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

Synthesis of Biologically Active *N*-Heterocycles and Amines via Catalytic Hydroamination of Alkynes

Dissertation

zur Erlangung des akademischen Grades eines
Doktor rerum naturalium (Dr. rer. nat.)

vorgelegt der

Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

von

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geb. am 29.12.1981

Rostock, Mai 2008

urn:nbn:de:gbv:28-diss2008-0096-0

Die vorliegende Arbeit entstand in der Zeit von Oktober 2005 bis Mai 2008 am Leibniz-Institut für Katalyse e.V. an der Universität Rostock.

Einreichung der Dissertation: 02.06.2008

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Rigorosum: 19.08.2008

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Wissenschaftliches Kolloquium: 16.09.2008

Herzlicher Dank gebührt meinem hochgeschätzten Lehrer

Prof. Dr. Matthias Beller

für die Aufnahme in seine Arbeitsgruppe, das große Interesse an meiner Arbeit, die unerschöpflichen wertvollen Anregungen und für die stets gewährte wissenschaftliche Freiheit.

Besonders bedanken möchte ich mich bei *Dr. Annegret Tillack* für die herzliche Aufnahme in die Aminierungsgruppe und ihre Freundschaft. Mit ihrer stets großen Hilfsbereitschaft und ihrem fachspezifischen Wissen hat sie viel zu meiner Arbeit beigetragen.

Der bereits erwähnten Aminierungsgruppe danke ich für die unzähligen Diskussionen und die gute Zusammenarbeit: *Dirk Hollmann*, *Nicolle Schwarz*, *Sebastian Bähn*, *Dr. Anahit Pews-Davtyan* und *Kathleen Mevius*.

Allen Freunden und Kollegen danke ich für die freundliche Atmosphäre am LIKAT: *Anne Brennführer*, *Angelika Preetz*, *Stephan Enthaler*, *Anne Grotevendt*, *Bianca Bitterlich*, *Hanns-Martin Kaiser*, *Kristin Schröder*, *Henry Postleb*, *Thomas Schulz*, *Christian Torborg*, *Björn Loges*, *Christian Fischer*, *Dr. Sandra Hübner*, *Dr. Jette Kischel*, *Dr. Iliyas Sayyed*, *Dr. Vivek Khedkar*, *Cathleen Buch*, *Dr. Andrea Christiansen*, *Stefan Schulz*, *Benjamin Schäffner*, *Dr. Marko Hapke*, *Dr. Haijun Jiao*, *Dr. Ralf Jackstell*, *Dr. Henrik Junge*, *Dr. Katrin Junge*, *Dr. Alexander Zapf*, *Dr. Irina Iovel*, *Dr. Helfried Neumann*, *Dr. Holger Klein*, *Dr. Jens Holz*, *Dr. Man Kin Tse*, *Dr. Torsten Dwars* und vielen mehr.

Für die Analytik gebührt mein Dank *Dr. Dirk Michalik* für die lehrreichen NMR-Diskussionen, sowie *Dr. Christine Fischer*, *Dr. Wolfgang Baumann*, *Andreas Koch*, *Susanne Schareina*, *Susann Buchholz*, *Katrin Reincke*, *Astrid Lehmann* und *Karin Buchholz* für die Bearbeitung weiterer Analytik-Proben.

Ich danke dem Ruhepol unseres Labors *Dr. Thomas Schareina* für die interessanten Gespräche.

Dem Graduiertenkolleg 1213 danke ich für die finanzielle Unterstützung.

Der Firma Esteve danke ich für das interessante Projektthema und für die wissenschaftlichen Diskussionen mit *Dr. Jörg Holenz* und *Dr. José Luis Díaz*.

Nicht zuletzt gilt mein ganz besonderer Dank *meiner Familie* und *meinem Thomas*.

University of Rostock

Abstract

Synthesis of Biologically Active *N*-Heterocycles and Amines via Catalytic Hydroamination of Alkynes

by Karolin Krüger

Leibniz Institute for Catalysis at the University of Rostock

This thesis presents new syntheses of *N*-heterocycles and amines. Building up on our prior studies in titanium-catalyzed hydroamination of alkynes we discovered zinc salts as new hydroamination catalysts. Zinc chloride and zinc triflate were successfully applied in the intermolecular hydrohydrazination of terminal alkynes for the synthesis of various substituted indole derivatives, pyrazolines and pyrazoles as well as pyridazinones. Additional functionalization reactions on special synthesized indole structures lead to pharmaceutically and biologically interesting substances. Further achievements in the field of hydroamination of alkynes with aniline derivatives for the synthesis of secondary and tertiary amines are included.

Table of Contents

List of Abbreviations

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
boc	*tert*-Butyloxycarbonyl
t-Bu	*tert*-Butyl
i-Bu	*iso*-Butyl
$BuPAd_2$	Di-1-adamantyl-*n*-butylphosphin
Bz	Benzoyl
Cat.	Catalyst
cod	1,5-Cyclooctadiene
conv.	Conversion
Cp	Cyclopentadienyl
Cp*	Pentamethyl cyclopentadienyl
Cy	Cyclohexyl
dba	Dibenzylidene acetone
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
equiv	Equivalent
Et	Ethyl
et al.	et alii, et aliae or et alia
GC	Gas chromatography
h	Hour
HIPr	1,3-Bis-(2,6-diiso-propylphenyl)imidazolium
HMDS	Hexamethyldisilazane
L	Ligand
Me	Methyl
min	Minute
NMP	*N*-Methyl-2-pyrrolidone
o	*ortho*
OAc	Acetat
OMe	Methoxy
OTf	Triflate (trifluoromethanesulfonate)
Ph	Phenyl

Phen	Phenanthroline
i-Pr	*iso*-Propyl
R	Organic group
r. t.	Room temperature
T	Temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyl-dimethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl
X	Leaving group, halide
Xphos	2-Dicylcohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl

1 Preface

Chemistry is described as a central science, wherein phenomena are defined at a molecular level. Organic synthesis is at the heart of this science, in which development and invention of new synthetic methods and reagents are constantly enriched. With regard to chemical synthesis, "Green Chemistry" represents a central issue in the 21^{st} century. Many of the new approaches towards economically and environmentally sustainable synthesis focus on the replacement of inefficient chemical processes and the reduction of atmospheric pollution on the elimination of hazardous waste. In this respect, catalytic reagents being superior to stoichiometric reagents, much of the research activities have been devoted to the development of chemo- and biocatalyzed reactions. A state-of-the-art reaction should proceed with inexpensive, probably renewable reagents, in standard equipment to give the desired product selectively in quantitative yield with high atom economy. The catalytic synthesis of organic building blocks from cheap and available starting materials is one of the main research targets of chemists, specifically in the field of applied organic and industrial chemistry.

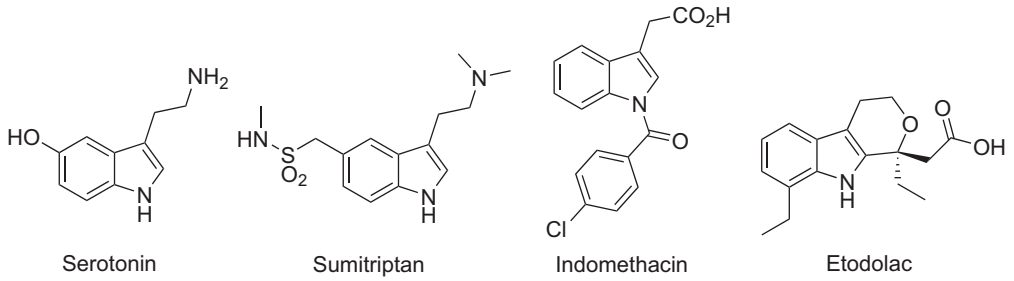
More specifically, there still exists considerable interest in the development of improved methodologies for the construction of carbon-nitrogen bonds. In this regard, the addition of nitrogen compounds across carbon-carbon multiple bonds continues to be an important subject for organic synthesis and catalysis for the design of building blocks for pharmaceutically and biologically active substances. Especially amines and their derivatives are of significant importance in human life and chemical industry. In general, these amination processes are perfectly suited to fulfil today's need of "Green Chemistry", due to the availability of substrates and 100% atom efficiency.

The present work is emphasized on the development and exploration of new methods in selective catalytic hydroamination of alkynes for the synthesis of biologically active *N*-heterocycles and amines.

2 Indoles from Alkynes

2.1 Introduction

The indole ring system is the most widely distributed heterocyclic ring system found in nature. Since indole was firstly isolated by treatment of indigo dye with oleum, its name is a combination of both words *indigo* and *oleum*. Among the numerous structurally diverse derivatives many indoles obtain biological activity such as tryptamine and tryptophol thus making the indole moiety an important component in many pharmaceutical compounds (Scheme 1).



Scheme 1: Biologically active indoles

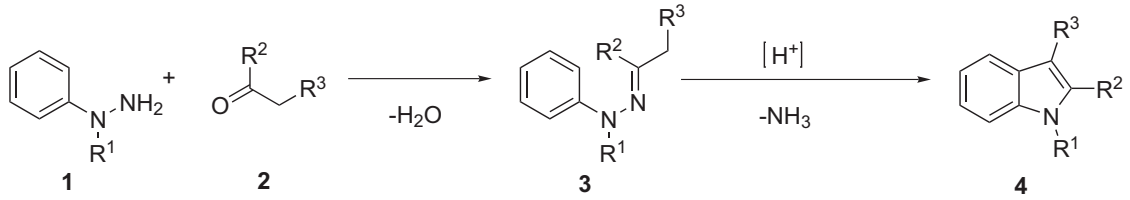
The diversity of this structure as well as their biological and pharmaceutical relevance has motivated academic and industrial researchers to develop new practical syntheses. Besides the well-established Fischer indole synthesis other syntheses exist, such as the Bischler-Möhlau synthesis from α-bromoacetophenone and an excess of aniline, the Batcho-Leimgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, the Gassmann synthesis from *N*-haloanilines, the Madelung-Houlihan cyclization and the reductive cyclization of *o*-nitrobenzylcarbonyl compounds.[1]

Recently, the interest shifts to more simple and direct methods for the synthesis of the indole skeleton. The increasing demand for greener and more sustainable chemistry makes the transition metal-catalyzed indole synthesis a widely applied and developed reaction type. With the aid of catalysis the formation of C-N bonds by addition of nitrogen-containing compounds across C-C unsaturated bonds could be realized. Hence, the electrophilic activation of alkynes towards intramolecular and intermolecular addition reactions to nitrogen-containing nucleophiles has become a useful method for the preparation of substituted indoles. In the past years this method has been improved in scope, mildness of the reaction conditions, functional group tolerance with regard to "Green Chemistry" and practicable atom-economic one-pot methods have been de-

veloped. In the following the development of the indole synthesis by reacting alkynes with different *N*-nucleophiles, such as arylhydrazines, anilines, arylisonitriles and nitroarenes, will be described. Known methods for the synthesis of functionalized indoles from alkynes will be mentioned and recently reported improvements are presented for the different reaction types in detail.

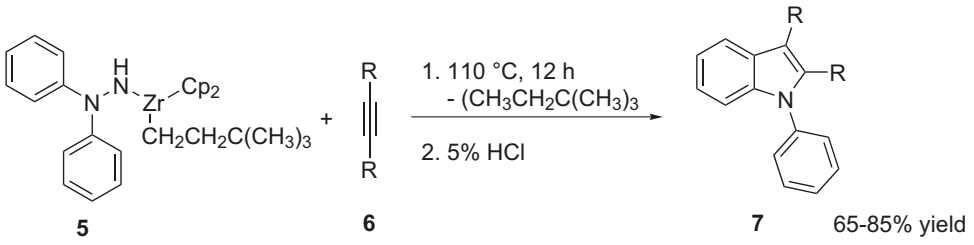
2.2 Metal-catalyzed Hydroamination of Alkynes with Arylhydrazines

Since the discovery in 1883, the Fischer indole reaction has remained an important method for the synthesis of a variety of indoles **4** via cyclization of *N*-arylhydrazones **3** (Scheme 2).[1] These *N*-arylhydrazones **3** were typically obtained by reacting arylhydrazines **1** with ketones or aldehydes **2** or by hydrohydrazination of alkynes.



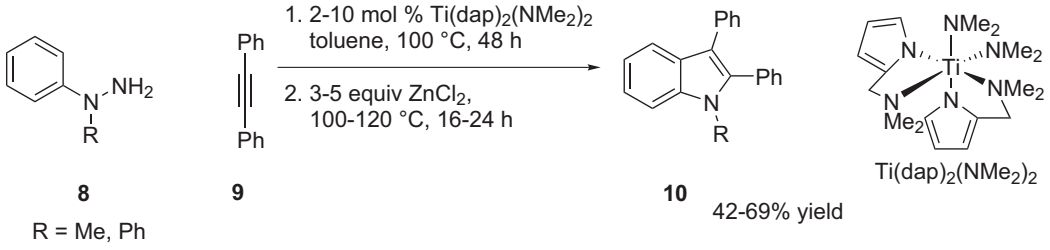
Scheme 2: Fischer indole cyclization

In 1991, Bergman and co-workers reported the first zirconium-mediated domino hydroamination-Fischer indole cyclization by trapping a hydrazidozirconocene complex **5** with alkynes **6** and subsequent addition of hydrochloric acid (Scheme 3).[2]



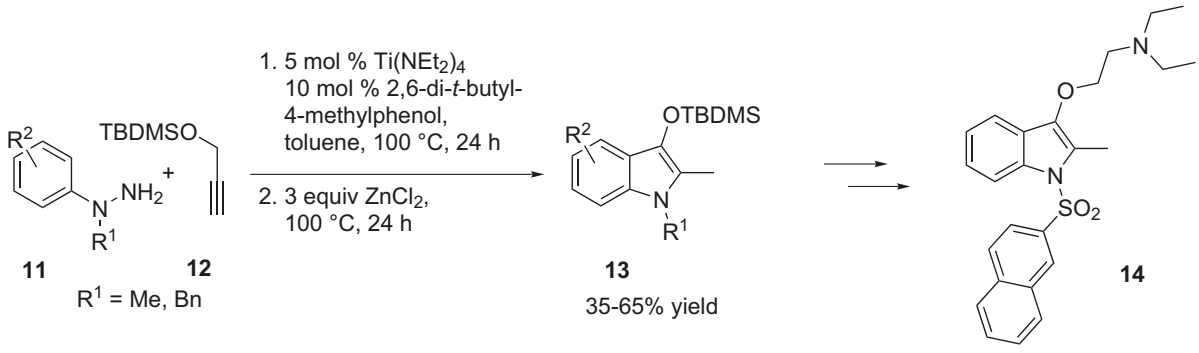
Scheme 3: Zirconium-mediated indole synthesis

Later on, Odom and co-workers described the first titanium-catalyzed intermolecular hydroamination of arylhydrazines **8** with alkynes **9** (Scheme 4).[3] The arylhydrazones obtained underwent further Fischer indole reaction by addition of $ZnCl_2$ to provide *N*-alkyl and *N*-aryl indoles **10** in high yield.



Scheme 4: Titanium-catalyzed synthesis of indoles

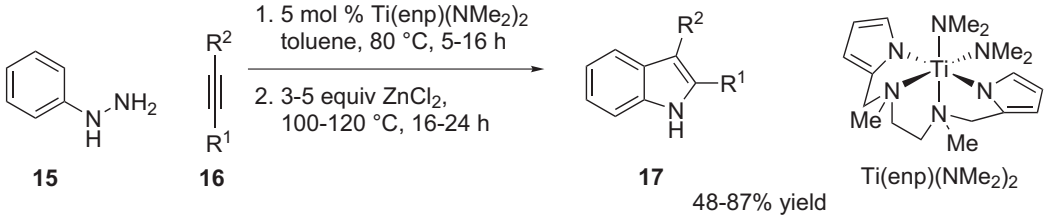
Based on this elegant approach, the titanium-catalyzed synthesis of tryptamines and tryptamine homologues, and trypthophols and tryptophol derivatives, starting from commercially available arylhydrazines and alkynes was developed in our group.[4] Ackermann and Born also reported the use of a combination of $TiCl_4$ and t-$BuNH_2$ as catalyst for domino hydroamination-Fischer indole cyclizations.[5] A problem which prevents widespread use of this methodology is the sensitivity of the titanium complexes towards functional groups, and the necessity for hydrazine protection and indole deprotection steps. Based on our work in the tryptophol synthesis starting from 3- and 4-silyloxyalkynes[4] we studied the reaction of arylhydrazines **11** with silyl-protected propargyl alcohol **12** in the presence of $Ti(NEt_2)_4$ and 2,6-di-t-butyl-4-methylphenol (Scheme 5).[6] After the addition of $ZnCl_2$ a variety of new electron-rich functionalized 3-silyloxy-2-methylindoles **13** were accessible with high regioselectivity.[7] These 3-silyloxyindoles were further used as intermediates for the synthesis of potential 5-HT_6-receptor ligands **14**.[8]



Scheme 5: Synthesis of 3-silyloxy-2-methylindoles

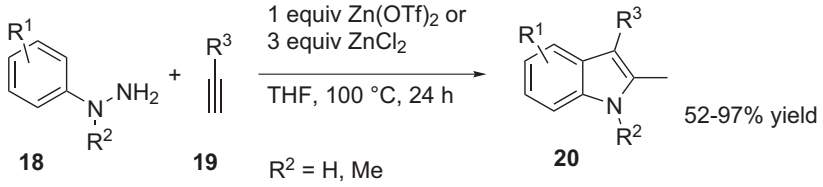
Recently, Odom and co-workers reported a titanium-catalyzed hydrohydrazination of unprotected arylhydrazines **15** with terminal and internal alkynes **16** for the synthesis of the free indole **17** (Scheme 6).[9] For unsymmetrical alkynes often a mixture of indole products was observed. This new reaction was enabled by changing the ancillary ligand

from two bidentate $[Ti(dap)_2(NMe_2)_2]$ to a tetradentate ligand $[Ti(enp)(NMe_2)_2]$, which leads to a higher protolytic stability of the ligand.



