 124.4 (q), 123.7, 123.0 (q), 122.0 (q), 121.6, 118.8, 108.4, 108.3, 46.8, 26.2, 18.1 (q), 9.4, –4.1.

MS (EI, 70 eV): *m*/*z* (%) = 493 (100), 402 (4), 345 (2), 319 (3), 261 (2), 218 (3), 153 (2), 112 (16), 91 (12), 73 (33), 57 (12), 44 (15).

HRMS: *m*/*z* calcd for $C_{32}H_{35}NO_2Si$: 493.24316; found: 493.242367.

***tert*-Butyl 5-(4-Hydroxynaphthalen-1-yl)indole-1-carboxylate (26)**

FTIR (ATR): 3358, 3150, 3110, 3044, 2981, 2932, 1368, 1334, 1239, 1155, 1133, 1078, 1044, 1022, 812, 763, 726 cm^{-1}.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.28 (m, 1 H), 8.21 (d, *J* = 8.5 Hz, 1 H), 7.89 (m, 1 H), 7.67 (d, *J* = 3.7 Hz, 1 H), 7.63 (d, *J* = 1.6 Hz, 1 H), 7.50 (m, 1 H), 7.42 (m, 2 H), 7.27 (d, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 7.6 Hz, 1 H), 6.62 (d, *J* = 3.7 Hz, 1 H), 5.82 (s, 1 H, OH), 1.71 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.0 (q), 149.9 (q), 135.4 (q), 134.1 (q), 133.4 (q), 133.0 (q), 130.7 (q), 127.1, 126.8, 126.4 (two signals, detected by CORE), 126.2, 125.0, 124.5 (q), 122.4, 121.9, 114.7, 108.1, 107.5, 83.8 (q), 28.2.

MS (EI, 70 eV): *m*/*z* (%) = 359 (40), 304 (31), 303 (96), 260 (52), 259 (100), 258 (83), 242 (21), 231 (17), 230 (39), 229 (11), 228 (27), 202 (19), 101 (10), 57 (30).

HRMS: *m*/*z* calcd for $C_{23}H_{21}NO_3$: 359.15160; found: 359.151449.

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3.5 Synthesis of 3-(2-*N,N*-Diethylaminoethoxy)indoles as Potential 5-HT_6 Receptor Ligands

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Contributions: In this paper I contributed to a significant amount of the argumentation and the synthetic work. I performed synthesis of compounds **9a**, **9b**, **9c** and **9d**. My contribution as co-author of this paper is approximately 30%.

Synthesis of 3-(2-*N,N*-diethylaminoethoxy)indoles as potential 5-HT$_6$ receptor ligands

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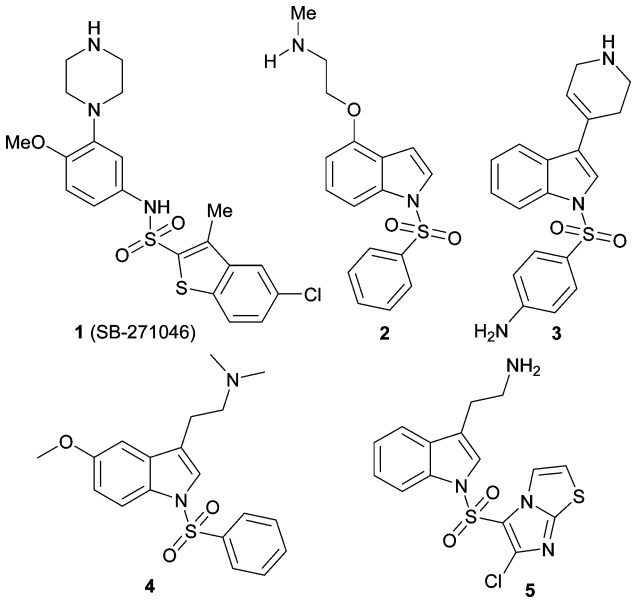
The synthesis of new pharmaceutically interesting 3-(2-*N,N*-diethylaminoethoxy)indole derivatives is described. Starting from 3-silyloxy-2-methylindoles, deprotection and *in situ* aminoalkylation provided 3-(2-*N,N*-diethylaminoethoxy)indoles in good yield. Further sulfonylation of these novel indoles gave access to potential 5-HT$_6$ receptor ligands.

Introduction

The 5-hydroxytryptamine$_6$ (5-HT$_6$) receptor is one of the latest subtypes of the mammalian serotonin receptor family to have been identified.[1] The high affinity of a wide range of antipsychotics for the receptor, coupled with its almost exclusive distribution in the brain, prompted much interest into the potential role of the 5-HT$_6$ as a target for central nervous system (CNS)-mediated diseases such as schizophrenia, Alzheimer's disease (cognitive function), anxiety, and obesity.[2] A variety of 5-HT$_6$ selective agents have been reported, however, there is still a need for more selective and active compounds.[3]

For example, in 1998 Bromidge and co-workers presented SB-271046 (**1**) as one of the first 5-HT$_6$ selective antagonists which entered into clinical trials (Phase I, not continued).[4] As shown in Scheme 1 SB-271046 is a 2-benzo-thiophene-sulfonamide derivative, which is substituted with a 4-methoxy-3-piperazinyl-phenyl group. Recently, this basic unit was replaced by a 4-(2-aminoethoxy)indole derivative **2** in 2005 by Zhou and co-workers.[5] Comparing the latest reported 5-HT$_6$ receptor ligands, it is evident that the majority of active compounds are indole derivatives, especially with a tryptamine scaffold.[6] Some typical examples are shown in Scheme 1.

Due to their importance as one of the most represented building blocks in natural bioactive products and known marketed drugs, there is a continuing interest in the development of catalytic methods for the synthesis of indoles.[7] For us especially, domino sequences whereby a reactive intermediate is generated from easily available substrates with the aid of a catalyst were of interest. Apart from domino hydroformylation–Fischer indole reactions,[8] alkyne-hydroamination–Fischer indole sequences were studied.[9] Most recently, we demonstrated that commercially available aryl-hydrazines and alkynes yielded a variety of potentially bio-active functionalized tryptamine and trypthophol derivatives, as well as 3-silyloxy-2-methylindoles in the presence of either Zn(OTf)$_2$ or ZnCl$_2$.[10]



Scheme 1 SB-271046 (**1**) and N-sulfonylindole derivatives **2–5** as 5-HT$_6$ receptor ligands.

Herein, we describe for the first time the synthesis of 3-(2-*N,N*-diethylaminoethoxy)-2-methylindoles. Deprotection and sulfonylation gave a novel class of biarylsulfonylindoles as 5-HT$_6$ receptor ligands.

Results and discussion

Based on the recently developed synthesis of 3-silyloxy-2-methylindoles **8**, we thought it should be possible to prepare 3-alkoxylated indoles. So far, this class of compounds has scarcely been investigated.[11] Of special interest to us was amino-functionalized alkoxy chains because of their resemblance to natural tryptamines.

Initially, seven electron-rich indole derivatives were synthesized in good yields *via* titanium-catalyzed hydroamination (Ti(NEt$_2$)$_4$–2,6-di-*tert*-butyl-4-methylphenol) of the silyl-protected propargylic alcohol (Scheme 2).[9a] Due to the exclusive Markovnikov hydroamination, only the 2,3-disubstituted indoles were obtained.[12] Next, the desired 3-(2-*N,N*-diethylaminoethoxy)indoles **9** were

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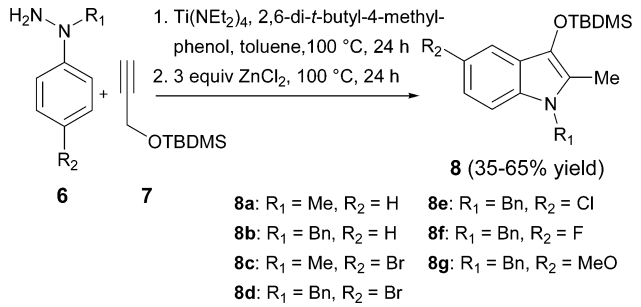
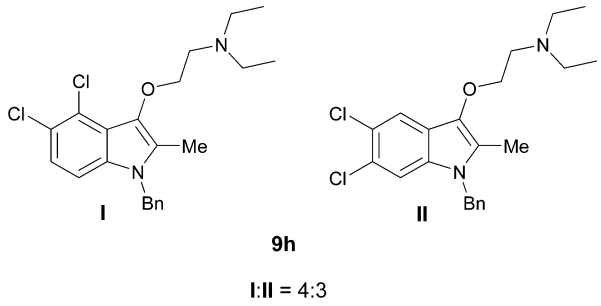


Scheme 2 Ti-catalyzed synthesis of electron-rich 3-silyloxy-2-methylindoles (**8**).

prepared by treating the appropriate 3-silyloxy-2-methylindole **8a–g** with 2-*N,N*-diethylaminoethyl chloride.

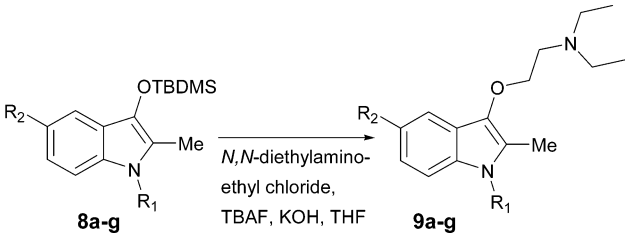
After some optimization, it turned out that a mixture of potassium hydroxide and tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran gave the best results for the *in situ* desilylation reaction. The resulting 3-hydroxyindoles were not stable and had to be directly alkylated. Under these conditions, the new indole derivatives **9a–g** were obtained in good to moderate yields (30–70%) (Table 1). In general, the *N*-methyl-protected indoles gave higher yields compared to the *N*-benzyl-protected indoles. However, in agreement with previous results on the synthesis of substituted tryptophols,[9c] the Fischer indole synthesis of 3,4-dichlorophenylhydrazine with **7** gave a mixture of two regioisomers of the corresponding 3-silyloxy-2-methylindole **8h**. This purified indole was used without particular analytical investigations for the synthesis of 3-(2-*N,N*-diethylaminoethoxy)indole (**9h**). Due to the presence of two isomers in the case of **8h**, we also observed the formation of compound **9h** as a mixture of two isomers (Scheme 3).

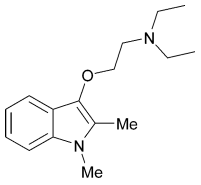
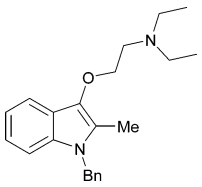
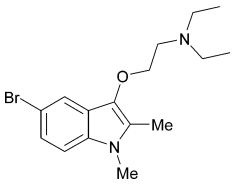
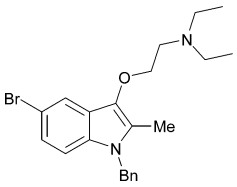
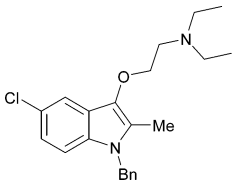
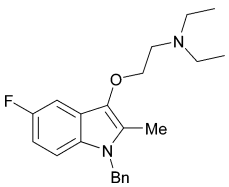
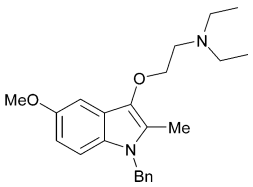


Scheme 3 Regioisomers **I** and **II** of the dichlorosubstituted derivative **9h**.

Then, we turned our attention to the deprotection of the benzyl group of the indole system. The different debenzylation methods were tested with compound **9b**, which was the most readily available product. Initially, reductive debenzylation in the presence of palladium on carbon was tried.[13] Despite variation of the solvent and hydrogen pressure or adding acetic acid, we did not obtain the free indole. The use of aluminium trichloride in benzene presents another well established method for *N*-debenzylation.[14] But neither applying aluminium trichloride nor using the known system of potassium *tert*-butoxide in dimethylsulfoxide and oxygen,[15] were effective in the *N*-debenzylation of **9b**. Apparently, the steric hindrance of an additional substituent in the 2-position makes the debenzylation of these electron-rich indoles difficult. Finally, the use of sodium in excess in liquid ammonia

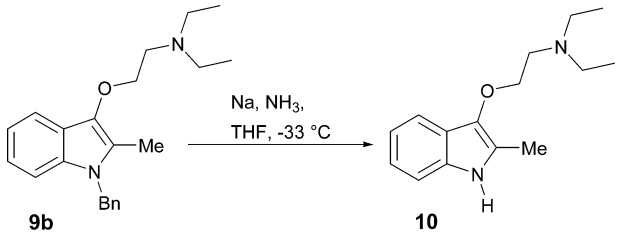
Table 1 Synthesis of 3-(2-*N,N*-diethylaminoethoxy)indoles [a]



Entry	Indole		Yield (%) [b]
1		**9a**	70
2		**9b**	60
3		**9c**	65
4		**9d**	30
5		**9e**	65
6		**9f**	50
7		**9g**	46

[a] Reaction conditions: 3-silyloxy-2-methylindole (1.0 equiv), 2-*N,N*-diethylaminoethyl chloride (1.1 equiv), KOH (1.1 equiv), TBAF (2.0 equiv), THF, 50 °C. [b] Isolated yield.

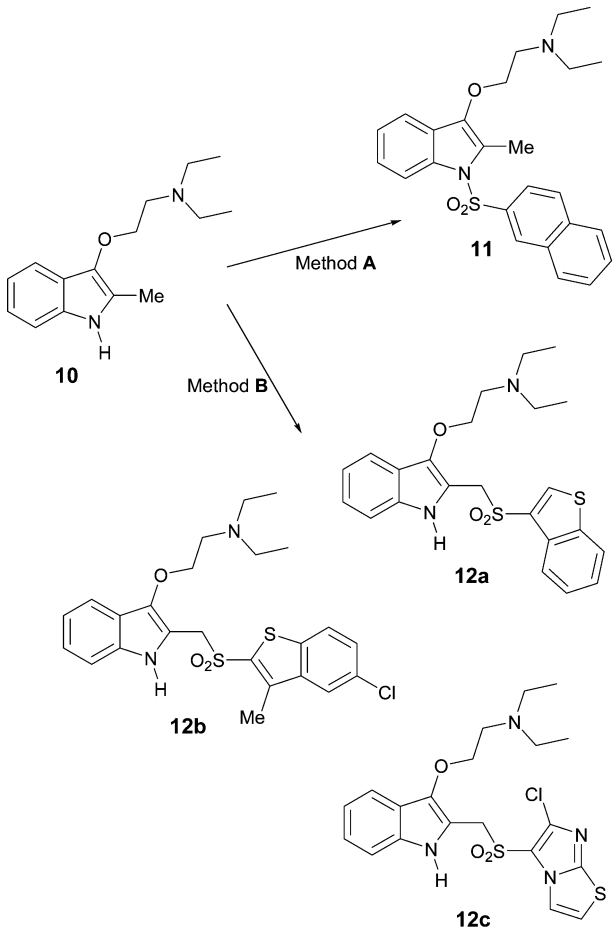
at −33 °C afforded the *N*-deprotected indole in high yield (95%) (Scheme 4).[16] Although this method worked well on most of the indoles, unfortunately, it was not usable for debenzylation of the 5-chlorinated 3-(2-*N,N*-diethylaminoethoxy)indole **9e**.



Scheme 4 Deprotection of the *N*-benzyl-3-(2-*N,N*-diethylaminoethoxy)-indole (**9b**).

Connected with this, not only debenzylation occurred, but also reductive dehalogenation at the 5-position of the indole. After successful debenzylation, different sulfonylation protocols were investigated applying 3-(2-*N,N*-diethylaminoethoxy)indole **10** as a substrate. Here, phase transfer sulfonylations with 2-naphthalenesulfonyl chloride (50% solution of sodium hydroxide, benzene, tetra-*n*-butylammonium hydrogen sulfate)[17] as well as typical nucleophilic substitution conditions (potassium hydroxide in ethanol) did not result in any desired product.[18] However, reaction of **10** with sodium hydride[19] and subsequent treatment with 2-naphthalenesulfonyl chloride gave *N*-naphthalenesulfonylindole **11** in 24% yield (Scheme 5). To our delight this product showed significant activity in initial binding studies towards the $5HT_6$-receptor.

Using the latter sulfonylation protocol, we tried to synthesize additional biarylsulfonylindoles of heteroaromatic sulfonic acids such as benzo[*b*]thiophen-3-ylsulfonyl chloride, 5-chloro-3-methylbenzo[*b*]thiophen-2-ylsulfonyl chloride and 6-chloroimidazo[2,1-*b*]thiazol-5-ylsulfonyl chloride. Unfortunately, the use of the less reactive arylsulfonic chlorides was not successful in the sulfonylation reaction of the free indole. Interestingly, by applying *n*-butyllithium[20] as a base in these reactions, we observed deprotonation at the methyl group in the 2-position of the indole, which is then subsequently sulfonylated. Based on this observation, we also synthesized the 2-(benzo[*b*]thiophen-3-ylsulfonyl)methyl-3-(2-*N*,*N*-diethylaminoethoxy)indole **12a** in 23% yield. In addition, we prepared the 2-(5-chloro-3-methylbenzo[*b*]thiophen-2-ylsulfonyl)methyl-3-(2-*N*,*N*-diethylaminoethoxy)indole **12b** and the 2-(6-chloroimidazo[2,1-*b*]thiazol-5-ylsulfonyl)methyl-3-(2-*N*,*N*-diethylaminoethoxy)indole **12c** both in similar yield (20%) (Scheme 5). The reaction of **10** with 2-naphthalenesulfonyl chloride in the presence of *n*-butyllithium gave the *N*-sulfonylated product **11** in 14% yield. The appropriate 2-methyl sulfonylated product was found only in traces. Because of the instability of the biarylsulfonylindoles **11** and **12**, the corresponding oxalates were prepared.



Scheme 5 Sulfonylation of the free 3-(2-*N,N*-diethylaminoethoxy)indole **10** with biarylsulfonyl chlorides in the presence of sodium hydride (method **A**) or *n*-butyllithium (method **B**).

Conclusions

To summarize, a variety of 3-(2-*N,N*-diethylaminoethoxy)indole derivatives were synthesized. By subsequent deprotection of the indole and sulfonylation with biarylsulfonyl chlorides, two novel classes of potential $5\text{-}HT_6$ receptor ligands could be prepared. Besides the desired 2-naphthalenesulfonylindole **11**, an unexpected sulfonylation of the 2-methyl group of the indole system created further interesting biarylsulfonylindoles **12a–c**.

Experimental

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka and Acros and unless otherwise noted were used without further purification. The compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS. ^{1}H NMR spectra (300.13 MHz and 500.13 MHz) and ^{13}C NMR spectra (75.5 MHz and 125.8 MHz) were recorded on Bruker spectrometers Avance 300 and Avance 500 in $CDCl_3$ and DMSO-d_6. The calibration of spectra was carried out on solvent signals ($CDCl_3$: δ (^{1}H) = 7.25, δ (^{13}C) = 77.0; DMSO-d_6: δ (^{1}H) = 2.50, δ (^{13}C) = 39.7). EI mass spectra were recorded on an MAT 95XP spectrometer (Thermo ELECTRON CORPORATION). GC was performed on a Hewlett Packard HP 6890 chromatograph with a 30 m HP5 column.

The preparation of compounds **8a–g** is described in the literature.[9a] The derivative **8h** was prepared by this method as well, but after purification by column chromatography, the product

mixture was used for the synthesis of compound **9h** without particular analytical investigations.

General procedure for the reaction of the 3-silyloxy-2-methylindoles with 2-*N,N*-diethylaminoethyl chloride to give the 3-(2-*N,N*-diethylaminoethoxy)indoles (9a–h)

To powdered potassium hydroxide (1.50 mmol) in a round bottom flask under an argon atmosphere, 15 mL dry THF and TBAF (2.75 mL of 1 M solution in THF, 2.75 mmol) were added. After the addition of the appropriate 3-silyloxy-2-methylindole (1.37 mmol) and *N,N*-diethylaminoethyl chloride (1.50 mmol), the mixture was stirred at 50 °C overnight. When the mixture had cooled to room temperature, H_2O (15 mL) was added. Then the separated aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The organic layers were dried (Na_2SO_4) and the solvents were evaporated *in vacuo.* The residue was chromatographed on a silica gel column (eluent: $CHCl_3$–10% MeOH) to give the 3-(2-*N,N*-diethylaminoethoxy)indole derivatives as brown oils.

1,2-Dimethyl-3-(2-*N,N*-diethylaminoethoxy)indole (9a). Yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.57$ (d, 1H, $J = 8.0$ Hz), 7.22 (d, 1H, $J = 8.2$ Hz), 7.13 (ddd, 1H, $J = 1.2$ Hz, $J = 6.9$ Hz, $J = 8.2$ Hz), 7.05 (ddd, 1H, $J = 1.2$ Hz, $J = 6.9$ Hz, $J = 8.0$ Hz), 4.16 (t, 2H, $J = 6.3$ Hz), 3.57 (s, 3H), 2.94 (t, 2H, $J = 6.3$ Hz), 2.72 (q, 4H, $J = 7.2$ Hz), 2.35 (s, 3H), 1.11 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 134.5$, 133.6, 124.7, 120.6, 120.5, 118.4, 116.7, 108.5, 72.1, 52.4, 47.3, 29.1, 11.2, 8.7 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 260 (10) [M$^+$], 160 (24), 145 (4), 117 (7), 100 (100), 86 (56), 77 (5), 72 (27), 57 (9), 45 (36). HRMS (CI, M + H$^+$): calcd. for $C_{16}H_{24}N_2O$: 261.1967; found: 261.1952.

1-Benzyl-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9b). Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$–7.59 (m, 1H), 7.25–7.15 (m, 4H), 7.09–7.02 (m, 2H), 6.93–6.90 (m, 2H), 5.23 (s, 2H), 4.17 (t, 2H, $J = 6.4$ Hz), 2.90 (t, 2H, $J = 6.4$ Hz), 2.65 (q, 4H, $J = 7.2$ Hz), 2.28 (s, 3H), 1.06 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.9$, 135.1, 133.7, 128.6, 127.1, 125.8, 124.6, 121.1, 120.9, 118.8, 117.0, 109.0, 72.6, 52.6, 47.5, 46.3, 11.7, 8.8 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 336 (6) [M$^+$], 279 (2), 237 (7), 221 (4), 208 (2), 195 (58), 180 (6), 165 (9), 117 (5), 100 (100), 91 (36), 86 (12), 71 (5), 57 (7), 43 (16). HRMS (EI): calcd. for $C_{22}H_{28}N_2O$: 336.2196; found: 336.2193.

5-Bromo-1,2-dimethyl-3-(2-*N,N*-diethylaminoethoxy)indole (9c). Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$ (d, 1H, $J = 1.9$ Hz), 7.17 (dd, 1H, $J = 8.5$ Hz, $J = 1.9$ Hz), 7.07 (d, 1H, $J = 8.5$ Hz), 4.09 (t, 2H, $J = 6.3$ Hz), 3.57 (s, 3H), 2.89 (t, 2H, $J = 6.3$ Hz), 2.68 (q, 4H, $J = 7.3$ Hz), 2.33 (s, 3H), 1.09 (t, 6H, $J = 7.3$ Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 134.2$, 132.5, 126.3, 123.4, 122.5, 119.5, 112.0, 110.1, 73.0, 52.8, 47.5, 29.5, 11.7, 8.9 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 339 (3), 338 (2) [M$^+$], 266 (4), 239 (10), 159 (2), 130 (4), 100 (100) 86 (36), 72 (13), 56 (5), 44 (11). HRMS (EI): calcd. for $C_{16}H_{23}BrN_2O$: 338.0988; found: 338.0976.

1-Benzyl-5-bromo-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9d). Yield: 30%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (br s, 1H), 7.25–7.16 (m, 3H), 7.13 (d, 1H, $J = 8.4$ Hz), 7.02 (d, 1H, $J = 8.4$ Hz), 6.88 (d, 2H, $J = 7.4$ Hz), 5.22 (s, 2H), 4.12 (t, 2H, $J = 6.2$ Hz), 2.88 (t, 2H, $J = 6.2$ Hz), 2.67 (q, 4H, $J = 7.3$ Hz), 2.28 (s, 3H), 1.08 (t, 6H, $J = 7.3$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.5$, 134.6, 132.4, 128.8, 127.4, 126.3, 125.8, 123.8, 122.8, 119.6, 112.3, 110.7, 72.9, 52.7, 47.5, 46.6, 11.7, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 415 (6), 414 (2) [M$^+$], 149 (5), 101 (11), 100 (100), 91 (68), 86 (33), 44 (12). HRMS (EI): calcd. for $C_{22}H_{27}BrN_2O$: 414.1301; found: 414.1298.

1-Benzyl-5-chloro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9e). Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.57$ (d, 1H, $J = 2.0$ Hz), 7.26–7.21 (m, 3H), 7.07 (d, 1H, $J = 8.5$ Hz), 7.01 (dd, 1H, $J = 2.0$ Hz, $J = 8.5$ Hz), 6.89 (m, 2H), 5.21 (s, 2H), 4.13 (t, 2H, $J = 6.3$ Hz), 2.88 (t, 2H, $J = 6.3$ Hz), 2.67 (q, 4H, $J = 7.3$ Hz), 2.28 (s, 3H), 1.07 (t, 6H, $J = 7.3$ Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 137.5$, 134.8, 132.2, 128.6, 127.3, 126.4, 125.8, 124.1, 122.2, 121.2, 116.6, 110.2, 73.0, 52.7, 47.5, 46.5, 11.7, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 370 (2) [M$^+$], 271 (7), 237 (2), 207 (3), 179 (3), 151 (7), 110 (3), 100 (100), 91 (78), 86 (40), 72 (15), 56 (9), 44 (16). HRMS (EI): calcd. for $C_{22}H_{27}ClN_2O$: 370.1805; found: 370.1807.

1-Benzyl-5-fluoro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9f). Yield: 50%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.21 (m, 4H), 7.09 (dd, 1H, $J = 9.0$ Hz, $J = 4.0$ Hz), 6.92 (m, 2H), 6.83 (dt, 1H, $J = 9.0$ Hz, $J = 2.5$ Hz), 5.24 (s, 2H), 4.27 (t, 2H, $J = 6.0$ Hz), 3.10 (t, 2H, $J = 6.0$ Hz), 2.91 (q, 4H, $J = 7.2$ Hz), 2.31 (s, 3H), 1.22 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.5$ (d, $J = 234$ Hz), 137.5, 134.8 (d, $J = 4.5$ Hz), 130.2, 128.7, 127.3, 126.9, 125.7, 120.9 (d, $J = 9.7$ Hz), 109.9 (d, $J = 9.7$ Hz), 109.2 (d, $J = 26.0$ Hz), 101.8 (d, $J = 24.5$ Hz), 71.4, 51.2, 47.5, 46.6, 10.7, 9.2 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 354 (2) [M$^+$], 255 (3), 135 (6), 101 (9), 100 (100), 91 (50), 86 (23), 43 (17). HRMS (EI): calcd. for $C_{22}H_{27}FN_2O$: 354.2102, found: 354.2109.

1-Benzyl-5-methoxy-2-methyl-3-(2-*N,N*-diethylaminoethoxy)-indole (9g). Yield: 46%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.19 (m, 3H), 7.06 (d, 1H, $J = 8.8$ Hz), 7.02 (d, 1H, $J = 2.5$ Hz), 6.92 (m, 2H), 6.73 (dd, 1H, $J = 8.8$ Hz, $J = 2.5$ Hz), 5.20 (s, 2H), 4.31 (t, 2H, $J = 6.0$ Hz), 3.85 (s, 3H), 3.13 (t, 2H, $J = 6.0$ Hz), 3.00–2.90 (m, 4H), 2.27 (s, 3H), 1.24 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.7$, 137.8, 134.6, 129.0, 128.6, 127.2, 125.8, 125.5, 120.9, 110.9, 110.0, 98.9, 70.9, 55.9, 52.1, 47.5, 46.4, 10.5, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 366 (20) [M$^+$], 267 (26), 266 (14), 265 (20), 251 (11), 176 (9), 147 (16), 106 (19), 101 (45), 100 (100), 92 (14), 91 (92), 86 (67), 72 (29), 57 (12), 56 (15), 44 (32). HRMS (EI): calcd. for $C_{23}H_{30}N_2O_2$: 366.2302; found: 366.2308.