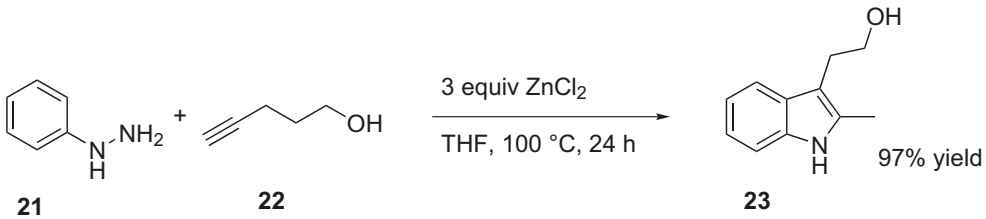
Scheme 6: Titanium-catalyzed synthesis of free indoles

Very recently, our investigations showed no necessity of a titanium catalyst for the one-pot synthesis of substituted indoles **20**. Starting from commercially available arylhydrazines **18** and terminal alkynes **19**, a range of pharmaceutically relevant indole building blocks was obtained in excellent Markovnikov regioselectivity in the presence of either $Zn(OTf)_2$ or $ZnCl_2$ (Scheme 7).[10] These Zn-based Lewis acids catalyze the hydrohydrazination of the alkyne as well as the Fischer indole cyclization. The particular advantage of this reaction is that by using Zn-salts, there is no need for protecting groups at the alkyne and the arylhydrazine unit.



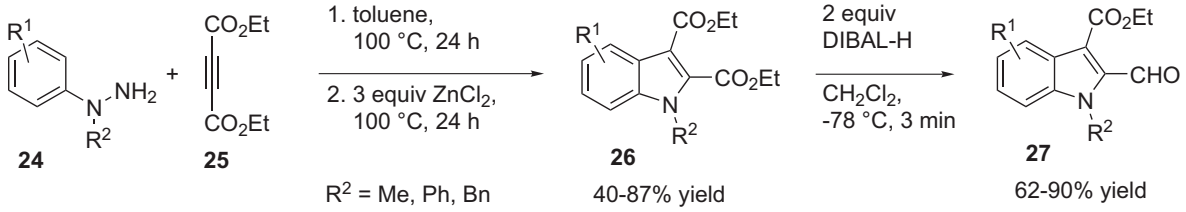
Scheme 7: Zinc-mediated indole synthesis

For example, the free tryptophol derivative **23** was directly available from the unprotected pentyn-1-ol **22** and *N*-phenylhydrazine **21** in excellent yield in the presence of $ZnCl_2$ (Scheme 8).



Scheme 8: Synthesis of a free tryptophol derivative

In addition, a transition-metal-free one-pot method synthesis of indole-2,3-dicarboxylates **26** from arylhydrazines **24** and acetylene dicarboxylates **25** was reported (Scheme 9).[11] Via domino amination-Fischer-indole-cyclization sequence the corresponding products are easily obtained from commercially available substrates in good yields. In a first step the arylhydrazine and acetylene dicarboxylate reacted to the corresponding arylhydrazone. Subsequent treatment of the reaction mixture with 3 equiv of $ZnCl_2$ allowed the cyclization of this *in situ*-generated arylhydrazone to give the corresponding diethyl indole-2,3-dicarboxylate **26**. Noteworthy, when $ZnCl_2$ is added in the beginning of reaction, the desired product is also obtained, albeit in lower yield. Based on this work we developed a selective reduction of **26** to 2-formyl-1-alkylindole-3-carboxylates **27**.[12]

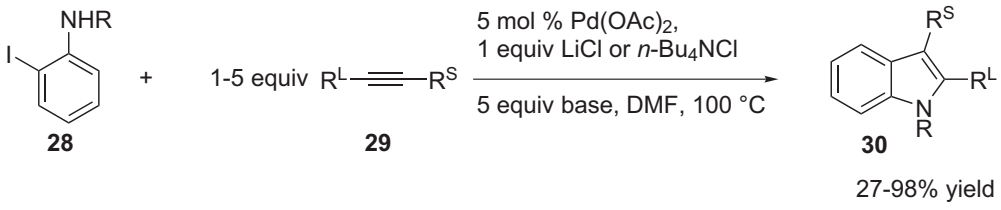


Scheme 9: One-pot method for the synthesis of indole-2,3-dicarboxylates

2.3 Indoles from Aniline Derivatives

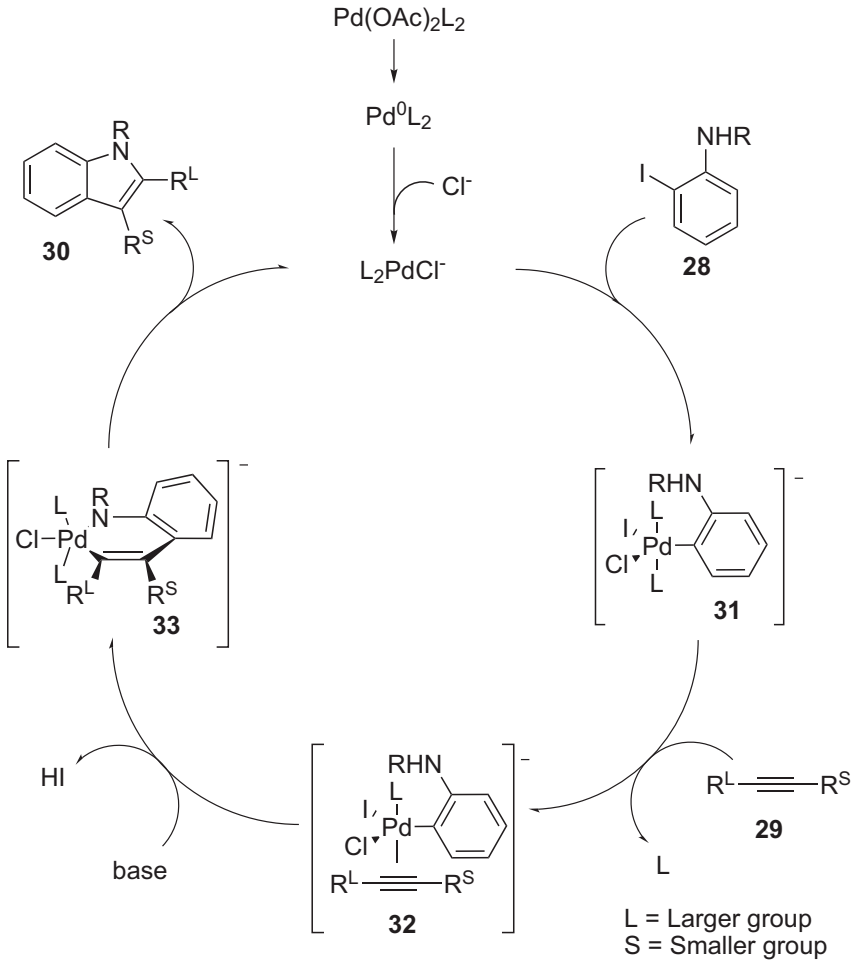
2.3.1 Annulation of *o*-Haloanilines with Alkynes

An attractive method for the synthesis of complex 2,3-disubstituted indoles **30** in a single operation is presented by the Larock heteroannulation. In 1991, Larock and co-workers reported this useful method for the preparation of indoles via palladium-catalyzed heteroannulation of internal alkynes **29** with *o*-iodoanilines and corresponding *N*-protected derivatives **28** (Scheme 10).[13] The cyclization is regioselective with unsymmetrical alkynes, wherein the more sterically hindered group (R^L) of the alkyne is recovered in the 2-position of the indole.



Scheme 10: Larock heteroannulation for the synthesis of 2,3-disubstituted indoles

As shown in Scheme 11 the reaction involves the reduction of $Pd(OAc)_2$ to Pd(0) and coordination of the chloride to form a chloride-ligated zerovalent palladium species. Oxidative addition of Pd(0) to the aryl iodide and coordination of the alkyne to the palladium center gave the aryl-Pd intermediate **32**.

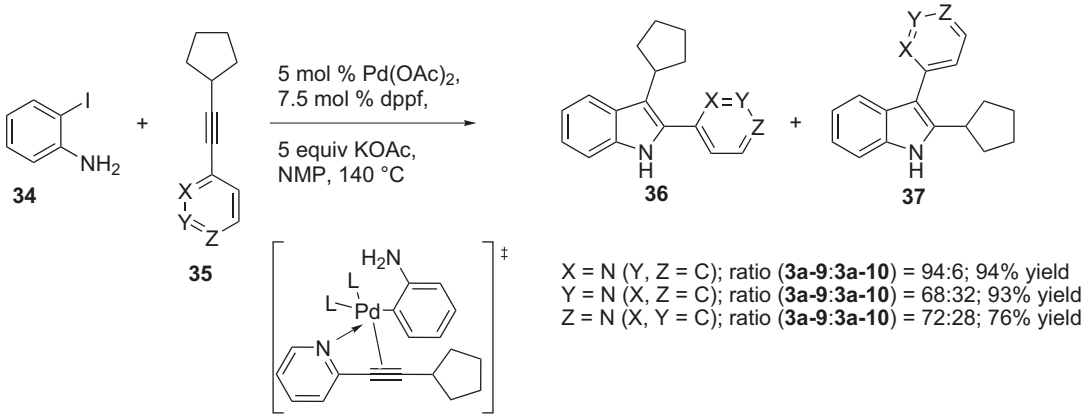


Scheme 11: Mechanism of the Larock heteroannulation

Here, the more sterically demanding group (R^L) is inserted away from the sterically encumdered aryl group. Subsequent regioselective *syn*-insertion into the aryl-Pd bond, nitrogen displacement of the halide in the resulting vinylic Pd intermediate to form a six-membered palladacycle **33** and reductive elimination forms the indole with regeneration of Pd(0).[14]

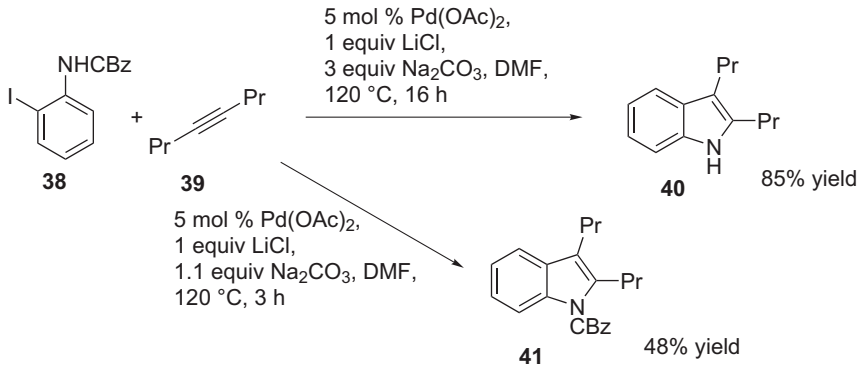
A special approach in the regioselective Larock heteroannulations was published by Roschangar and co-workers.[15] In the presence of $Pd(OAc)_2$ and dppf *o*-alkynylpyridines **35** and *o*-iodoaniline (**34**) were reacted to 3-substituted-2-pyridinylindoles **36** (Scheme 12). Different regioselectivities were observed depending on the pyridinyl moiety. For

example, alkynes with pyridine-2-yl substituent provided a significantly higher ratio of regioisomeric indoles **36** and **37** (94:6) compared to alkynes with pyridine-3-yl or pyridine-4-yl substituents (68:32 or 72:28). The pyridine-2-yl moiety, which is known to act as a ligand for palladium complexes, favours *syn*-insertion of the arylpalladium complex in a way to maintain coordination of palladium to the pyridyl nitrogen via a four-membered ring. Such a coordination effect plays no important role for the pyridine-3-yl and pyridine-4-yl substitutents.



Scheme 12: Regioselective synthesis of 3-substituted-2-pyridinylindoles

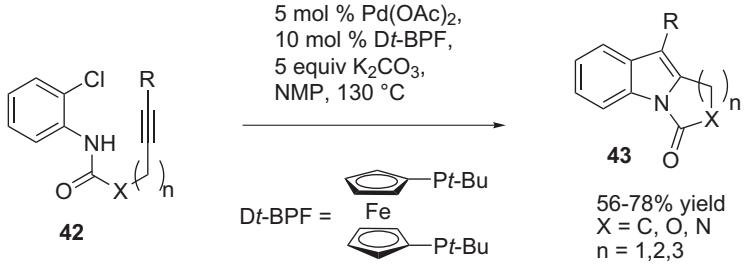
Based on Larock's protocol carbamate substrates were used for the palladium-catalyzed indolization with alkynes.[16] In the presence of 1.1 equiv Na_2CO_3 the annulation reaction of benzyl-2-iodophenylcarbamate (**38**) and 4-octyne (**39**) resulted in the carbobenzoxy (CBz) protected indole **41** in 48% yield after three hours (Scheme 13).[17] Using an excess of base and a longer reaction time the unprotected indole **40** was isolated in higher yield (85%).



Scheme 13: Application of carbamates for the synthesis of indoles

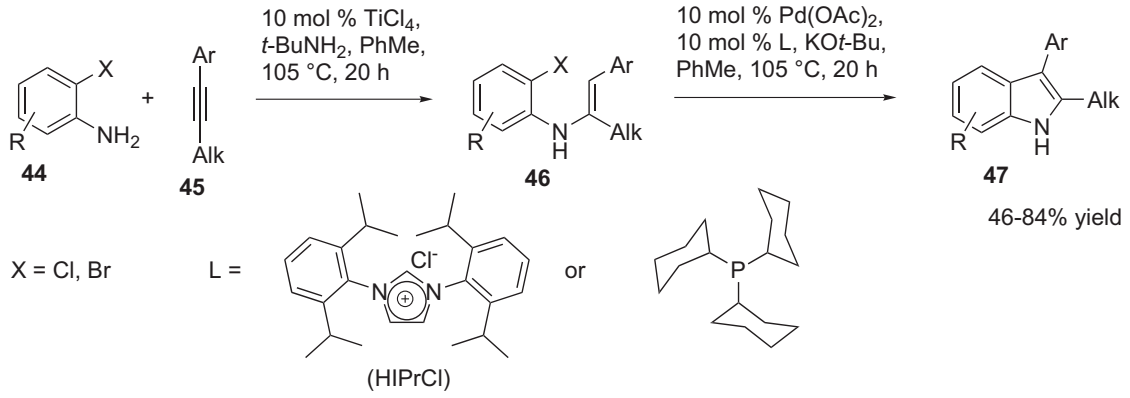
Moreover, Lebel and co-worker described a multicomponent process for the synthesis of indole derivatives by a one-pot Curtius rearrangement/palladium-catalyzed indoliza-

tion process, in which the *o*-iodophenylcarbamate substrate is formed *in situ* from the corresponding *o*-iodobenzoic acid. An intramolecular heteroannulation of carbamate and urea derivatives **42** for the synthesis of a polycyclic indole skeleton **43** was reported by Lu and Senanayake (Scheme 14).[18] Based on their discovery in regioselective palladium-catalyzed indolization of *o*-bromo- or *o*-chloroanilines with internal alkynes[19] the authors applied $Pd(OAc)_2$ and 1,1'-bis(di-*t*-butylphosphino)ferrocene (D*t*-BPF) as ligand. Five-, six- and seven-membered rings were formed without problems.



Scheme 14: Intramolecular heteroannulation of carbamate and urea derivatives

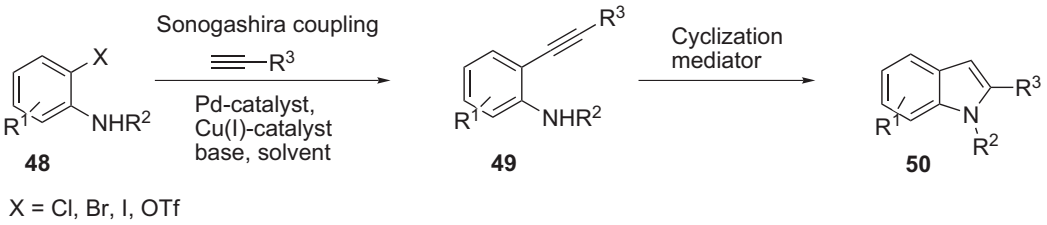
Another elegant concept of reacting *o*-haloanilines was reported by Ackermann and co-workers, who developed a highly regioselective annulation reaction of unsymmetrically substituted alkynes **45** by *o*-bromo- or *o*-chloroanilines **44** to 3-aryl-2-alkyl-indoles **47** (Scheme 15).[20] This one-pot synthesis started with a regioselective $TiCl_4$-catalyzed intermolecular hydroamination followed by a subsequent palladium-catalyzed intramolecular aza-Heck reaction. The best results for the Heck reaction were obtained by applying palladium complexes with either PCy_3 or the imidazolium salt HIPrCl as precursor for a sterically hindered carbene. In addition, Ackermann and co-worker published a ruthenium-catalyzed hydroamination as the first step of this one-pot procedure followed by the Heck reaction.[21]



Scheme 15: $TiCl_4$-catalyzed intermolecular hydroamination followed by a subsequent palladium-catalyzed intramolecular aza-Heck reaction

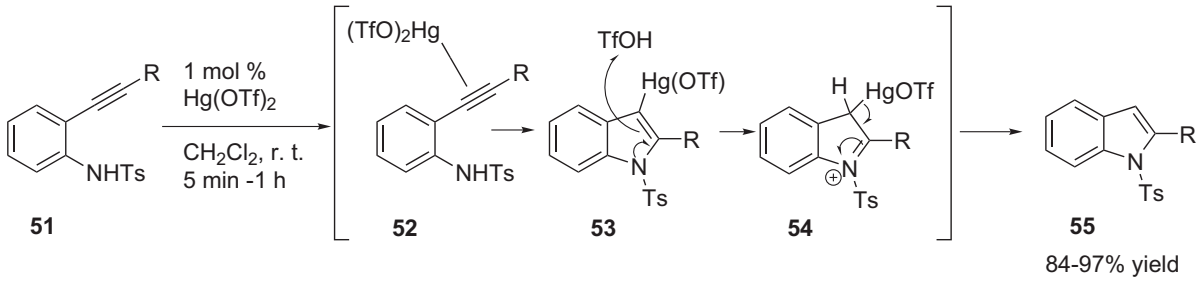
2.3.2 Cyclization of *o*-Alkynylaniline Derivatives

Transition-metal-catalyzed hydroamination of *o*-alkynylaniline derivatives **49** is one of the most efficient approaches for the preparation of 2-substituted indoles **50**. This method usually requires two steps, introduction of an alkynyl moiety to an arene **48** through the Sonogashira reaction[22] and subsequent cyclization (Scheme 16). The main reaction strategy consists of a 5-*endo*-dig cyclization of *o*-alkynylaniline derivatives.



Scheme 16: Sonogashira reaction and cyclization of *o*-alkynylanilines

In this context it is interesting to note that many procedures have been reported for indole syntheses from *o*-alkynylaniline derivatives, including basic conditions[23], ammonium fluoride-mediated reactions[24] and transition metal-catalyzed reactions. In the following different transition metals for the cyclization reaction are mentioned and the most recent appropriate examples will be presented. In the past years molybdenum[25] and indium complexes[26] were reported to be active for the indole cyclization reaction of *o*-alkynylaniline derivatives. Recently, another unusual method was presented by Nishizawa and co-workers.[27] Using $Hg(OTf)_2$ in catalytic amounts *N*-tosyl-*o*-alkynylaniline derivatives **51** were reacted to afford 2-substituted *N*-tosyl-indole derivatives **55** in excellent yield under mild reaction conditions (Scheme 17).

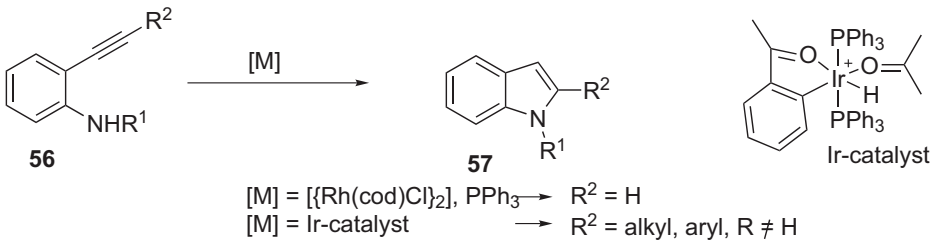


Scheme 17: $Hg(OTf)_2$-catalyzed indole cyclization

The reaction is initiated by π-complexation of the alkyne with $Hg(OTf)_2$ (**52**). Nucleophilic attack of nitrogen generates TfOH to form intermediate **53**. This *in situ* released TfOH protonates **53** to the nitronium ion **54**, which undergoes demercuration

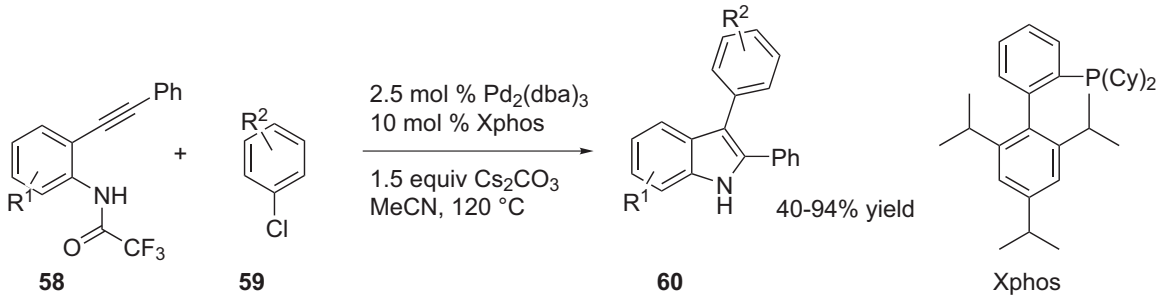
to produce indole **55** under generating the catalyst $Hg(OTf)_2$. Nevertheless, the use of toxic metals even in low amount is fraught with human health risk.

Trost and co-worker published a rhodium-catalyzed cycloisomerization reaction to give indole **57** (R^2 = H)(Scheme 18).[28] Herein only terminal alkynes were reacted successfully to yield 2,3-unsubstituted indoles. The opposite reactivity was reported by Crabtree and co-workers using an iridium-catalyst.[29] This catalytic process was limited to internal alkynes for the synthesis of 2-substituted indole derivatives **57** (R^2 = alkyl, aryl)(Scheme 18).



Scheme 18: Rhodium- and iridium-catalyzed indole synthesis

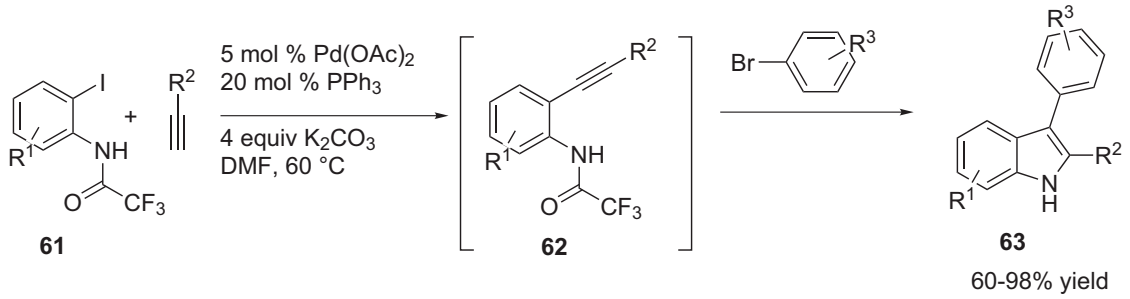
The most frequently used transition metal reagents or catalysts for these ring-closing reactions of *o*-alkynylaniline derivatives are palladium complexes. In the past years the work was concentrated to the synthesis of 2,3-disubstituted indoles **60** via palladium-catalyzed reaction of aryl iodides, bromides, and triflates with *o*-alkynyltrifluoroacetanilides **58**. Cacchi and co-workers published an extension of this procedure to aryl chlorides **59** (Scheme 19)[30], due to their greater availability and their lower costs. Best results are obtained with $Pd_2(dba)_3$ and 2-dicylcohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (Xphos) as ligand to give 2,3-disubstituted indoles **60** in moderate to excellent yields.



Scheme 19: Reaction of *o*-alkynyltrifluoroacetanilides with aryl chlorides

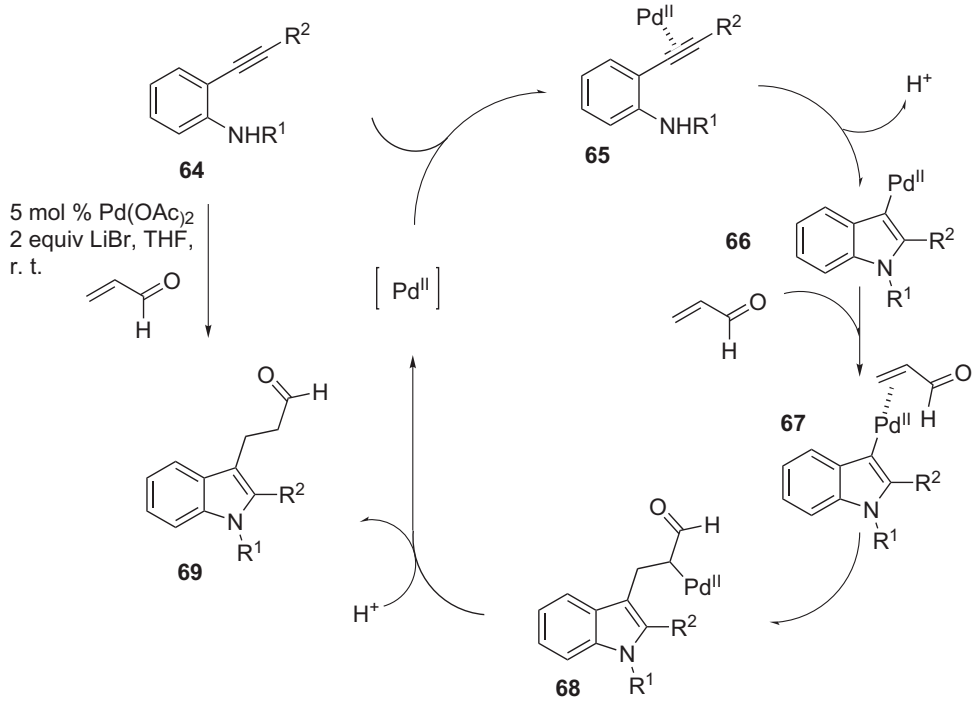
Lu and Senanayake also reported a one-pot, three component Sonogashira-Cacchi domino reaction of 2,3-disubstituted indoles **63**.[31] This sequential process involved

the *in situ* formation of the *o*-alkynyltrifluoroacetanilide **62** by Sonogashira coupling, cyclization by aminopalladation and reductive elimination (Scheme 20).



Scheme 20: *In situ* formation of *o*-alkynyltrifluoroacetanilides and cyclization

Yasuhara and Sakamoto reported the synthesis of 2-substituted 3-alkenylindoles through the reaction of *N*-protected *o*-alkynylanilines with electron deficient alkenes in the presence of palladium and copper chloride as an oxidant.[32] Domino cyclization with subsequent Heck reaction resulted in these 2-substituted 3-alkenylindoles through β-hydride elimination. Recently, Lu and co-worker published the palladium(II)-catalyzed reaction of *N*-protected 2-alkynylanilines **64** with α, β-unsaturated carbonyl compounds for the synthesis of 2-substituted 3-alkylindoles **69** in the presence of LiBr without occurrence of β-hydride elimination (Scheme 21).[33]

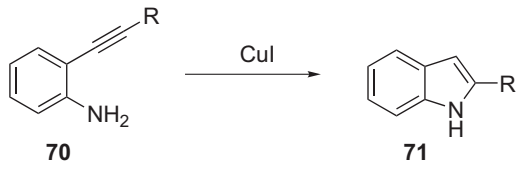


Scheme 21: Palladium-catalyzed reaction for the synthesis of 2-substituted 3-alkylindoles

Mechanistically, the Pd(II) species coordinates with the triple bond of **64** to intermediate **65**. Aminopalladation to the Pd intermediate **66** followed by insertion of the double bond of the acrolein (**68**) and protonolysis of the newly formed carbon-palladium bond yields indole **69** in the presence of halide ions (Scheme 21). A similar reaction type was reported by Arcadi and co-workers using a Au(III) catalyst.[34]

Campagne and co-workers published the use of a catalytic combination of $FeCl_3$-$PdCl_2$ in dichloroethane for the synthesis of 2,3-substituted indoles.[35] They proposed that the role of iron could be the facilitation of the *in situ* reoxidation of Pd(0) to Pd(II).

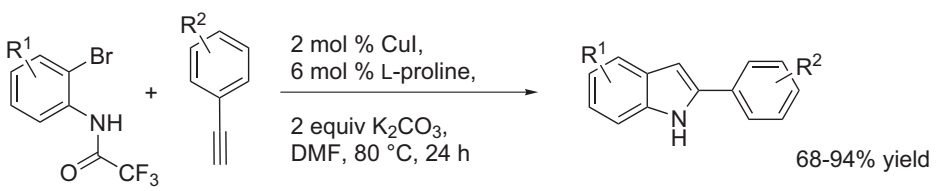
Another attractive method for the cyclization is based on a by copper(I) or copper(II) salt-catalyzed reaction of *o*-alkynylaniline derivatives **70** to 2-substituted indoles **71**.[36] The use of economically attractive copper(I) salts, usually copper(I) iodide, is known as the Castro indole synthesis (Scheme 22).



70 **71**

Scheme 22: Castro indole synthesis

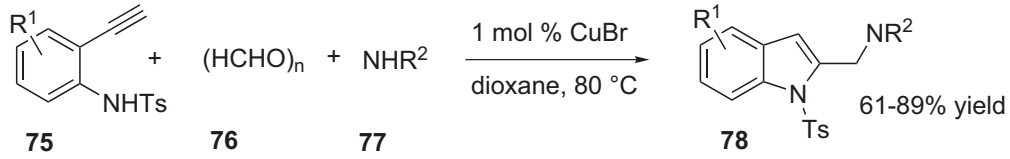
Based on the successful application of aryl bromides as substrates in the CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction[37] Ma and co-worker reported a domino coupling/cyclization process of terminal alkynes **73** and *o*-bromotrifluoroacetanilides **72** (Scheme 23).[38] This conversion firstly involved a CuI/L-proline-catalyzed coupling between the alkyne and the aryl bromide and secondly a CuI-catalyzed cyclization to the indole moiety **74**. The reaction proceeded under mild conditions through the *ortho*-substituent effect directed by $NHCOCF_3$.



72 **73** **74**

Scheme 23: Copper iodide-catalyzed domino coupling/cyclization process

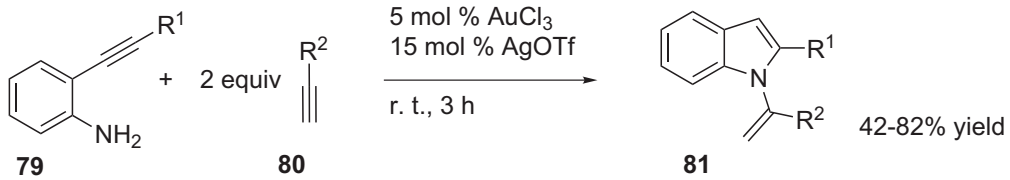
Ohno and Fujii developed a domino three-component coupling and cyclization reaction for the synthesis of 2-(aminomethyl)indoles **78** (Scheme 24).[39] In the presence of copper(I) bromide *N*-protected alkynylanilines **75** were treated with paraformaldehyde **76** and secondary amines **77** to give **78** with water as waste product. This reaction proceeded presumably through Mannich-type multicomponent coupling reaction (MCR) followed by indole cyclization.