1-Benzyl-4,5-dichloro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)-indole (I)/1-benzyl-5,6-dichloro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (II) (9h). Yield: 30%. (**I**) ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$–7.20 (m, 3H), 7.08 (d, 1H, $J = 8.8$ Hz), 6.96 (d, 1H, $J = 8.8$ Hz), 6.88–6.85 (m, 2H), 5.20 (s, 2H), 4.09 (t, 2H, $J = 6.3$ Hz), 2.85 (t, 2H, $J = 6.3$ Hz), 2.64 (q, 4H, $J = 7.2$ Hz), 2.29 (s, 3H), 1.05 (t, 6H, $J = 7.2$ Hz) ppm.^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 136.9$, 134.8, 133.1, 128.9, 128.4, 127.6, 125.7, 123.7, 122.4, 121.5, 120.1, 108.6, 73.1, 52.3, 47.6, 46.7, 11.7, 9.0 ppm. (**II**) ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$–7.20 (m, 3H), 7.66 (s, 1H), 7.22 (s, 1H), 6.88–6.85 (m, 2H), 5.16 (s, 2H), 4.06 (t, 2H, $J = 6.6$ Hz), 2.95 (t, 2H, $J = 6.6$ Hz), 2.67 (q, 4H, $J = 7.2$ Hz), 2.25 (s, 3H), 1.07 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (126 MHz,

$CDCl_3$) δ = 137.0, 134.7, 132.6, 128.9, 127.6, 127.0, 125.7, 124.9, 123.0, 121.0, 118.1, 110.7, 74.9, 52.8, 47.6, 46.7, 11.6, 8.9 ppm. MS (CI, M + H^+): *m/z* (relative intensity): 405. HRMS (CI, M − H^+) calcd. for $C_{22}H_{26}Cl_2N_2O$: 403.1338; found: 403.1334.

2-Methyl-3-(2-*N,N*-diethylaminoethoxy)indole (10). To a deep blue solution of Na (684 mg, 29.7 mmol) in NH_3 (*ca.* 20 mL) at −78 °C, a solution of compound **9b** (1.0 g, 2.97 mmol) in dry THF (10 mL) was added dropwise. The mixture was stirred at −33 °C for 2 h, quenched with NH_4Cl at −78 °C, allowed to warm to room temperature, and concentrated. The residue was diluted with H_2O and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvents were removed *in vacuo* to give a yellow oil in 95% yield (700 mg, 2.84 mmol). The crude material was used for the next reaction.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (br s, 1H, NH), 7.54 (m, 1H), 7.09 (m, 1H), 7.11–7.01 (m, 2H), 4.14 (t, 2H, J = 6.6 Hz), 2.89 (t, 2H, J = 6.6 Hz), 2.66 (q, 4H, J = 7.2 Hz), 2.33 (s, 3H), 1.07 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 132.7, 122.5, 121.9, 120.9, 118.9, 116.9, 110.6, 72.3, 52.6, 47.5, 11.6, 10.2 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 246 (1) [M^+], 160 (1), 146 (11), 117 (5), 100 (100), 86 (40), 72 (11), 56 (7), 44 (18). HRMS (EI): calcd. for $C_{15}H_{22}N_2O$: 246.1987; found: 246.2006.

1-(*N*-Naphthalene-2-ylsulfonyl)-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (11). The above mentioned crude **10** (700 mg, 2.84 mmol) in dry THF (8 mL) was added dropwise to NaH (682 mg, 28.4 mmol, 65% content in a mineral oil suspension that was washed with dry *n*-hexane three times before use) suspended in dry THF (10 mL) at room temperature under argon, and then the mixture was stirred for 10 min. A dry THF (3 mL) solution of 2-naphthalenesulfonylchloride (1.9 g, 8.5 mmol) was added to the mixture, and the resulting solution was stirred at 50 °C for 2 h. The reaction was quenched by adding aq. Na_2CO_3 (20 mL) and the mixture was extracted with $CHCl_3$ (3 × 20 mL). After drying with Na_2SO_4, removal of the solvent and chromatography of the crude material with $CHCl_3$–10% MeOH gave compound **11** as brown oil in 24% yield (300 mg, 0.69 mmol).

^{1}H NMR (300 MHz, DMSO), **11** (**oxalate**): δ = 9.53 (br, 2H), 8.70 (d, 1H, J = 2.2 Hz), 8.22 (d, 1H, J = 8.2 Hz), 8.18 (d, 1H, J = 8.5 Hz), 8.04 (d, 1H, J = 8.8 Hz), 7.99 (d, 1H, J = 8.2 Hz), 7.75–7.66 (m, 2H), 7.65 (dd, 1H, J = 8.8 Hz, J = 2.0 Hz), 7.59 (d, 1H, J = 7.9 Hz), 7.35 (m, 1H), 7.26 (t, 1H, J = 7.6 Hz), 4.28 (t, 2H, J = 5.4 Hz), 3.38 (t, 2H, J = 5.4 Hz), 3.13 (q, 4H, J = 7.3 Hz), 2.60 (s, 3H), 1.17 (t, 6H, J = 7.3 Hz) ppm. ^{13}C NMR (75 MHz, DMSO), **11** (**oxalate**): δ = 164.4, 140.3, 134.9, 134.4, 133.8, 131.6, 130.2, 129.9, 129.8, 128.3, 128.2, 128.0, 124.9 (2), 124.1, 124.0, 120.9, 117.9, 114.7, 68.5, 50.9, 47.0, 11.4, 8.9 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 436 (1) [M^+], 160 (1), 146 (11), 117 (5), 100 (100), 86 (40), 72 (11), 56 (7), 44 (18), 29 (6). HRMS (EI): calcd. for $C_{25}H_{28}N_2O_3S$: 436.1815; found: 436.1808.

General procedure for the formation of the oxalate

The product oil was diluted in a small amount of dry ethanol. After addition of oxalic acid in excess (1.1 equiv), the solution was stored in a fridge. The formed precipitate was isolated. The yield after the formation of the oxalate from the product oil for compound **11** constituted 55%.

General procedure for the sulfonylation with *n*-butyl lithium

n-Butyl lithium (1.6 M in hexane, 1.33 mL, 2.1 mmol) was added to a solution of the free indole **10** (2.03 mmol) in anhydrous THF (5 mL) at −78 °C during 20 min. After complete addition, the mixture was stirred at −78 °C for 10 min, and was thereafter allowed to reach room temperature over 1 h. After cooling to −78 °C, a solution of sulfonyl chloride (2.3 mmol) in anhydrous THF (3 mL) was added over 20 min at −78 °C. The resulting mixture was allowed to slowly reach room temperature over 3 days, was thereafter poured into water (20 mL) containing brine (5 mL), and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were washed with water (50 mL) and dried over $MgSO_4$. After removal of the solvents *in vacuo*, the desired product was isolated by column chromatography in $CHCl_3$–MeOH as brown oil. This isolated oil was used for the preparation of the oxalate.

2-(Benzo[*b*]thiophen-3-ylsulfonyl)methyl-3-(2-*N,N*-diethylaminoethoxy)indole (12a) (oxalate). Yield: 23% free indole, 70% oxalate (from product oil). ^{1}H NMR (300 MHz, DMSO): δ = 11.02 (s, 1H), 9.82 (br, 2H), 8.55 (s, 1H), 8.17 (ddd, 1H, J = 8.0 Hz, J = 1.3 Hz, J = 0.8 Hz), 8.05 (ddd, 1H, J = 8.0 Hz, J = 1.3 Hz, J = 0.8 Hz), 7.55–7.42 (m, 3H), 7.35 (dt, 1H, J = 8.0 Hz, J = 1.0 Hz), 7.11 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz), 6.98 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz), 4.88 (s, 2H), 4.04 (t, 2H, J = 5.3 Hz), 3.11–3.04 (m, 6H), 1.16 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 164.7, 140.2, 139.4, 137.4, 134.1, 134.0, 132.5, 125.8, 123.7, 122.8, 122.5, 119.3, 119.0, 117.8, 113.0, 112.2, 68.3, 52.8, 50.7, 47.0, 8.9 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 442 (28) [M^+ − oxalic acid], 245 (30), 181 (30), 145 (69), 134 (83), 100 (78), 86 (100), 72 (58), 64 (17), 56 (44), 44 (90). HRMS (EI): calcd. for $C_{23}H_{26}N_2O_3S_2$: 442.1379; found: 442.1384.

2-(5-Chloro-3-methylbenzo[*b*]thiophen-2-ylsulfonyl)-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (12b) (oxalate)

Yield: 20% free indole, 46% oxalate (from product oil). ^{1}H NMR (300 MHz, DMSO): δ = 11.00 (s, 1H), 8.14 (d, 1H, J = 8.7 Hz), 8.09 (d, 1H, J = 2.1 Hz), 7.64 (dd, 1H, J = 8.7 Hz, J = 2.1 Hz), 7.58 (d, 1H, J = 8.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.13 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.2 Hz), 7.00 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.1 Hz), 4.94 (s, 2H), 4.18 (t, 2H, J = 5.1 Hz), 3.27 (t, 2H, J = 5.1 Hz), 3.08 (q, 4H, J = 7.2 Hz), 2.38 (s, 3H), 1.15 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 164.4, 140.8, 140.0, 138.5, 137.7, 135.6, 134.0, 130.8, 128.3, 125.2, 124.1, 122.7, 119.3, 119.1, 117.9, 112.8, 68.6, 53.9, 51.0, 47.1, 11.9, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 490 (1) [M^+ − oxalic acid], 422 (2), 244 (6), 214 (4), 181 (100), 147 (29), 100 (63), 86 (20), 72 (10), 64 (16), 56 (16), 44 (9). HRMS (EI): calcd. for $C_{24}H_{27}ClN_2O_3S_2$: 490.1146; found: 490.1140.

2-(6-Chloroimidazo[2,1-*b*]thiazol-5-ylsulfonyl)methyl-3-(2-*N,N*-diethylaminoethoxy)indole (12c) (oxalate). Yield: 20% free indole, 64% oxalate (from product oil). ^{1}H NMR (300 MHz, DMSO): δ = 10.90 (s, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 4.5 Hz), 7.39 (d, 1H, J = 4.5 Hz), 7.30 (d, 1H, J = 8.0 Hz),

7.11 (ddd, 1H, $J = 8.0$ Hz, $J = 7.0$ Hz, $J = 1.0$ Hz), 6.99 (ddd, 1H, $J = 8.0$ Hz, $J = 7.0$ Hz, $J = 1.0$ Hz), 4.92 (s, 2H), 4.24 (t, 2H, $J = 5.3$ Hz), 3.34 (t, 2H, $J = 5.3$ Hz), 3.17 (q, 4H, $J = 7.2$ Hz), 1.22 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, DMSO): $\delta =$ 164.4, 151.1, 138.9, 137.8, 134.0, 122.7, 119.9, 119.3, 119.1, 117.8, 116.9, 116.9, 112.4, 112.2, 68.6, 53.5, 51.1, 47.2, 9.1 ppm. MS (CI, M + H$^+$, 70 eV): m/z (relative intensity): 467 (7) [M$^+$ − oxalic acid], 445 (8), 403 (67), 245 (39), 159 (40), 100 (100), 86 (15), 72 (10). HRMS (CI, M + H$^+$): calcd. for $C_{20}H_{23}ClN_4O_3S_2$: 467.0973; found: 467.0963.

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3.6 Palladium-Catalyzed Amination and Sulfonylation of 5-Bromo-3-[2-(diethylamino)ethoxy)indoles to Potential $5HT_6$ Receptor Ligands

Nicolle Schwarz, Anahit Pews-Davtyan, Dirk Michalik, Karolin Krüger, Annegret Tillack, Antoni Torrens, José Luis Diaz, Matthias Beller*, Eur. J. Org. Chem.* **2008**, 5425-5435.

Contributions: In this paper I contributed to a significant amount of the argumentation and the synthetic work. I performed synthesis about half of the compounds. My contribution as co-author of this paper is more than 60%.

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Palladium-Catalyzed Amination and Sulfonylation of 5-Bromo-3-[2-(diethylamino)ethoxy]indoles to Potential 5-HT_6 Receptor Ligands

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Keywords: Indole / Sulfonylation / Amination / Palladium

A general and efficient palladium-catalyzed amination of 5-bromo-3-[2-(diethylamino)ethoxy]indoles has been developed. Best results are obtained in the presence of $Pd(OAc)_2$ and 2-[di(1-adamantyl)phosphanyl]-1-phenylpyrrole as ligand. Subsequent sulfonylation gave novel indole derivatives, which are of interest as potentially biological active 5-HT_6 receptor ligands.

Introduction

Among the known biologically active amines, especially indoles continue to attract significant synthetic and medicinal interest.[1] A variety of substituted indoles bind selectively to different receptors with high affinity and have been referred as "privileged pharmacological structures". Thus, it is not surprising that indoles have become an important component in many of today's pharmaceuticals.[2] 5-Hydroxytryptamine$_6$ (5-HT_6) receptors are an essential subtype of the identified serotonin receptors 5-HT_{1-7}.[3] Their selective attraction for a wide range of drugs used in central nervous system related diseases (e.g. Alzheimer's disease, anxiety, and schizophrenia) has stimulated significant recent work in this field.[4] In addition, 5-HT_6 receptor ligands are known to facilitate the reduction of food intake, fat absorption and body weight in genetic and dietary models of obesity. Interestingly, the 5-HT_6 receptor has no known functional splice variants and it appears to be expressed almost exclusively in the central nervous system (CNS).[5]

Since the discovery of selective ligands for 5-HT_6 receptors by high-throughput-screening in 1998, several medicinal-chemistry-driven approaches have delivered novel lead structures. Among the active compounds the majority are indole derivatives, especially with tryptamine scaffold (Figure 1).[6] For some time we have been interested in the improvement and exploration of methodologies for the synthesis and functionalization of indoles.[7,8] For example, we developed a one-pot synthesis of tryptamines and tryptopholes via titanium-catalyzed hydrohydrazination of chloro- and silyloxo-substituted alkynes.[9] Based on this work, more recently we studied the catalytic hydrohydrazination of propargyl alcohol derivatives to give 3-silyloxy-2-methylindoles (Scheme 1).[10]

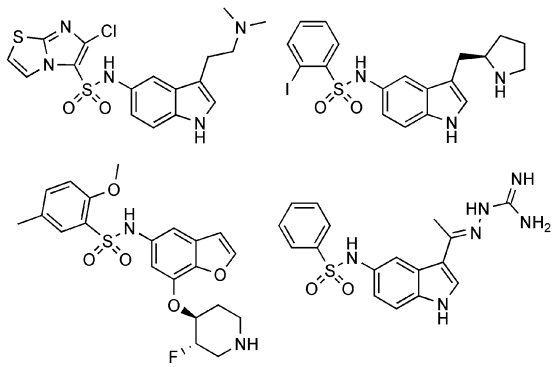

Figure 1. 5-HT_6 receptor ligands containing indoles or indole-like structures.

Scheme 1. Catalytic synthesis of 3-siloxyindoles.

In continuation of these studies, we report here the synthesis of novel 3-[2-(diethylamino)ethoxy]-2-methylindoles,[11] their palladium-catalyzed amination and subsequent sulfonylation of the corresponding coupled indoles.

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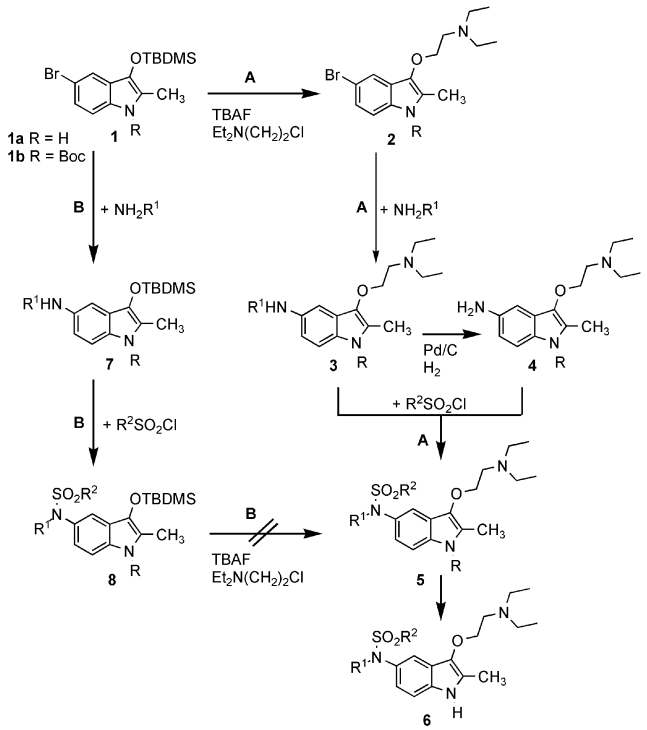
Results and Discussion

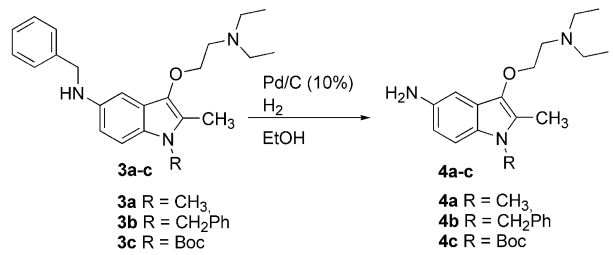
As shown in Scheme 2 initially we envisioned two different synthetic strategies (**A** and **B**) to obtain the desired compounds **5** and **6**. The synthetic route **A** starts with 5-bromo-2-methyl-3-silyloxyindole **1** with in situ deprotection of the silyl group, followed by nucleophilic substitution with 2-(diethylamino)ethyl chloride to give **2**. Palladium-catalyzed Buchwald–Hartwig amination[12] towards **3**, subsequent hydrogenation to **4** and finally sulfonylation should lead to the desired products **5** and **6**. Route **B** demonstrates another access to these structures starting from the same compound. Here, 5-bromo-2-methyl-3-silyloxyindole **1** should be catalytically aminated to the according indole derivatives **7**. Subsequent sulfonylation of the arylamino-indoles **7** would give the sulfonylated intermediates **8**. Then, the aminoalkyl side chain has to be introduced in the last step to give the target compounds **5** and **6**.

In exploratory experiments the palladium-catalyzed amination of 5-bromo-3-[2-(diethylamino)ethoxy]indole **2** with benzylamine in presence of different ligands was investigated. Best results are obtained applying $Pd(OAc)_2$/1-phenyl-2-[di(1-adamantyl)phosphanyl]pyrrole **L** as in situ catalyst at 100 °C for 20 h in toluene in the presence of LiHMDS (or Cs_2CO_3) as base. This catalyst system has also been proven successful in several other catalytic coupling reactions before.[13a,13b] As shown in Scheme 3 and Table 1 aminations with benzylamine as well as aliphatic amines [*n*-hexylamine and 2-(4-fluorophenyl)ethylamine] worked well and led to the corresponding products in good yields (56–85%). In general, the yields of the Boc-protected indoles are decreased in comparison with the *N*-methyl and *N*-benzyl-protected ones. All attempts to couple *tert*-butyl 5-bromo-3-[2-(diethylamino)ethoxy]-2-methylindole-1-carboxylate (**2c**) with secondary amines (imidazole, pyrazole, 2-aminopyrimidine) gave the free NH-indole derivative [2-(5-bromo-2-methyl-1*H*-indol-3-yloxy)ethyl]diethylamine **2d**.

The lower stability of the Boc-derivatives is explained by partial deprotection under the reaction conditions. In order to prepare the pharmaceutically more interesting free 5-aminoindoles, catalytic debenzylation of **3a**–**c** was investigated (Scheme 4, Table 2). For this purpose hydrogenation reactions **3a**–**b** have been performed in a 20 mL autoclave at room temperature with a hydrogen pressure of 50 bar for 8 h. In the case of compound **3c** lower hydrogen pressure (5 bar), shorter reaction time and elevated temperatures (60 °C) were needed, to avoid the formation of 3-indoline as a by-product. Formation of the free NH_2-group in position 5 of the indole proceeded smoothly and gave the corresponding 5-amino-3-[2-(diethylamino)ethoxy]indoles **4a**–**c** in good to high yields (50–91%).

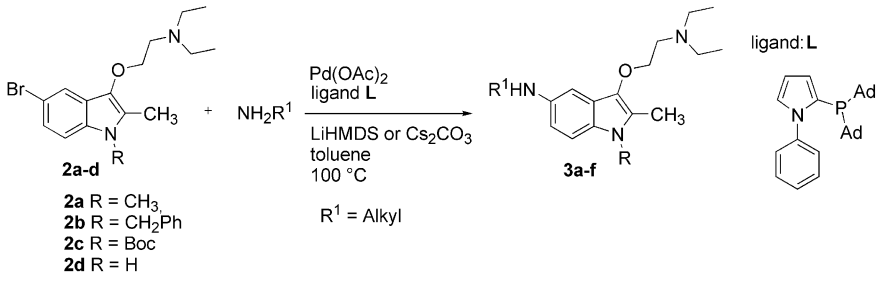


Scheme 2. Synthetic routes of 5-sulfonylamine-3-[2-(diethylamino)-ethoxy]indoles.



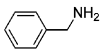
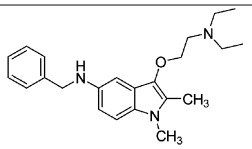
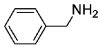
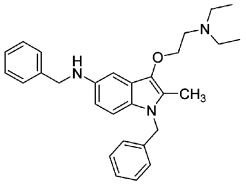
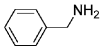
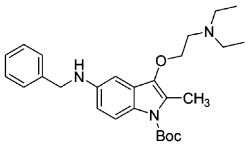
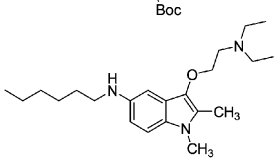
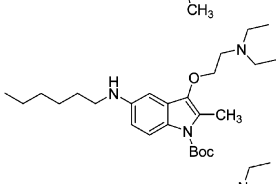
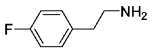
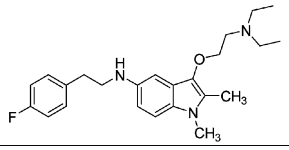
Scheme 4. Palladium-catalyzed hydrogenation of 5-benzylamino-3-[2-(diethylamino)ethoxy]indoles.

Next, we attempted the sulfonylation of **3c**, **3e**, and **4a**–**c** with different aryl- and heteroarylsulfonyl chlorides as shown in Scheme 5. The selection of the sulfonyl groups is



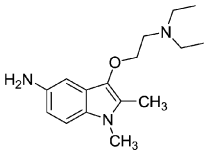
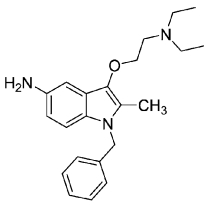
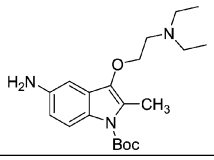
Scheme 3. Palladium-catalyzed amination of 5-bromo-3-[2-(diethylamino)ethoxy]lindoles.

Table 1. Pd-catalyzed amination of 5-bromo-3-[2-(diethylamino)-ethoxy]indoles.

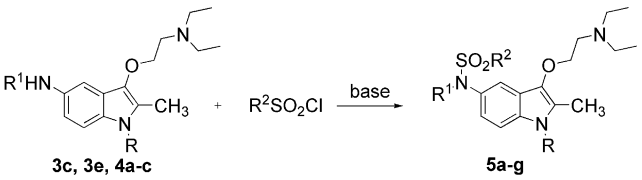
Entry	Starting material	Amine	Product	3	% Yield[a]
1	**2a**			**3a**[b]	85
2	**2b**			**3b**[b]	60
3	**2c**			**3c**[c]	72
4	**2a**			**3d**[b]	70
5	**2c**			**3e**[c]	56
6	**2a**			**3f**[b]	70

[a] Isolated yield based on the indole. [b] *Reaction conditions:* 5-bromo-3-[2-(diethylamino)ethoxy]indole (1 mmol), amine (1.3 mmol), 2 mol-% $Pd(OAc)_2$, 4 mol-% ligand **L**, LiHMDS (1.3 mmol), solvent: toluene 3 mL, 100 °C, 20 h. [c] *Reaction conditions*: 5-bromo-3-[2-(diethylamino)ethoxy]indole (1 mmol), amine (1.5 mmol), 6 mol-% $Pd(OAc)_2$, 12 mol-% ligand **L**, Cs_2CO_3 (1.0 mmol), solvent: toluene 3 mL, 100 °C, 20 h.

Table 2. Pd-catalyzed hydrogenation.

Entry	Starting material	Product	4	% Yield[a]
1	**3a**		**4a**[b]	81
2	**3b**		**4b**[b]	91
3	**3c**		**4c**[c]	50

[a] Isolated yield based on indole derivative. [b] *Reaction conditions:* Indole derivative (1 mmol), Pd/C (10%) (200 mg), H_2, 50 bar, room temp., 8 h in 40 mL of ethanol. [c] *Reaction conditions:* Indole derivative (1 mmol), Pd/C (10%) (200 mg), H_2, 5 bar, 60 °C, 3.5 h in 40 mL of ethanol.

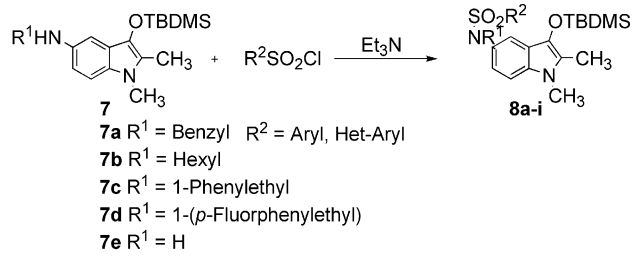


Scheme 5. Sulfonylation of 5-amino-3-[2-(diethylamino)ethoxy]-indoles with different sulfonyl chlorides.

based on a pharmacophore-framework model for known 5-HT$_6$ receptor ligands, which was postulated in 2004 by Holenz et al.[6] based on a medicinal-chemistry-guided analysis of reference compounds. Favourable sulfonyl motives came from a modelling study of Pullagurla et al., including naphthyl, benzothiophenyl, imidazo[2,1-*b*]thiazolyl and *p*-aminophenyl substituents.[14]

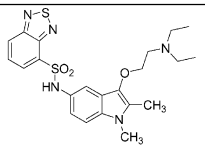
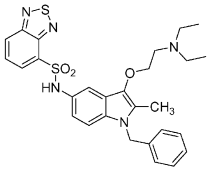
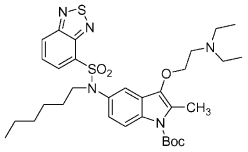
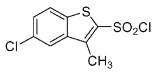
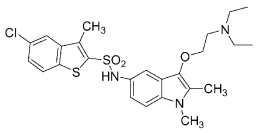
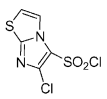
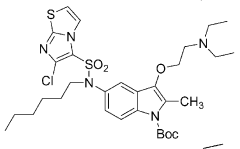
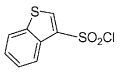
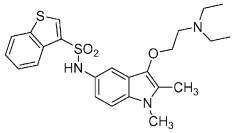
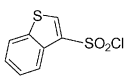
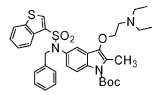
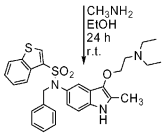
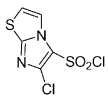
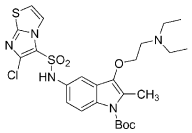
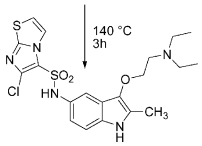
The newly synthesized sulfonylated indoles are listed in Table 3. Treatment of the respective 5-aminoindole with the different aryl- and heteroarylsulfonyl chlorides in Et_3N at 40 °C or in CH_2Cl_2 in the presence of Cs_2CO_3 at room temperature for 2 h gave the corresponding sulfonylated indole derivatives **5a**–**h** in general in good yields (Table 3, entries 1–4, 6–7 and 9, 50–98%). An exception is the reaction with 6-chloroimidazo[2,1-*b*]thiazole-5-sulfonyl chloride (Table 3, entry 5) which gave a lower yield due to the decreased reactivity of this sulfonyl chloride. In accordance with the pharmacophore-framework model for 5-HT$_6$ receptor ligands the newly prepared compounds in Table 3 possess two hydrophobic areas and an indole core. Because the receptor-ligand affinity increases additionally with a free NH-group in position 1, we have deprotected compound **5g** and **5h** to the biologically more active indole derivatives **6a** and **6b**. We obtained these indole derivatives in high yields up to 88% (Table 3, entries 8 and 10).

Finally, we studied the sulfonylation of the 3-siloxy-protected 5-aminoindoles **7a**–**e**[13a] to give **8a**–**i** (Scheme 6).