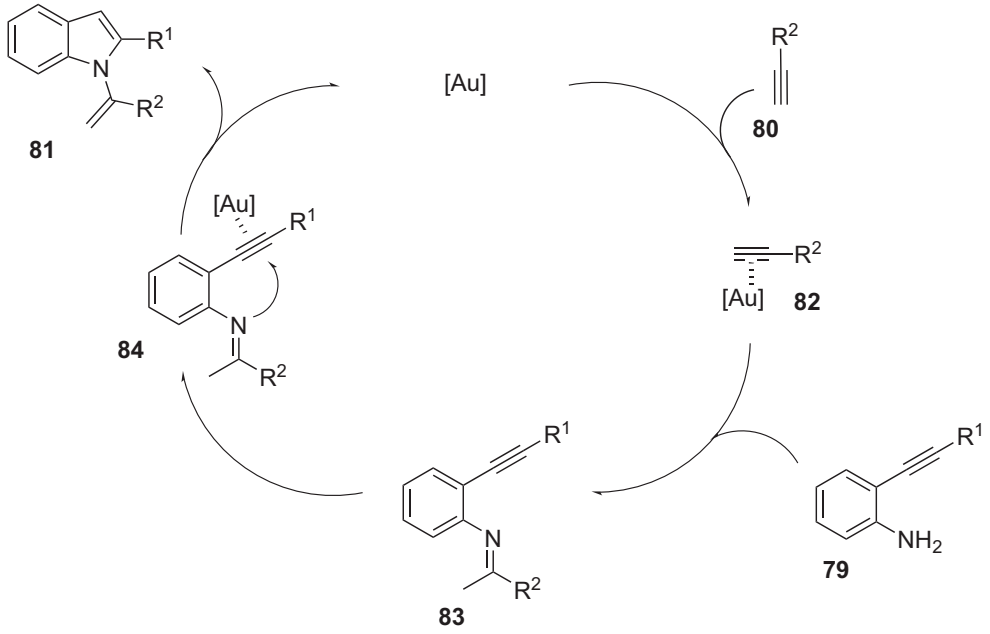
Scheme 24: Domino three-component coupling and cyclization reaction for the synthesis of 2-(aminomethyl)indoles

As mentioned before Au(III) is also known as a cyclization catalyst to afford 2-substituted indoles.[40] Hence, Marinelli and co-workers reported the cyclization of *o*-alkynylanilines in the presence of $NaAuCl_4 \cdot H_2O$ using the ionic liquid [bmim]BF_4 as a more environmentally benign reaction medium.[41]

Li and co-workers developed a double-hydroamination reaction of *o*-alkynylanilines **79** with terminal alkynes **80** leading to *N*-vinylindoles **81** (Scheme 25).[42] After optimization the best result is obtained at room temperature without any solvent in the presence of $AuCl_3$/AgOTf. A mechanism for the Au(III)-catalyzed double hydroamination is shown in Scheme 26. Firstly, the terminal alkyne **80** is activated by $Au(OTf)_3$ to generate the intermediate **82**. This reacts further with **79** to yield the first hydroamination product **83**. Subsequently the carbon-carbon triple bond is again activated by $Au(OTf)_3$ and produces the intermediate **84** via nucleophilic addition of the imine nitrogen. After protonation at the C-3-position of the indole the final product **81** is formed and the catalyst regenerated.



Scheme 25: Gold-catalyzed synthesis of *N*-vinylindoles

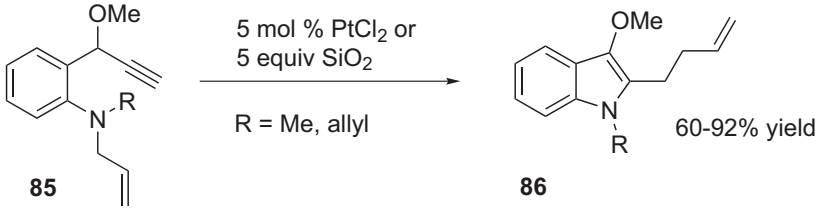


Scheme 26: Mechanistic aspects in the synthesis of *N*-vinylindoles by gold catalysis

Besides Au(III) catalysts also AgOTf was reported by Rutjes and co-workers to catalyze the cyclization of *o*-alkynylanilines to give isotryptophan derivatives.[43]

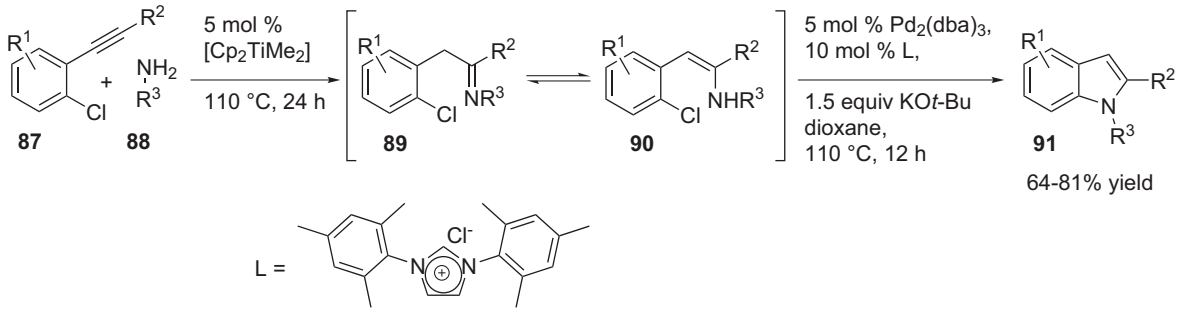
A transition-metal free method for the synthesis of 2,3-substituted indoles is the electrophilic cyclization promoted by iodine.[44] This strategy constitutes a convenient and general method synthetic method for the synthesis of 3-iodoindoles.

Fensterbank and Malacria published an alternative 5-*exo*-dig isomerization to the 5-*endo*-dig cyclization.[45] 2,3-Functionalized indoles and especially 3-alkoxyindoles **86** (Scheme 27) were prepared in the presence of $PtCl_2$ or protons. The *N*,*N*-diallyl precursor underwent the transformation, where an additional transfer of an allyl group from the nitrogen to the terminal alkyne carbon atom occurred. Formally, this constituted an aminoallylation of the triple bond followed by an isomerization of the unsaturated bond. In the case of the *N*-allyl-*N*-methyl substrate also the allyl moiety was transferred.



Scheme 27: Synthesis of 3-alkoxyindoles through 5-*exo*-dig isomerization

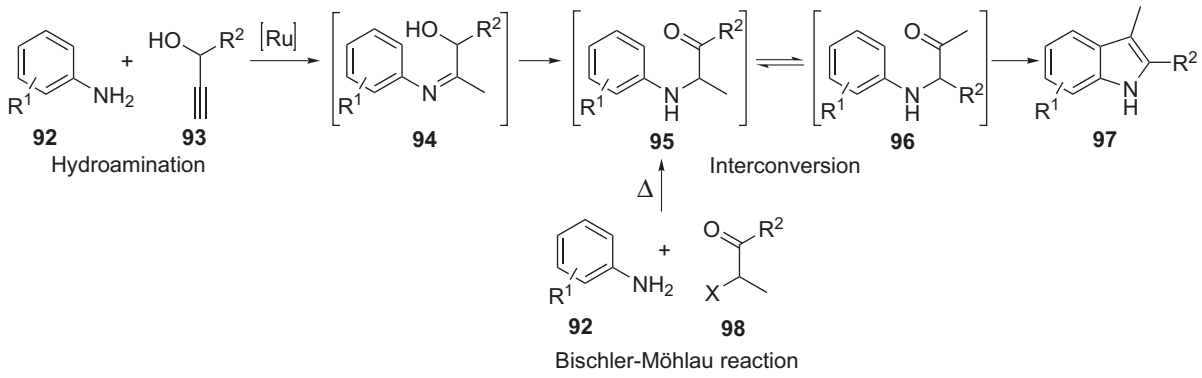
Doye and co-workers reported a one-pot procedure by combining a titanium-catalyzed hydroamination of *ortho*-chloro-substituted 1-phenyl-2-alkylalkynes **87** with a Pd-catalyzed *N*-arylation of imines which resulted in a new method for the synthesis of indoles **91** (Scheme 28).[46] The major expectation was that under basic conditions, the imines **89**, which are regioselectively formed during the hydroamination in the presence of the titanium catalyst [Cp_2TiMe_2], will be in equilibrium with the corresponding enamines **90**. In addition, an *ortho*-chloro-substituent in the benzene ring offered the possibility to convert **90** into indoles by a Pd-catalyzed *N*-arylation/cyclization (Buchwald-Hartwig reaction).



Scheme 28: Titanium-catalyzed hydroamination followed by palladium-catalyzed *N*-arylation/cyclization

2.3.3 Reaction of Anilines with Propargylalcohol Derivatives

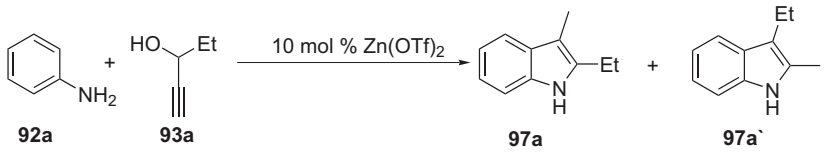
Another approach besides the classical Fischer indole synthesis[47] via arylhydrazones is represented by the Bischler-Möhlau indole synthesis.[48] Starting from anilines **92** and α-haloketones **98** the indole moiety **97** was generated under harsh conditions. A more pratical, halogen-free process was developed by Wakatsuki and co-workers.[49] Based on their results in ruthenium-catalyzed hydroamination reactions[50] they provided a one-pot synthesis of 2-substituted 3-methylindoles **97** using anilines **92** and propargylalcohol derivatives **93** as starting materials (Scheme 29). In the presence of [$Ru_3(CO)_{12}$] and aniline hydrochloride as additive hydroamination of the C-C triple bond occurs followed by an isomerization of the resulting aminoalcohol **94** to aminoketone **95** (Bischler-Möhlau-type intermediate). In the presence of aniline hydrochloride there is fast interconversion between the regioisomers **95** and **96**. Also catalyzed by the additive these two intermediates undergo cyclization to the corresponding indole, wherein the 1,2-nitrogen migration product **97** cyclized from **96** is the major indole product.



Scheme 29: One-pot synthesis of 2-substituted 3-methylindoles via ruthenium-catalyzed hydroamination/cyclization

Based on this methodology Liu and co-workers published a $Zn(OTf)_2$-catalyzed synthesis of these 2-substituted-3-methyl indoles.[51] Herein, $Zn(OTf)_2$ is responsible for the hydroamination of the propargyl alcohol, the isomerization as well as for the cyclization step.

Table 1: $Zn(OTf)_2$-catalyzed regioselective synthesis of indole derivatives.

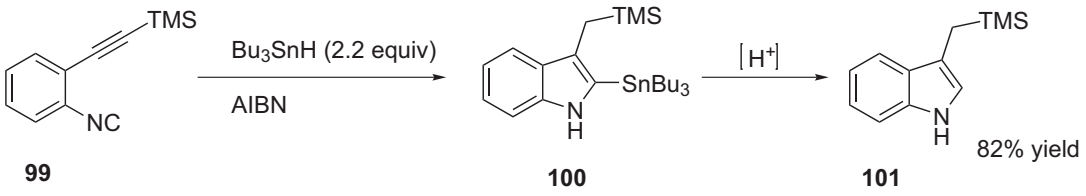


Entry	Solvent	Temperature [°C]	Time [h]	Product (Yield [%])
1		130	4	97a/97a‘= 4.5 (95)
2	benzene	100	14	97a (89)
3	toluene	100	8	97a (97)

After optimization of the reaction conditions, toluene was found to be the best solvent where only one regioisomeric product **97a** is observed (Table 1). Using this regioselective indole synthesis from anilines and propargylalcohol derivatives 2-substituted 3-methylindoles are synthesized due to the use of a terminal alkyne.

2.4 Indoles from Isocyanides

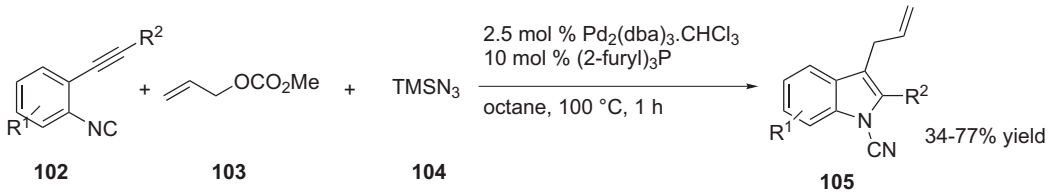
Isocyanides provide an additional nitrogen source as starting material for the synthesis of the indole skeleton.[52] These stable compounds are applied in a broad number of organic reactions.[53] The reaction characteristics of isocyanides is distinguished by the α-addition, the α-metallation and the radical reaction as three different reaction types. Based on the Fukayama isonitrile-alkene free-radical coupling reaction[54] the group of Rainier developed an analog alkyne-isonitrile free-radical reaction for the synthesis of indoles (Scheme 30).[55]



Scheme 30: Synthesis of indoles from *o*-alkynylarylisocyanides via radical cyclization

Starting from aryl isocyanides having pendant alkyne 5-*exo*-dig radical cyclization provided indolenine intermediate **100**. This 2-stannylindole could be destannylated by acidic work up to the 3-substituted indole **101**. For the formation of 2,3-disubstituted indoles the 2-stannylindole **100** could be expanded directly by palladium-mediated coupling reactions (Stille) or oxidation of the tin-carbon bond with iodine resulting in 2-iodoindoles which further underwent palladium-catalyzed coupling reactions.[56]

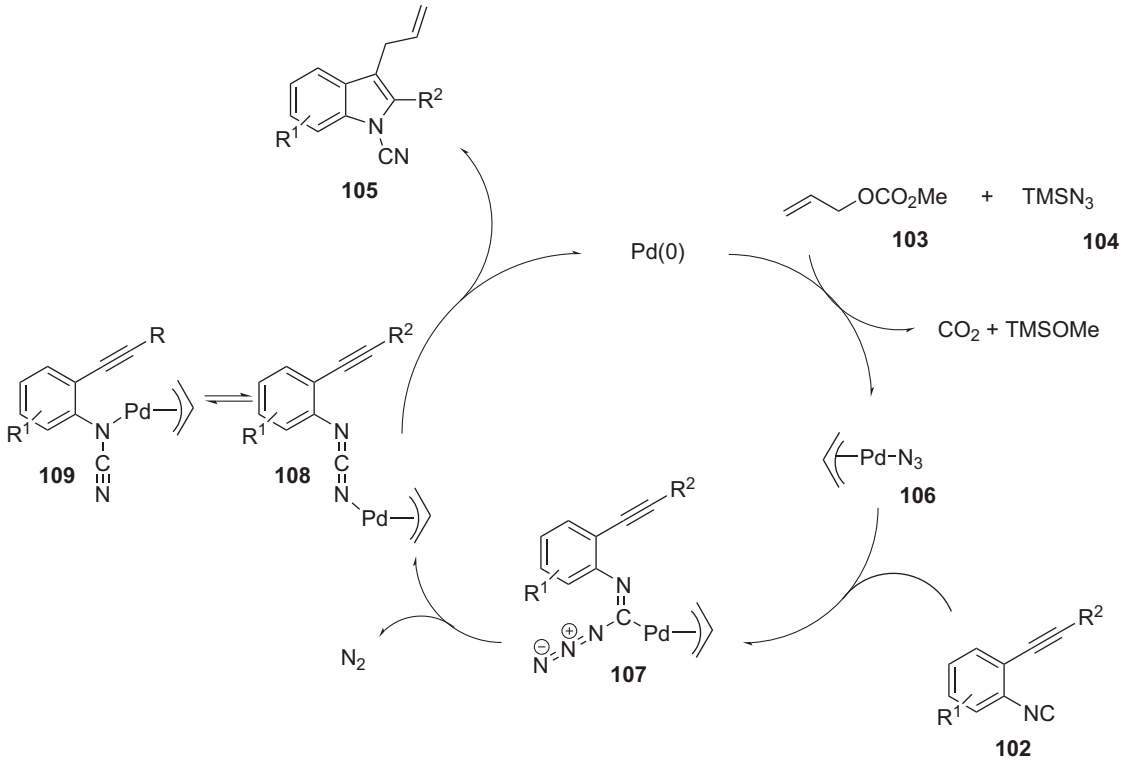
o-Alkynylphenylisocyanides have been employed in the synthesis of various substituted *N*-cyanoindoles **105** via a multicomponent coupling reaction (MCR) of aryl isocyanides **102**, allylmethyl carbonate **103** and trimethylsilyl azide **104** (Scheme 31).[57] A wide range of functional groups were tolerated at the *p*-, *m*- and *o*-position of the aromatic ring.



Scheme 31: Multicomponent coupling reaction for the synthesis of *N*-cyanoindoles

A proposed mechanism is shown in Scheme 32. Firstly, the π-allylpalladium azide **106** is formed through the reaction of Pd(0) with allyl methyl carbonate **103** and

$TMSN_3$ **104**. The isocyanide **102** is then inserted in the Pd-N_3 bond to generate the π-allylpalladium intermediate **107**. Under release of N_2 followed by the 1,2-migration of π-allylpalladium part from the carbon atom to the α-nitrogen in **107** would provide the palladium-carbodiimide complex **108** via a π-allylpalladium mimic of the Curtius rearrangement. The palladium-carbodiimide complex **108** isomerized in equilibrium with the palladium-cyanamide complex **109**. The *N*-cyanoindoles **105** were formed through the insertion of the alkyne moiety into the Pd-N bond in intermediate **109** followed by reductive elimination of Pd(0).