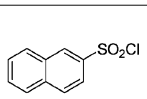
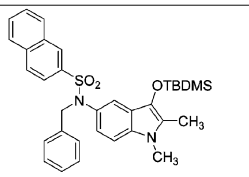
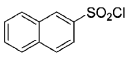
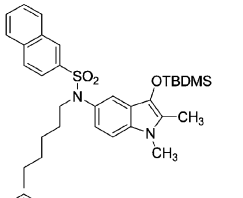
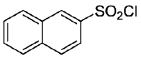
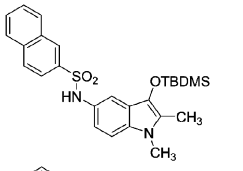
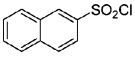
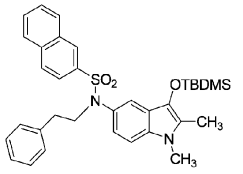
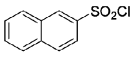
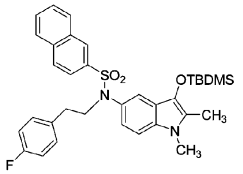
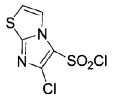
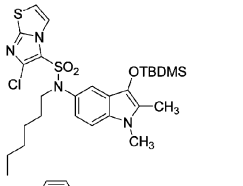
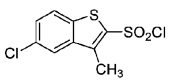
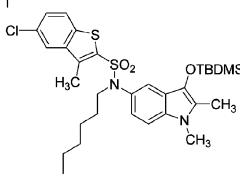
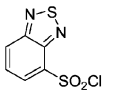
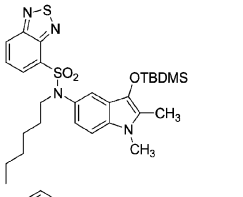
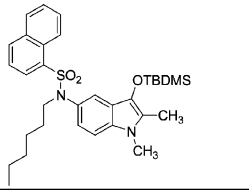
Scheme 6. Sulfonylation of 5-amino-3-(silyloxy)indoles with different sulfonyl chlorides.

Table 3. Sulfonylation of 5-amino-3-[2-(diethylamino)ethoxy]indoles with different sulfonyl chlorides.

Entry	Starting material	Sulfonyl chloride	Product	5 and 6	% Yield[a]
1	**4a**			**5a**[b]	54
2	**4b**			**5b**[b]	63
3	**3e**			**5c**[c]	98
4	**4a**			**5d**[b]	50
5	**3e**			**5e**[b]	28
6	**4a**			**5f**[b]	81
7	**3c**			**5g**[c]	91
8	**5g**			**6a**[d]	78
9	**4c**			**5h**[e]	81
10	**5h**			**6b**[f]	88

[a] Isolated yield based on the indole. [b] *Reaction conditions:* Indole derivative (1 mmol), arylsulfonyl chloride (1 mmol), triethylamine (5 mL), 40 °C, 24 h. [c] *Reaction conditions*: Indole derivative (1 mmol), arylsulfonyl chloride (3 mmol), Cs_2CO_3 (2 mmol), solvent: CH_2Cl_2 (10 mL), 40 °C, 24 h. [d] *Reaction conditions:* Indole derivative (0.1 mmol), methylamine in 10 mL of ethanol (33%), room temp., 24 h. [e] *Reaction conditions:* indole derivative (0.5 mmol), sulfonyl chloride (0.5 mmol), $NaHCO_3$ (2 equiv.), solvent: acetonitrile (5 mL), room temp., 15 h. [f] *Reaction conditions:* indole derivative (0.5 mmol), 140 °C, 3 h.

Table 4. Sulfonylation of 5-amino-3-(silyloxy)indoles.[a]

Entry	Starting material	Sulfonyl chloride	Product	8	% Yield[b]
1	**7a**			**8a**	70
2	**7b**			**8b**	90
3	**7e**			**8c**	51
4	**7c**			**8d**	51
5	**7d**			**8e**	75
6	**7b**			**8f**	25
7	**7b**			**8g**	62
8	**7b**			**8h**	75
9	**7b**			**8i**	80

[a] *Reaction conditions:* Indole derivative (1 mmol), arylsulfonyl chloride (1 mmol), triethylamine (5 mL), 40 °C, 2 h. [b] Isolated yield based on the indole.

The sulfonylation proceeded similar compared to the sulfonylations shown in Scheme 3. Again, most sulfonylated indoles **8a**–**i** were isolated in good yields (Table 4, entries 1–5, 7–9; 51–90%). Despite several attempts, the in situ deprotection with TBAF and nucleophilic substitution of 2-(diethylamino)ethyl chloride to compounds **5** and **6** according to route **B** could not be achieved.

Conclusions

In summary, a series of new potential 5-HT$_6$ receptor ligands has been synthesized. For the first time palladium-catalyzed coupling reactions of 3-[2-(diethylamino)ethoxy]-indoles have been performed. Catalytic amination applying Pd(OAc)$_2$/1-phenyl-2-[di(1-adamantyl)phosphanyl]pyrrole as catalyst system gave the corresponding 5-aminoindoles in good yields. Straightforward sulfonylation with different aryl- and heteroarylsulfonyl chlorides proceeded smoothly and led to the targeted products.

Experimental Section

General: All reactions were carried out under argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros and Strem and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 300, AV 400 and AV 500 spectrometers. The ^{1}H and ^{13}C NMR chemical shifts are referenced to trimethylsilane (TMS) [δ(TMS) = 0 (^{1}H)], and to the solvent resonance [δ(CDCl$_3$) = 77.0 (^{13}C)]. EI mass spectra were recorded on an AMD 402 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded on a FT-IR Nicolet 6700 (Thermo ELECTRON CORPORATION). The synthesis of compounds **2a**–**b** and **7a**–**d** have been already described in earlier publications.[11,13a]

Three-Step Synthesis of the Starting Material *tert*-Butyl 5-Bromo-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (2c)

Step 1. 5-Bromo-3-(*tert*-butyldimethylsilanyloxy)-2-methyl-1*H*-indole (1a): In a round-bottomed flask under argon atmosphere (4-bromophenyl)hydrazine (0.09 mol), *tert*-butyldimethylsilyloxy-2-propyne (0.07 mol) and ZnCl$_2$ (0.09 mmol) were dissolved in 50 mL of THF. The reaction mixture was heated to 100 °C under reflux for 24 h. After removal of the solvent the mixture was purified by column chromatography (eluent: ethyl acetate gradient 0–25% in heptane with 1–2% triethylamine). The isolated product gave a light-brown solid in a yield of 50% ^{1}H NMR (300.13 MHz, CDCl$_3$): δ = 7.53 (d, J = 1.9 Hz, 1 H), 7.37 (br., 1 H, NH), 7.14 (dd, J = 8.5, J = 1.9 Hz, 1 H), 7.04 (d, J = 8.5 Hz, 1 H), 2.30 (s, 3 H), 1.07 (s, 9 H), 0.15 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 131.3 (Cq), 130.4 (Cq), 124.5 (Cq), 123.8, 121.6 (Cq), 119.7, 112.1 (Cq), 111.8, 25.7, 18.1 (Cq), 10.6, –4.2 ppm. MS (EI, 70 eV): *m*/*z* (%) = 340 (22), 339 [M$^+$, 93], 285 (17), 284 (10), 283 (16), 205 (5), 204 (19), 203 (100), 188 (19), 145 (9), 144 (47), 73 (41). HRMS: calcd. for C$_{15}$H$_{22}$BrNOSi: 339.06485; found 339.064659. FTIR (KBr): $\tilde{\nu}$ = 3399, 2954, 2929, 2856, 1724, 1471, 1314, 1285, 1255, 1238, 1156, 888, 861, 838, 791, 780, 583 cm^{-1}.

Step 2. *tert*-Butyl 5-Bromo-3-(*tert*-butyldimethylsilanyloxy)-2-methyl-1*H*-indole-1-carboxylate (1b): In a round-bottomed flask under argon atmosphere indole **1a** (10 mmol), di-*tert*-butyl dicarbonate (12 mmol) and DMAP (0.35 mmol) were dissolved in dry THF and stirred overnight at room temperature. After complete conversion (TLC control) the solvent was removed and the residue was cleaned by column chromatography (eluent: ethyl acetate gradient 0–25% in heptane). The isolated product gave a light-yellow solid material in a yield of 90%. ^{1}H NMR (300.13 MHz, CDCl$_3$): δ = 7.99 (d, J = 8.9 Hz, 1 H), 7.49 (d, J = 2.0 Hz, 1 H), 7.29 (dd, J = 8.9, J = 2.0 Hz, 1 H), 2.44 (s, 3 H), 1.66 (s, 9 H), 1.08 (s, 9 H), 0.17 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 150.5 (Cq), 134.7 (Cq), 132.2, 127.0 (Cq), 126.3, 123.6, 119.6 (Cq), 116.9 (Cq), 115.6 (Cq), 83.7 (Cq), 28.3, 25.8, 18.2 (Cq), 12.9, –4.1 ppm. MS (EI, 70 eV): *m*/*z* (%) = 441 (11), 440 (3), 439 (11) [M$^+$], 386 (24), 385 (100), 384 (23), 383 (97), 341 (58), 340 (13), 339 (57), 284 (12), 283 (14), 282 (12), 204 (12), 203 (64), 145 (4), 144 (26), 75 (15), 74 (6), 73 (83), 59 (12), 58 (7), 57 (91). HRMS: calcd. for C$_{20}$H$_{30}$BrNO$_3$Si: 439.11728; found 439.116436. FTIR (ATR): $\tilde{\nu}$ = 3077, 3004, 2976, 2958, 2930, 2896, 2858, 1724, 1454, 1360, 1320, 1267, 1251, 1217, 1150, 1129, 1068, 1010, 887, 835, 820, 799, 783, 764, 729 cm^{-1}.

Step 3. *tert*-Butyl 5-Bromo-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (2c): In a round-bottomed flask carboxylate **1b** (3.4 mmol) and tetrabutylammonium fluoride (TBAF) (4.1 mmol) were dissolved in dry THF and stirred for 10 min at room temperature. After Na$_2$CO$_3$ (6.8 mmol) was added, the reaction mixture was stirred for further 10 min at room temperature. Finally (2-chloroethyl)diethylamine (6.8 mmol) was added and the solution was heated up to 45 °C for 4 h. After removal of the solvent the residue was cleaned by column chromatography (eluent CH$_2$ Cl$_2$/ethanol, 20:1). The isolated product obtained as pale yellow oil with a yield of 68%. ^{1}H NMR (300.13 MHz, CDCl$_3$): δ = 8.00 (d, J = 8.9 Hz, 1 H), 7.64 (d, J = 2.0 Hz, 1 H), 7.29 (dd, J = 8.9, J = 2.0 Hz, 1 H), 4.05 (t, J = 6.3 Hz, 2 H), 2.84 (t, J = 6.3 Hz, 2 H), 2.63 (q, J = 7.2 Hz, 4 H), 2.49 (s, 3 H), 1.65 (s, 9 H), 1.06 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 150.4 (Cq), 138.9 (Cq), 132.4 (Cq), 126.6 (Cq), 126.4, 126.0 (Cq), 119.5, 117.1, 115.8 (Cq), 84.0 (Cq), 72.7 (CH$_2$), 52.8 (CH$_2$), 47.5 (CH$_2$), 28.2, 12.5, 11.7 ppm. MS (EI, 70 eV): *m*/*z* (%) = 426 (1), 425 (1) [M$^+$], 424 (1), 385 (7), 384 (1), 383 (6), 341 (3), 279 (4), 225 (6), 197 (4), 167 (11), 149 (31), 101 (25), 100 (100), 72 (17), 57 (76). HRMS: calcd. for C$_{20}$H$_{29}$BrN$_2$O: 425.14362; found 425.14343. FTIR (ATR): $\tilde{\nu}$ = 3052, 2969, 2930, 2873, 2805, 1728, 1453, 1369, 1348, 1319, 1221, 1172, 1148, 1130, 1116, 1061, 1015, 765, 745 cm^{-1}.

[2-(5-Bromo-2-methyl-1*H*-indol-3-yloxy)ethyl]diethylamine (2d): ^{1}H NMR (300.13 MHz, CDCl$_3$): δ = 7.67 (d, J = 2.0 Hz, 1 H), 7.60 (br., 1 H, NH), 7.16 (dd, J = 8.5, J = 2.0 Hz, 1 H), 7.06 (d, J = 8.5 Hz, 1 H), 4.09 (t, J = 6.3 Hz, 2 H), 2.86 (t, J = 6.3 Hz, 2 H), 2.65 (q, J = 7.2 Hz, 4 H), 2.35 (s, 3 H), 1.07 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 134.7 (Cq), 131.3 (Cq), 124.1 (Cq), 123.9, 123.7 (Cq), 119.6, 112.4 (Cq), 112.1, 72.7 (CH$_2$), 52.7 (CH$_2$), 47.4 (CH$_2$), 11.7, 10.3 ppm. MS (EI, 70 eV): *m*/*z* (%) = 324 (0.3) [M$^+$], 226 (3), 225 (1), 224 (3), 145 (3), 117 (5), 101 (8), 100 (100), 87 (3), 86 (47). HRMS: calcd. for C$_{15}$H$_{21}$BrN$_2$OSi: 324.08318; found 324.081805. FTIR (ATR): $\tilde{\nu}$ = 3410, 3300, 2964, 2919, 2850, 1453, 1284, 1234, 1154, 1122, 1034, 862, 791, 732, 668 cm^{-1}.

Compounds 3a–f, General Procedure for the Coupling Synthesis of 5-Amino-3-[2-(diethylamino)ethoxy]-1*H*-indole Derivatives 2a–c: In an Ace-pressure tube under argon atmosphere, a 5-bromo-3-[2-(diethylamino)ethoxy]indole derivative of type **2a**–**c** (1 mmol), amine (1.3 mmol), Pd(OAc)$_2$ (2 mol-%, 6 mol-% for **3c** and **3e**), 1-phenyl-2-[di(1-adamantyl)phosphanyl]pyrrole **L** (4 mol-%; 12 mol-% for **3c**

and **3e**) and lithium hexamethyldisilazane (LiHMDS) (1.3 mmol or 1.5 mmol Cs_2CO_3 for **3c** and **3e**) were dissolved in toluene (3 mL). The pressure tube was fitted with a Teflon cap and heated up to 100 °C for 20 h. After removal of the solvent in vacuo, the corresponding indole product was isolated as oil by column chromatography (eluent: ethyl acetate gradient 0–20% in heptane with 1–2% triethylamine).

Benzyl{3-[2-(diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}amine (3a): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.44–7.26 (m, 5 H), 7.05 (d, J = 8.4 Hz, 1 H), 6.77 (d, J = 2.4 Hz, 1 H), 6.59 (dd, J = 8.4, J = 2.4 Hz, 1 H), 4.37 (s, 2 H), 4.08 (t, J = 6.5 Hz, 2 H), 3.54 (s, 3 H), 3.30 (br., 1 H, NH), 2.90 (t, J = 6.5 Hz, 2 H), 2.69 (q, J = 7.2 Hz, 4 H), 2.31 (s, 3 H), 1.09 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 141.6 (Cq), 140.1 (Cq), 134.2 (Cq), 128.6 (Cq), 128.5, 127.7, 127.0, 125.3 (Cq), 121.4 (Cq), 110.5, 109.4, 99.0, 72.0 (CH_2), 52.5 (CH_2), 49.8 (CH_2), 47.5 (CH_2), 29.4, 11.5, 8.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 366 (2), 365 (1) [M$^+$], 288 (1), 262 (19), 261 (6), 250 (3), 249 (2), 175 (4), 174 (9), 173 (26), 118 (1), 101 (7), 100 (100), 99 (2), 86 (9), 44 (7). HRMS: calcd. for $C_{23}H_{31}N_3O$: 365.24616; found 365.245156. FTIR (ATR): $\tilde{\nu}$ = 3392, 3060, 3027, 2966, 2630, 2871, 2820, 1774, 1451, 1370, 1256, 1169, 1069, 1028, 787, 737, 670 cm^{-1}.

Benzyl{1-benzyl-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indol-5-yl}amine (3b): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.44–7.19 (m, 8 H), 6.97 (d, J = 8.7 Hz, 1 H), 6.92 (dd, J = 7.7, J = 1.7 Hz, 2 H), 6.82 (d, J = 2.1 Hz, 1 H), 6.53 (dd, J = 8.7, J = 2.1 Hz, 1 H), 5.17 (s, 2 H), 4.35 (s, 2 H), 4.09 (t, J = 6.6 Hz, 2 H), 2.86 (t, J = 6.6 Hz, 2 H), 2.63 (q, J = 7.1 Hz, 4 H), 2.24 (s, 3 H), 1.05 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 141.8 (Cq), 140.0 (Cq), 138.4 (Cq), 134.8 (Cq), 128.7, 128.5, 128.4 (Cq), 127.7, 127.1, 125.9, 125.1 (Cq), 121.9 (Cq), 110.7, 110.0, 99.0, 72.5 (CH_2), 52.7 (CH_2), 49.7 (CH_2), 47.6 (CH_2), 46.4 (CH_2), 11.8, 8.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 441 (1) [M$^+$], 252 (3), 251 (4), 181 (2), 161 (3), 145 (2), 100 (100), 91 (54). HRMS: calcd. for $C_{29}H_{35}N_3O$: 441.27746; found 441.277177. FTIR (KBr): $\tilde{\nu}$ = 3061, 3028, 2968, 2930, 2871, 2813, 1625, 1494, 1452, 1373, 1354, 1269, 1168, 1028, 733, 697 cm^{-1}.

***tert*-Butyl 5-Benzylamino-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (3c):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.9 Hz, 1 H), 7.41–7.25 (m, 5 H), 6.70 (d, J = 2.4 Hz, 1 H), 6.60 (dd, J = 8.9, J = 2.4 Hz, 1 H), 4.37 (s, 2 H), 4.01 (t, J = 6.5 Hz, 2 H), 2.82 (t, J = 6.5 Hz, 2 H), 2.61 (q, J = 7.1 Hz, 4 H), 2.47 (s, 3 H), 1.64 (s, 9 H), 1.04 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.8 (Cq), 144.0 (Cq), 139.6 (Cq), 139.6 (Cq), 128.5, 127.5, 127.1 (Cq), 125.5 (Cq), 125.2 (Cq), 116.4, 111.5, 99.1, 82.9 (Cq), 72.1 (CH_2), 52.7 (CH_2), 49.0 (CH_2), 47.5 (CH_2), 28.3, 12.4, 11.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 451 (1) [M$^+$], 351 (3), 252 (18), 251 (5), 250 (6), 161 (22), 160 (4), 159 (5), 134 (3), 133 (9), 101 (11), 100 (100), 92 (5), 91 (27), 86 (40), 85 (5), 72 (18), 71 (10), 57 (16), 56 (23), 44 (51), 43 (9), 42 (11), 40 (32). HRMS: calcd. for $C_{27}H_{37}N_3O_3$: 451.28294; found 451.283100. FTIR (ATR): $\tilde{\nu}$ = 3416, 3062, 3028, 2969, 2927, 2872, 2810, 1720, 1470, 1452, 1367, 1330, 1275, 1221, 1168, 1129, 1062, 734, 697 cm^{-1}.

{3-[2-(Diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}hexylamine (3d): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.03 (d, J = 8.6 Hz, 1 H), 6.73 (d, J = 2.1 Hz, 1 H), 6.56 (dd, J = 8.6, J = 2.1 Hz, 1 H), 4.17 (t, J = 6.2 Hz, 2 H), 3.53 (s, 3 H), 3.14 (t, J = 7.1 Hz, 2 H), 3.01 (t, J = 6.2 Hz, 2 H), 2.82 (q, J = 7.1 Hz, 4 H), 2.31 (s, 3 H), 1.71–1.58 (m, 2 H), 1.50–1.26 (m, 6 H), 1.17 (t, J = 7.1 Hz, 6 H), 0.90 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 142.0 (Cq), 134.0 (Cq), 128.5 (Cq), 125.1 (Cq), 121.3 (Cq), 110.7, 109.4, 98.8, 71.6 (CH_2), 52.4 (CH_2), 47.6 (CH_2), 45.6 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 29.3, 27.0 (CH_2), 22.6 (CH_2), 14.0, 11.0, 9.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 359 (5) [M$^+$], 259 (6), 244 (1), 187 (3), 173 (4), 100 (100), 86 (6), 44 (5). HRMS: calcd. for $C_{22}H_{37}N_3O$: 359.29311; found 359.292382. FTIR (ATR): $\tilde{\nu}$ = 3313, 2959, 2932, 2856, 2808, 2590, 2461, 1626, 1475, 1460, 1367, 1253, 1176, 1024, 781, 732 cm^{-1}.

***tert*-Butyl 3-[2-(Diethylamino)ethoxy]-5-hexylamino-2-methyl-1*H*-indole-1-carboxylate (3e):** ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.8 Hz, 1 H), 6.66 (d, J = 2.3 Hz, 1 H), 6.55 (dd, J = 8.8, J = 2.3 Hz, 1 H), 4.06 (t, J = 6.4 Hz, 2 H), 3.13 (t, J = 7.2 Hz, 2 H), 2.86 (t, J = 6.4 Hz, 2 H), 2.64 (q, J = 7.2 Hz, 4 H), 2.46 (s, 3 H), 1.63 (s, 9 H), 1.50–1.25 (m, 8 H), 1.06 (t, J = 7.2 Hz, 6 H), 0.89 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.9 (Cq), 144.5 (Cq), 139.7 (Cq), 127.0 (Cq), 125.4 (Cq), 125.3 (Cq), 116.4, 111.6, 98.9, 82.9 (Cq), 72.2 (CH_2), 52.8 (CH_2), 47.6 (CH_2), 44.9 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 28.4, 26.9 (CH_2), 22.7 (CH_2), 14.1, 12.4, 11.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 446 (1), 445 (5) [M$^+$], 346 (2), 345 (9), 290 (3), 246 (16), 245 (7), 244 (3), 176 (3), 175 (23), 174 (5), 147 (4), 146 (3), 145 (7), 100 (100), 99 (8), 98 (8), 97 (17), 86 (42), 85 (10), 84 (12), 83 (21), 58 (8), 57 (45), 44 (58). HRMS: calcd. for $C_{26}H_{43}N_3O_3$: 445.32989; found 445.330462. FTIR (ATR): $\tilde{\nu}$ = 3400, 2964, 2927, 2856, 1721, 1367, 1329, 1314, 1221, 1168, 1127, 1061, 1018, 846, 764, 678 cm^{-1}.

{3-[2-(Diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}[2-(4-fluorophenyl)ethyl]amine (3f): ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 7.19 (m, 2 H), 7.05 (d, J = 8.6 Hz, 1 H), 7.00 (m, 2 H), 6.78 (d, J = 2.0 Hz, 1 H), 6.51 (dd, J = 8.6, J = 2.0 Hz, 1 H), 4.13 (t, J = 6.3 Hz, 2 H), 4.01 (br., 1 H, NH), 3.54 (s, 3 H), 3.43 (t, J = 6.9 Hz, 2 H), 2.95–2.91 (m, 4 H), 2.72 (q, J = 7.1 Hz, 4 H), 2.32 (s, 3 H), 1.10 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 161.5 (d, J = 244 Hz, Cq), 141.1 (Cq), 135.3 (d, J = 3.0 Hz, Cq), 134.2 (Cq), 130.2 (d, J = 7.5 Hz), 128.7 (Cq), 125.2 (Cq), 121.5 (Cq), 115.3 (d, J = 21.0 Hz), 110.8, 109.4, 99.4, 72.3, 52.7, 47.5, 46.7, 34.8, 29.3, 11.5, 8.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 397 (4) [M$^+$], 297 (3), 281 (1), 188 (6), 173 (7), 159 (4), 130 (1), 100 (100), 86 (8), 44 (7). HRMS: calcd. for $C_{24}H_{32}FN_3O$: 397.25239; found 397.251869. FTIR (ATR): $\tilde{\nu}$ = 2966, 2930, 2871, 2821, 1508, 1476, 1446, 1371, 1256, 1220, 1169, 1157, 1067, 1014, 824, 786 cm^{-1}.

Compounds 4a–c. General Procedure for the Hydrogenation of 5-Benzylamino-3-[2-(diethylamino)ethoxy]-1*H*-indole Derivatives 3a–c: In a 20-mL autoclave 5-benzylamino-3-[2-(diethylamino)ethoxy]indole derivative (1 mmol) was dissolved in 40 mL of ethanol, before Pd/C (10%) (200 mg) was added. Under a pressure of 50 bar (5 bar for **4c**) H_2, the reaction mixture was stirred for 8 h (3.5 h for **4c**) at room temperature (60 °C for **4c**). After removal of the solvent in vacuo, the hydrogenated indole derivative was isolated as an oil by column chromatography [eluent heptane/ethyl acetate (5:1) with 5% triethylamine].

{3-[2-(Diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}amine (4a): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 6.95 (d, J = 8.6 Hz, 1 H), 6.78 (d, J = 2.1 Hz, 1 H), 6.51 (dd, J = 8.6, J = 2.1 Hz, 1 H), 3.99 (t, J = 6.5 Hz, 2 H), 3.45 (s, 3 H), 3.21 (br., 2 H, NH_2), 2.79 (t, J = 6.5 Hz, 2 H), 2.56 (q, J = 7.1 Hz, 4 H), 2.23 (s, 3 H), 0.99 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.6 (Cq), 134.0 (Cq), 129.1 (Cq), 125.4 (Cq), 121.5 (Cq), 111.4, 109.2, 102.2, 72.6 (CH_2), 52.7 (CH_2), 47.5 (CH_2), 29.3, 11.8, 8.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 275 (4) [M$^+$], 176 (3), 175 (12), 160 (4), 159 (2), 101 (7), 100 (100), 91 (4), 86 (13), 72 (8), 44 (9). HRMS: calcd. for $C_{16}H_{25}N_3O$: 275.19921; found 275.199332. FTIR (KBr): $\tilde{\nu}$ = 3420, 3342, 3219, 2966, 2933, 2872, 2819, 1628, 1495, 1470, 1372, 1322, 1257, 1165, 1068, 793 cm^{-1}.

{1-Benzyl-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indol-5-yl}-amine (4b): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.23–7.20 (m, 3 H), 6.97 (d, J = 8.6 Hz, 1 H), 6.93–6.90 (m, 3 H), 6.53 (dd, J = 8.6, J = 2.2 Hz, 1 H), 5.18 (s, 2 H), 4.11 (t, J = 6.6 Hz, 2 H), 3.10 (br., 2 H, NH_2), 2.88 (t, J = 6.6 Hz, 2 H), 2.65 (q, J = 7.1 Hz, 4 H), 2.25 (s, 3 H), 1.07 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.9 (Cq), 138.3 (Cq), 134.5 (Cq), 129.0 (Cq), 128.7, 127.1, 125.9, 125.4 (Cq), 121.9 (Cq), 111.7, 109.8, 102.3, 72.6 (CH_2), 52.7 (CH_2), 47.5 (CH_2), 46.4 (CH_2), 11.8, 8.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 351 (3) [M$^+$], 251 (2), 236 (1), 159 (1), 132 (2), 100 (100), 91 (26). HRMS: calcd. for $C_{22}H_{29}N_3O$: 351.23051; found 351.230802. FTIR (KBr): $\tilde{\nu}$ = 3035, 2970, 2921, 1626, 1490, 1456, 1437, 1371, 1356, 1329, 1268, 1165, 732 cm^{-1}.

***tert*-Butyl 5-Amino-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (4c):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.9 Hz, 1 H), 6.79 (d, J = 2.2 Hz, 1 H), 6.62 (dd, J = 8.9, J = 2.2 Hz, 1 H), 4.06 (t, J = 6.4 Hz, 2 H), 3.59 (br., 2 H, NH_2), 2.86 (t, J = 6.4 Hz, 2 H), 2.64 (q, J = 7.1 Hz, 4 H), 2.47 (s, 3 H), 1.65 (s, 9 H), 1.07 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.8 (Cq), 141.7 (Cq), 139.4 (Cq), 127.8 (Cq), 125.7 (Cq), 125.3 (Cq), 116.4, 112.8, 102.1, 83.1 (Cq), 72.2 (CH_2), 52.8 (CH_2), 47.5 (CH_2), 28.5, 12.4, 11.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 362 (2), 361 (8) [M$^+$], 261 (3), 162 (9), 161 (8), 147 (2), 146, (5), 145 (5), 101 (19), 100 (100), 86 (67), 72 (17), 57 (40). HRMS: calcd. for $C_{20}H_{31}N_3O_3$: 361.23599; found 361.235080. FTIR (ATR): $\tilde{\nu}$ = 3443, 3369, 3211, 3027, 2969, 2929, 2873, 2810, 1720, 1365, 1327, 1254, 1218, 1166, 1129, 1060, 1033 cm^{-1}.

Compounds 5a–h. General Procedure for the Sulfonylation of 5-Amino-3-[2-(diethylamino)ethoxy]-1*H*-indole Derivatives 3c, 3e, 4a–c: In an Ace-pressure tube under argon atmosphere the corresponding 5-amino-substituted 3-[2-(diethylamino)ethoxy]indole derivative (1 mmol) and the arylsulfonyl chloride (1 mmol) (see Table 3) were dissolved in 5 mL of triethylamine (for the synthesis of **5a**–**b**, **5e**–**f**) and heated at 40 °C for 2 h. In the case of **5c** and **5g** 10 mL of CH_2Cl_2 as solvent and 2 equiv. Cs_2CO_3 as base at room temp. were used. The pressure tube was fitted with a Teflon® cap. After removal of the solvent in vacuo the corresponding indole product was isolated by column chromatography as oil or solid material with heptane/ethyl acetate (5:1) and 1% triethylamine.