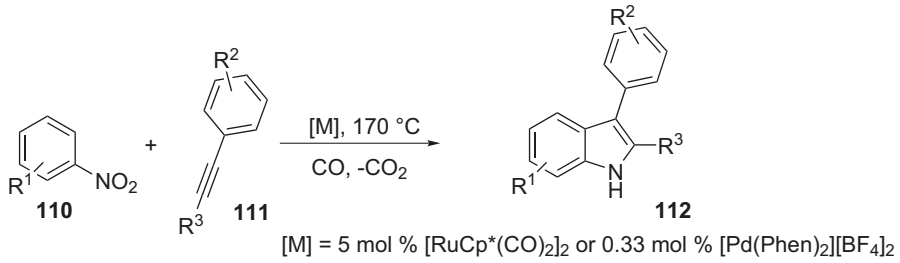


Scheme 32: Mechanism for the synthesis of *N*-cyanoindoles

2.5 Cycloaddition of Nitro- and Nitrosoarenes with Alkynes

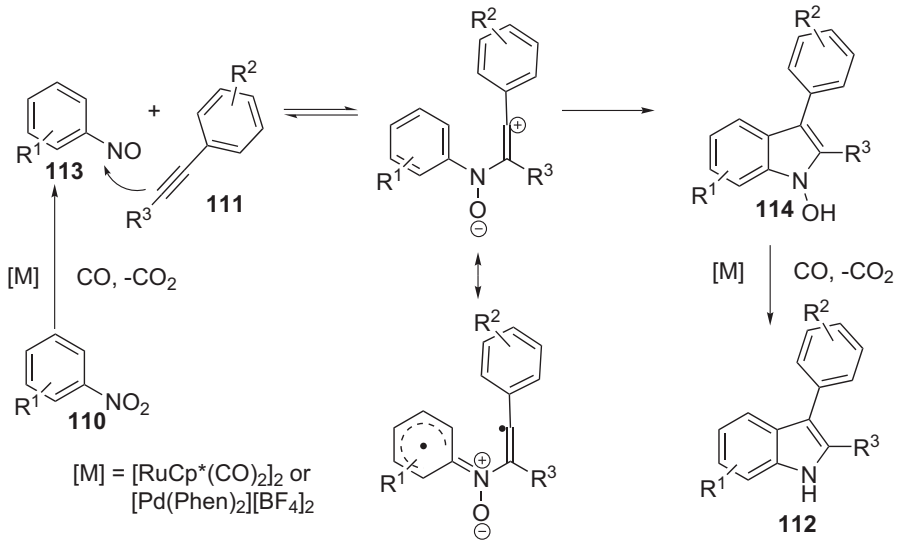
In 2002, Nicholas and Penoni reported a $[RuCp^*(CO)_2]_2$-catalyzed reaction of nitroarenes **110** with alkynes **111** to give indoles **112** (Scheme 33).[58] Through the indole formation complete 3-position regioselectivity is observed, however, the indole yields were only moderate.

A more active catalyst for the synthesis of indoles **112** from nitroarenes **110** was published by Ragaini and co-workers.[59] Palladium-phenanthroline complexes such as $[Pd(Phen)_2][BF_4]_2$ catalyzed this reaction with aryl alkynes and CO to give 3-arylindoles.



Scheme 33: Ruthenium- and palladium-catalyzed reaction of nitroarenes with alkynes

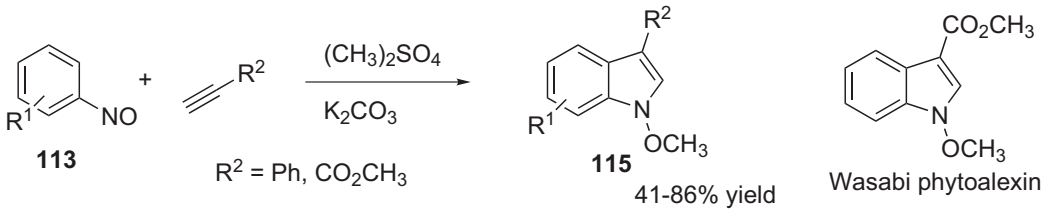
In the presence of alkylalkynes no cyclized product was formed. $[RuCp^*(CO)_2]_2$ and $[Pd(Phen)_2][BF_4]_2$ represent active catalysts for reductive carbonylation reactions of nitro-arenes.[60] Due to mechanistic aspects shown in Scheme 34 the catalytic reduction of nitroarenes **110** by CO initially produces nitrosoarenes **113** which further react with the alkyne **111** outside the coordination sphere of the metal. The nitrosoarene should interact reversibly with the alkyne to give an intermediate having a polarized diradical character. Cyclization would give the corresponding *N*-hydroxyindole **114** which is reduced in a last step to the indole **112** in the presence of CO and the catalyst. The radical character of the intermediate adducts explains the need for an aryl group on the alkyne, wherein the aryl ring stabilizes charges or a radical in the α-position.



Scheme 34: Mechanism for the reaction of alkynes with nitrosoarenes generated from nitroarenes

The uncatalyzed reaction of nitrosoarenes with alkynes to give *N*-hydroxyindoles **114** under refluxing conditions in benzene was already observed by Nicholas and coworkers.[61] Reductive carbonylation catalyzed by $[RuCp^*(CO)_2]_2$ or hydrogenation on Pd/C of **114** resulted in **112**. Recently, the same group published the synthesis of

the more stable *N*-methoxyindoles **115** (Scheme 35).[62] In the presence of K_2CO_3/ $(CH_3)_2SO_4$ in refluxing benzene the reaction of nitrosoarenes with terminal alkynes formed the 3-substituted *N*-methoxyindoles in good yields.



Scheme 35: Synthesis of 3-substituted *N*-methoxyindoles

The analog reaction with methyl propiolate provided a one-pot preparation of phytoalexin analogues from Wasabi.[63]

2.6 Conclusion

Alkynes still play an important role as starting material for the synthesis of a variety of indole derivatives. Different methods using *N*-nucleophiles were developed for the reaction with the electron-rich system of the unsaturated compound. The addition of arylhydrazines and aniline derivates to alkynes for the synthesis of functionalized indoles constitutes the most frequently applied reaction type. In addition, arylisonitriles and nitro- and nitrosoarenes are useful for new, short, and highly flexible synthetic approaches for the preparation of biologically interesting indoles. In the past years synthetic chemists have improved these methods in scope, mildness of the reaction conditions, functional group tolerance with regard to "Green Chemistry" and practicable atom-economic one-pot methods have been developed. However, for most of these improved methods room for optimizations in the mentioned areas remain. Future studies will provide new or improved indole synthetic sequences as well as new preparative applications for biologically active indole-based molecules.

2.7 References

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3 Objectives of this Work

There is a 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. Based on our attention in indole synthesis we looked for alternative catalysts for the intermolecular hydrohydrazination of alkynes. A problem which prevents widespread use of this reaction is the sensitivity of the previously used titanium complexes towards functional groups, and the necessity for hydrazine protection and indole deprotection steps. In "*Angewandte Chemie*" (Publication 4.1, **2008**) a zinc-mediated and -catalyzed hydrohydrazination of alkynes is described for the first time, which allowed for a general synthesis of protected and unprotected indoles. Starting from commercially available arylhydrazines and terminal alkynes, a range of pharmaceutically relevant indole building blocks is obtained in excellent Markovnikov regioselectivity in the presence of either $Zn(OTf)_2$ or $ZnCl_2$. Based on these observations the zinc-catalyzed hydroamination of terminal alkynes with primary and secondary aromatic amines was investigated. With the use of a catalytic amount of $Zn(OTf)_2$ for the hydroamination of the alkyne and subsequent reduction of the formed imine with $NaBH_3CN$ a variety of secondary and tertiary amines could be isolated in up to 99% yield and with over 99% Markovnikov regioselectivity (Publication 4.2, *ChemSusChem* **2008**). A novel regioselective synthesis of aryl-substituted pyrazolines has been developed by reacting substituted phenylhydrazines with 3-butynol in the presence of a catalytic amount of $Zn(OTf)_2$ (Publication 4.4, *Org. Lett.* **2008**). Subsequent one-pot oxidation of the pyrazoline derivatives with air led to the corresponding pyrazoles. In a similar manner, the hydrohydrazination of 4-pentynoic acid with different arylhydrazines proceeded smoothly in the presence of zinc chloride. This domino amination-amidation sequence leads to aryl-substituted 4,5-dihydro-3(2H)-pyridazinones (Publication 4.5, *Tetrahedron Lett.* **2008**). We also reported a transition-metal-free one-pot synthesis of indole-2,3-dicarboxylates from arylhydrazines and acetylene dicarboxylates (Publication 4.7, *Eur. J. Org. Chem.* **2007**). Based on this work, we have developed a selective and fast reduction of these indole-2,3-dicarboxylates to obtain alkyl 2-formyl-1-alkyl-indole-3-carboxylates (Publication 4.8, *Tetrahedron* **2008**).

Next to this mainly methodical work a range of new potentially 5-HT_6 receptor ligands were synthesized in cooperation with the pharmaceutical company Esteve. The basis of these molecules constituted the synthesis of functionalized 3-silyloxy-2-methylindoles, which was published in *Synlett* (Publication 4.6, **2007**). A key step of this reaction represented the use of the titanium-catalyzed hydroamination of silyl-protected propargyl alcohol and commercially available arylhydrazines. Later it was shown, that there was no need for a titanium-catalyst (Publication 4.1, *Angew. Chem.* **2008**). In addition, 3-silyloxy-2-methylindoles are converted to the corresponding 3-(*N*,*N*-diethylaminoethoxy)-indoles. By subsequent deprotection of the indole and sulfonylation with biarylsulfonyl chlorides, two novel classes of potential 5-HT_6 receptor ligands could be prepared (Publication 4.3, *Org. Biomol. Chem.* **2008**). Besides the desired 2-naphthalenesulfonylindole, an unexpected sulfonylation of the 2-methyl group of the indole system created further interesting biarylsulfonylindoles. For further design of building blocks for pharmaceutically and biologically active substances the palladium-catalyzed amination of 3-silyloxy-substituted bromo-indole with primary and secondary amines was developed (Publication 4.9, *Tetrahedron Lett.* **2007**). 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 high yield. An additional application of the 3-silyloxy-substituted bromo-indole was introduced for the synthesis of 3,5-dioxyindole derivatives via palladium-catalyzed diaryl ether formation (Publication 4.10, *Synthesis* **2007**). Different alkylated phenols reacted in the presence of $Pd(OAc)_2$ and *N*-phenyl-2-(di-1-adamantylphosphino)pyrrole to give potentially bioactive indole derivatives.

4 Publications

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

Karolin Alex, Annegret Tillack, Nicolle Schwarz, Matthias Beller*, *Angew. Chem.* **2008**, *120*, 2337-2340; *Angew. Chem. Int. Ed.* **2008**, *47*, 2304-2307.

Contributions

My contribution as co-author of this paper accounts to approximately 80%.

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**

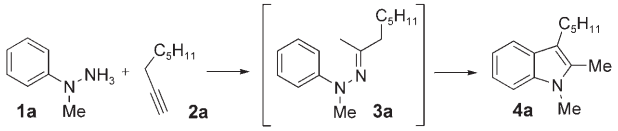
There is continuing interest in the development of improved methods for the synthesis of indoles owing to their importance as one of the most represented building block in natural bioactive products and marketed drugs.[1,2] Thus, indole and its derivatives have been termed "privileged pharmacological 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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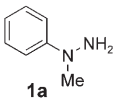
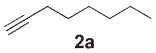
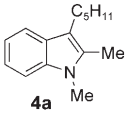
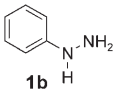
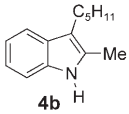
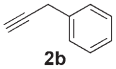
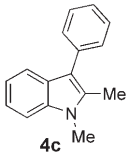
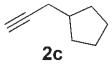
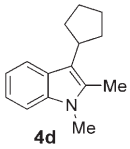
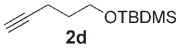
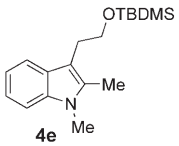
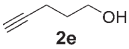
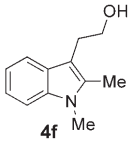
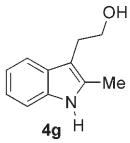
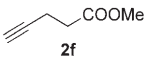
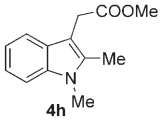
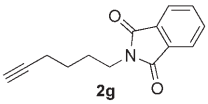
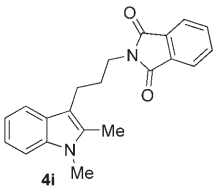
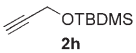
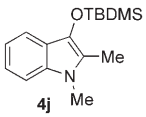
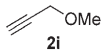
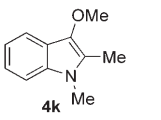
[**] This work has been funded by the State of Mecklenburg–Western Pomerania, the Bundesministerium für Bildung und Forschung, the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213 and Leibniz Prize), and the Fonds der Chemischen Industrie. We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, and K. Mevius for their excellent technical and analytical support.

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.

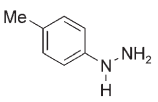
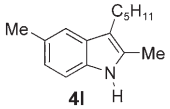
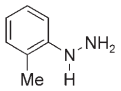
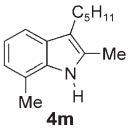
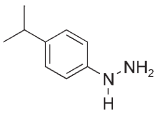
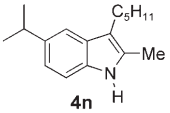
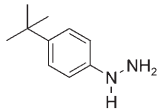
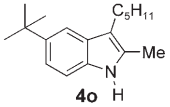
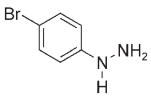
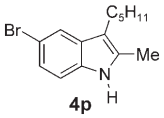
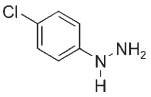
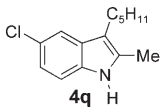
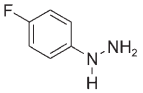
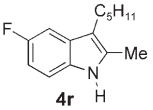
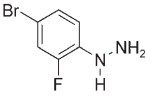
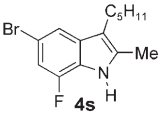
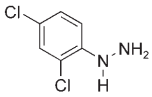
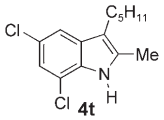
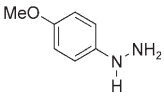
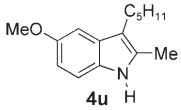
We were interested in the scope and limitations of the procedure with different alkynes (Table 2). For this purpose, we studied the reaction of *N*-methyl-*N*-phenylhydrazine and *N*-phenylhydrazine with various alkynes in the presence of $Zn(OTf)_2$ and $ZnCl_2$. Notably, applying the unprotected hydrazine 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).

Received: August 20, 2007
Revised: September 29, 2007
Published online: February 8, 2008

Keywords: alkynes · hydrohydrazinations · indole · zinc

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4.2 General Zn-catalyzed Intermolecular Hydroamination of Terminal Alkynes

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

Contributions

My contribution as co-author of this paper accounts to approximately 80%.

DOI: 10.1002/cssc.200700160

General Zinc-Catalyzed Intermolecular Hydroamination of Terminal Alkynes

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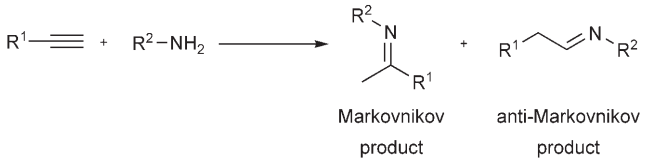
Catalytic hydroaminations are one of the most sustainable C–N bond-forming processes as a result of 100% atom economy and the availability of substrates. Here, it is shown that the intermolecular hydroamination of terminal alkynes with anilines proceeds smoothly in the presence of catalytic amounts of 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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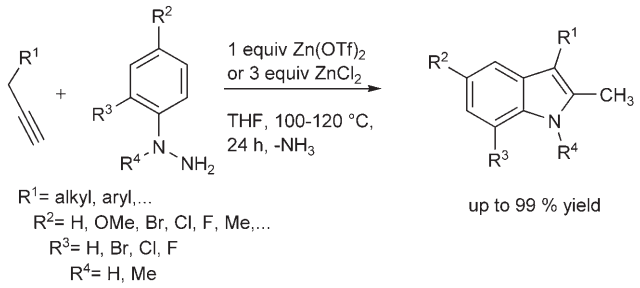
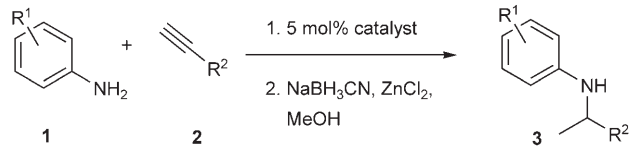


Scheme 2. Synthesis of indoles by hydrohydrazination of terminal alkynes (OTf = trifluoromethanesulfonate).

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

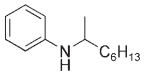
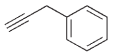
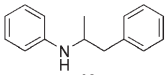
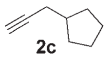
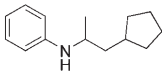
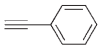
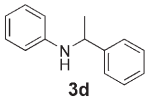
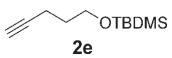
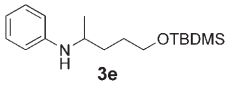
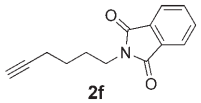
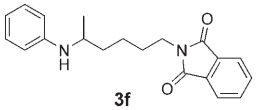
[a] Reaction conditions: 1) **2a** (1 mmol), **1a** (1–2 mmol), catalyst (5 mol%), solvent (2 mL), 24 h; 2) reduction: $NaBH_3CN$ (2 mmol), $ZnCl_2$ (1 mmol), MeOH (5 mL), 20 h, room temperature. [b] Determined by GC with dodecane as internal standard.

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]

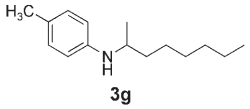
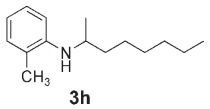
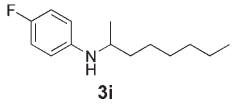
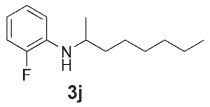
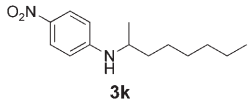
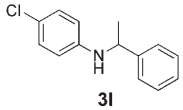
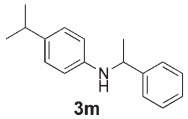
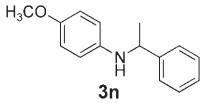
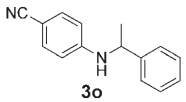
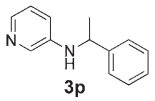
Entry	Alkyne	Hydroamination product	Yield [%][b]
1	 **2a**	 **3a**	78
2	 **2b**	 **3b**	99
3	 **2c**	 **3c**	98
4	 **2d**	 **3d**	98
5	 **2e**	 **3e**	86
6	 **2f**	 **3f**	77

[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-

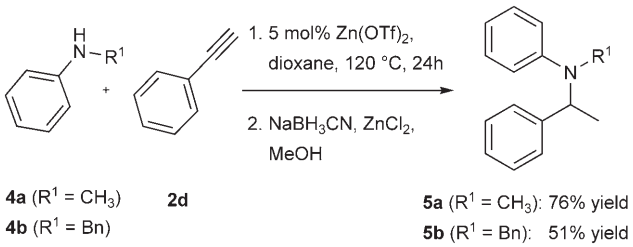
Table 3. Hydroamination of 1-octyne (**2a**) and phenylacetylene (**2d**) with various substituted anilines **1**.[a]

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}.

Acknowledgements

This work was funded by the State of Mecklenburg-Western Pomerania, the Bundesministerium für Bildung und Forschung (BMBF), the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213, and Leibniz Prize), and the Fonds der Chemischen Industrie (FCI). We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, and K. Mevius for their excellent technical and analytical support.

Keywords: alkynes · amines · homogeneous catalysis · hydroamination · zinc

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Received: December 14, 2007
Published online on March 12, 2008

4.3 Synthesis of 3-(2-*N*,*N*-Dietyhlaminoethoxy)indoles as Potential 5-HT$_6$ Receptor Ligands

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Contributions

Compound **9e**, **10**, **11** and **12** were synthesized by myself. My contribution as co-author of this paper accounts to approximately 50%.

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

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Received 5th February 2008, Accepted 5th March 2008
First published as an Advance Article on the web 31st March 2008
DOI: 10.1039/b802054j

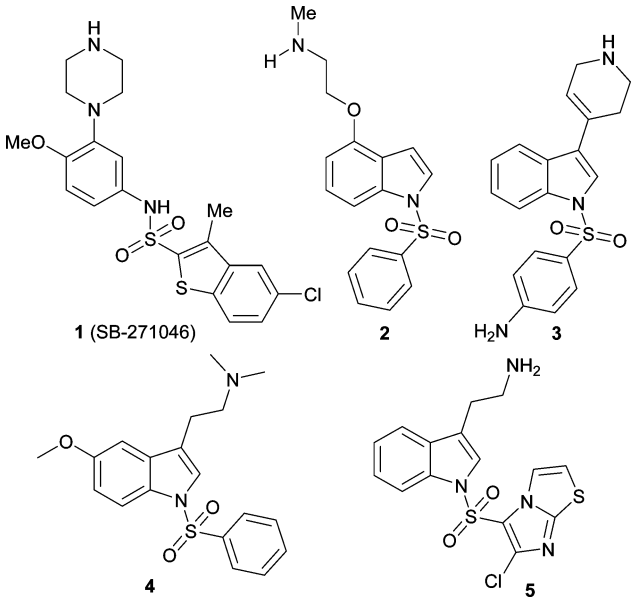
The synthesis of new pharmaceutically interesting 3-(2-*N,N*-diethylaminoethoxy)indole derivatives is described. Starting from 3-silyloxy-2-methylindoles, deprotection and *in situ* aminoalkylation provided 3-(2-*N,N*-diethylaminoethoxy)indoles in good yield. Further sulfonylation of these novel indoles 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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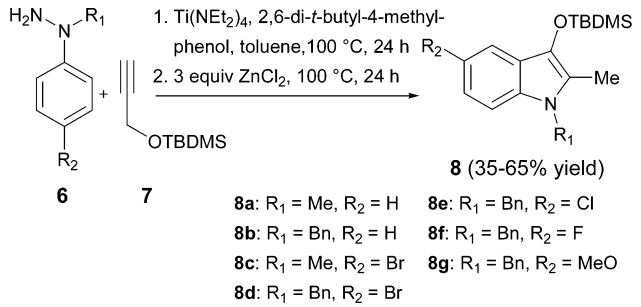
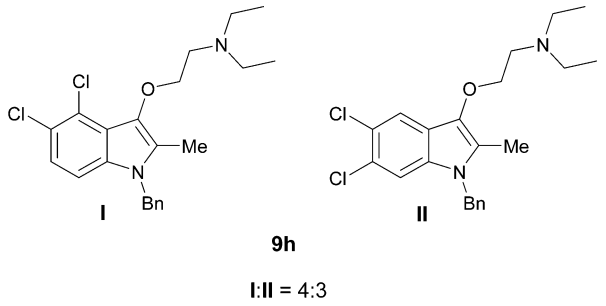


Scheme 2 Ti-catalyzed synthesis of electron-rich 3-silyloxy-2-methylindoles (**8**).

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

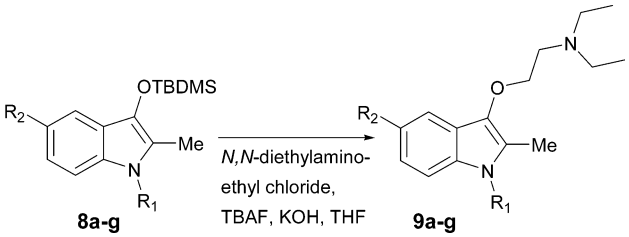
After some optimization, it turned out that a mixture of potassium hydroxide and tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran gave the best results for the *in situ* desilylation reaction. The resulting 3-hydroxyindoles were not stable and had to be directly alkylated. Under these conditions, 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).

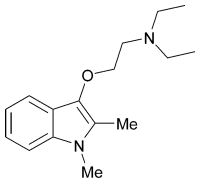
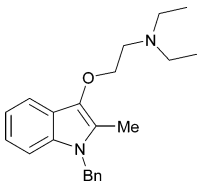
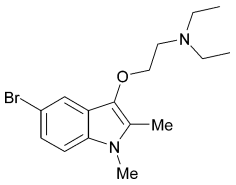
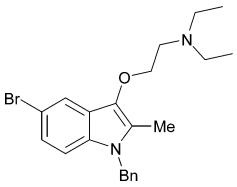
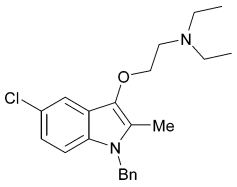
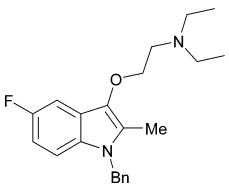
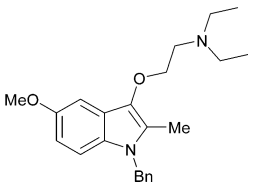


Scheme 3 Regioisomers **I** and **II** of the dichlorosubstituted derivative **9h**.

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

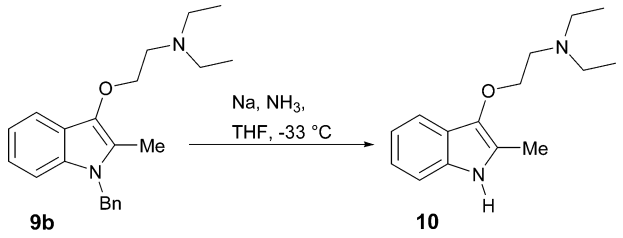
Table 1 Synthesis of 3-(2-*N,N*-diethylaminoethoxy)indoles [a]



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.

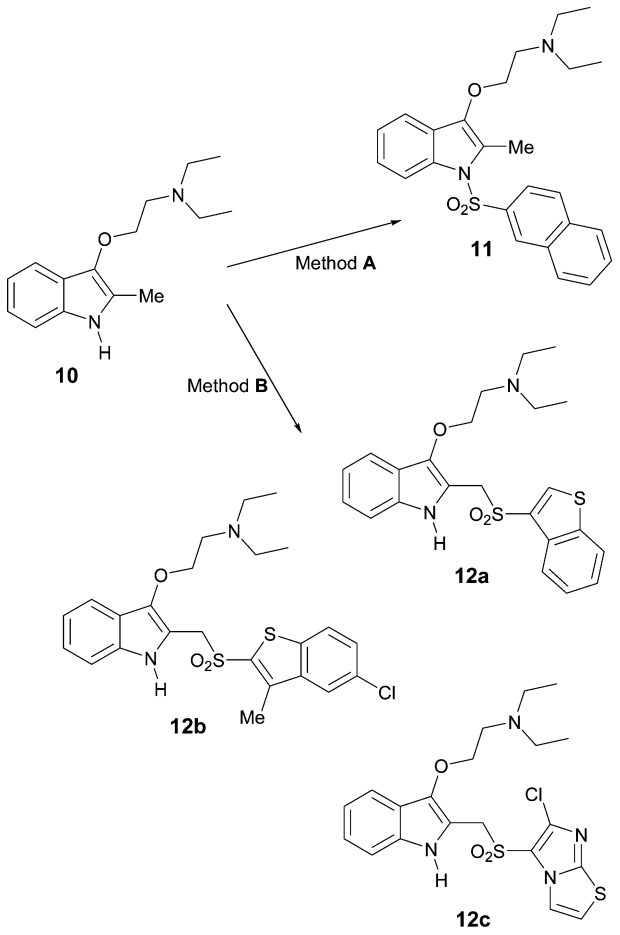
at −33 °C afforded the *N*-deprotected indole in high yield (95%) (Scheme 4).[16] Although this method worked well on most of the indoles, unfortunately, it was not usable for debenzylation of the 5-chlorinated 3-(2-*N,N*-diethylaminoethoxy)indole **9e**.



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.

Acknowledgements

This work has been funded by the Laboratories Dr. Esteve S.A., the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), and the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213 and Leibnizprice). We thank Dr W. Baumann, Dr C. Fischer, S. Buchholz, and S. Schareina for their excellent technical and analytical support.

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4.4 Zn-catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination

Karolin Alex, Annegret Tillack, Nicolle Schwarz, Matthias Beller*, *Org. Lett.* **2008**, *10*, 2377-2379.

Contributions

My contribution as co-author of this paper accounts to approximately 80%.

ORGANIC LETTERS

2008
Vol. 10, No. 12
2377−2379

Zinc-Catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination

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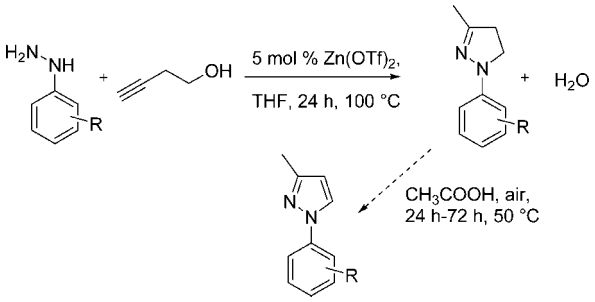
Received March 14, 2008

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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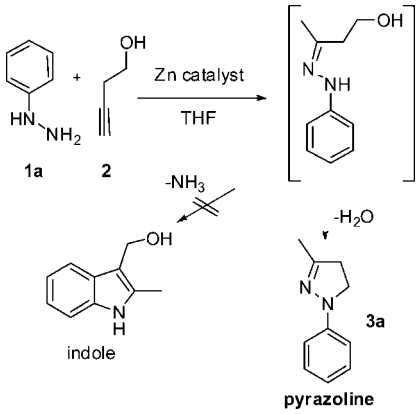
10.1021/ol800592s CCC: $40.75
Published on Web 05/27/2008

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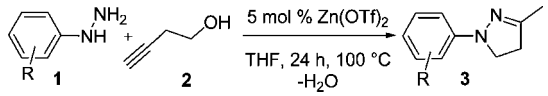
Table 2. Reaction of Arylhydrazines **1** with 3-Butynol **2** to Various Substituted Pyrazolines[a]



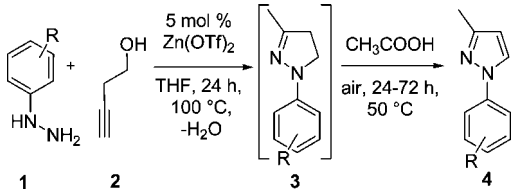
entry	hydrazine **1**	pyrazoline **3**	yield (%)[b]
1	**1a**	**3a**	96
2	**1b**	**3b**	96
3	**1c**	**3c**	88
4	**1d**	**3d**	98
5	**1e**	**3e**	52
6	**1f**	**3f**	99
7	**1g**	**3g**	96
8	**1h**	**3h**	87
9	**1i**	**3i**	99
10	**1j**	**3j**	98
11	**1k**	**3k**	97

[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.

Acknowledgment. This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung and Forschung), the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213, and Leibniz-price), and the Fonds der Chemischen Industrie (FCI). We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, and K. Mevius for their excellent technical and analytical support.

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.

OL800592S

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

Karolin Alex, Annegret Tillack, Nicolle Schwarz, Matthias Beller*, *Tetrahedron Lett.* **2008**, *49*, 4607-4609.

Contributions

My contribution as co-author of this paper accounts to approximately 80%.

Tetrahedron Letters 49 (2008) 4607–4609

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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ARTICLE INFO

Article history:
Received 8 April 2008
Revised 18 May 2008
Accepted 19 May 2008
Available online 23 May 2008

Keywords:
Hydrazine
Hydroamination
Intermolecular
Pentynoic acid
Pyridazinone
Zinc

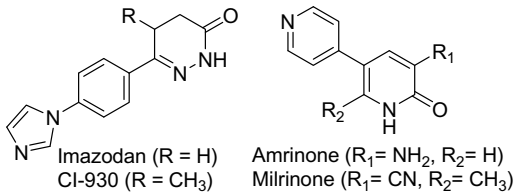
ABSTRACT

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]

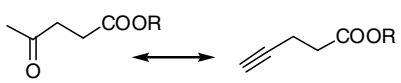


Scheme 1. Selected examples of biologically active pyridazinones.

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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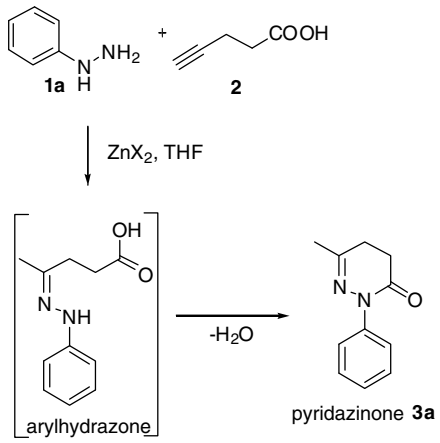
E-mail address: matthias.beller@catalysis.de (M. Beller).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.084



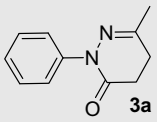
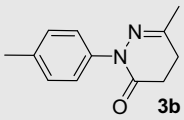
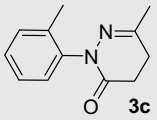
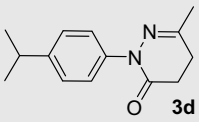
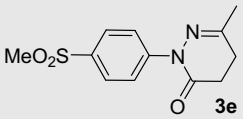
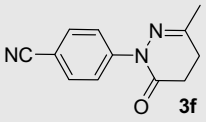
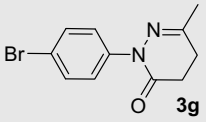
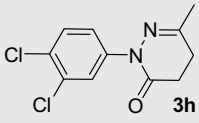
Scheme 3. Synthesis of pyridazinone **3a**.

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.