***N*-{3-[2-(Diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}-2,1,3-benzothiadiazole-5-sulfonamide (5a):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.11 (dd, J = 8.9, J = 1.0 Hz, 1 H), 8.08 (dd, J = 7.0, J = 1.0 Hz, 1 H), 7.53 (dd, J = 8.9, J = 7.0 Hz, 1 H), 7.11 (d, J = 2.0 Hz, 1 H), 6.93 (d, J = 8.8 Hz, 1 H), 6.69 (dd, J = 8.8, J = 2.0 Hz, 1 H), 3.97 (t, J = 6.1 Hz, 2 H), 3.47 (s, 3 H), 2.89 (t, J = 6.1 Hz, 2 H), 2.76 (q, J = 7.2 Hz, 4 H), 2.25 (s, 3 H), 1.13 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.1 (Cq), 149.2 (Cq), 134.4 (Cq), 133.0 (Cq), 132.0, 130.8 (Cq), 123.2, 127.0 (Cq), 126.4 (Cq), 126.2, 120.6 (Cq), 116.9, 111.7, 109.1, 72.0 (CH_2), 52.4 (CH_2), 47.5 (CH_2), 29.3, 11.1, 8.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 474 (1), 473 (2) [M$^+$], 472 (1), 374 (6), 373 (9), 372 (2), 176 (12), 175 (52), 174 (38), 173 (22), 161 (4), 160 (11), 159 (11), 148 (5), 147 (11), 146 (3), 145 (5), 137 (3), 136 (12), 135 (2), 101 (37), 100 (100), 99 (5), 98 (7), 86 (72), 85 (3), 84 (6), 73 (5), 72 (30), 71 (8), 70 (7), 69 (6), 57 (9), 56 (15), 55 (5). HRMS: calcd. for $C_{22}H_{27}N_5O_3S_2$: 473.15498; found 473.154213. FTIR (KBr): $\tilde{\nu}$ = 3448, 3203, 3085, 2962, 2925, 2835, 1521, 1488, 1374, 1347, 1332, 1271, 1252, 1213, 1162, 1143, 966, 834, 819, 764, 733, 669, 612, 594, 482 cm^{-1}.

***N*-{1-Benzyl-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indol-5-yl}-2,1,3-benzothiadiazole-5-sulfonamide (5b):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.14 (dd, J = 8.8, J = 1.1 Hz, 1 H), 8.10 (dd, J = 7.0, J = 1.2 Hz, 1 H), 7.56 (dd, J = 8.8, J = 7.0 Hz, 1 H), 7.24–7.17 (m, 3 H), 7.13 (d, J = 2.0 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 6.86–6.80 (m, 2 H), 6.66 (dd, J = 8.7, J = 2.0 Hz, 1 H), 5.11 (s, 2 H), 3.93 (t, J = 6.4 Hz, 2 H), 2.77 (t, J = 6.4 Hz, 2 H), 2.61 (q, J = 7.1 Hz, 4 H), 2.20 (s, 3 H), 1.05 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.2 (Cq), 149.3 (Cq), 137.4 (Cq), 135.1 (Cq), 132.1 (Cq), 132.0, 131.0 (Cq), 128.7, 128.3, 127.4, 127.2 (Cq), 126.3 (Cq), 126.3, 125.8, 121.2 (Cq), 117.4, 112.1, 109.6, 72.8 (CH_2), 52.6 (CH_2), 47.5 (CH_2), 46.5 (CH_2), 11.8, 9.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 550 (1), 549 (1) [M$^+$], 351 (1), 252 (4), 251 (7), 250 (2), 236 (1), 235 (2), 162 (1), 161 (3), 160 (2), 137 (1), 136 (7), 135 (1), 101 (9), 100 (100), 99 (2), 92 (4), 91 (44), 86 (15), 85 (2), 58 (3), 57 (5), 56 (5), 44 (12). HRMS: calcd. for $C_{28}H_{31}N_5O_3S_2$: 549.18628; found 549.187203. FTIR (KBr): $\tilde{\nu}$ = 3452, 2970, 2929, 2872, 1626, 1495, 1474, 1454, 1375, 1353, 1289, 1210, 1155, 1142, 967, 754, 731, 608 cm^{-1}.

***tert*-Butyl 5-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)(hexyl)amino]-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (5c):** ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.8, J = 1.3 Hz, 1 H), 7.94 (d, J = 9.0 Hz, 1 H), 7.91 (dd, J = 7.1, J = 1.3 Hz, 1 H), 7.51 (dd, J = 8.8, J = 7.1 Hz, 1 H), 7.06 (d, J = 2.0 Hz, 1 H), 6.78 (dd, J = 9.0, J = 2.0 Hz, 1 H), 4.02 (t, J = 7.1 Hz, 2 H), 3.83 (t, J = 6.2 Hz, 2 H), 2.72 (t, J = 6.2 Hz, 2 H), 2.57 (q, J = 7.2 Hz, 4 H), 2.45 (s, 3 H), 1.62 (s, 9 H), 1.50–1.25 (m, 8 H), 1.01 (t, J = 7.2 Hz, 6 H), 0.84 (m, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 155.5 (Cq), 150.4 (Cq), 149.7 (Cq), 139.4 (Cq), 133.0 (Cq), 132.7 (Cq), 132.6, 131.7 (Cq), 128.1, 126.5 (Cq), 126.0, 124.6 (Cq), 124.5, 117.6, 116.1, 84.0 (Cq), 72.5 (CH_2), 52.9 (CH_2), 52.6 (CH_2), 47.4 (CH_2), 31.4 (CH_2), 28.9 (CH_2), 28.2, 26.1 (CH_2), 22.5 (CH_2), 14.0, 12.4, 11.7 ppm. MS (EI, 70 eV): *m*/*z* (%) = 643 (1) [M$^+$], 346 (1), 345 (2), 246 (5), 245 (3), 244 (2), 187 (2), 186 (1), 169 (3), 168 (10), 167 (2), 147 (2), 146 (1), 145 (3), 101 (7), 100 (100), 99 (6), 86 (27), 85 (7), 84 (10), 71 (15), 70 (15), 69 (24), 57 (30), 56 (39), 45 (9), 44 (99), 43 (36). HRMS: calcd. for $C_{32}H_{45}N_5O_5S_2$: 643.28566; found 643.284226. FTIR (neat): $\tilde{\nu}$ = 3442, 3093, 3060, 2965, 2929, 2871, 2809, 2725, 1732, 1471, 1353, 1272, 1256, 1225, 1208, 1162, 1070, 1021, 970, 853, 831, 754, 730, 622, 604, 593 cm^{-1}.

5-Chloro-*N*-{3-[2-(diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}-3-methyl-1-benzothiophene-2-sulfonamide (5d): ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.6 Hz, 1 H), 7.60 (d, J = 2.0 Hz, 1 H), 7.34 (dd, J = 8.6, J = 2.0 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 6.91 (dd, J = 8.7, J = 2.0 Hz, 1 H), 5.56 (br. s, 1 H, NH), 3.97 (t, J = 6.2 Hz, 2 H), 3.54 (s, 3 H), 2.87 (t, J = 6.2 Hz, 2 H), 2.74 (q, J = 7.2 Hz, 4 H), 2.30 (s, 3 H), 2.21 (s, 3 H), 1.09 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.5 (Cq), 137.7 (Cq), 136.9 (Cq), 136.1 (Cq), 134.5 (Cq), 132.5 (Cq), 131.1 (Cq), 127.5, 126.7 (Cq), 126.4 (Cq), 123.6, 123.2, 120.6 (Cq), 118.6, 113.5, 109.1, 71.8 (CH_2), 52.4 (CH_2), 47.4 (CH_2), 29.5, 12.1, 10.9, 8.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 520 (1), 519 (2) [M$^+$], 421 (5), 420 (9), 419 (8), 275 (1), 274 (1), 184 (7), 183 (10), 182 (20), 181 (24), 176 (15), 175 (69), 174 (51), 173 (27), 101 (49), 100 (100), 99 (6), 98 (8), 87 (5), 86 (97), 85 (2), 73 (7), 72 (44), 71 (7), 70 (7), 57 (4), 56 (16), 55 (1). HRMS: calcd. for $C_{25}H_{30}ClN_3O_3S_2$: 519.14116; found 519.139652. FTIR (KBr): $\tilde{\nu}$ = 3448, 2966, 2921, 2856, 2668, 1857, 1128, 1486, 1373, 1335, 1326, 1277, 1244, 1156, 1117, 1080, 987, 862, 799, 647, 575, 563, 547 cm^{-1}.

***tert*-Butyl 5-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)-sulfonyl](hexyl)amino}-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (5e):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.9 Hz, 1 H), 7.19 (d, J = 2.1 Hz, 1 H), 7.06 (d, J = 4.5 Hz, 1 H), 6.94 (d, J = 8.9, J = 2.1 Hz, 1 H), 6.70 (d, J = 4.5 Hz, 1 H),

3.89 (t, J = 6.1 Hz, 2 H), 3.76 (t, J = 7.0 Hz, 2 H), 2.81 (t, J = 6.1 Hz, 2 H), 2.63 (q, J = 7.1 Hz, 4 H), 2.47 (s, 3 H), 1.64 (s, 9 H), 1.46–1.18 (m, 8 H), 1.65 (t, J = 7.1 Hz, 6 H), 0.83 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.4 (Cq), 149.3 (Cq), 139.4 (Cq), 137.6 (Cq), 133.0 (Cq), 132.5 (Cq), 126.8 (Cq), 124.7 (Cq), 124.1, 120.5, 119.0 (Cq), 117.0, 116.2, 113.4, 84.2 (Cq), 72.5 (CH_2), 52.7 (CH_2), 51.7 (CH_2), 47.4 (CH_2), 31.3 (CH_2), 28.2 (CH_2), 28.2, 26.0 (CH_2), 22.5 (CH_2), 14.0, 12.5, 11.6 ppm. MS (EI, 70 eV): m/z (%) = 667 (3), 666 (8) [M^+], 568 (2), 567 (3), 566 (4), 447 (5), 446 (15), 445 (7), 444 (4), 347 (13), 346 (16), 345 (11), 344 (7), 300 (2), 299 (8), 161 (37), 160 (11), 159 (100), 158 (10), 101 (6), 100 (39), 99 (11), 86 (5), 85 (24), 84 (4), 83 (14). HRMS: calcd. for $C_{31}H_{44}ClN_5O_5S_2$: 666.25452; found 666.25510. FTIR (ATR): $\tilde{\nu}$ = 3148, 3121, 2959, 2929, 2870, 2858, 1737, 1619, 1453, 1355, 1324, 1269, 1248, 1118, 1133, 1069, 1020, 728, 670 cm^{-1}.

***N*-{3-[2-(Diethylamino)ethoxy]-1,2-dimethyl-1*H*-indol-5-yl}-1-benzothiophene-3-sulfonamide (5f):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.21–8.14 (m, 1 H), 7.93 (s, 1 H), 7.87–7.79 (m, 1 H), 7.47–7.37 (m, 2 H), 7.05 (d, J = 2.0 Hz, 1 H), 7.00 (d, J = 8.7 Hz, 1 H), 6.76 (dd, J = 8.7, J = 2.0 Hz, 1 H), 3.87 (t, J = 6.2 Hz, 2 H), 3.52 (s, 3 H), 2.76 (t, J = 6.2 Hz, 2 H), 2.60 (q, J = 7.1 Hz, 4 H), 2.28 (s, 3 H), 1.03 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.1 (Cq), 135.1, 134.7 (Cq), 133.7 (Cq), 132.6 (Cq), 132.5 (Cq), 126.7 (Cq), 126.3 (Cq), 125.6, 125.5, 123.2, 122.8, 120.7 (Cq), 118.8, 113.8, 109.0, 72.5 (CH_2), 52.5 (CH_2), 47.3 (CH_2), 29.4, 11.5, 8.9 ppm. MS (EI, 70 eV): m/z (%) = 471 (2) [M^+], 470 (1), 373 (3), 372 (10), 371 (9), 370 (2), 176 (10), 175 (47), 174 (36), 173 (21), 161 (3), 160 (7), 159 (14), 134 (25), 133 (4), 132 (7), 131 (5), 101 (36), 100 (100), 99 (5), 86 (67), 85 (3), 84 (5), 72 (26), 71 (8), 70 (7), 69 (7), 58 (8), 57 (10), 56 (16), 55 (5). HRMS: calcd. for $C_{24}H_{29}N_3O_3S_2$: 471.16448; found 471.164566. FTIR (ATR): $\tilde{\nu}$ = 3257, 3104, 2965, 2927, 2872, 2853, 1372, 1276, 1250, 1142, 1064, 076, 797, 756, 731, 706, 668 cm^{-1}.

***tert*-Butyl 5-{[(1-Benzothiophen-3-yl)sulfonyl](benzyl)amino}-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (5g):** ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.98 (m, 1 H), 7.97 (s, 1 H), 7.92 (d, J = 8.8 Hz, 1 H), 7.88 (m, 1 H), 7.46–7.33 (m, 2 H), 7.24–7.14 (m, 5 H), 6.96 (d, J = 2.1 Hz, 1 H), 6.85 (dd, J = 8.8, J = 2.1 Hz, 1 H), 4.89 (s, 2 H), 3.70 (t, J = 6.3 Hz, 2 H), 2.68 (t, J = 6.3 Hz, 2 H), 2.55 (q, J = 7.1 Hz, 4 H), 2.44 (s, 3 H), 1.62 (s, 9 H), 1.02 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.4 (Cq), 140.1 (Cq), 139.4 (Cq), 136.0 (Cq), 135.0, 134.1 (Cq), 133.0 (Cq), 132.8 (Cq), 132.8 (Cq), 128.7, 128.3, 127.6, 126.2 (Cq), 125.5, 125.5, 125.2, 124.3 (Cq), 124.0, 122.7, 117.6, 115.9, 83.9 (Cq), 72.2 (CH_2), 55.4 (CH_2), 52.6 (CH_2), 47.3 (CH_2), 28.2, 12.4, 11.7 ppm. MS (EI, 70 eV): m/z (%) = 647 (1) [M^+], 341 (2), 151 (4), 150 (3), 149 (15), 135 (4), 134 (13), 133 (5), 101 (6), 100 (81), 99 (14), 71 (49), 70 (27), 69 (52), 57 (78), 56 (55), 55 (62), 44 (100), 43 (71). HRMS: calcd. for $C_{35}H_{41}N_3O_5S_2$: 647.24821; found 647.249346. FTIR (neet): $\tilde{\nu}$ = 3109, 3064, 3035, 2970, 2925, 2868, 2811, 2255, 1731, 1471, 1455, 1355, 1325, 1259, 1225, 1160, 1139, 1066, 911, 757, 733, 590 cm^{-1}.

***tert*-Butyl 5-{[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)-sulfonyl]amino}-3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indole-1-carboxylate (5h):** In a round-bottomed flask under argon atmosphere to a solution of **4c** (0.5 mmol), $NaHCO_3$ (2 equiv.) and 6-chloroimidazo[2,1-*b*]thiazole-5-sulfonyl chloride (0.5 mmol) were added in 5 mL of acetonitrile. The reaction mixture was stirred at room temperature for 15 h. The product was isolated by column chromatography (eluent: ethanol gradient 5–50% in CH_2Cl_2) in a yield of 81% as a white powder. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.8 Hz, 1 H), 7.70 (d, J = 4.5 Hz, 1 H), 7.31 (d, J = 2.3 Hz, 1 H), 7.01 (dd, J = 8.8, J = 2.3 Hz, 1 H), 6.86 (d, J = 4.5 Hz, 1 H), 5.24 (br., 1 H, NH), 4.01 (t, J = 6.1 Hz, 2 H), 2.88 (t, J = 6.1 Hz, 2 H), 2.74 (q, J = 7.1 Hz, 4 H), 2.45 (s, 3 H), 1.63 (s, 9 H), 1.09 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 150.4 (Cq), 149.5 (Cq), 139.1 (Cq), 137.3 (Cq), 132.0 (Cq), 130.1 (Cq), 126.7 (Cq), 124.6 (Cq), 120.3, 119.8, 118.6 (Cq), 116.4, 114.0, 112.1, 84.0 (Cq), 72.0 (CH_2), 52.5 (CH_2), 47.3 (CH_2), 28.2, 12.4, 11.2 ppm. MS (EI, 70 eV): m/z (%) = 581 (1) [M^+], 382 (1), 381 (1), 158 (12), 101 (18), 100 (100), 86 (83), 72 (16), 57 (15), 56 (24). HRMS (ESI$^+$, [M + H]$^+$) Calcd. for $C_{25}H_{32}ClN_5O_5S_5$: 582.16061; found 582.16052. FTIR (Nujol): $\tilde{\nu}$ = 3436, 3109, 2924, 2854, 2716, 1728, 1612, 1542, 1460, 1376, 1323, 1271, 1249, 1179, 1129, 1067, 1022, 933, 725, 622 cm^{-1}.

***N*-Benzyl-*N*-{3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indol-5-yl}-1-benzothiophene-3-sulfonamide (6a):** Ester **5g** was solved in a 33% methylamine/ethanol solution (10 mL) and stirred at room temperature for 24 h. After removal of the solvent in vacuo the corresponding indole product was isolated by column chromatography (eluent: ethanol gradient 5–20% in CH_2Cl_2) as solid material in a yield of 78%. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.98 (m, J = 7.3 Hz, 1 H), 7.97 (s, 1 H), 7.88 (m, J = 7.3 Hz, 1 H), 7.50 (br. s, 1 H, NH), 7.44–7.31 (m, 2 H), 7.25–7.14 (m, 5 H), 6.97 (d, J = 1.9 Hz, 1 H), 6.94 (d, J = 8.6 Hz, 1 H), 6.66 (dd, J = 8.6, J = 1.9 Hz, 1 H), 4.89 (s, 2 H), 3.77 (t, J = 6.2 Hz, 2 H), 2.71 (t, J = 6.2 Hz, 2 H), 2.59 (q, J = 7.1 Hz, 4 H), 2.29 (s, 3 H), 1.04 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.1 (Cq), 136.4 (Cq), 135.4 (Cq), 134.8, 134.3 (Cq), 133.3 (Cq), 131.9 (Cq), 130.0 (Cq), 128.7, 128.3, 127.5, 125.4, 125.4, 124.2, 123.7 (Cq), 123.2, 122.6, 121.8 (Cq), 118.0, 110.8, 72.3 (CH_2), 55.8 (CH_2), 52.5 (CH_2), 47.3 (CH_2), 11.6, 10.3 ppm. MS (EI, 70 eV): m/z (%) = 547 (1) [M^+], 448 (1), 447 (1), 351 (1), 350 (1), 252 (5), 251 (5), 250 (4), 161 (4), 134 (16), 133 (3), 101 (8), 100 (100), 99 (8), 71 (25), 70 (15), 57 (41), 56 (16), 55 (29). HRMS: calcd. for $C_{30}H_{33}N_3O_3S_2$: 547.19578; found 547.197375. FTIR (ATR): $\tilde{\nu}$ = 3308, 3106, 2966, 2928, 2851, 1492, 1454, 1346, 1291, 1259, 1233, 1146, 1086, 1063, 1024, 969, 844, 803, 757, 732, 699 cm^{-1}.

6-Chloro-*N*-{3-[2-(diethylamino)ethoxy]-2-methyl-1*H*-indol-5-yl}imidazo[2,1-*b*]thiazole-5-sulfonamide (6b): In a round-bottomed flask under argon atmosphere **5h** was heated up to 140 °C for 3 h. After column chromatography (eluent: ethanol gradient 10–30% in CH_2Cl_2) a light-cream powder was obtained in 88% yield. ^{1}H NMR (300.13 MHz, [D_6]acetone, referenced to solvent signal δ = 2.05): δ = 9.67 (br., 1 H, NH), 7.71 (d, J = 4.5 Hz, 1 H), 7.35 (d, J = 4.5 Hz, 1 H), 7.30 (d, J = 2.1 Hz, 1 H), 7.12 (dd, J = 8.5, J = 0.5 Hz, 1 H), 6.87 (dd, J = 8.5, J = 2.1 Hz, 1 H), 3.96 (t, J = 6.3 Hz, 2 H), 2.78 (t, J = 6.3 Hz, 2 H), 2.61 (q, J = 7.1 Hz, 4 H), 2.30 (s, 3 H), 1.02 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]-acetone, referenced to solvent signal δ = 29.9): δ = 150.4 (Cq), 138.1 (Cq), 135.8 (Cq), 132.5 (Cq), 128.0 (Cq), 125.4 (Cq), 122.8 (Cq), 121.2, 119.7 (Cq), 118.6, 115.9, 113.2, 112.2, 73.6 (CH_2), 53.7 (CH_2), 47.4 (CH_2), 12.6, 10.3 ppm. MS (EI, 70 eV): m/z (%) = 481 (0.3) [M^+], 382 (1), 174 (1), 173 (1), 161 (5) (5) 160, 145 (2), 101 (7), 100 (100), 86 (48), 72 (7), 58 (4). HRMS (ESI$^+$, [M + H]$^+$) Calcd. for $C_{20}H_{24}ClN_5O_3S_2$: 482.10819; found 482.10949. FTIR (ATR): $\tilde{\nu}$ = 3308, 3129, 3059, 2964, 2923, 2853, 1459, 1435, 1269, 1240, 1211, 1177, 1139, 1122, 1103, 1042, 1022, 926, 882, 814, 791, 727, 671 cm^{-1}.

[3-(*tert*-Butyldimethylsilanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]amine (7e): Ammonia (gaseous) was liquified in a flask at –80 °C. After addition of sodium (10 equiv.) to liquid ammonia a solution of benzyl[3-(*tert*-butyldimethylsilanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]amine (0.9 mmol) in THF (4 mL) was added carefully over sy-

ringe. The reaction mixture was stirred for 2 h at –30 °C. The dark violet solution was charged with NH_4Cl carefully until all sodium was destroyed. After 1 h water was added to the reaction mixture, extracted with dichloromethane and dried with Mg_2SO_4. The solvent was removed and the crude product was cleaned by column chromatography (eluent: ethyl acetate gradient 5–20% in hexane). The product was obtained as brown oil with a yield of 130 mg (20%). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 7.00 (d, J = 8.5 Hz, 1 H), 6.78 (d, J = 2.2 Hz, 1 H), 6.60 (dd, J = 8.5, J = 2.2 Hz, 1 H), 3.54 (s, 3 H), 2.93 (br., 2 H, NH_2), 2.25 (s, 3 H), 1.07 (s, 9 H), 0.15 (s, 6 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 137.7 (Cq), 129.5 (Cq), 129.4 (Cq), 123.2 (Cq), 122.2 (Cq), 111.5, 108.9, 102.8, 29.4, 25.9, 18.2 (Cq), 9.2, –4.2 ppm. MS (EI, 70 eV): *m*/*z* (%) = 292 (19), 290 (100) [M$^+$], 233 (25), 218 (6), 192 (7), 175 (5), 160 (14), 159 (13), 73 (5).. HRMS: calcd. for $C_{16}H_{26}N_2OSi$: 290.18089; found 290.180559. FTIR (Nujol): $\tilde{\nu}$ = 3446, 2952, 2923, 2854, 1844, 1648, 1559, 1506, 1457, 1419, 1376, 1318, 1251, 1160, 1066, 891, 778 cm^{-1}.

Compounds 8a–i. General Procedure for the Sulfonylation of 5-Amino-3-(silanyloxy)indole Derivatives: Under argon atmosphere the indole derivative (1 mmol) and the arylsulfonyl chloride (2 mmol) were dissolved in triethylamine (5 mL) and heated to 40 °C for 2 h. After the reaction was complete by TLC control, the solvent was removed in vacuo. The product was isolated by column chromatography with hexane/ethyl acetate (10:1) as a solid material.

***N*-Benzyl-*N*-[3-(*tert*-butyldimethylsilanyloxy)-1,2-dimethyl-1*H*-indol-5-yl]naphthalene-2-sulfonamide (8a):** ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 8.27 (d, J = 1.7 Hz, 1 H), 7.91 (d, J = 8.7 Hz, 1 H), 7.91–7.87 (m, 2 H), 7.71 (dd, J = 8.7, J = 1.7 Hz, 1 H), 7.63, 7.57 (2 ddd, 2 H), 7.27–7.24 (m, 2 H), 7.21–7.14 (m, 3 H), 7.01 (d, J = 8.8 Hz, 1 H), 6.95 (d, J = 2.0 Hz, 1 H), 6.71 (dd, J = 8.8, J = 2.0 Hz, 1 H), 4.87 (s, 2 H), 3.51 (s, 3 H), 2.22 (s, 3 H), 0.88 (s, 9 H), –0.16 (s, 6 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 136.6 (Cq), 136.6 (Cq), 134.8 (Cq), 132.8 (Cq), 132.2 (Cq), 130.4 (Cq), 129.6 (Cq), 129.3, 128.9, 128.8, 128.7, 128.5, 128.2, 127.8, 127.4, 127.2, 123.5 (Cq), 123.3, 122.2, 121.4 (Cq), 118.0, 108.5, 56.2 (CH_2), 29.5, 25.7, 18.0 (Cq), 9.1, –4.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 571 (16), 570 (38) [M$^+$], 380 (46), 379 (99), 378 (15), 277 (6), 276 (5), 205 (28), 204 (5), 203 (31), 191 (5), 93 (9), 92 (13), 91 (100), 78 (10), 77 (21), 74 (11), 73 (96), 57 (38). HRMS: calcd. for $C_{33}H_{38}N_2O_3SSi$: 570.236511; found 570.23669. FTIR (ATR): $\tilde{\nu}$ = 3057, 3301, 2956, 2929, 2854, 1337, 1321, 1247, 1156, 1131, 1077, 820, 807, 786, 754, 699, 666 cm^{-1}.

Naphthalene-2-sulfonamide 8b: ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 8.21 (d, J = 1.8 Hz, 1 H), 7.89–7.85 (m, 3 H), 7.65 (dd, J = 8.8, J = 1.8 Hz, 1 H), 7.61, 7.55 (2m, 2 H), 7.09 (d, J = 8.8 Hz, 1 H), 7.01 (d, J = 2.2 Hz, 1 H), 6.84 (dd, J = 8.8, J = 2.2 Hz, 1 H), 3.66 (t, J = 7.0 Hz, 2 H), 3.58 (s, 3 H), 2.26 (s, 3 H), 1.45–1.18 (m, 8 H), 0.89 (s, 9 H), 0.84 (t, J = 7.3 Hz, 3 H), –0.10 (s, 6 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 138.2 (Cq), 136.3 (Cq), 134.6 (Cq), 132.8 (Cq), 130.4 (Cq), 129.7 (Cq), 129.3, 128.7, 127.8, 128.7, 128.3, 127.1, 123.7 (Cq), 123.3, 122.1, 121.5 (Cq), 117.5, 108.6, 51.7 (CH_2), 31.4 (CH_2), 28.3 (CH_2), 26.1 (CH_2), 22.5 (CH_2), 29.5, 25.6, 17.9 (Cq), 13.9, 9.1, –4.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 565 (18), 373 (100), 304 (4), 303 (15), 302 (4), 243 (6), 185 (5), 160 (8), 128 (10), 127 (8), 83 (11), 82 (6), 73 (12), 57 (17), 55 (18). HRMS: calcd. for $C_{32}H_{44}N_2O_3SSi$: 564.28364; found 564.283310. FTIR (KBr): $\tilde{\nu}$ = 3444, 3060, 2958, 2929, 2852, 1732, 1487, 1464, 1377, 1337, 1249, 1163, 1129, 1074, 891, 839, 813, 782, 749, 666, 616, 544 cm^{-1}.

Naphthalene-2-sulfonamide 8c: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.27 (d, J = 1.5 Hz, 1 H), 7.83 (m, 3 H), 7.69 (dd, J = 8.6, J = 1.9 Hz, 1 H), 7.61–7.57 (m, 1 H), 7.55–7.51 (m, 1 H), 7.04–7.01 (m, 2 H), 6.85 (dd, J = 8.8, J = 2.0 Hz, 1 H), 6.49 (br. s, 1 H, NH), 3.53 (s, 3 H), 2.22 (s, 3 H), 0.93 (s, 9 H), –0.12 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 136.2 (Cq), 134.9 (Cq), 132.3 (Cq), 132.1 (Cq), 130.3 (Cq), 129.3, 129.1, 128.8, 128.6, 127.8, 127.2, 126.6 (Cq), 123.9 (Cq), 122.7, 121.6 (Cq), 118.6, 113.6, 108.9, 29.5, 25.7, 18.0 (Cq), 9.2, –4.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 481 (23), 480 (70) [M$^+$], 291 (6), 290 (23), 289 (100), 232 (5), 231 (5), 161 (2), 160 (7), 159 (5), 129 (2), 128 (7), 127 (8), 79 (3), 78 (5), 77 (11), 57 (5), 56 (4). HRMS: calcd. for $C_{26}H_{32}N_2O_3SSi$: 480.18974; found 480.189326. FTIR (ATR): $\tilde{\nu}$ = 3237, 3056, 2930, 2857, 1376, 1331, 1273, 1247, 1161, 1153, 1130, 1074, 895, 836, 816, 795, 777, 743, 675 cm^{-1}.