Acknowledgments

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-price), and the Fonds der Chemischen Industrie (FCI). We thank Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, S. Schareina, and K. Mevius for their excellent technical and analytical support.

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

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Contributions

Compound **4f** and Table 2 were prepared by myself. My contribution as co-author of this paper accounts to approximately 30%.

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

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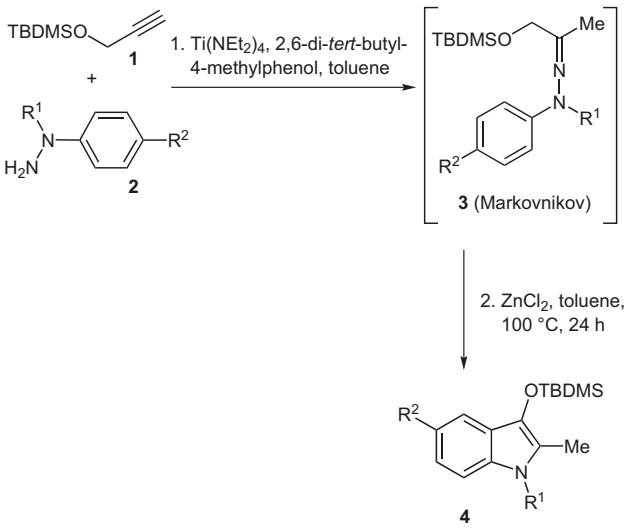
Received 24 January 2007

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).

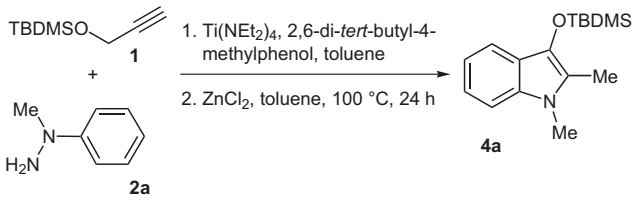


Scheme 1 Hydrohydrazination of silyl-protected propargyl alcohol to 3-silyloxy-2-methylindoles

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

SYNLETT 2007, No. 7, pp 1091–1095
Advanced online publication: 13.04.2007
DOI: 10.1055/s-2007-973892; Art ID: G02807ST

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]

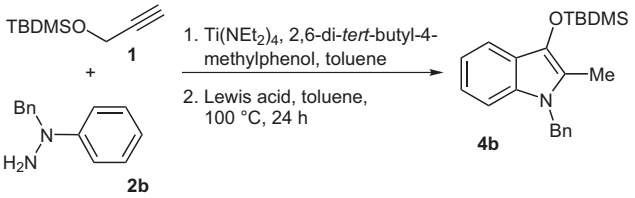
Selected results of the model reaction of *tert*-butyldimethylsiloxy-2-propyne (**1**)[18] with *N*-methyl-*N*-phenylhydrazine (**2a**) are shown in Table 1. The best yield of indole **4** (65%) is achieved applying 5 mol% $Ti(NEt_2)_4$ and 10 mol% 2,6-*tert*-butyl-4-methyl-phenol at 100 °C in the presence 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.

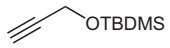
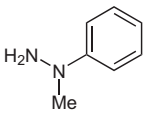
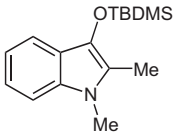
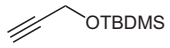
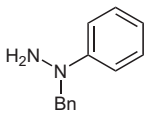
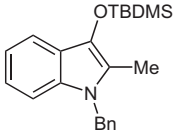
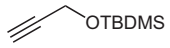
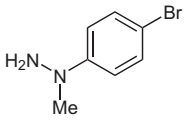
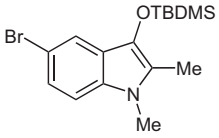
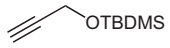
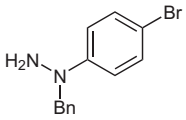
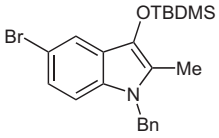
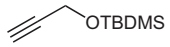
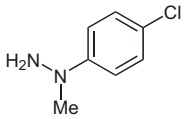
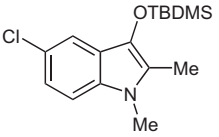
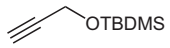
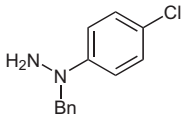
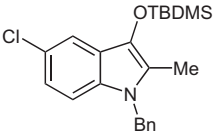
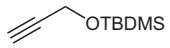
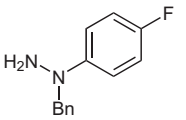
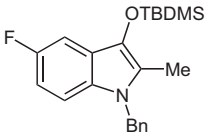
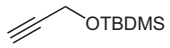
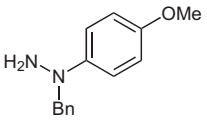
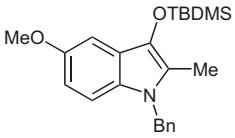
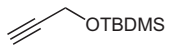
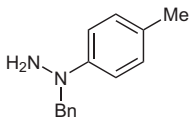
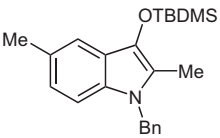
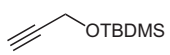
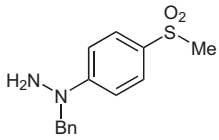
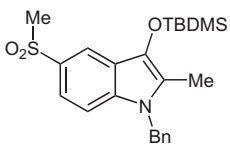
Table 2 Reaction of *tert*-butyldimethylsiloxy-2-propyne (**1**) with *N*-Benzyl-*N*-phenylhydrazine (**2b**)[a]



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.

4.7 A Convenient and General Method for the Synthesis of Indole-2,3-Dicarboxylates and 2-Aryl-Indole-3-Carboxylates

Iliyas Ali Sayyed, Karolin Alex, Annegret Tillack, Nicolle Schwarz, Dirk Michalik, Matthias Beller*, *Eur. J. Org. Chem.* **2007**, 4525-4528.

Contributions

In this paper, I was involved in planning of 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 accounts to approximately 20%.

DOI: 10.1002/ejoc.200700310

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

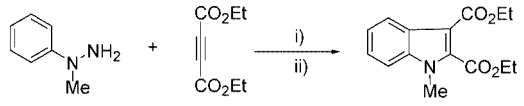
A transition-metal-free, simple and efficient one-pot method for the synthesis of indole-2,3-dicarboxylates and 2-arylindole-3-carboxylates is described. The corresponding products are obtained by a domino hydroamination/Fischer indole cyclization in good-to-excellent yields from easily available 1-alkyl-1-phenylhydrazines 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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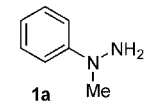
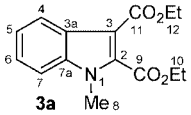
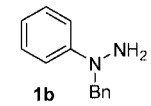
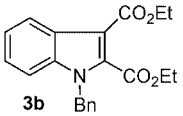
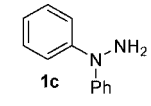
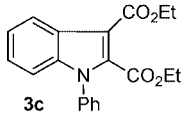
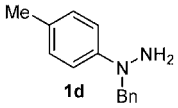
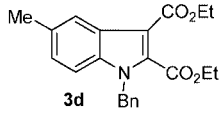
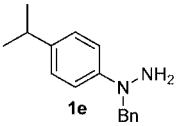
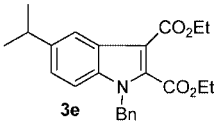
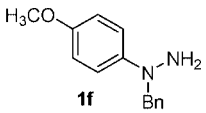
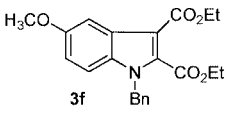
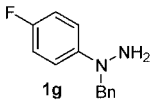
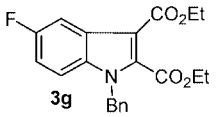
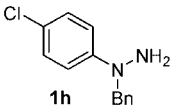
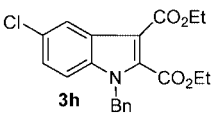
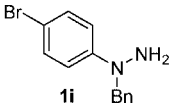
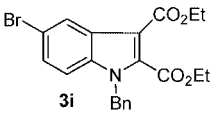
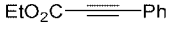
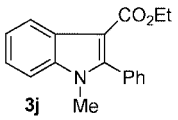
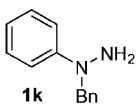
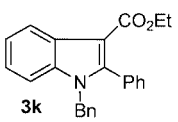
Because of the limited information available, we decided to perform a systematic study to improve the yield of this domino hydroamination/cyclization sequence. Selected experiments are shown in Table 1. The use of an excess amount of phenylhydrazine **1a** (1.5 equiv.) improved the yield of **3a** slightly. 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]

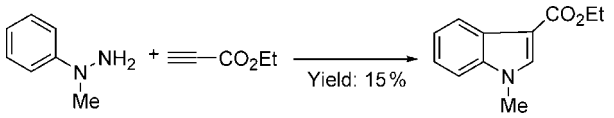
Entry	Hydrazine	Alkyne	Product	Yield [%][b]
1	 **1a**		 **3a**	87
2	 **1b**		 **3b**	67
3	 **1c**		 **3c**	60
4	 **1d**		 **3d**	65
5	 **1e**		 **3e**	60
6	 **1f**		 **3f**	55
7	 **1g**		 **3g**	75
8	 **1h**		 **3h**	40
9	 **1i**		 **3i**	26
10	 **1j**		 **3j**	55
11	 **1k**		 **3k**	60

[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.

Acknowledgments

This work has been supported by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Leibniz-price), and the Fonds der Chemischen Industrie (FCI). We thank all members of the analytical group for their support.

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Received: April 5, 2007
Published Online: July 10, 2007

4.8 Selective Reduction and Functionalization of Diethyl 1-alkyl-1H-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 and contributed significantly to the draft of the manuscript. My contribution as co-author of this paper accounts to approximately 20%.

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Tetrahedron 64 (2008) 4590–4595
Tetrahedron
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Selective reduction and functionalization of diethyl 1-alkyl-1*H*-indole-2,3-dicarboxylates

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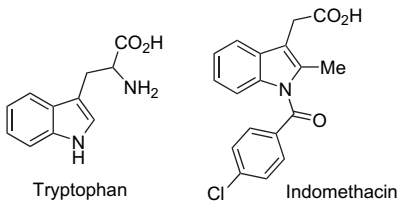
Received 25 January 2008; received in revised form 28 February 2008; accepted 3 March 2008
Available online 7 March 2008

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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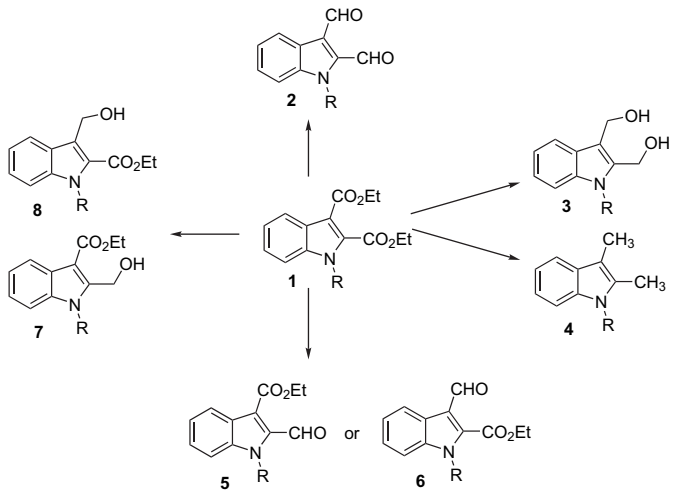
doi:10.1016/j.tet.2008.03.011



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**.

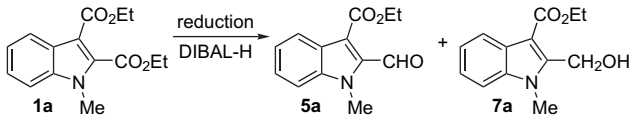
2. Results and discussion

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.

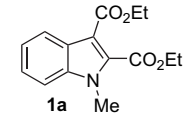
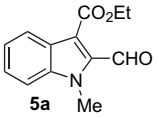
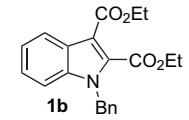
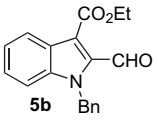
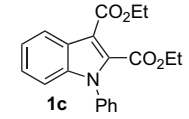
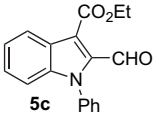
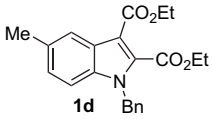
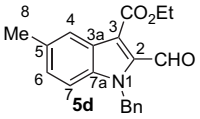
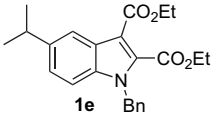
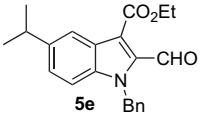
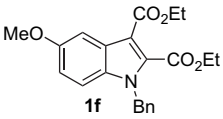
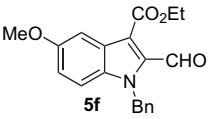
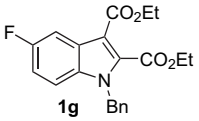
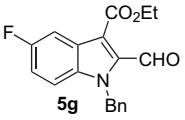
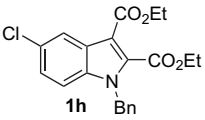
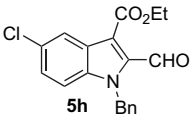
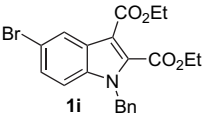
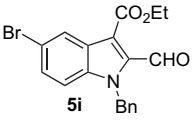
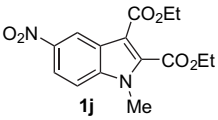
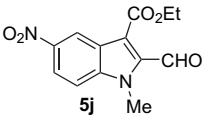
Table 1
Reduction of **1a** under different conditions



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.

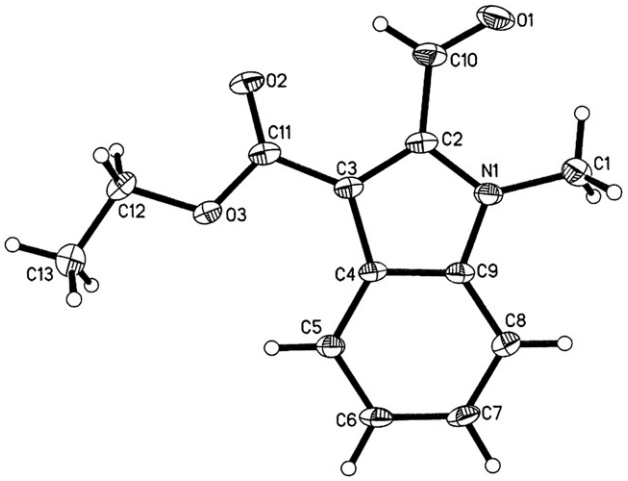


Figure 1. X-ray crystal structure of ethyl 2-formyl-1-methyl-1*H*-indole-3-carboxylate **5a**. The thermal ellipsoids correspond to 30% probability.

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.

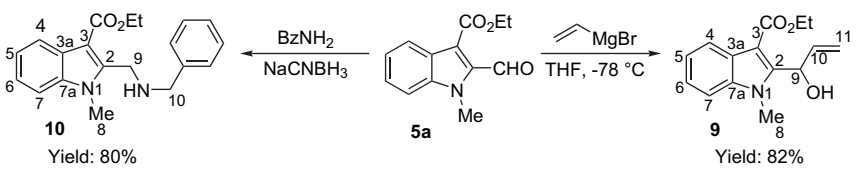
4. Experimental

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). ^{1}H 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). ^{1}H 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). ^{1}H 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). ^{1}H 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. ^{1}H 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. ^{1}H 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.

Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Graduiertenkolleg and Leibniz-price), and the Fonds der Chemischen Industrie (FCI). We thank all the members of the analytical group for their support.

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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.

4.9 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 was involved in planning of 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 accounts to approximately 10%.