Naphthalene-2-sulfonamide 8d: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.19 (d, J = 1.5 Hz, 1 H), 7.89–7.83 (m, 3 H), 7.64–7.51 (m, 3 H), 7.30–7.12 (m, 4 H), 7.02 (d, J = 2.1 Hz, 1 H), 6.90 (dd, J = 8.7, J = 2.1 Hz, 1 H), 3.93 (m, 2 H), 3.62 (s, 3 H), 2.80 (m, 2 H), 2.28 (s, 3 H), 0.89 (s, 9 H), –0.11 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.5 (Cq), 136.1 (Cq), 134.7 (Cq), 133.0 (Cq), 132.1 (Cq), 130.4 (Cq), 129.6 (Cq), 129.3, 128.9, 128.8, 128.7, 128.4 (2×), 127.7, 127.2, 126.4, 123.9 (Cq), 123.3, 122.3, 121.6 (Cq), 117.5, 108.8, 53.2 (CH_2), 35.2 (CH_2), 29.6, 25.6, 18.0 (Cq), 9.2, –4.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 585 (15), 584 (35) [M$^+$], 394 (12), 393 (28), 392 (2), 303 (34), 302 (100), 246 (7), 245 (17), 218 (4), 217 (12), 216 (3), 188 (4), 187 (10), 128 (13), 127 (13), 73 (16). HRMS: calcd. for $C_{34}H_{40}N_2O_3SSi$: 584.25234; found 584.25293. FTIR (ATR): $\tilde{\nu}$ = 3083, 3061, 3026, 2958, 2930, 2855, 1331, 1249, 1152, 1129, 1072, 937, 890, 833, 817, 783, 750, 692, 665 cm^{-1}.

Naphthalene-2-sulfonamide 8e: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.17 (d, J = 1.7 Hz, 1 H), 7.87–7.82 (m, 3 H), 7.61–7.52 (m, 3 H), 7.11 (d, J = 8.6 Hz, 1 H), 7.10–7.05 (m, 2 H), 7.00 (d, J = 2.0 Hz, 1 H), 6.95–6.90 (m, 2 H), 6.84 (dd, J = 8.5, J = 2.0 Hz, 1 H), 3.90 (m, 2 H), 3.59 (s, 3 H), 2.76 (m, 2 H), 2.26 (s, 3 H), 0.88 (s, 9 H), –0.11 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 161.6 (d, J = 244 Hz, Cq), 136.0 (Cq), 134.7 (Cq), 134.1 (d, J = 3.2 Hz, Cq), 132.9 (Cq), 132.1 (Cq), 130.4 (Cq), 130.3 (d, J = 7.8 Hz), 129.5 (Cq), 129.2, 128.8, 128.8, 128.4, 127.8, 127.2, 123.9 (Cq), 123.2, 122.1, 121.6 (Cq), 117.6, 115.2 (d, J = 21.5 Hz), 108.8, 53.1 (CH_2), 34.3 (CH_2), 29.6, 25.6, 17.9 (Cq), 9.1, –4.5 ppm. MS (EI. 70 eV): *m*/*z* (%) = 603 (14), 602 (34) [M$^+$], 413 (2), 412 (8), 411 (18), 304 (8), 303 (32), 302 (100), 246 (5), 245 (13), 217 (7), 216 (2), 187 (7), 186 (2), 185 (5), 128 (7), 127 (7), 109 (5), 73 (9). HRMS: calcd. for $C_{34}H_{39}FN_2O_3SSi$: 602.24292; found 602.243034. FTIR (ATR): $\tilde{\nu}$ = 3064, 3042, 2959, 2932, 2855, 1509, 1337, 1248, 1219, 1152, 1130, 1106, 1075, 938, 891, 855, 835, 815, 781, 749, 665 cm^{-1}.

6-Chloroimidazo[2,1-*b*]thiazole-5-sulfonamide 8f: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.07 (d, J = 2.0 Hz, 1 H), 6.91 (d, J = 4.5 Hz, 1 H), 6.88 (d, J = 8.6 Hz, 1 H), 6.60 (dd, J = 8.6, J = 2.0 Hz, 1 H), 6.51 (d, J = 4.5 Hz, 1 H), 3.66 (t, J = 7.0 Hz, 2 H), 3.44 (s, 3 H), 2.24 (s, 3 H), 1.36–1.01 (m, 8 H), 0.90 (s, 9 H), 0.70 (t, J = 7.0 Hz, 3 H), –0.09 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 149.1 (Cq), 137.2 (Cq), 132.9 (Cq), 130.4 (Cq), 128.4 (Cq), 124.1 (Cq), 121.6 (Cq), 120.7, 120.6, 119.4 (Cq), 118.2, 113.0, 108.8, 52.1 (CH_2), 31.4 (CH_2), 29.6, 28.2 (CH_2), 26.1 (CH_2), 25.8, 22.5 (CH_2), 18.1 (Cq), 14.0, 9.2, –4.3 ppm. MS (EI, 70 eV): *m*/*z* (%) = 595 (12), 594 (34) [M$^+$], 531 (4), 530 (11), 495 (10), 494 (12), 424 (19), 423 (8), 422 (38), 375 (18), 374 (76), 373 (100), 304 (12), 303 (52), 302 (9), 290 (13), 262 (15), 158 (14), 73 (31). HRMS: calcd. for $C_{27}H_{39}ClN_4O_3S_2Si$: 594.19159; found 594.192313. FTIR (KBr): $\tilde{\nu}$ = 3150, 3117, 2954, 2925, 2852, 2709, 2479, 1842, 1736, 1486, 1455, 1360, 1324, 1269, 1248, 1178, 1133, 1084, 1068, 946, 890, 839, 807, 781, 727, 668, 619 cm^{-1}.

5-Chloro-3-methylbenzo[*b*]thiophene-2-sulfonamide 8g: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.6 Hz, 1 H), 7.65 (d, J = 2.0 Hz, 1 H), 7.41 (dd, J = 8.6, J = 2.0 Hz, 1 H), 7.11 (d, J = 2.0 Hz, 1 H), 7.09 (d, J = 8.7 Hz, 1 H), 6.85 (dd, J = 8.7, J = 2.0 Hz, 1 H), 3.73 (t, J = 6.6 Hz, 2 H), 3.59 (s, 3 H), 2.27 (s, 3 H), 2.04 (s, 3 H), 1.50–1.15 (m, 8 H), 0.91 (s, 9 H), 0.83 (t, J = 6.6 Hz, 3 H), –0.06 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.8 (Cq), 137.6 (Cq), 136.4 (Cq), 135.8 (Cq), 132.9 (Cq), 131.2 (Cq), 130.5 (Cq), 128.9 (Cq), 127.4, 123.9 (Cq), 123.6, 123.4, 121.8, 121.6 (Cq), 117.7, 108.6, 52.2 (CH_2), 31.4 (CH_2), 29.6, 28.3 (CH_2), 26.1 (CH_2), 25.6, 22.5 (CH_2), 18.0 (Cq), 14.0, 12.1, 9.2, –4.4 ppm. MS (EI, 70 eV): *m*/*z* (%) = (rel, intensity): 619 (23), 618 (61) [M^+], 555 (4), 554 (10), 375 (13), 374 (54), 373 (100), 304 (6), 303 (24), 302 (7), 290 (8), 258 (4), 257 (11), 218 (4), 217 (7), 183 (6), 182 (11), 181 (14), 73 (19), 57 (9), 43 (12). HRMS: calcd. for $C_{31}H_{43}ClN_2O_3S_2Si$: 618.216211; found 618.21674. FTIR (KBr): $\tilde{\nu}$ = 3448, 2954, 2921, 2860, 1486, 1464, 1378, 1341, 1250, 1158, 1145, 1081, 894, 864, 839, 810, 783, 662, 573, 558 cm^{-1}.

2,1,3-Benzothiadiazole-4-sulfonamide 8h: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.8, J = 1.1 Hz, 1 H), 7.93 (dd, J = 7.1, J = 1.1 Hz, 1 H), 7.50 (dd, J = 8.8, J = 7.1 Hz, 1 H), 7.05 (d, J = 9.2 Hz), 6.84–6.80 (m, 2 H), 4.10 (t, J = 7.0 Hz, 2 H), 3.55 (s, 3 H), 2.23 (s, 3 H), 1.55–1.20 (m, 8 H), 0.91 (s, 9 H), 0.87 (t, J = 7.0 Hz, 3 H), –0.16 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.6 (Cq), 149.8 (Cq), 132.8 (Cq), 132.6, 132.2 (Cq), 130.2 (Cq), 129.1 (Cq), 128.2, 125.8, 123.8 (Cq), 122.4, 121.4 (Cq), 117.6, 108.7, 53.7 (CH_2), 31.5 (CH_2), 29.6, 29.0 (CH_2), 26.2 (CH_2), 25.6, 22.6 (CH_2), 18.0 (Cq), 14.0, 9.1, –4.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 573 (13), 572 (36) [M^+], 374 (72), 373 (100), 372 (8), 304 (13), 303 (55), 302 (6), 290 (10), 289 (4), 217 (11), 216 (5), 188 (6), 187 (11), 168 (9), 136 (15), 109 (9), 75 (12), 74 (5), 73 (65), 57 (12), 56 (8), 44 (15). HRMS: calcd. for $C_{28}H_{40}N_4O_3S_2Si$: 572.23056; found 572.229155. FTIR (ATR): $\tilde{\nu}$ = 3058, 2952, 2927, 2856, 1344, 1247, 1158, 1137, 1068, 963, 892, 834, 826, 778, 750, 665 cm^{-1}.

Naphthalene-1-sulfonamide 8i: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.66–8.61 (m, 1 H), 8.03 (dd, J = 7.5, J = 1.2 Hz, 1 H), 7.95 (d, J = 8.2 Hz, 1 H), 7.90–7.84 (m, 1 H), 7.56–7.50 (m, 2 H), 7.35 (dd, J = 8.2, J = 7.5 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H), 7.00 (d, 1 H, J = 8.8 Hz), 6.83 (dd, 1 H, J = 8.8 Hz, J = 2.0 Hz), 3.72 (t, 2 H, J = 7.0 Hz), 3.54 (s, 3 H), 2.24 (s, 3 H), 1.45–1.10 (m, 8 H), 0.96 (s, 9 H), 0.80 (t, 3 H, J = 7.0 Hz), –0.08 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 134.6 (Cq), 134.2 (Cq), 133.8 (Cq), 132.7 (Cq), 130.9, 130.3 (Cq), 129.1, 129.0 (Cq), 128.6, 127.6, 126.5, 125.6, 124.0, 123.6 (Cq), 122.0, 121.4 (Cq), 118.5, 108.5, 51.4 (CH_2), 31.4 (CH_2), 29.5, 28.3 (CH_2), 26.1 (CH_2), 25.7, 22.5 (CH_2), 18.0 (Cq), 14.0, 9.1, –4.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 565 (18), 564 (48) [M^+], 374 (35), 373 (100), 304 (4), 303 (15), 302 (4), 243 (6), 185 (5), 161 (2), 160 (8), 128 (10), 127 (8), 83 (11), 73 (12), 57 (17), 56 (10), 55 (18). HRMS: calcd. for $C_{32}H_{44}N_2O_3SSi$: 564.28364; found 564.285035. FTIR (KBr): $\tilde{\nu}$ = 3452, 3060, 2950, 2921, 2856, 1488, 1377, 1321, 1249, 1159, 1128, 1082, 893, 838, 797, 772, 672, 612, 503 cm^{-1}.

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3.7 A Convenient and General Method for the Synthesis of Indole-2,3-dicarboxylates and 2-Arylindole-3-carboxylates

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A Convenient and General Method for the Synthesis of Indole-2,3-dicarboxylates and 2-Arylindole-3-carboxylates

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Keywords: Alkynes / Hydroamination / Indoles

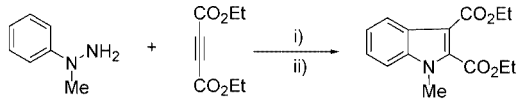
A transition-metal-free, simple and efficient one-pot method for the synthesis of indole-2,3-dicarboxylates and 2-arylindole-3-carboxylates is described. The corresponding products are obtained by a domino hydroamination/Fischer indole cyclization in good-to-excellent yields from easily available 1-alkyl-1-phenylhydrazines and acetylene carboxylates.

The catalytic addition of organic amines and their derivatives to alkenes and alkynes (hydroamination) to produce nitrogen-containing molecules is of significant importance for synthetic chemists in basic research as well as for those in the chemical industry.[1] Today intermolecular hydroaminations are known to be catalyzed by a variety of transition metals (d- and f-block metals),[2] alkali metals[3] and Brönsted and Lewis acids.[4] However, most of these catalysts are rather limited with respect to their substrate tolerance.

Various biologically active amine alkaloids, especially indoles, continue to attract the interest of organic chemists. Though many catalytic methods exist for the synthesis of indoles,[5] still the most famous synthesis for indoles and their derivatives constitutes the Fischer indole synthesis.[6] We have been interested for some time in the improvement and exploration of methodologies for the synthesis of indole heterocycles.[7] For example, we developed a one-pot synthesis of tryptamines and tryptopholes by a titanium-catalyzed hydrohydrazination of chloro- and silyloxo-substituted alkynes.[7a,8] In continuation of this work, we became interested in the hydrohydrazination reaction of acetylenedicarboxylates, which are easily available. Some related carboxy-2,3-disubstituted indole derivatives are known to be potent inhibitors of thromboxane synthase,[9] phospholipase-A_2,[10] cyclooxygenase-2,[11] steroid-5α-reluctase[12] and glycine/NMDA antagonists.[13] In addition to their biological activity, indole-2,3-dicarboxylate esters may serve as valuable synthetic intermediates for other indole derivatives and more complex indole heterocycles.[14]

On the basis of our previous hydroamination protocols, we initially investigated the reaction of *N*-methyl-*N*-phenylhydrazine (**1a**) with diethyl acetylenedicarboxylate (**2**) in the presence of 10 mol-% of $Ti(NEt_2)_4$ as the catalyst at 100 °C. Subsequent treatment of the reaction mixture with 3 equiv. of $ZnCl_2$ allowed the cyclization of the in-situ-generated hydrazone to give the corresponding diethyl 1-methylindole-2,3-dicarboxylate **3a** in 55% yield (Table 1, Entry 1).

Table 1. Reaction of 1-methyl-1-phenylhydrazine (**1a**) with diethyl acetylenedicarboxylate (**2**).[a]



1a **2** **3a**

Entry	Hydrazine **1a** [equiv.]	Alkyne **2** [equiv.]	Yield **3a** [%]
1[b]	1.0	1.0	55
2	1.0	1.0	63
3[c]	1.0	1.0	30
4[d]	1.0	1.0	60
5	1.5	1.0	66
6	1.0	1.5	78
7	1.0	2.0	87

[a] Reaction conditions: i) toluene, 100 °C, 24 h; ii) $ZnCl_2$ (3 equiv.), 100 °C, 24 h. [b] 10 mol-% $Ti(NEt_2)_4$, 20 mol-% 2,6-di-*tert*-butyl-4-methylphenol. [c] Reaction temperature 80 °C. [d] Reaction temperature 120 °C.

Interestingly, the same reaction occurred in 63% yield when performed in the absence of any titanium catalyst (Table 1, Entry 2). This observation is in agreement with the previous work of Acheson[15] and Miki et al.[16] who prepared selected dimethyl indole-2,3-dicarboxylates in yields of 13–62%. Interestingly, in 1935 Diels and Reese had already described the condensation of 1-benzyl-1-phenylhydrazine with acetylenedicarboxylate; however, no product yield of the respective indole-2,3-dicarboxylate was given.[17]

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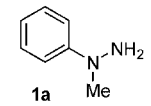
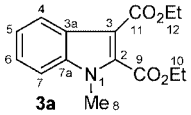
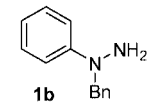
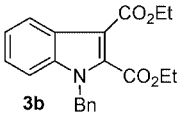
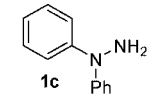
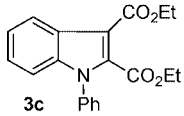
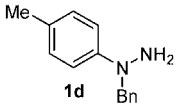
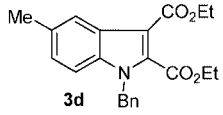
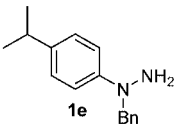
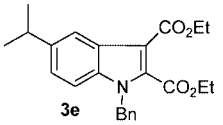
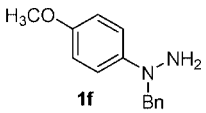
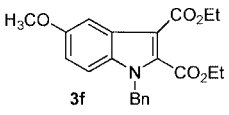
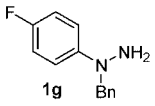
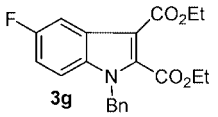
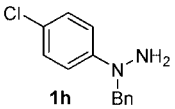
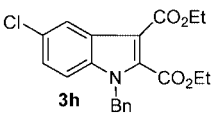
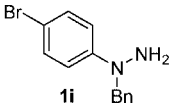
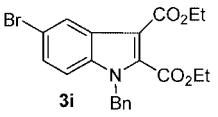
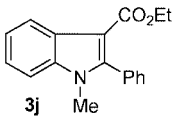
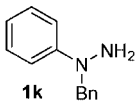
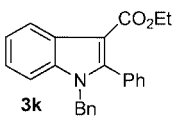
Because of the limited information available, we decided to perform a systematic study to improve the yield of this domino hydroamination/cyclization sequence. Selected experiments are shown in Table 1. The use of an excess amount of phenylhydrazine **1a** (1.5 equiv.) improved the yield of **3a** slightly. In contrast, a considerable increase in the yield of the corresponding indoledicarboxylate was observed when an excess of alkyne **2** was used. Hence, 1.5 and 2.0 equiv. of **2** gave 78 and 87% yield of **3a**, respectively. This is explained by oligomerization side reactions of **2**. We also examined the effect of temperature to improve the yield of the indole product. However, neither an increase in the

Table 2. Synthesis of indole-2,3-dicarboxylates.[a]

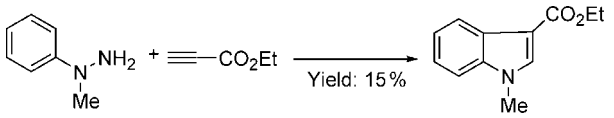
Entry	Hydrazine	Alkyne	Product	Yield [%][b]
1	 **1a**		 **3a**	87
2	 **1b**		 **3b**	67
3	 **1c**		 **3c**	60
4	 **1d**		 **3d**	65
5	 **1e**		 **3e**	60
6	 **1f**		 **3f**	55
7	 **1g**		 **3g**	75
8	 **1h**		 **3h**	40
9	 **1i**		 **3i**	26
10	 **1j**		 **3j**	55
11	 **1k**		 **3k**	60

[a] Reaction conditions: i) hydrazine (1 equiv.), acetylenedicarboxylate (2 equiv.), toluene, 100 °C, 24 h; ii) $ZnCl_2$ (3 equiv.), 100 °C, 24 h. [b] Yield of isolated products.

reaction temperature to 120 °C nor a lowering to 80 °C gave a better yield of **3a**. Also, attempts to improve the yield further by using different solvents such as benzene, methanol, THF, 1,4-dioxane and NMP were not fruitful. Noteworthy is that when $ZnCl_2$ was added in the beginning of reaction, the desired product was also obtained, albeit in lower yield.

As already described by Acheson et al.[15] we were also able to isolate the intermediate hydrazone of the reaction between *N*-methyl-*N*-phenylhydrazine (**1a**) and acetylenedicarboxylate **2** in the absence of $ZnCl_2$. After 24 h at 100 °C in toluene, a hydrazone/indole ratio of 83:17 was found. The hydrazone immediately underwent Fischer indole cyclization in the presence of the Lewis acid. At this point it is noteworthy that Schwesinger et al. demonstrated that the reaction of phenylhydrazine and acetylenedicarboxylate also yielded the corresponding hydrazone.[18] However, as a result of the strong intramolecular hydrogen bond, subsequent Fischer indole cyclization to yield the indole-2,3-dicarboxylate was prevented. Apparently, the presence of two substituents at the hydrazine nitrogen atom facilitates the Fischer indole cyclization. Thus, we next applied the improved hydroamination–cyclization protocol to indole products **3a**–**k** (Table 2).

However, lower yields (26–40%) were obtained for the reaction of *N*-(4-bromophenyl)- and *N*-(4-chlorophenyl)-*N*-benzylhydrazine, presumably owing to the lower reactivity in the Fischer indole cyclization step. Notably, the methodology is also applicable to other activated acetylenecarboxylic acid derivatives. Hence, the regioselective synthesis of 2-arylindolecarboxylate derivatives is possible from ethyl 3-phenyl-1-propynecarboxylate in 55–60% yield (Table 2, Entries 10 and 11). To the best of our knowledge these are the first examples of such a direct synthesis of 2-arylindole-3-carboxylates. Moreover, by applying the more labile ethyl propiolate, 15% of the desired product was obtained under similar reaction conditions (Scheme 1). Here, the lower product yield can be explained by the increased propensity of ethyl propiolate to undergo self condensation.



Scheme 1. Reaction with ethyl propiolate.

In conclusion, we presented the synthesis of various diethyl indole-2,3-dicarboxylates by a domino hydroamination/Fischer indole cyclization synthesis. The corresponding products are obtained easily from commercially available substrates in general in good yield. We believe that this methodology constitutes the most convenient access to this class of compounds.

Experimental Section

Representative Procedure: An Ace pressure tube under an argon atmosphere was charged with 1-methyl-1-phenylhydrazine (0.366 g, 3.0 mmol), diethyl acetylenedicarboxylate (1.02 g, 6.0 mmol) and dry toluene (5 mL). The pressure tube was fitted with a Teflon cap and heated at 100 °C for 24 h in an oil bath. Then, the reaction mixture was cooled to r.t. and anhydrous $ZnCl_2$ (1.22 g, 9.0 mmol) was added. The reaction mixture was further heated at 100 °C for 24 h. The excess toluene was distilled off under reduced pressure, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 9:1) to afford **3a** as a gummy liquid. Isolated yield: 0.717 g (87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (br. d, $^3J_{4,5}$ = 8.0 Hz, 1 H, 4-H), 7.37–7.33 (m, 2 H, 6,7-H), 7.28 (m, 1 H, 5-H), 3.83 [s, 3 H, Me(8)], 4.48 [q, ^3J = 7.3 Hz, 2 H, CH_2(10)], 4.38 [q, ^3J = 7.2 Hz, 2 H, CH_2(12)], 1.42 [t, ^3J = 7.3 Hz, 3 H, Me(10)], 1.40 [t, ^3J = 7.2 Hz, 3 H, Me(12)] ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 164.1 (C-11), 162.8 (C-9), 136.8 (C-7a), 135.0 (C-2), 125.4 (C-3a), 124.3 (C-6), 122.3, 122.5 (C-4,5), 110.0 (C-7), 108.0 (C-3), 62.3 [CH_2(10)], 60.2 [CH_2(12)], 31.3 [Me(8)], 14.0 [Me(10)], 14.4 [Me(12)] ppm (numbering according to Table 2, Entry 1). IR (neat): $\tilde{\nu}$ = 3055, 2982, 2938, 2905, 1733, 1717, 1700, 1615, 1539, 1471, 1444, 1412, 1379, 1273, 1247, 1210, 1157, 1103, 1034, 1014, 860, 788, 753, 742 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 275 (100) [M]$^+$, 230 (40), 229 (30), 203 (28), 202 (91), 200 (20), 158 (18), 157 (22), 89 (6). HRMS (EI): calcd. for $C_{15}H_{17}NO_4$ 275.1153; found 275.1152.

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3.8 Selective Reduction and Functionalization of Diethyl 1-alkyl-1*H*-indole-2,3-dicarboxylates

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Contributions: In this paper, I was involved in planning of experiments, the discussion and argumentation of the results. I was contributed significantly to the draft of the manuscript and supported the synthetic work. My contribution as co-author of this paper is approximately 15%.

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Selective reduction and functionalization of diethyl 1-alkyl-1*H*-indole-2,3-dicarboxylates

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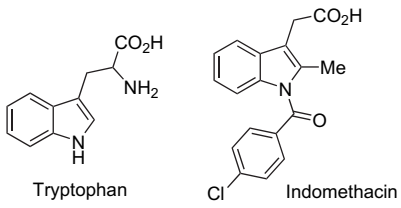
Abstract

A convenient and highly selective reduction of easily accessible indole-2,3-dicarboxylates is described. Ten different 1-alkyl-2-formyl-1*H*-indole-3-carboxylates are obtained in high yield and represent interesting building blocks for novel indoles.

1. Introduction

Indole and its derivatives have been termed as 'privileged pharmacologic structures' since they bind to many biological receptors with high affinity.[1] In addition, the indole moiety is found in numerous natural products and is an important building block of several families of alkaloids.[2] Many of them have significant biological activity such as Indomethacin[3] (anti-inflammatory), Vincristine[4] (anti-cancer), Fluvastatin[5] (cholesterol-lowering), Vinblastine[6] (anti-cancer), and tryptophan, which is an essential amino acid[7] (Scheme 1).



Scheme 1. Selected biologically active indoles.

Due to their importance as one of the most represented building blocks in natural products and known marketed drugs, there is a continuing interest in the development of improved methods for the synthesis of indoles.[8,9] In recent years especially domino sequences provided efficient complementary access to various indoles.[10] Though, many catalytic methods exist for the preparation of indoles, still the most famous route for the construction of the indole ring constitutes the Fischer indole synthesis.[9]

For some time, we have been interested in the improvement and exploration of methodologies for the synthesis and functionalization of indoles. For example, we developed a titanium-catalyzed as well as zinc-mediated synthesis of functionalized tryptamines and tryptophol derivatives starting from commercially available arylhydrazines and alkynes.[11] More recently, we reported also a transition-metal-free one-pot synthesis of indole-2,3-dicarboxylates **1** from arylhydrazines and acetylene dicarboxylates.[12] Based on this work, we became interested in the selective reduction of indole-2,3-dicarboxylates (Scheme 2). Obviously, such a selective protocol would offer direct access to a variety of novel indole derivatives. Here, we report our results on this project.

Clearly, reduction of carboxylic acids, esters, and amides is an essential tool for the synthesis of aldehydes, alcohols, and amines.[13] Especially, selective reduction to aldehydes is important, as the highly reactive formyl group can be easily employed in numerous C–C-, and C–N-coupling reactions as well as other transformations.

As shown in Scheme 2, chemoselective reduction of 1*H*-indole-2,3-dicarboxylates **1** could provide different functionalized

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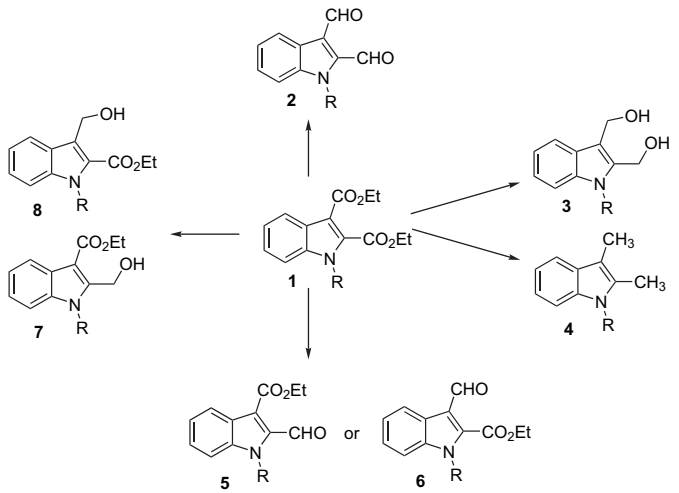


Scheme 2. Potential reductions of the indole-2,3-dicarboxylates.

indoles such as 1-alkyl-1*H*-indole-2,3-dicarbaldehyde **2**, (1-alkyl-1*H*-indole-2,3-diyl)-dimethanol **3**, 1-alkyl-2,3-dimethyl-1*H*-indole **4**, isomeric 2,3-formylindole-carboxylates **5** or **6**, and 2,3-hydroxymethylindole-carboxylates **7** or **8**.

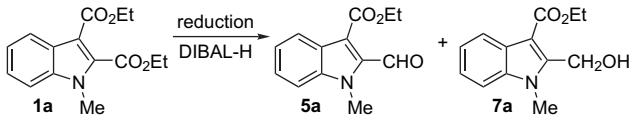
2. Results and discussion

At the starting point of our investigations, we studied the reaction of indole 2,3-diester **1a** in the presence of standard metal hydrides at different temperatures. However, in the presence of $NaBH_4$ and $NaCNBH_3$ only the recovered starting material was obtained.

Unfortunately, under more drastic conditions treatment of **1a** with $LiAlH_4$ (reflux temperature) afforded a complex mixture of several products.

As shown in Table 1 reduction using DIBAL-H at room temperature was more selective but also afforded a mixture of products. Here, aldehyde **5a** and alcohol **7a** along with the recovered starting material are observed. When the reduction was carried out in the presence of an excess (2.5 equiv) of DIBAL-H at −78 °C for 5 min, full conversion is seen and the alcohol **7a** is obtained as major product in 60% yield along with some aldehyde **5a**. Reducing the amount of DIBAL-H (2.0 equiv) as well as the reaction time (3 min) afforded the aldehyde **5a** with an excellent yield of 90% as the only product of the reaction. To the best of our knowledge, there is no report on chemoselective reduction of one of the ester group of indole-2,3-dicarboxylates to give 2-formyl-1-alkyl-1*H*-indole-3-carboxylates.

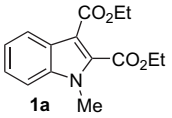
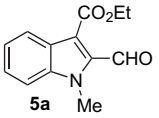
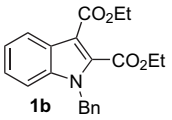
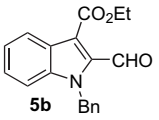
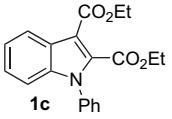
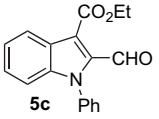
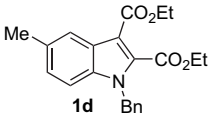
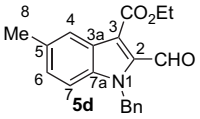
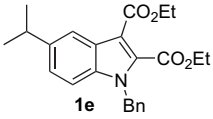
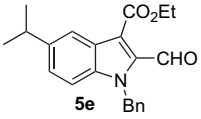
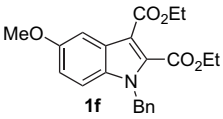
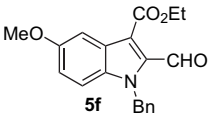
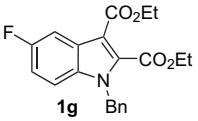
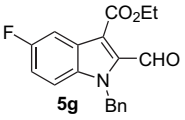
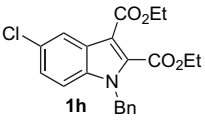
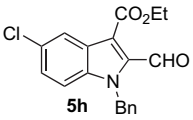
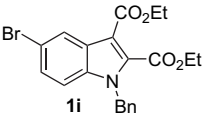
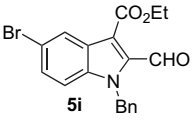
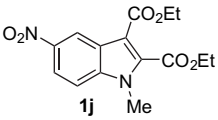
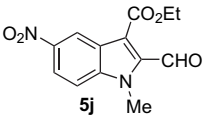
Table 1
Reduction of **1a** under different conditions



Entry	DIBAL-H (equiv)	Temp (°C)	Time (min)	Yield[a] (%) (**5a**)	Yield[a] (%) (**7a**)	Yield[a] (%) (**1a**)
1	1.5	0	5	23	24	50
2	2.0	0	5	9	40	49
3	2.5	−78	5	30	60	—
4	2.0	−78	5	60	30	—
5	2.0	−78	3	90	—	—

[a] Isolated yield.

Table 2
Chemoselective reduction of indole-2,3-dicarboxylates: substrate scope[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **1a**	 **5a**	90
2	 **1b**	 **5b**	62
3	 **1c**	 **5c**	75
4	 **1d**	 **5d**	75
5	 **1e**	 **5e**	86
6	 **1f**	 **5f**	60
7	 **1g**	 **5g**	90
8	 **1h**	 **5h**	67
9	 **1i**	 **5i**	67
10	 **1j**	 **5j**	60

[a] Reaction conditions: indole 2,3-dicarboxylates (1.0 equiv), DIBAL-H (2.0 equiv), CH_2Cl_2, −78 °C, 3 min.
[b] Isolated yield.

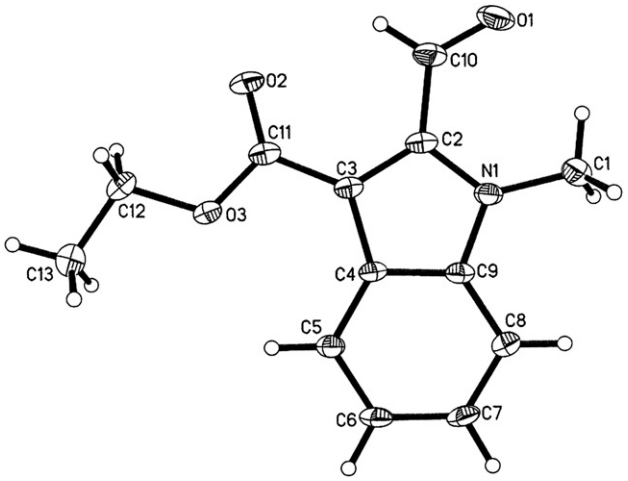


Figure 1. X-ray crystal structure of ethyl 2-formyl-1-methyl-1*H*-indole-3-carboxylate **5a**. The thermal ellipsoids correspond to 30% probability.

At this point, it should be noted that there are only few methods known in the literature for the preparation of 2-formyl-indole-3-carboxylates.[14]

The promising results obtained with the model compound encouraged us to study the general scope and limitations of this protocol for the reduction of different substituted indole-2,3-dicarboxylates (Table 2). Fluoro-, chloro-, and bromo-substituted diethyl indole-2,3-dicarboxylates **1g–1i** readily underwent reduction with DIBAL-H to afford the corresponding aldehydes **5g–5i** in good yield (67–90% yield) with no over-reduction of the halide substituents observed. Likewise, the nitro-substituted indole **1j** gave the corresponding aldehyde **5j** in 60% isolated yield. Previously, the product **1j** has been obtained by nitration of **1a**.[15] Noteworthy, all isolated indole-2-aldehydes are stable solids, which did not oxidize easily in air. In all cases, spectroscopic characterization of the products by NMR revealed the presence of one aldehyde and one ester group. The position of the formyl group is established unambiguously by NOE measurements. For example, in the two-dimensional NOESY spectrum of **5d** correlations are found for the proton H-4 with methyl substituent on the phenyl ring, the OCH_2, and the OCH_2CH_3 confirming the ester group being placed in C-3 position. In addition, we were able to confirm the regioselective reduction by X-ray crystallographic analysis of **5a** (Fig. 1).[16] Suitable crystals were obtained by recrystallization from dichloromethane.

Obviously, 2-formyl indole-3-carboxylates are versatile building blocks for selective reactions either at the 2- or 3-position of the indole ring. Therefore, we turned our attention to further functionalization reactions of **5a**. In some preliminary studies, the reductive amination with benzylamine in the presence of $NaCNBH_3$ proceeded smoothly at the formyl group to give **10** in 80% yield (Scheme 3). Notably, there is no side reaction at the ester group observed.

Moreover, addition of organometallic reagents progressed highly selectively at the 2-position. Hence, the reaction of the vinyl magnesium bromide with **5a** yielded the corresponding allylic alcohol **9** in 82%. As expected in the NOESY spectrum of compound **9** correlations are found for the proton H-4 with OCH_2 and OCH_2CH_3 as well as NMe with the protons H-7, H-9, H-10, and H-11 confirming the proposed structure.

3. Conclusion

In conclusion, we have developed a convenient and fast reduction of 1*H*-indole-2,3-dicarboxylates. The resulting products **5a–j** are obtained with excellent selectivity in good yield. It is predicted that alkyl 2-formyl-1-alkyl-1*H*-indole-3-carboxylates constitute useful building blocks, which will lead in three easy steps to a variety of novel 2,3-disubstituted indoles from commercially available arylhydrazines and acetylene dicarboxylates.

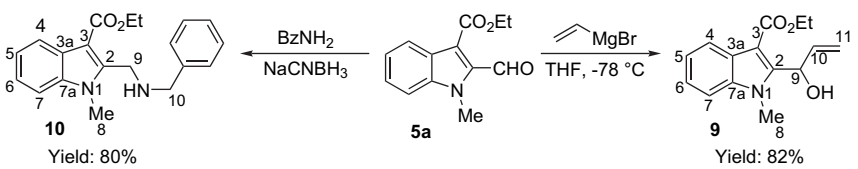
4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros, and Strem, and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, HRMS, and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 300, AV 400, and AV 500 spectrometers. The ^{1}H and ^{13}C NMR chemical shifts are reported relative to the center of solvent resonance ($CDCl_3$: 7.25 (^{1}H), 77.0 (^{13}C)). For compounds **5d**, **9**, and **10**, a complete assignment of the ^{1}H- and ^{13}C-signal is given based on two-dimensional NMR spectra (COSY, NOESY, and C,H-correlation). EI mass spectra were recorded on an AMD 402 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded on an FTIR Nicolet 6700 (Thermo ELECTRON CORPORATION). GC was performed on a Hewlett–Packard HP 6890 chromatograph with a 30 m HP5 column. All yields reported in Tables 1 and 2 refer to isolated yields.

4.2. General procedure for the preparation of aldehydes

A solution of diethyl 1-alkyl-1*H*-indole-2,3-dicarboxylate (0.25 mmol) in CH_2Cl_2 at −78 °C was treated with DIBAL-H (0.42 ml, 0.5 mmol, 1 M solution in toluene). The reaction



Scheme 3. Potential reduction examples of the indole-2,3-dicarboxylates.

mixture was stirred at −78 °C for 3 min and then quenched with 1 M HCl and MeOH. After warming up to room temperature, H_2O was added and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel with hexane–EtOAc (95:5) as the eluent afforded the aldehydes **5a–j**.

*4.2.1. Ethyl 2-formyl-1-methyl-1H-indole-3-carboxylate (**5a**)*

Isolated yield: 90% (mp: 76–77 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.47 (t, J=7.2 Hz, 3H), 4.05 (s, 3H), 4.45 (q, J=7.2 Hz, 2H), 7.26–7.45 (m, 3H), 8.23 (br d, J=8.0 Hz, 1H), 10.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 32.5 (CH_3), 60.8 (CH_2), 110.5 (CH), 115.0, 123.2 (CH), 123.8 (CH), 125.5, 126.9 (CH), 136.3, 136.7, 164.3, 186.5 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=231 (M^+, 76), 203 (21), 202 (42), 188 (21), 186 (32), 175 (26), 159 (16), 158 (100), 157 (26), 131 (16), 130 (17), 103 (12), 89 (12), 77 (12). HRMS (EI) calcd for $C_{13}H_{13}NO_3$: 231.0890; found: 231.0889. FTIR: (KBr, cm^{-1})= 3077, 3025, 2987, 2906, 1699, 1662, 1612, 1516, 1447, 1396, 1383, 1338, 1267, 1218, 1175, 1160, 1106, 1036, 908, 890, 785, 752, 740, 726, 517.

*4.2.2. Ethyl 1-benzyl-2-formyl-1H-indole-3-carboxylate (**5b**)*

Isolated yield: 62% (mp: 112–113 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.48 (t, J=7.2 Hz, 3H), 4.48 (q, J=7.2 Hz, 2H), 5.87 (s, 2H), 7.04 (m, 2H), 7.17–7.42 (m, 6H), 8.31 (br d, J=8.0 Hz, 1H), 10.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 48.4 (CH_2), 60.9 (CH_2), 111.2 (CH), 115.9, 123.3 (CH), 123.9 (CH), 125.7, 126.4 (2CH), 127.2 (CH), 127.5 (CH), 128.6 (2CH), 135.8, 136.8, 138.6, 164.2, 186.1 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=307 (M^+, 16), 262 (12), 261 (42), 260 (37), 233 (14), 232 (36), 204 (17), 157 (11), 149 (37), 123 (48), 121 (18), 119 (21), 115 (14), 111 (15), 109 (15), 105 (22), 97 (23), 95 (29), 91 (100), 83 (29), 81 (24), 77 (27), 69 (71), 57 (50). HRMS (EI) calcd for $C_{19}H_{17}NO_3$: 307.1208; found: 307.1202. FTIR: (KBr, cm^{-1})=3058, 3030, 2932, 1699, 1671, 1518, 1469, 1450, 1415, 1384, 1338, 1274, 1238, 1175, 1161, 1146, 1026, 913, 868, 785, 747, 730.

*4.2.3. Ethyl 2-formyl-1-phenyl-1H-indole-3-carboxylate (**5c**)*

Isolated yield: 75% (mp: 83–84 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.48 (t, J=7.2 Hz, 3H), 4.50 (q, J=7.2 Hz, 2H), 7.05 (m, 1H), 7.22–7.37 (m, 4H), 7.51 (m, 3H), 8.36 (m, 1H), 10.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=14.5 (CH_3), 61.0 (CH_2), 111.9 (CH), 115.9, 123.6 (CH), 123.6 (CH), 125.4, 127.2 (CH), 127.6 (2CH), 128.8 (CH), 129.3 (2CH), 136.7, 137.4, 139.8, 164.3, 184.3 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=293 (M^+, 32), 264 (40), 248 (36), 247 (95), 237 (12), 221 (15), 220 (100), 219 (53), 218 (35), 193 (18), 191 (49), 190 (20), 165 (27), 158 (15), 77 (12), 57 (13), 55 (10). HRMS (EI) calcd for $C_{18}H_{15}NO_3$: 293.1046; found: 293.1044. FTIR: (KBr, cm^{-1})=3054, 2980, 2952, 2899, 1700, 1679, 1597, 1516, 1502, 1482, 1454, 1395, 1381, 1343, 1263, 1241, 1183, 1123, 1065, 1020, 1065, 1020, 940, 773, 753, 698, 562.

*4.2.4. Ethyl 1-benzyl-2-formyl-5-methyl-1H-indole-3-carboxylate (**5d**)*

Isolated yield: 75% (mp: 97–98 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=1.48 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 2.48 (s, 3H, $Me_{(8)}$), 4.49 (q, ^3J=7.2 Hz, 2H, OCH_2), 5.87 (s, 2H, H-8), 7.04 (m, 2H, *o*-Ph), 7.18–7.25 (m, 4H, H-6, *m*-, *p*-Ph), 7.30 (d, $^3J_{6,7}$=8.5 Hz, 1H, H-7), 8.09 (br s, 1H, H-4), 10.79 (s, 1H, CHO). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm)=14.5 (OCH_2CH_3), 21.7 ($Me_{(8)}$), 48.5 (C-8), 60.8 (OCH_2), 110.9 (C-7), 115.3 (C-3), 123.1 (C-4), 126.0 (C-3), 126.4 (*o*-Ph), 127.5 (*p*-Ph), 128.7 (*m*-Ph), 129.3 (C-6), 133.1 (C-5), 135.7 (C-2), 137.0, 137.2 (C-7a, *i*-Ph), 164.4 (COO), 186.1 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=321 (M^+, 28), 276 (18), 275 (71), 274 (62), 256 (57), 247 (20), 218 (15), 111 (14), 97 (20), 95 (16), 91 (100), 83 (20), 71 (20), 69 (22), 57 (31), 55 (28). HRMS (EI) calcd for $C_{20}H_{19}NO_3$: 321.1359; found: 321.1358. FTIR: (KBr, cm^{-1})=3066, 3033, 2985, 2922, 1693, 1669, 1515, 1482, 1452, 1413, 1384, 1351, 1304, 1270, 1234, 1164, 1133, 1030, 1011, 909, 871, 799, 772, 718, 694.

*4.2.5. Ethyl 1-benzyl-2-formyl-5-isopropyl-1H-indole-3-carboxylate (**5e**)*

Isolated yield: 86% (mp: 73–74 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.31 (d, J=7.0 Hz, 6H), 1.49 (t, J=7.2 Hz, 3H), 3.05 (sep, J=7.0 Hz, 1H), 4.49 (q, J=7.2 Hz, 2H), 5.85 (s, 2H), 7.05 (m, 2H), 7.19–7.35 (m, 5H), 8.15 (m, 1H), 10.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 24.2 (2 CH_3), 34.2 (CH), 48.5 (CH_2), 60.8 (CH_2), 111.0 (CH), 115.5, 120.3 (CH), 125.9, 126.4 (2CH), 127.0 (CH), 127.4 (CH), 128.6 (2CH), 135.6, 136.9, 137.4, 144.2, 164.3, 186.0 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=349 (M^+, 34), 304 (21), 303 (80), 302 (90), 276 (12), 275 (16), 274 (64), 260 (17), 232 (10), 91 (100), 65 (11). HRMS (EI) calcd for $C_{22}H_{23}NO_3$: 349.1672; found: 349.1669. FTIR: (KBr, cm^{-1})=3064, 3033, 2959, 2929, 2870, 1701, 1671, 1621, 1606, 1516, 1482, 1454, 1411, 1383, 1353, 1282, 1235, 1187, 1163, 1130, 1030, 998, 906, 890, 806, 705.

*4.2.6. Ethyl 1-benzyl-2-formyl-5-methoxy-1H-indole-3-carboxylate (**5f**)*

Isolated yield: 60% (mp: 101–102 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.48 (t, J=7.2 Hz, 3H), 3.89 (s, 3H), 4.48 (q, J=7.2 Hz, 2H), 5.86 (s, 2H), 7.02–7.09 (m, 3H), 7.22–7.33 (m, 4H), 7.73 (d, J=2.0 Hz, 1H), 10.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 48.6 (CH_2), 55.6 (CH_3), 60.8 (CH_2), 103.2 (CH), 112.2 (CH), 114.9, 119.3 (CH), 126.4 (2CH), 126.7, 127.5 (CH), 128.7 (2CH), 134.1, 135.6, 136.9, 156.7, 164.4, 185.9 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=337 (M^+, 35), 292 (14), 291 (51), 290 (53), 263 (17), 262 (47), 149 (11), 97 (14), 91 (100), 83 (18), 71 (16), 69 (22), 57 (28). HRMS (EI) calcd for $C_{20}H_{19}NO_4$: 337.1308; found:

337.1301. FTIR: (KBr, cm^{-1})=3117, 3030, 3007, 2981, 2927, 2843, 1697, 1661, 1617, 1575, 1509, 1487, 1467, 1408, 1384, 1342, 1303, 1219, 1205, 1179, 1148, 1126, 1081, 1031, 988, 918, 867, 846, 816, 775, 742, 711.

4.2.7. Ethyl 1-benzyl-2-formyl-5-fluoro-1H-indole-3-carboxylate (**5g**)

Isolated yield: 90% (mp: 103–104 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.49 (t, J=7.2 Hz, 3H), 4.49 (q, J=7.2 Hz, 2H), 5.87 (s, 2H), 7.03 (m, 2H), 7.16 (dt, $J_{H,F}$=9.0 Hz, J=9.0, 2.5 Hz, 1H), 7.22–7.28 (m, 3H), 7.35 (dd, J=9.0 Hz, $J_{H,F}$=4.5 Hz, 1H), 7.94 (dd, $J_{H,F}$=9.5 Hz, J=2.5 Hz, 1H), 10.84 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 48.7 (CH_2), 61.0 (CH_2), 108.5 (d, $J_{F,C}$=25.2 Hz, CH), 112.5 (d, $J_{F,C}$=9.5 Hz, CH), 115.5 (d, $J_{F,C}$=5.5 Hz), 116.5 (d, $J_{F,C}$=27.4 Hz, CH), 126.2 (d, $J_{F,C}$=11.0 Hz), 126.4 (2CH), 127.7 (CH), 128.7 (2CH), 135.1, 136.5, 136.8, 159.6 (d, $J_{F,C}$=241.0 Hz), 163.9, 186.1 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=325 (M^+, 28), 280 (20), 279 (72), 278 (65), 251 (20), 250 (61), 222 (24), 92 (10), 91 (100), 65 (16). HRMS (EI) calcd for $C_{19}H_{16}FNO_3$: 325.1108; found: 325.1100. FTIR: (KBr, cm^{-1})=3105, 3043, 2982, 2926, 1705, 1657, 1513, 1493, 1461, 1413, 1390, 1260, 1237, 1214, 1176, 1160, 1144, 1126, 1028, 993, 939, 876, 857, 810, 786, 714.

4.2.8. Ethyl 1-benzyl-2-formyl-5-chloro-1H-indole-3-carboxylate (**5h**)

Isolated yield: 67% (mp: 88–89 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.47 (t, J=7.2 Hz, 3H), 4.47 (q, J=7.2 Hz, 2H), 5.84 (s, 2H), 7.00 (m, 2H), 7.14–7.33 (m, 5H), 8.27 (br s, 1H), 10.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 48.7 (CH_2), 61.1 (CH_2), 112.4 (CH), 115.2, 123.2 (CH), 126.4 (2CH), 126.5, 127.7 (CH), 127.8 (CH), 128.8 (2CH), 129.4, 136.4, 136.5, 136.9, 163.8, 186.0 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=341 (M^+, 20), 297 (16), 296 (28), 295 (46), 294 (48), 267 (20), 266 (37), 204 (10), 91 (100), 65 (13). HRMS (EI) calcd for $C_{19}H_{16}ClNO_3$: 341.0813; found: 341.0811. FTIR: (KBr, cm^{-1})=3101, 3068, 3057, 2958, 2983, 2925, 2856, 1695, 1676, 1515, 1499, 1462, 1453, 1412, 1384, 1347, 1291, 1259, 1233, 1160, 1129, 1069, 1031, 996, 987, 923, 877, 866, 801, 781, 759, 738, 701.

4.2.9. Ethyl 1-benzyl-2-formyl-5-bromo-1H-indole-3-carboxylate (**5i**)

Isolated yield: 67% (mp: 109–110 °C). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.48 (t, J=7.2 Hz, 3H), 4.49 (q, J=7.2 Hz, 2H), 5.85 (s, 2H), 7.01 (m, 2H), 7.20–7.30 (m, 4H), 7.47 (dd, J=9.0, 2.0 Hz, 1H), 8.45 (d, J=2.0 Hz, 1H), 10.82 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 48.6 (CH_2), 61.1 (CH_2), 112.8 (CH), 115.0, 117.1, 126.3 (2CH), 126.4 (CH), 127.0, 127.7, 128.8 (2CH), 130.3, 136.3, 136.4, 137.1, 163.8, 186.0 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=387 (M^{+2}, 15), 385 (M^+, 15), 341 (39), 340 (39), 339 (39), 338 (28), 312 (28), 310 (22), 304 (12), 91 (100), 65 (10). HRMS (EI) calcd for $C_{19}H_{16}BrNO_3$: 385.0308; found: 385.0302. FTIR: (KBr, cm^{-1})=3100, 3037, 2981, 2923, 1695, 1676, 1515, 1452, 1412, 1383, 1347, 1290, 1259, 1234, 1160, 1130, 1112, 1056, 1030, 987, 921, 878, 865, 799, 781, 732, 698.

4.2.10. Ethyl 1-methyl-2-formyl-5-nitro-1H-indole-3-carboxylate (**5j**)

Isolated yield: 60% (mp: 185–186 °C). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.49 (t, J=7.2 Hz, 3H), 4.20 (s, 3H), 4.50 (q, J=7.2 Hz, 2H), 8.16 (dd, J=9.0, 2.0 Hz, 1H), 8.40 (d, J=9.0 Hz, 1H), 8.42 (d, J=2.0 Hz, 1H), 10.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=14.4 (CH_3), 33.0 (CH_3), 61.3 (CH_2), 107.6 (CH), 114.7, 117.7 (CH), 124.6 (CH), 129.5, 137.3, 139.7, 146.3, 163.4, 186.8 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=276 (M^+, 56), 248 (23), 247 (23), 220 (30), 203 (100), 202 (28), 185 (20), 157 (25), 128 (18), 102 (12), 87 (11). FTIR: (KBr, cm^{-1})=3121, 3091, 1703, 1672, 1515, 1471, 1406, 1397, 1340, 1260, 1218, 1162, 1123, 1070, 1027, 933, 887, 837, 736.

4.3. Ethyl 2-(1-hydroxyallyl)-1-methyl-1H-indole-3-carboxylate (**9**)

To a solution of ethyl 2-formyl-1-alkyl-1*H*-indole3-carboxylate (0.151 mmol) in 5 mL dry THF at −78 °C was treated with allyl-magnesium-bromide (0.166 mmol). The reaction mixture was stirred at −78 °C for 30 min. After removal of the solvent and purification by column chromatography (eluent: hexane–EtOAc=80:20) yielded **9** (82%) as colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm)=1.48 (t, ^3J=7.2 Hz, 3H, Me), 3.78 (s, 3H, NMe), 4.38–4.48 (m, 2H, OCH_2), 5.15–5.21 (m, 2H, H-11), 5.70 (m, 1H, H-9), 6.17 (ddd, $^3J_{10,11(trans)}$=17.0 Hz, $^3J_{10,11(cis)}$=10.4 Hz, $^3J_{9,10}$=5.7 Hz, 1H, H-10), 6.35 (d, J=10.5 Hz, 1H, OH), 7.25–7.31 (m, 2H, H-5,6), 7.34 (m, 1H, H-7), 8.13 (m, 1H, H-4). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm)=14.4 (Me), 30.6 (NMe), 60.6 (OCH_2), 68.1 (C-9), 104.1 (C-3), 109.7 (C-7), 115.7 (C-11), 122.0 (C-4), 122.3 (C-5), 122.9 (C-6), 126.3 (C-3a), 136.6 (C-7a), 137.4 (C-10), 149.0 (C-2), 167.7 (CO). MS (EI, 70 eV): *m/z* (relative intensity)=259 (M^+, 36), 214 (24), 213 (100), 186 (29), 185 (31), 184 (54), 170 (10), 169 (13), 168 (15), 158 (21), 157 (23), 130 (10). HRMS (EI) calcd for $C_{15}H_{17}NO_3$: 259.1202; found: 259.1200. FTIR: (neat, cm^{-1})=3409, 3054, 2980, 2936, 1689, 1661, 1523, 1472, 1404, 1376, 1351, 1330, 1287, 1219, 1163, 1104, 1032, 990, 928, 878, 790, 753, 741.

4.4. Ethyl 2-(benzylamino)methyl-1H-indole-3-carboxylate (**10**)

A solution of ethyl 2-formyl-1-alkyl-1*H*-indole-3-carboxylate (0.216 mmol), benzylamine (0.259 mmol), and $NaCNBH_3$ (0.216 mmol) in 6 mL methanol was stirred for 20 h at room temperature. After removal of the solvent and purification by column chromatography (eluent: EtOAc) yielded **10** (80%) as colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm)=1.43 (t, ^3J=7.2 Hz, 3H), 2.24 (br, 1H, NH), 3.73 (s, 3H, $Me_{(8)}$),

3.89 (s, 2H, H-10), 4.27 (s, 2H, H-9), 4.42 (q, ^3J=7.2 Hz, 2H, OCH_2), 7.26–7.40 (m, 8H, H-5,6,7,Ph), 8.17 (m, 1H, H-4). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm)=14.5 (Me), 29.8 ($Me_{(8)}$), 42.8 (C-9), 53.5 (C-10), 59.6 (OCH_2), 105.0 (C-3), 109.5 (C-7), 121.8 (2), 122.6 (C-4,5,6), 126.2 (C-3a), 127.0 (*p*-Ph), 128.2 (*o*-Ph), 128.3 (*m*-Ph), 136.7 (C-7a), 140.0 (*i*-Ph), 145.9 (C-2), 165.8 (CO). MS (EI, 70 eV): *m*/*z* (relative intensity)=325 (26), 280 (16), 279 (56), 278 (61), 252 (11), 251 (17), 250 (53), 222 (23), 91 (100), 65 (14). FTIR: (neat, cm^{-1})=3300, 3105, 3042, 3031, 2925, 1704, 1657, 1513, 1492, 1461, 1452, 1412, 1389, 1372, 1351, 1260, 1236, 1214, 1176, 1160, 1143, 1126, 1027, 993, 939, 875, 856, 810, 784, 736, 713.

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16. *X-ray crystallographic study of complex* ***5a***. Data were collected with an STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structures were solved by direct methods [Sheldrick, G. M. *SHELXS-97*; University of Göttingen: Germany, 1997;] and refined by full-matrix least-squares techniques against F^2; [Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, 1997;]. XP (BRUKER AXS) was used for structural representations. Space group *P*21/*c*, monoclinic, a=14.294(3), b=9.846(2), c=7.841(2) Å, β=101.05(3)°, V=1130.8(4) Å^3, Z=4, ρ_{calcd}=1.358 g cm^{-3}, 3972 reflections measured, 2048 were independent of symmetry, of which 1291 were observed ($I>2\sigma(I)$), $R1$=0.056, $wR2$ (all data)=0.151, 154 parameters. The crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC (**3**). Copies of the data can be obtained free of charge on application to http://www.ccdc.cam.ac.uk/data_request/cif.

3.9 General Zn-Catalyzed Intermolecular Hydroamination of Terminal Alkynes

Karolin Alex, Annegret Tillack, Nicolle Schwarz, Matthias Beller, *ChemSusChem*, **2008**, *1*, 333-338.

Contributions: In this paper, I was involved in planning experiments, as well as the discussion and argumentation of the results. I contributed significantly to the draft of the manuscript. My contribution as co-author of this paper is approximately 10%.

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General Zinc-Catalyzed Intermolecular Hydroamination of Terminal Alkynes

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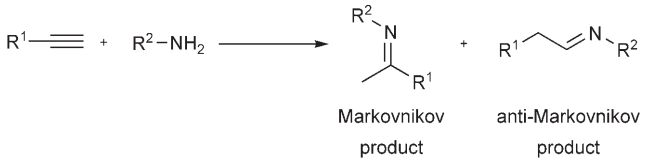
Catalytic hydroaminations are one of the most sustainable C–N bond-forming processes as a result of 100% atom economy and the availability of substrates. Here, it is shown that the intermolecular hydroamination of terminal alkynes with anilines proceeds smoothly in the presence of catalytic amounts of zinc triflate, an easily available and inexpensive zinc salt. Amination and subsequent reduction with $NaBH_3CN$ gives a variety of secondary and tertiary amines in up to 99% yield and with over 99% Markovnikov regioselectivity. Moreover, difficult functional groups such as nitro and cyano substituents are tolerated by the homogeneous catalyst.

Introduction

The addition of primary and secondary amines to C–C unsaturated bonds represents an attractive and green method for the synthesis of nitrogen-containing organic compounds. As a result of 100% atom economy and the availability of substrates, catalytic hydroaminations constitute probably the most sustainable C–N bond-forming processes.[1] While a general and efficient hydroamination of aliphatic alkenes is not yet possible and still a major challenge in modern catalysis research, alkynes are more reactive in hydroamination reactions. In general, terminal alkynes can provide two regioisomeric imines, the Markovnikov and the anti-Markovnikov product (Scheme 1). Typically, the Markovnikov regioisomer is thermodynamically favored.



Scheme 1. Hydroamination of terminal alkynes.

As a result of the continuing interest in alkyne hydroamination, several catalysts have been developed over the last decade for the intra- and intermolecular hydroamination of non-activated alkynes. Pioneering work in this area was reported by Barluenga et al., who employed mercury and thallium salts for the hydroamination of alkynes with anilines, and special work was done by Reppe using acetylene in the presence of zinc and cadmium salts.[2] Later on, the intermolecular hydroamination of alkynes was carried out with lanthanides (Sm, Lu, Nd) and actinoids (Ur, Th), early transition metals (Zr, Ti, V, Ta), Ru, Rh, Pd, Pt, Ag, and Au.[3] Despite the methodological progress, the application of most of these catalyst systems is narrowed by their air and/or moisture sensitivity and/or their limited ability to tolerate different functional groups.

In addition to the well-established organometallic complexes used for hydroaminations, also heterogeneous catalysts based on transition-metal-exchanged montmorillonite K-10 (Cu^{2+})[4] and solid catalysts based on supported ionic liquids (Zn, Cu, Pd, Rh)[5] were reported for the reaction of aniline derivatives with phenylacetylene. Among the different metal catalysts known for hydroaminations, extensive investigations have been reported on Ti-based catalysts because of the price of the metal and their low toxicity.[6] Notably, the Markovnikov or the anti-Markovnikov functionalization of alkynes can be controlled by applying a suitable ligand in the Ti complex.[7]

Besides the hydroamination with simple amines and alkynes, similar reactions with other nitrogen nucleophiles such as hydrazines are known. In this respect, the hydrohydrazination with subsequent Fischer indole synthesis is especially noteworthy.[8] Recently, we reported for the first time an intermolecular zinc-mediated and -catalyzed hydrohydrazination reaction of alkynes which allows for a general synthesis of indoles (Scheme 2).[9] On the basis of this investigation, we became interested in the use of zinc catalysts for the hydroamination of alkynes with amines. To the best of our knowledge, there is no homogeneous zinc catalyst known for any intermolecular hydroamination of alkynes with amines. Müller and co-workers demonstrated that the reaction of phenylacetylene with 4-isopropylaniline in the presence of $Zn(OTf)_2$ proceeded only with 3% conversion.[5] However, the thermodynamically more favorable intramolecular hydroamination of terminal alkynes is known to be catalyzed by homogeneous zinc catalysts, which has been nicely demonstrated by Müller and co-workers as well as by Blechert, Roesky et al.[10]

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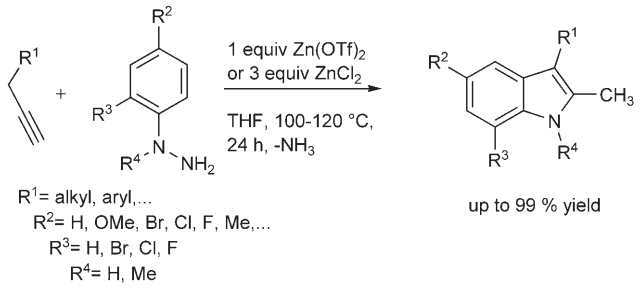
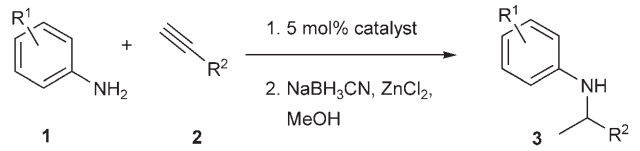


Scheme 2. Synthesis of indoles by hydrohydrazination of terminal alkynes (OTf = trifluoromethanesulfonate).

Results and Discussion

As the starting point of our investigation, we studied the reaction of aniline (**1a**; $R^1 = H$) with 1-octyne (**2a**; $R^2 = C_6H_{13}$) by varying the reaction conditions (Scheme 3; Table 1). After full



Scheme 3. Hydroamination of alkynes with aniline derivatives.

Table 1. Variation of the reaction conditions for the hydroamination of 1-octyne (**2a**) with aniline (**1a**).[a]

Entry	Catalyst	Solvent	T [°C]	Ratio **2a**/**1a**	Conv. [%][b]	Yield [%][b]
1	$Zn(OTf)_2$	THF	100	1:1.3	93	68
2	$ZnCl_2$	THF	100	1:1.3	25	21
3	$Zn(OTf)_2$	Toluene	100	1:1.3	100	76
4	$Zn(OTf)_2$	Toluene	120	1:1.3	100	86
5	$Zn(OTf)_2$	Dioxane	120	1:1.3	100	83
6	$Zn(OTf)_2$	Toluene	130	1:1.3	100	84
7	$Zn(OTf)_2$	Toluene	140	1:1.3	100	78
8	$Yb(OTf)_3$	Dioxane	120	1:1.3	<5	<5
9	AgOTf	Dioxane	120	1:1.3	52	22
10	$Zn(OTf)_2$	Toluene	120	1:2	100	87
11	$Zn(OTf)_2$	Toluene	120	1:1	100	76

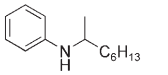
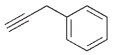
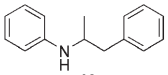
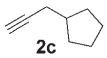
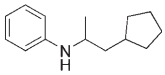
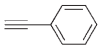
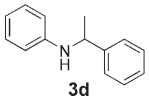
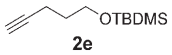
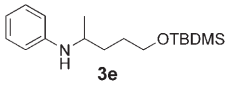
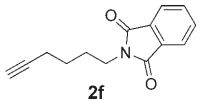
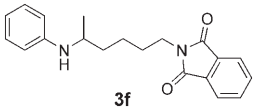
[a] Reaction conditions: 1) **2a** (1 mmol), **1a** (1–2 mmol), catalyst (5 mol%), solvent (2 mL), 24 h; 2) reduction: $NaBH_3CN$ (2 mmol), $ZnCl_2$ (1 mmol), MeOH (5 mL), 20 h, room temperature. [b] Determined by GC with dodecane as internal standard.

conversion, subsequent reduction using zinc-modified $NaBH_3CN$ in methanol at room temperature gave the secondary amine **3a**.[11] As a result of the highly selective Markovnikov functionalization, the branched isomer is produced with excellent regioselectivity (>99%) and yield.

To our delight, the model reaction proceeded in 68% yield in the presence of 5 mol% $Zn(OTf)_2$ at 100 °C. However, by applying $ZnCl_2$ under similar reaction conditions we obtained only a low conversion and yield (Table 1, entry 2). Besides these zinc salts, we tested $Yb(OTf)_3$ and AgOTf, which gave low product yields (Table 1, entries 8 and 9). By changing the solvent from THF to toluene, the yield increased to 76% (Table 1, entry 3). Also by changing the temperature from 100 °C to 120 °C in toluene as well as in dioxane, the product yield was further increased (Table 1, entries 4 and 5). However, above 120 °C the yield decreased (Table 1, entries 6 and 7). Variation of the ratio of 1-octyne to aniline had no significant impact on the product yield (Table 1, entries 4, 10, and 11).

Next, we studied the scope and limitations of our novel procedure with different alkynes (Table 2). For this purpose, we

Table 2. Reaction of aniline (**1a**) with different alkynes **2**.[a]

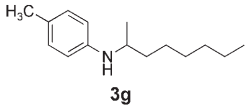
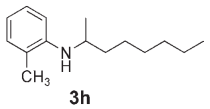
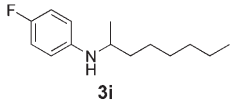
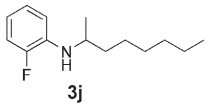
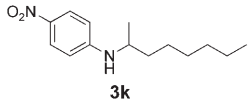
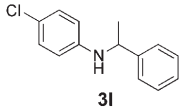
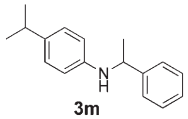
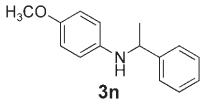
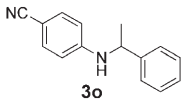
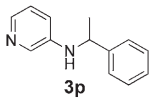
Entry	Alkyne	Hydroamination product	Yield [%][b]
1	 **2a**	 **3a**	78
2	 **2b**	 **3b**	99
3	 **2c**	 **3c**	98
4	 **2d**	 **3d**	98
5	 **2e**	 **3e**	86
6	 **2f**	 **3f**	77

[a] Reaction conditions: 1) alkyne **2** (1.5 mmol), aniline (**1a**; 1.95 mmol), $Zn(OTf)_2$ (5 mol%), toluene (2 mL), 24 h, 120 °C; 2) reduction: $NaBH_3CN$ (3 mmol), $ZnCl_2$ (1.5 mmol), MeOH (8 mL), 20 h, room temperature. [b] Yield of isolated product.

studied the reaction of aniline (**1a**) with various alkynes **2a–f** in the presence of 5 mol% $Zn(OTf)_2$. After hydroamination and in situ reduction, it was possible to isolate the secondary amines **3a–f** in good to excellent yields. As shown in Table 2, reaction of aniline with substituted alkynes such as 3-phenyl-1-propyne (**2b**), 3-cyclopentyl-1-propyne (**2c**), and phenylacetylene (**2d**) proceeded to give the products with up to 99% yield (Table 2). Also functionalized alkynes, such as 1-*tert*-butyldimethylsilyloxy-4-pentyne (**2e**) and *N*-(5-hexynyl)phthalimide (**2f**), gave the corresponding secondary amines in yields of 86% (**3e**) and 77% (**3f**), respectively.

The generality of the new zinc-catalyzed procedure was demonstrated by using different substituted aniline derivatives **1** with one aliphatic (1-octyne) and one aromatic alkyne (phenylacetylene). In general, hydroaminations of 1-octyne were more difficult. Here, products **3g–k** were obtained in 51–67% yield (Table 3, entries 1–5). The results reveal only a small substituent effect. Reaction of phenylacetylene with different ani-

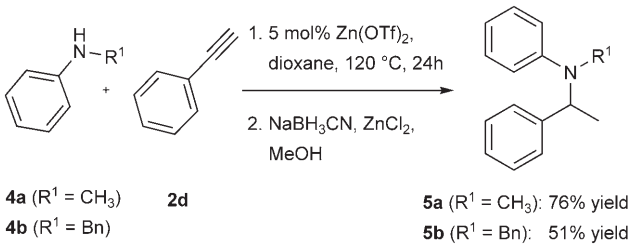
Table 3. Hydroamination of 1-octyne (**2a**) and phenylacetylene (**2d**) with various substituted anilines **1**.[a]

Entry	Hydroamination product	Yield [%][b]
1	 **3g**	58
2	 **3h**	67
3	 **3i**	66
4	 **3j**	51
5	 **3k**	67
6	 **3l**	95
7	 **3m**	97
8	 **3n**	91
9[c]	 **3o**	93
10	 **3p**	77

[a] Reaction conditions: 1) alkyne **2** (1.5 mmol), aniline derivatives **1** (1.95 mmol), $Zn(OTf)_2$ (5 mol%), toluene (2 mL), 24 h, 120 °C; 2) reduction: $NaBH_3CN$ (3 mmol), $ZnCl_2$ (1.5 mmol), MeOH (8 mL), 20 h, room temperature. [b] Yield of isolated product. [c] Dioxane (2 mL).

line derivatives led to the secondary amines **3l**–**p** in yields of up to 97%. Notably, in contrast to most transition-metal-catalyzed hydroamination reactions, nitro- and cyano-substituted anilines are tolerated. For example, NO_2-substituted anilines showed no reaction in titanium-catalyzed aminations[12] and CN-substituted anilines reacted only in low yield.[13] In addition, methoxy- and chloro-substituted anilines as well as 3-aminopyridine gave the desired products in the presence of the zinc catalyst. In all cases, over 99% regioselectivity for the corresponding Markovnikov isomer was observed.[14]

A significant advantage of the $Zn(OTf)_2$-catalyzed hydroamination compared to similar Ti-catalyzed reactions is the reactivity of secondary amines (Scheme 4). For example, the preparation of *N*-methyl-*N*-(1-phenylethyl)aniline (**5a**) and *N*-benzyl-*N*-(1-phenylethyl)aniline (**5b**) proceeded to give the corresponding tertiary amines in moderate to good yields.



Scheme 4. Zinc-catalyzed hydroamination of phenylacetylene (**2d**) with secondary amines **4** (Bn = benzyl).

Conclusion

In summary, we have shown for the first time that easily available zinc salts are active and practical catalysts for the intermolecular hydroamination of terminal alkynes with anilines. The reactions proceed in the presence of $Zn(OTf)_2$ with excellent regioselectivity (>99%) and with high yields. Notably, no expensive catalyst and even no ligands are required for this novel environmentally friendly reaction.

Experimental Section

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka, and Acros and unless otherwise noted were used without further purification. All compounds were characterized by ^1H NMR and ^{13}C NMR spectroscopy, low- and high-resolution mass spectrometry (MS and HRMS), and FTIR spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometer. ^1H NMR chemical shifts are reported relative to the TMS signal, and the ^{13}C NMR chemical shifts are reported relative to the center of solvent resonance ($CDCl_3$: δ = 77.23 ppm (^{13}C)). EI mass spectra were recorded on an MAT 95XP spectrometer (Thermo ELECTRON CORP.). GC was performed on a Hewlett Packard HP 6890 chromatograph with a 30 m HP5 column. IR spectra were recorded on a FT-IR Nicolet 6700 (Thermo ELECTRON CORP.).

General Procedure for the Zinc-Catalyzed Hydroamination Reaction

$Zn(OTf)_2$ (27.3 mg, 0.075 mmol) was dissolved in dry toluene or dry dioxane (3 mL) in an ACE pressure tube under argon atmosphere. Then aniline (1.95 mmol) and alkyne (1.5 mmol) were added to the solution, and the reaction mixture was heated at 120 °C for 24 h. After cooling the mixture to room temperature, a suspension of $NaBH_3CN$ (188.5 mg, 3 mmol) and $ZnCl_2$ (204.4 mg, 1.5 mmol) in methanol (8 mL) was added and the mixture was stirred for 20 h at room temperature. Saturated Na_2CO_3 solution (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×20 mL), and the organic layer was dried over $MgSO_4$. The organic solvent was removed in vacuo, and the amine product was purified by column chromatography with hexane/ethyl acetate (9:1) as eluent.

N-(Octan-2-yl)aniline[13] (**3a**): 78% yield, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$ (dd, 2H, $^3J = 8.7$ Hz, $^3J = 7.2$ Hz), 6.64 (tt, 1H, $^3J = 7.2$ Hz, $^4J = 1.2$ Hz), 6.56 (dd, 2H, $^3J = 8.7$ Hz, $^4J = 1.2$ Hz), 3.47–3.41 (m, 2H), 1.59–1.27 (m, 10H), 1.16 (d, 3H, $^3J = 6.4$ Hz), 0.88 ppm (t, 3H, $^3J = 6.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.9$, 129.5, 116.9, 113.3, 48.7, 37.5, 32.1, 29.6, 26.4, 22.8, 21.0, 14.3 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 205 (10) [M^+], 190 (6), 120 (100), 106 (3), 93 (4), 77 (6), 65 (2), 41 (3). HRMS (EI): *m/z* calcd for $C_{14}H_{23}N$: 205.1825; found: 205.1828. FTIR (ATR): 3404, 3051, 2957, 2926, 2855, 1600, 1503, 1316, 1179, 1153, 993, 865, 745, 691 cm^{-1}.

N-(1-Phenylpropan-2-yl)aniline[15] (**3b**): 99% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$–7.15 (m, 7H), 6.72–6.60 (m, 3H), 3.77–3.73 (m, 1H), 2.93 (dd, 1H, $J = 4.8$ Hz, $J = 13.4$ Hz), 2.68 (dd, 1H, $J = 7.3$ Hz, $J = 13.4$ Hz), 1.14 ppm (d, 3H, $^3J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.4$, 138.7, 129.7, 129.6, 128.5, 126.5, 117.4, 113.5, 49.5, 42.5, 20.4 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 211 (10) [M^+], 120 (100), 104 (2), 91 (6), 77 (6), 65 (2). HRMS (EI): *m/z* calcd for $C_{15}H_{17}N$: 211.1356; found: 211.1362. FTIR (ATR): 3403, 3052, 3025, 2965, 2924, 1599, 1502, 1452, 1429, 1315, 1254, 1178, 1152, 1091, 1029, 993, 867, 744, 690 cm^{-1}.

N-(1-Cyclopentylpropan-2-yl)aniline (**3c**): 98% yield, pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$ (dd, 2H, $^3J = 8.4$ Hz, $^3J = 7.2$ Hz), 6.65 (tt, 1H, $^3J = 7.2$ Hz, $^4J = 0.9$ Hz), 6.56 (dd, 2H, $^3J = 8.7$ Hz, $^4J = 0.9$ Hz), 3.48 (q, 1H, $^3J = 6$ Hz), 1.97–1.06 (m, 11H), 1.17 ppm (d, 3H, $^3J = 6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.9$, 129.5, 116.9, 113.2, 48.0, 44.1, 37.4, 33.3, 32.9, 25.3, 25.1, 21.3 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 203 (10) [M^+], 188 (4), 120 (100), 106 (2), 93 (5), 77 (7), 65 (2), 41 (4). HRMS (EI): *m/z* calcd for $C_{14}H_{21}N$: 203.1669; found: 203.1664. FTIR (ATR): 3404, 3051, 3017, 2974, 2865, 1599, 1502, 1451, 1426, 1375, 1317, 1255, 1178, 1152, 1076, 1029, 993 864, 744, 690 cm^{-1}.

N-(1-Phenylethyl)aniline[13] (**3d**): 98% yield, pale orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$–7.28 (m, 4H), 7.24–7.18 (m, 1H), 7.08 (dd, 2H, $^3J = 8.7$ Hz, $^3J = 7.5$ Hz), 6.63 (tt, 1H, $^3J = 7.5$ Hz, $^4J = 1.2$ Hz), 6.50 (dd, 2H, $^3J = 8.7$ Hz, $^4J = 1.2$ Hz), 4.47 (q, 1H, $^3J = 6$ Hz), 1.50 ppm (d, 3H, $^3J = 6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.4$, 145.4, 129.3, 128.8, 127.1, 126.0, 117.4, 113.5, 53.6, 25.2 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 197 (43) [M^+], 182 (100), 120 (9), 105 (74), 93 (50), 77 (41), 65 (6), 51 (11). HRMS (EI): *m/z* calcd for $C_{14}H_{15}N$: 197.1199; found: 197.1197. FTIR (ATR): 3409, 3051, 3022, 2965, 2923, 2866, 1599, 1502, 1448, 1427, 1315, 1278, 1256, 1205, 1179, 1139, 1076, 1029, 991, 868, 745, 690 cm^{-1}.

N-(5-(*tert*-Butyldimethylsilyloxy)pentan-2-yl)aniline (**3e**): 86% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.15$ (dd, 2H, $^3J = 8.4$ Hz, $^3J = 7.2$ Hz), 6.65 (tt, 1H, $^3J = 7.2$ Hz, $^4J = 0.8$ Hz), 6.56 (dd, 2H, $^3J = 8.4$ Hz, $^4J = 0.8$ Hz), 3.62 (t, 2H, $^3J = 6.0$ Hz), 3.48 (q, 1H, $^3J = 6.0$ Hz), 1.62–1.48 (m, 4H), 1.17 (d, 3H, $^3J = 6.0$ Hz), 0.89 (s, 9H), 0.05 ppm (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.9$, 129.5, 117.0, 113.3, 63.3, 48.5, 33.6, 29.6, 26.2, 21.1, 18.6, −5.1 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 293 (25) [M^+], 236 (11), 150 (33), 143 (12), 120 (100), 101 (10), 77 (12), 75 (19), 59 (5), 41 (7). HRMS (EI): *m/z* calcd for $C_{17}H_{31}NOSi$: 293.2169; found: 293.2174. FTIR (ATR): 3400, 2953, 2927, 2856, 1601, 1504, 1471, 1471, 1428, 1360, 1317, 1253, 1179, 1154, 1091, 1005, 938, 832, 773, 745, 690, 661 cm^{-1}.

N-(5-(Phenylamino)hexyl)phthalimide (**3f**): 77% yield, pale yellow solid, m.p.: 60–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$ (dd, 2H, $^3J = 5.4$ Hz, $^4J = 3.0$ Hz), 7.69 (dd, 2H, $^3J = 5.4$ Hz, $^4J = 3.0$ Hz), 7.13 (dd, 2H, $^3J = 8.7$ Hz, $^3J = 7.5$ Hz), 6.63 (tt, 1H, $^3J = 7.5$ Hz, $^4J = 1.2$ Hz), 6.54 (dd, 2H, $^3J = 8.7$ Hz, $^4J = 1.2$ Hz), 3.69 (t, 2H, $^3J = 6.6$ Hz), 3.44 (q, 1H, $^3J = 6.3$ Hz), 1.75–1.39 (m, 6H), 1.16 ppm (d, 3H, $^3J = 6.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.7$, 147.7, 134.0, 132.3, 129.3, 123.4, 116.9, 115.2, 48.4, 37.9, 36.7, 28.7, 23.5, 21.0 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 322 (11) [M^+], 307 (3), 160 (11), 120 (100), 104 (4), 93 (3), 77 (9), 65 (2), 51 (1). HRMS (EI): *m/z* calcd for $C_{20}H_{22}N_2O_2$: 322.1676; found: 322.1671. FTIR (ATR): 3452, 3378, 3023, 2952, 2929, 2863, 1765, 1703, 1599, 1513, 1496, 1436, 1399, 1369, 1333, 1258, 1218, 1153, 1062, 1034, 1010, 909, 861, 793, 746, 721, 711, 691 cm^{-1}.

4-Methyl-*N*-(octan-2-yl)aniline[13] (**3g**): 58% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (d, 2H, $^3J = 8.4$ Hz), 6.50 (dd, 2H, $^3J = 8.4$ Hz), 3.40 (q, 1H, $^3J = 6.4$ Hz), 2.23 (s, 3H), 1.58–1.27 (m, 10H), 1.15 (d, 3H, $^3J = 6.4$ Hz), 0.88 ppm (t, 3H, $^3J = 6.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 145.6$, 130.0, 126.3, 113.6, 49.1, 37.5, 32.1, 29.6, 26.4, 22.9, 21.0, 20.6, 14.3 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 219 (12) [M^+], 204 (7), 134 (100), 106 (4), 91 (5), 77 (2), 65 (2), 41 (3). HRMS (EI): *m/z* calcd for $C_{15}H_{25}N$: 219.1982; found: 219.1980. FTIR (ATR): 3404, 2956, 2924, 2855, 1618, 1517, 1456, 1376, 1316, 1300, 1248, 1181, 1156, 1119, 804, 723 cm^{-1}.

2-Methyl-*N*-(octan-2-yl)aniline[13] (**3h**): 67% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.12$–7.08 (m, 1H), 7.05–7.02 (m, 1H), 6.62–6.58 (m, 2H), 3.49 (q, 1H, $^3J = 6.4$ Hz), 3.28 (br s, 1H), 2.11 (s, 3H), 1.57–1.28 (m, 10H), 1.19 (d, 3H, $^3J = 6.4$ Hz), 0.88 ppm (t, 3H, $^3J = 6.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 145.8$, 130.4, 127.3, 121.8, 116.4, 110.2, 48.5, 37.5, 32.1, 29.6, 26.4, 22.8, 21.2, 17.8, 14.3 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 219 (11) [M^+], 204 (7), 134 (100), 106 (4), 91 (6), 77 (2), 65 (2), 41 (3). HRMS (EI): *m/z* calcd for $C_{15}H_{25}N$: 219.1982; found: 219.1986. FTIR (ATR): 3430, 2956, 2925, 2855, 1606, 1585, 1510, 1444, 1376, 1314, 1259, 1162, 1051, 985, 918, 741, 714 cm^{-1}.

4-Fluoro-*N*-(octan-2-yl)aniline[13] (**3i**): 66% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.88$–6.83 (m, 1H), 6.52–6.48 (m, 1H), 3.36 (q, 1H, $^3J = 6.1$ Hz), 3.26 (br s, 1H), 1.57–1.28 (m, 10H), 1.14 (d, 3H, $^3J = 6.3$ Hz), 0.88 ppm (t, 3H, $^3J = 7.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.5$ ($J = 232.7$ Hz), 144.3 ($J = 1.6$ Hz), 115.8 ($J = 22.1$ Hz), 114.2 ($J = 6.6$ Hz), 49.5, 37.4, 32.1, 29.6, 26.3, 22.9, 21.0, 14.3 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 223 (9) [M^+], 208 (5), 138 (100), 111 (4), 95 (3), 83 (2), 55 (2), 41 (3). HRMS (EI): *m/z* calcd for $C_{14}H_{22}NF$: 223.1731; found: 223.1729. FTIR (ATR): 3415, 2957, 2926, 2855, 1613, 1506, 1457, 1402, 1377, 1314, 1218, 1154, 1098, 816, 768, 724 cm^{-1}.

2-Fluoro-*N*-(octan-2-yl)aniline (**3j**): 51% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.99$–6.92 (m, 2H), 6.69–6.65 (m, 1H), 6.59–6.54 (m, 1H), 3.68 (br s, 1H), 3.46 (q, 1H, $^3J = 6.3$ Hz), 1.61–1.24 (m, 10H), 1.19 (d, 3H, $^3J = 6.3$ Hz), 0.88 ppm (t, 3H, $^3J = 7.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.8$ ($J = 236.1$ Hz), 136.4 ($J = 11.0$ Hz), 124.7 ($J = 3.0$ Hz), 116.0 ($J = 7.1$ Hz), 114.6 ($J = 18.6$ Hz), 112.6 ($J = 3.5$ Hz), 48.8, 37.8, 32.3, 29.9, 26.4, 23.2, 21.2, 14.5 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 223 (9) [M^+], 208 (4), 138 (100), 111 (5), 91 (2), 83 (2), 55 (2), 41 (3). HRMS (EI): *m/z* calcd for $C_{14}H_{22}NF$: 223.1731; found: 223.1729. FTIR (ATR): 3433, 2957, 2926, 2856, 1619, 1511, 1455, 1377, 1335, 1295, 1249, 1187, 1160, 1095, 1035, 911, 834, 789, 735 cm^{-1}.

4-Nitro-*N*-(octan-2-yl)aniline[16] (**3k**): 67% yield, pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$ (d, 2H, $^3J = 9.2$ Hz), 6.49 (d, 2H, $^3J = 9.3$ Hz), 4.39 (br s, 1H), 3.58–3.54 (m, 1H), 1.66–1.26 (m, 10H, 1.22 (d, 3H, $^3J_{2,9} = 6.4$ Hz), 0.88 ppm (t, 3H, $^3J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.0$, 137.6, 126.8, 111.3, 48.8, 37.1, 31.9, 29.4, 26.2, 22.8, 20.7, 14.3 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 250 (12) [M^+], 220 (17), 205 (6), 165 (100), 135 (71), 119 (26), 97 (7), 83 (8), 69 (12), 57 (15), 43 (12). HRMS (EI): *m/z* calcd for $C_{14}H_{22}N_2O_2$: 250.1676; found: 250.1682. FTIR (ATR): 3361, 2956, 2926, 2855,

1597, 1519, 1501, 1466, 1377, 1291, 1273, 1184, 1155, 1106, 996, 830, 753, 724, 694, 662 cm^{-1}.

4-Chloro-*N*-(1-phenylethyl)aniline[17] (**3l**): 95% yield, pale yellow solid, m.p.: 55–57 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5H), 7.02 (d, 2H, ^3J = 9.0 Hz), 6.41 (d, 2H, ^3J = 9.0H), 4.43 (q, 1H, ^3J = 7.2 Hz), 4.04 (br s, 1H), 1.50 ppm (d, 3H, ^3J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 144.9, 129.1, 128.9, 127.3, 126.0, 122.0, 114.6, 53.8, 25.1 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 231 (34) [M^+], 216 (50), 127 (37), 105 (100), 90 (8), 77 (21), 63 (4), 51 (6). HRMS (EI): *m/z* calcd for $C_{14}H_{14}NCl$: 231.0809; found: 231.0812. FTIR (ATR): 3404, 3028, 2974, 2953, 2916, 2888, 2862, 1853, 1598, 1496, 1445, 1371, 1356, 1312, 1291, 1278, 1253, 1208, 1176, 1142, 1093, 1006, 947, 913, 809, 759, 703 cm^{-1}.

4-Isopropyl-*N*-(1-phenylethyl)aniline (**3m**): 97% yield, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 4H), 7.24–7.19 (m, 1H), 6.95 (d, 2H, ^3J = 8.3 Hz), 6.45 (d, 2H, ^3J = 8.5 Hz), 4.43 (q, 1H, ^3J = 6.7 Hz), 2.76–2.72 (m, 1H), 1.49 (d, 3H, ^3J = 6.7 Hz), 1.16 ppm (d, 6H, ^3J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.7, 145.6, 137.9, 128.8, 127.2, 127.0, 126.1, 113.4, 54.0, 33.3, 25.3, 24.4 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 239 (51) [M^+], 224 (100), 208 (7), 162 (4), 135 (5), 120 (59), 105 (49), 91 (7), 77 (16), 65 (3), 51 (3), 39 (2). HRMS (EI): *m/z* calcd for $C_{17}H_{21}N$: 239.1669; found: 239.1674. FTIR (ATR): 3408, 3059, 3022, 2956, 2924, 2866, 1614, 1515, 1448, 1408, 1371, 1315, 1288, 1253, 1186, 1140, 1053, 1016, 942, 817, 759, 698 cm^{-1}.

4-Methoxy-*N*-(1-phenylethyl)aniline[18] (**3n**): 91% yield, pale yellow solid, m.p.: 54–56 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 4H), 7.23–7.18 (m, 1H), 6.68 (d, 2H, ^3J = 9.0 Hz), 6.46 (d, 2H, ^3J = 9.0H), 4.40 (q, 1H, ^3J = 6.6 Hz), 3.68 (s, 3H), 1.49 ppm (d, 3H, ^3J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1, 145.6, 141.7, 128.8, 127.0, 126.1, 114.9, 114.8, 55.9, 54.5, 25.3 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 227 (89) [M^+], 212 (100), 168 (7), 123 (51), 105 (82), 95 (5), 77 (25), 63 (5), 51 (7). HRMS (EI): *m/z* calcd for $C_{15}H_{17}NO$: 227.1305; found: 227.1307. FTIR (ATR): 3376, 3005, 2982, 2962, 2920, 2861, 2836, 1617, 1504, 1451, 1368, 1353, 1302, 1269, 1231, 1178, 1142, 1108, 1081, 1030, 944, 852, 814, 750, 697, 655 cm^{-1}.

4-(1-Phenylethylamino)benzonitrile[19] (**3o**): 93% yield, pale yellow solid, m.p.: 98–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 7H), 6.46 (d, 2H, ^3J = 8.9 Hz), 4.61 (br s, 1H), 4.54–4.50 (m, 1H), 1.55 ppm (d, 3H, ^3J = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 143.8, 133.8, 129.1, 127.6, 125.8, 120.6, 113.1, 99.0, 53.3, 24.9 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 222 (22) [M^+], 207 (30), 129 (8), 118 (13), 105 (100), 95 (4), 77 (14), 69 (12), 57 (17), 41 (12). HRMS (EI): *m/z* calcd for $C_{15}H_{14}N_2$: 222.1152; found: 222.1148. FTIR (ATR): 3374, 3347, 3032, 2966, 2925, 2868, 2208, 1602, 1524, 1451, 1374, 1342, 1280, 1207, 1171, 1143, 1090, 1027, 944, 906, 826, 812, 756, 696 cm^{-1}.

3-(2-Phenylethylamino)pyridine (**3p**): 77% yield, white solid, m.p.: 105–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, 1H, ^4J = 2.7 Hz), 7.88 (dd, 1H, ^3J = 4.8 Hz, ^4J = 1.5 Hz), 7.35–7.22 (m, 5H), 6.95 (dd, 1H, ^3J = 4.8 Hz, ^3J = 8.4 Hz), 6.69 (ddd, 1H, ^3J = 8.4 Hz, ^4J = 2.7 Hz, ^4J = 1.5 Hz), 4.43 (m, 1H), 4.17 (br s, 1H), 1.53 ppm (d, 3H, ^3J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 143.4, 138.8, 136.8, 129.0, 127.4, 125.9, 123.8, 119.2, 53.5, 25.2 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 198 (65) [M^+], 183 (83), 121 (7), 105 (100), 94 (50), 77 (18), 67 (3), 51 (8). HRMS (EI): *m/z* calcd for $C_{13}H_{14}N_2$: 198.1152; found: 198.1155. FTIR (ATR): 3230, 3151, 3094, 3033, 2966, 2922, 2879, 1590, 1528, 1475, 1447, 1413, 1346, 1299, 1245, 1204, 1143, 1108, 1089, 1014, 946, 797, 765, 700 cm^{-1}.

N-Methyl-*N*-(1-phenylethyl)aniline (**5a**): 76% yield, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 4H), 7.27–7.22 (m, 3H), 6.85–6.82 (m, 2H), 6.75–6.70 (m, 1H), 5.13 (q, 1H, ^3J = 6.9 Hz), 2.67 ppm (s, 3H), 1.54 (d, 3H, ^3J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.4, 143.0, 129.4, 128.6, 127.2, 127.1, 116.8, 113.3, 56.7, 32.1, 16.5 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 211 (41) [M^+], 196 (100), 180 (10), 134 (18), 105 (89), 91 (5), 77 (42), 65 (3), 51 (10), 39 (4). HRMS (EI): *m/z* calcd for $C_{15}H_{17}N$: 211.1356; found: 211.1355. FTIR (ATR): 3059, 3025, 2972, 2933, 2874, 2814, 1595, 1501, 1446, 1370, 1309, 1214, 1156, 1110, 1026, 990, 906, 861, 745, 721, 690 cm^{-1}.

N-Benzyl-*N*-(1-phenylethyl)aniline[20] (**5b**): 51% yield, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.10 (m, 12H, 6.77–6.66 (m, 3H), 5.26 (q, 1H, ^3J = 7.0 Hz), 4.47 (dd, 2H, J = 7.6 Hz), 1.58 ppm (d, 3H, ^3J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.4, 143.0, 140.3, 129.2, 128.7, 128.5, 127.1, 127.1, 126.6, 117.3, 114.3, 57.2, 50.5, 19.0 ppm. MS (EI, 70 eV): *m/z* (rel. int.): 287 (48) [M^+], 272 (73), 210 (7), 183 (43), 105 (82), 91 (100), 77 (43), 65 (11), 51 (10), 39 (3). HRMS (EI): *m/z* calcd for $C_{21}H_{21}N$: 287.1669; found: 287.1667. FTIR (ATR): 3057, 3022, 2982, 2924, 2876, 2853, 1594, 1501, 1451, 1389, 1332, 1294, 1254, 1203, 1165, 1074, 1025, 987, 918, 885, 865, 772, 732, 689 cm^{-1}.

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3.10 Zn-Catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination

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Zinc-Catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination

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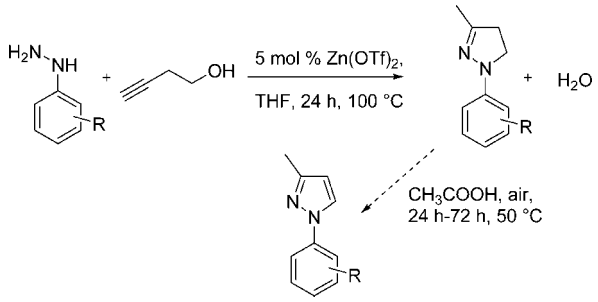
ABSTRACT



A novel regioselective synthesis of aryl-substituted pyrazolines and pyrazoles has been developed. Substituted phenylhydrazines react with 3-butynol in the presence of a catalytic amount of zinc triflate to give pyrazoline derivatives. The resulting products are easily oxidized in a one-pot procedure to the corresponding pyrazoles.

Pyrazoline and pyrazole derivatives play an important role in the pharmaceutical and agrochemical industries. For example, pyrazolines have been reported to show a wide range of biological activity, including antidepressant, anticancer, and antibacterial activity.[1] On the other hand, the pyrazole motif is found in blockbuster drugs such as celecobix (Celebrex),[2] sildenafil (Viagra),[3] and rimonabant (Acomplia).[4]

In general, pyrazoles are obtained by condensation of 1,3-diketones with hydrazine derivatives.[5] Unfortunately, this reaction often results in a mixture of regioisomers. Notably, the use of α,β-unsaturated ketones with hydrazines presents a modification of the common method, wherein pyrazole and pyrazoline derivatives can be synthesized with high regioselectivity.[6] In addition, several other methods have also been reported for the preparation of pyrazoles.[7]

In recent years, catalytic processes have also become of interest. In this regard, Buchwald et al. demonstrated an elegant copper-catalyzed domino coupling/hydroamidation reaction,[8] and Mori et al. developed an efficient palladium-catalyzed four-component coupling[9] for the synthesis of pyrazoles.

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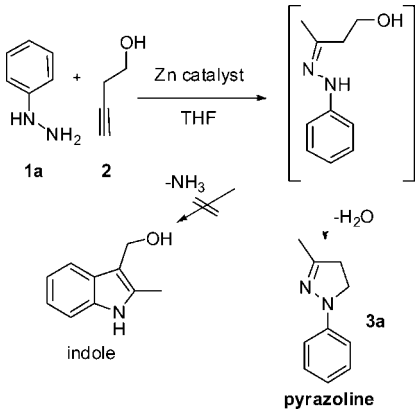
Over the past years, we investigated catalytic reactions of arylhydrazines with alkynes in more detail.[10] Most recently, we succeeded in an intermolecular zinc-mediated and -catalyzed hydrohydrazination reaction of alkynes, which allows a general synthesis of substituted indoles.[11] Following these investigations, we discovered that the reaction of phenylhydrazine **1a** with 3-butynol **2** in the presence of a stochiometric amount of zinc chloride did not result in the expected indole motif. Instead, the formation of the pyrazoline **3a** occurred via hydrohydrazination of the alkyne and condensation reaction (Scheme 1).

Scheme 1. Synthesis of Pyrazoline **3a**



Apparently, in the first step the hydrohydrazination of 3-butynol gave the corresponding arylhydrazone. In general, the arylhydrazone undergoes Fischer indole cyclization in the presence of a stochiometric amount of Lewis acid, such as $ZnCl_2$.[11] However, in the case of 3-butynol, the pyrazoline was formed by an unusual nucleophilic substitution of the hydroxy group.

To study this novel pyrazoline formation in more detail, we investigated the influence of different catalysts, solvents, and temperatures on the reaction of phenylhydrazine **1a** with 3-butynol **2**. Selected results are presented in Table 1. The model reaction proceeded in excellent yield (93%) in the presence of a stochiometric amount of $ZnCl_2$ (Table 1, entry 1). Unfortunately, when 5 mol % of $ZnCl_2$ was used, only 36% yield was observed. Similarly, in the presence of a catalytic amount of $Zn(OAc)_2$ we obtained only low conversion and yield (Table 1, entry 2). To our delight applying 5 mol % $Zn(OTf)_2$ an excellent product yield (98%) was observed (Table 1, entry 3). Dioxane gave a somewhat lower yield compared to tetrahydrofuran and toluene as solvent (Table 1, entries 4 and 5). Also in the presence of a stoichiometric amount of phenylhydrazine a high product yield was obtained (Table 1, entry 10).

Table 1. Reaction of Phenylhydrazine **1a** with 3-Butynol **2** under Different Conditions[a]

entry	catalyst	solvent	T (°C)	time (h)	conv[b] (%)	yield[b] (%)
1	$ZnCl_2$	THF	100	24	67 (100[c])	36 (93[c])
2	$Zn(OAc)_2$	THF	100	24	26	12
3	$Zn(OTf)_2$	THF	100	24	100	98
4	$Zn(OTf)_2$	dioxane	100	24	63	57
5	$Zn(OTf)_2$	toluene	100	24	100	96
6	$Zn(OTf)_2$	THF	80	24	64	62
7	$Zn(OTf)_2$	THF	120	24	100	93
8	$Zn(OTf)_2$	THF	100	9	85	76
9	$Zn(OTf)_2$	THF	100	16	94	94
10[d]	$Zn(OTf)_2$	THF	100	24	91	85

[a] Reaction conditions: 3-butynol (1.0 mmol), phenylhydrazine (1.3 mmol), 5 mol % of catalyst, solvent (2 mL). [b] Yield is determined by GC analysis with dodecane as internal standard. [c] 100 mol % of catalyst. [d] Phenylhydrazine (1.0 mmol).

Next, we studied reactions of 3-butynol **2** with various substituted arylhydrazines **1a**−**k** under optimized conditions in the presence of 5 mol % $Zn(OTf)_2$. In general, hydrohydrazination and condensation reactions proceeded smoothly, and it was possible to isolate the pyrazoline derivatives **3a**−**k** in good to excellent yields (Table 2).

For example, reaction of *p*-tolylhydrazine (**1b**) proceeded in 96% yield, while the more sterical hindered *o*-tolylhydrazine (**1c**) gave a lower yield of 88% (Table 2, entry 3). A similar effect was observed for the reaction of the *p*-chlorophenylhydrazine, which led to pyrazoline **3d** in 98% yield compared to the *o*-chlorophenyl-substituted pyrazoline **3e** (52% yield) (Table 2, entries 4 and 5).

In addition, bromo-, cyano-, methylsulfonyl-, and isopropylphenyl-substituted pyrazolines were synthesized in up to 99% yield (Table 2, entries 6−9). Dichloro-substituted phenylhydrazines in *para* and *meta* positions gave the corresponding pyrazolines **3j** and **3k** in 98% and 97% yields, respectively.

In agreement with previous studies the aryl-substituted pyrazolines were easily oxidized to the corresponding pyrazoles. Due to the ease of reaction conditions and environmental advantages we applied air as oxidant.[12,13] As shown in Scheme 2 after successful formation of the pyrazolines, we added acetic acid to the reaction mixture and heated the reaction mixture for additional 24−72 h in air. The reaction time depended largely on the substituent on the aryl group. While *p*-methyl- and *p*-isopropylphenyl-substituted pyrazolines were easily oxidized (Table 3, entries

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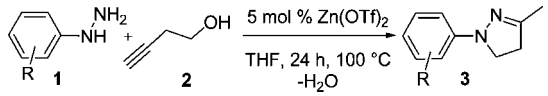
Table 2. Reaction of Arylhydrazines **1** with 3-Butynol **2** to Various Substituted Pyrazolines[a]



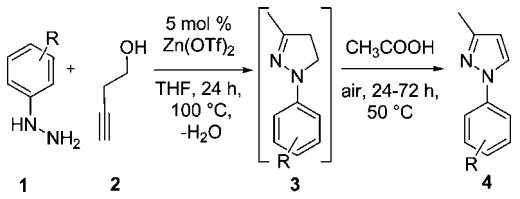
entry	hydrazine **1**	pyrazoline **3**	yield (%)[b]
1	**1a**	**3a**	96
2	**1b**	**3b**	96
3	**1c**	**3c**	88
4	**1d**	**3d**	98
5	**1e**	**3e**	52
6	**1f**	**3f**	99
7	**1g**	**3g**	96
8	**1h**	**3h**	87
9	**1i**	**3i**	99
10	**1j**	**3j**	98
11	**1k**	**3k**	97

[a] Reaction conditions: 3-butynol (1.5 mmol), phenylhydrazine derivative (1.95 mmol), 5 mol % of $Zn(OTf)_2$, THF (3 mL), 24 h, 100 °C. [b] Isolated yield.

1, 3), the more deactivated *o*-methyl- and *p*-bromophenyl-substituted pyrazolines needed a longer reaction time for full conversion (Table 3, entries 2, 4).

Interestingly, there was no significant difference in yield between the synthesis of the pyrazoles by one-pot or sequential reactions. For example, **4a** was obtained in 56% yield by adding acetic acid directly to the reaction mixture compared to 61% yield observed with the pure pyrazoline **3b** (Table 3, entry 1). Advantageously, a purification of the reaction mixture is not necessary for the direct synthesis of pyrazoles **4**. Notably, when 4-pentynol instead of 3-butynol

Scheme 2. One-Pot Formation of the Pyrazoles



is used, indole derivatives are obtained via a domino amination−cyclization sequence. Apparently, in the case of 3-butynol, the formation of the five-membered ring is preferred compared to the Fischer indole cyclization.

Table 3. Synthesis of Different Pyrazole Derivatives Starting from Phenylhydrazines **1** and 3-Butynol **2**[a]

entry	pyrazole **4**	time (h)	yield (%)[b]
1	**4a**	24	56 (61[c])
2	**4b**	48	48 (60[c])
3	**4c**	24	63
4	**4d**	72	67

[a] Reaction conditions: (step 1) 3-butynol (1.5 mmol), phenylhydrazine derivative (1.95 mmol), 5 mol % of $Zn(OTf)_2$, THF (3 mL), 24 h, 100 °C; (step 2) CH_3COOH, air, 24−72 h, 50 °C. [b] Isolated yield. [c] Yield only for the last step using the purified pyrazoline as educt.

In summary, we have developed a novel method for the synthesis of aryl-substituted pyrazolines and pyrazoles. Various substituted arylhydrazines react with 3-butynol in the presence of a catalytic amount of $Zn(OTf)_2$ to give pyrazoline derivatives in excellent yields. Subsequent one-pot oxidation with air led to the corresponding pyrazoles. This methodology is complementary to the classical pyrazoline synthesis from hydroxy ketones.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data of all compounds mentioned in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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3.11 First Synthesis of 4,5-Dihydro-3(2*H*)-pyridazinones via Zn-mediated Hydrohydrazination

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Contributions: In this paper, I was involved in planning the experiments, the discussion and argumentation of the results and contributed significantly to the draft of the manuscript. My contribution as co-author of this paper is approximately 10%.

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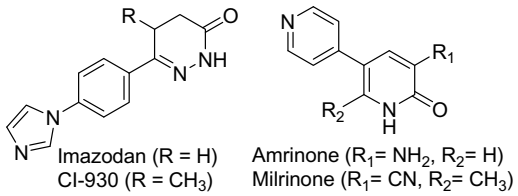
ABSTRACT

The hydrohydrazination of 4-pentynoic acid with different arylhydrazines proceeds smoothly in the presence of zinc chloride. The domino amination–amidation sequence leads to aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones.

Pyridazines represent an important class of biologically active compounds.[1] Especially pyridazinone derivatives are well known for their treatment in cardiovascular and heart diseases because of their blood pressure reduction properties as well as platelet-aggregation-inhibition and cardiotonic effects.[2] Besides, aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones such as imazodan are reported to show ionotropic properties comparable to milrinone and amrinone (Scheme 1).[3]

In general, the synthesis of 4,5-dihydro-3(2*H*)-pyridazinones proceeds via reaction of γ-ketoacids and their derivatives with alkylhydrazines or phenylhydrazines to give the corresponding hydrazones.[4] The resulting hydrazones are known to be converted by a simple condensation reaction to pyridazinones.[5] Other syntheses of pyridazinones are based for example on condensation of Wittig reagents with arylhydrazones or condensation of α-keto-esters with hydrazinocarbonyl-acetic acid esters.[6]

For some time, we have been involved in catalytic intermolecular hydroamination reactions of alkynes with amines[7,8] and arylhydrazines (hydrohydrazination).[9] Notably, in these domino reactions alkynes behave somewhat similar to carbonyl compounds. Indeed, imines as well as interesting heterocycles such as indoles[9,10] and pyrazolines[11] are directly available from alkynes. Most recently, we demonstrated that zinc chloride and zinc triflate are especially well-suited as catalysts for such reactions of terminal alkynes.[12]

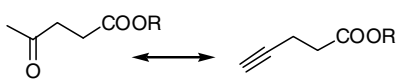


Scheme 1. Selected examples of biologically active pyridazinones.

With respect to the analogy of alkynes and carbonyl compounds, we thought that 4-pentynoic acid derivatives should behave similar to γ-ketoacid derivatives (Scheme 2).

Based on this idea, herein we describe for the first time the synthesis of different aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones from alkynes.

To our delight, the reaction of phenylhydrazine (**1a**) with 4-pentynoic acid (**2**) in the presence of 1 equiv $ZnCl_2$ resulted in the formation of the corresponding pyridazinone **3a** (Scheme 3). In agreement with previous work the hydrohydrazination reaction proceeds with complete regioselectivity toward the Markovnikov product.[13]



Scheme 2. Analogy of γ-ketoacids and 4-pentynoic acid.

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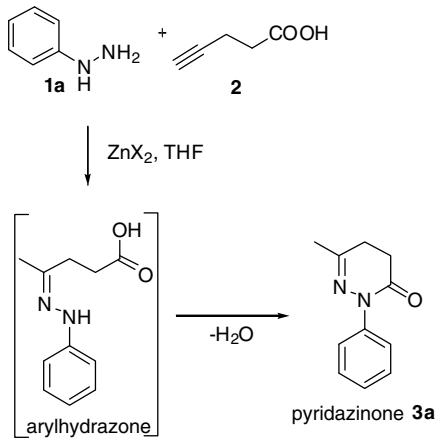


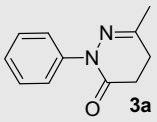
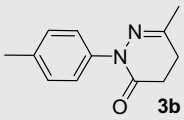
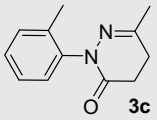
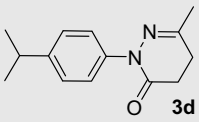
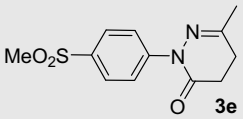
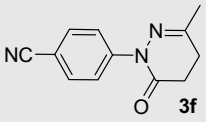
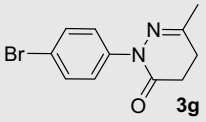
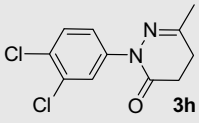
Scheme 3. Synthesis of pyridazinone **3a**.

In order to study this novel pyridazinone formation in more detail, we examined the influence of different reaction conditions (variation of Lewis acids, solvents, temperature), and changes in reaction time on the reaction of phenylhydrazine (**1a**) with 4-pentynoic acid (**2**). Selected results are presented in Table 1.

Initially, we investigated the effects of different Zn salts as well as $Yb(OTf)_3$ or $FeCl_3$ as Lewis acids. All the Zn salts showed full conversion and the best yield (81%) is obtained applying $Zn(OTf)_2$ (Table 1, entries 1–5). Increasing the amount of $Zn(OTf)_2$ from 1 equiv to 3 equiv the yield dropped down (Table 1, entries 1 and 8). Advantageously, using 3 equiv of $ZnCl_2$ the desired product is observed in 90% yield (Table 1, entry 7). It is important to note that applying catalytic amounts of zinc salts gave significantly lower yields. The necessity to apply stoichiometric amounts of the Zn salt is explained due to deactivation by the product similar to Friedel–Crafts acylation reactions.[14] As solvents, dioxane and toluene gave a much lower yield compared to tetrahydrofuran (Table 1, entries 9 and 10). In general, the alkyne is consumed relatively fast, but the best yields are obtained after 24 h (Table 1, entries 11 and 12). Apparently, the intramolecular amidation reaction seems to be the rate-determining step. By comparing the stoichiometric ratio of the starting materials the highest product yield is obtained with a slight excess of phenylhydrazine (Table 1, entries 7, 13, and 14).

Next, we studied reactions of 4-pentynoic acid (**2**) with substituted arylhydrazines **1** under optimized conditions in the presence of the cheap and easily available $ZnCl_2$. After Zn-mediated hydrohydrazination and subsequent condensation reactions, it is possi-

Table 2
Reaction of arylhydrazines **1** with 4-pentynoic acid (**2**) to various aryl-substituted pyridazinones **3**[a]

Entry	Pyridazinone **3**	Yield[b] (%)
1	 **3a**	72
2	 **3b**	61
3	 **3c**	47
4	 **3d**	64
5	 **3e**	53
6	 **3f**	67
7	 **3g**	71
8	 **3h**	57

[a] Reaction conditions: 4-pentynoic acid (1.5 mmol), arylhydrazine (1.95 mmol), 3 equiv $ZnCl_2$, THF (3 mL), 24 h, 100°C.
[b] Isolated yield.

Table 1
Reaction of phenylhydrazine (**1a**) with 4-pentynoic acid (**2**) under different conditions[a]

Entry	Lewis acid	Equiv	Solvent	Time (h)	Ratio (alkyne:hydrazine)	Conversion[b] (%)	Yield[b] (%)
1	$Zn(OTf)_2$	1	THF	24	1:1.3	100	81
2	$Zn(OAc)_2$	1	THF	24	1:1.3	100	69
3	$Yb(OTf)_3$	1	THF	24	1:1.3	89	14
4	$FeCl_3$	1	THF	24	1:1.3	32	0
5	$ZnCl_2$	1	THF	24	1:1.3	100	56
6	$ZnCl_2$	2	THF	24	1:1.3	100	74
7	$ZnCl_2$	3	THF	24	1:1.3	100	90
8	$Zn(OTf)_2$	3	THF	24	1:1.3	100	57
9	$ZnCl_2$	3	Dioxane	24	1:1.3	100	45
10	$ZnCl_2$	3	Toluene	24	1:1.3	100	35
11	$ZnCl_2$	3	THF	9	1:1.3	100	59
12	$ZnCl_2$	3	THF	16	1:1.3	100	71
13	$ZnCl_2$	3	THF	24	1:1	100	74
14	$ZnCl_2$	3	THF	24	1:2	100	56

[a] Reaction conditions: phenylhydrazine, 4-pentynoic acid, solvent (2 mL), 100 °C.
[b] Yield and conversion were determined by GC analysis with dodecane as internal standard.

ble to isolate the pyridazinone derivatives **3a–h** directly in moderate to good yields (Table 2). For example, reaction of *p*-tolylhydrazine proceeded over both steps in 61% yield (Table 2, entry 2), while the more sterical hindered *o*-tolylhydrazine gave a lower yield of 47% (Table 2, entry 3). Compared to the *p*-tolyl-substituted pyridazinone a similar yield is observed for the *p*-isopropyl-substituted pyridazinone derivative with 64% yield (Table 2, entry 4). Besides alkyl-substituted arylhydrazines, we also tested phenylhydrazines with electron-withdrawing substituents. These methylsulfonyl-, cyano-, and 4-bromophenyl-substituted pyridazinones are synthesized in up to 71% yield (Table 2, entries 5–7). In addition, the 3,4-dichloro-substituted phenylhydrazine in *para*- and *meta*-position gave the corresponding pyridazinone **3h** in 57% yield (Table 2, entry 8).

In conclusion, we have developed a novel method for the synthesis of aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones based on domino hydrohydrazination and condensation reactions. Eight substituted arylhydrazines react with 4-pentynoic acid in the presence of $ZnCl_2$ to give the corresponding pyridazinone derivatives in a one-pot process in moderate to good yields. Notably, this convenient and practical procedure does not require any special handling, unusual reagents, and proceeds without the exclusion of air or water.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.084.

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