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Tetrahedron Letters 48 (2007) 2897–2900

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

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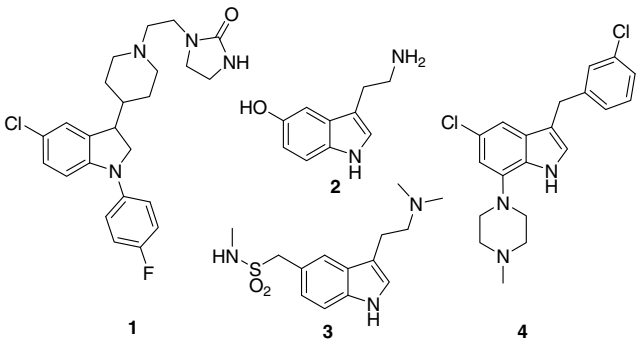
Received 23 January 2007; revised 15 February 2007; accepted 16 February 2007
Available online 22 February 2007

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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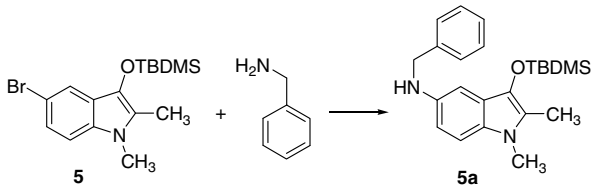
doi:10.1016/j.tetlet.2007.02.082

Table 1. Reaction of 3-*tert*-butyldimethylsilyloxy-5-bromo-indole with benzylamine in the presence of different ligands and bases[a]



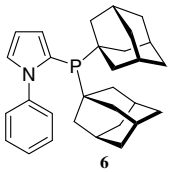
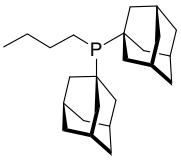
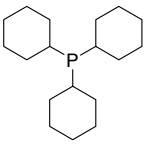
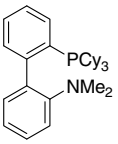
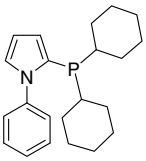
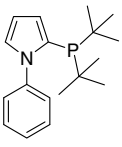
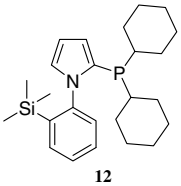
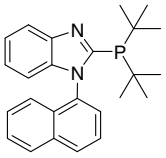
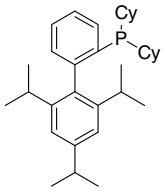
Entry	Ligand	Base	Yield[b] (%)
1		LiHMDS[c]	85
2		K_3PO_4	5
3		Cs_2CO_3	70
4		NaO^{t}Bu	40
5		Without	0
	6		
6		LiHMDS	<10
	7		
7		LiHMDS	<10
	8		
8		LiHMDS	51
	9		
9		LiHMDS	25
	10		
10		LiHMDS	75
	11		
11		LiHMDS	95
	12		

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.

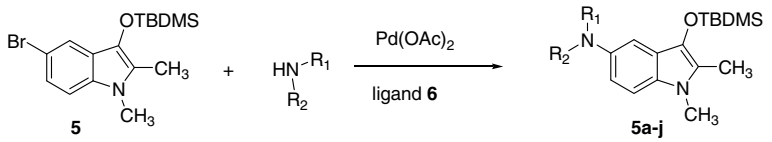
In the present Letter we describe for the first time the palladium-catalyzed amination of 3-silyloxy-5-bromoindole with primary and secondary amines in the presence of $Pd(OAc)_2$ and *N*-phenyl-2-(di-1-adamantylphosphino)-pyrrole as ligand to give new indole derivatives.

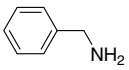
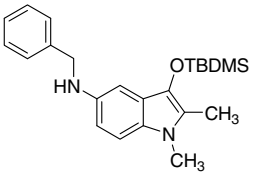
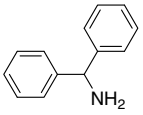
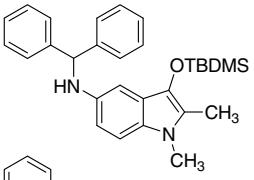
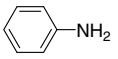
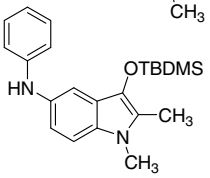
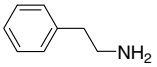
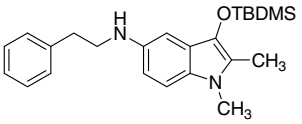
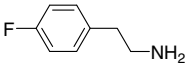
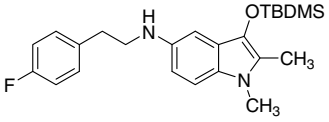
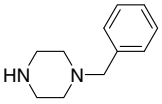
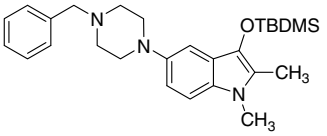
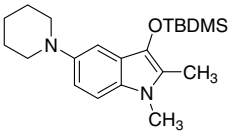
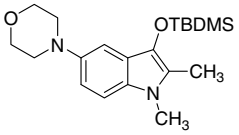
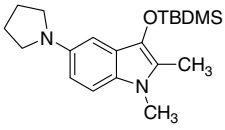
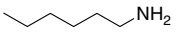
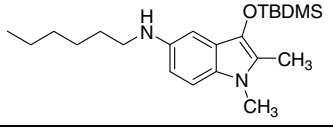
In exploratory experiments, we studied the effect of base and ligands on the reaction of 3-*tert*-butyldimethylsilyloxy-5-bromo-2-methylindole **5** and benzylamine to the corresponding indole **5a**. As shown in Table 1 the best yield of indole **5a** (85%) is achieved with 1.3 equiv of 1 M solution 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

This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Leibniz-price, Graduiertenkolleg 1213), and the Fonds der Chemischen Industrie (FCI). We thank Dr. J. Holenz and Dr. J. L. Díaz Fernández (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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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.

4.10 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**, 3722-3730.

Contributions

In this paper, I was involved in planning of 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 accounts to approximately 10%.

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

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Received 14 August 2007; revised 17 August 2007

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.

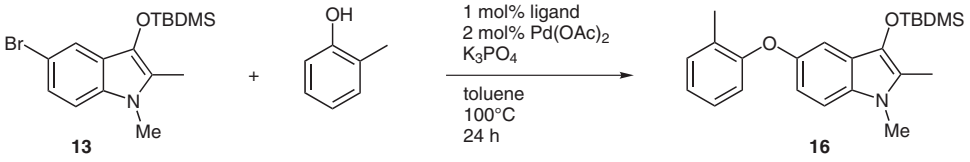
Therefore, we examined the influence of different bases, metal precursors, temperatures (100–160 °C), and the catalyst concentration (0.5–6 mol% Pd). The results of this optimization study are shown in Table 2. Neither the change of base nor the variation of the palladium source raised the product yield. 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).

SYNTHESIS 2007, No. 23, pp 3722–3730
Advanced online publication: 10.10.2007
DOI: 10.1055/s-2007-990819; Art ID: Z18907SS

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



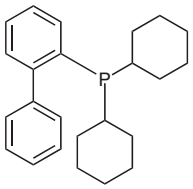
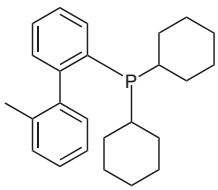
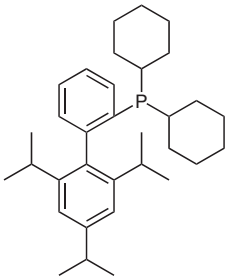
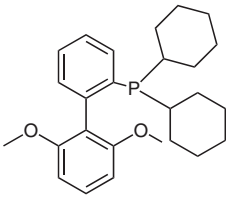
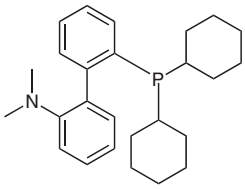
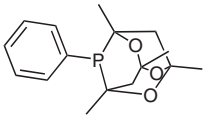
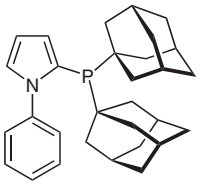
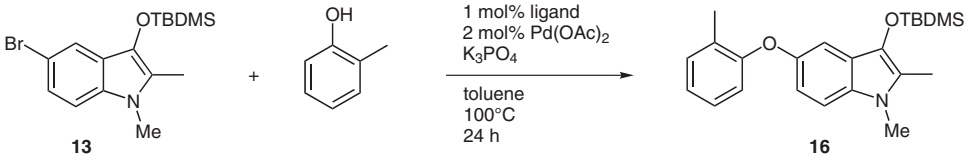
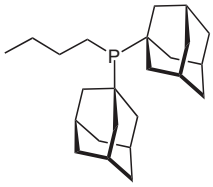
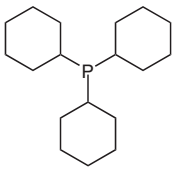
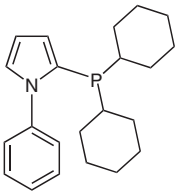
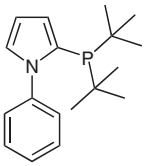
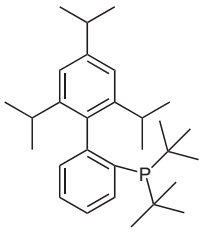
Entry	Ligand		Yield (%)[b]
1		**1**	<1
2		**2**	<1
3		**3**	1
4		**4**	<1
5		**5**	<1
6		**6**	<1
7		**7**	34

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



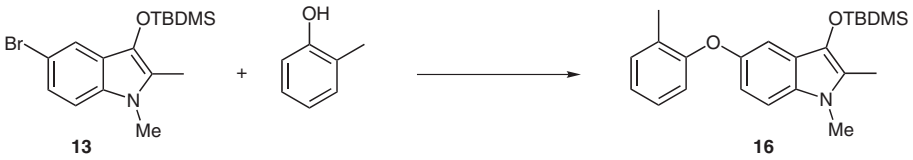
Entry	Ligand		Yield (%)[b]
8		**8**	<1
9		**9**	<1
10		**10**	<1
11		**11**	2
12		**12**	15

[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]



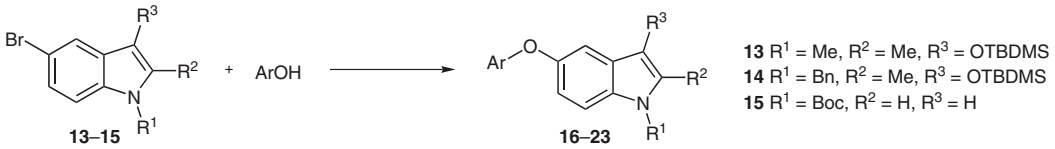
13 **16**

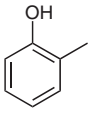
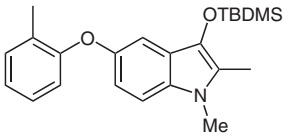
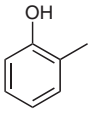
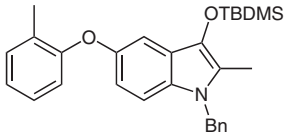
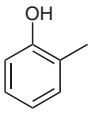
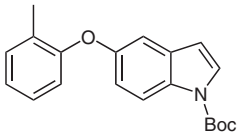
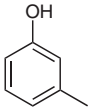
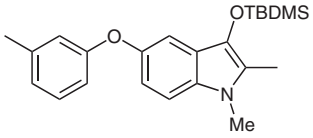
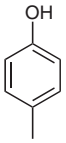
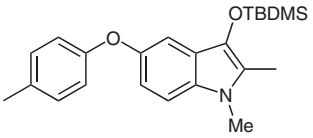
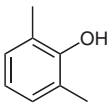
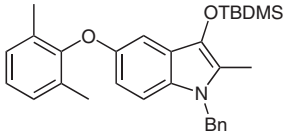
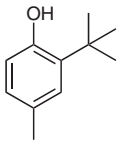
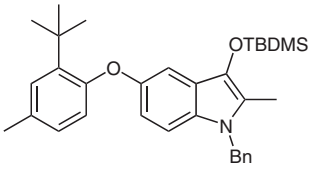
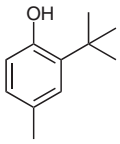
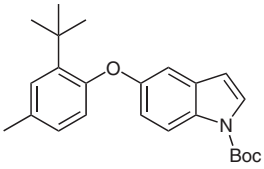
Entry	Pd source	Catalyst (mol%)	Ligand **7** (mol%)	Solvent	Base	Temperature (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	0.5	1	toluene	K_3PO_4	100	25
2	$Pd(OAc)_2$	1	2	toluene	K_3PO_4	100	34
3	$Pd(OAc)_2$	2	4	toluene	K_3PO_4	100	75
4	$Pd(OAc)_2$	2	4[c]	toluene	K_3PO_4	100	60
5	$Pd(OAc)_2$	2	4	toluene	K_3PO_4	120	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.

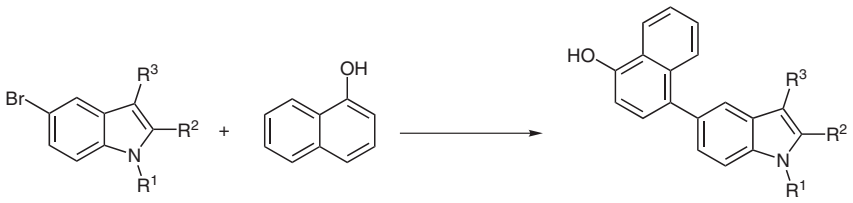
5-Bromo-3-(*tert*-butyldimethylsiloxy)-1,2-dimethyl-1*H*-indole (13)[10d]

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).

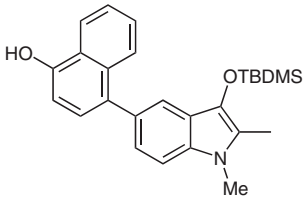
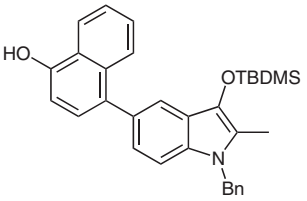
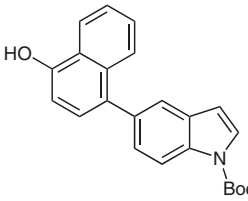
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 132.5 (q), 129.9 (q), 124.2 (q), 123.4, 123.3 (q), 119.7, 111.8 (q), 110.1, 29.8, 26.1, 18.3 (q), 9.5, –3.8.

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.

Acknowledgment

This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Leibniz prize, Graduiertenkolleg 1213), and the Fonds der Chemischen Industrie (FCI). We thank Dr. W. Baumann, Dr. D. Michalik, Dr. C. Fischer, S. Buchholz, S. Schareina, and K. Mevius for their excellent technical and analytical support.

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Publications

JOURNAL CONTRIBUTIONS

1. "Zinc-Promoted Hydrohydrazination of Terminal Alkynes - An Efficient Domino Synthesis of Indoles" K. Alex, A. Tillack, N. Schwarz, M. Beller, *Angew. Chem.* **2008**, *120*, 2337-2340; *Angew. Chem. Int. Ed.* **2008**, *47*, 2304-2307.

2. "General Zn-catalyzed Intermolecular Hydroamination of Terminal Alkynes" K. Alex, A. Tillack, N. Schwarz, M. Beller, *ChemSusChem* **2008**, *1*, 333-338.

3. "Synthesis of 3-(2-*N*,*N*-Dietyhlaminoethoxy)indoles as Potential 5-HT_6 Receptor Ligands" K. Alex, N. Schwarz, V. Khedkar, I. A. Sayyed, A. Tillack, D. Michalik, J. Holenz, J. L. Diaz, M. Beller, *Org. Biomol. Chem.* **2008**, *6*, 1802 - 1807.

4. "Zn-catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination" K. Alex, A. Tillack, N. Schwarz, M. Beller, *Org. Lett.* **2008**, *10*, 2377-2379.

5. "First Synthesis of 4,5-Dihydro-3(2H)-pyridazinones via Zn-mediated hydrohydrazination" K. Alex, A. Tillack, N. Schwarz, M. Beller, *Tetrahedron Lett.* **2008**, *49*, 4607-4609.

6. "Titanium-Catalyzed Hydroamination of Propargyl Alcohol Derivatives: Synthesis of 3-Silyloxy-2-methylindoles via Hydrohydrazination" N. Schwarz, K. Alex, I. A. Sayyed, V. Khedkar, A. Tillack, M. Beller, *Synlett* **2007**, 1091-1095.

7. "A Convenient and General Method for the Synthesis of Indole-2,3-Dicarboxylates and 2-Aryl-Indole-3-Carboxylates" I. A. Sayyed, K. Alex, A. Tillack, N. Schwarz, D. Michalik, M. Beller, *Eur. J. Org. Chem.* **2007**, 4525-4528.

8. "Selective Reduction and Functionalization of Diethyl 1-alkyl-1H-indole-2,3-dicarboxylates" I. A. Sayyed, K. Alex, A. Tillack, N. Schwarz, A. Spannenberg, D. Michalik, M. Beller, *Tetrahedron* **2008**, *64*, 4590-4595.

9. "A Novel Palladium Catalyst for the Amination of Electron-rich Indole Derivatives" N. Schwarz, A. Tillack, K. Alex, I. A. Sayyed, R. Jackstell, M. Beller, *Tetrahedron Lett.* **2007**, *48*, 2897-2900.

10. "Palladium-Catalyzed C-O and C-C Coupling Reactions of Electron-Rich Indoles" N. Schwarz, A. Pews-Davtyan, K. Alex, A. Tillack, M. Beller, *Synthesis* **2007**, 3722-3730.

PATENT

M. Beller, K. Alex, J. L. Diaz, EP 07384011.8, 19.01.2007 ("Substituted Indole Sulfonamide Compounds, their Preparation and Use as Medicaments").

TALKS

1. "An Efficient Domino Synthesis of Indoles via a Zinc-promoted Hydrohydrazination of Terminal Alkynes" K. Alex, *IXth Netherlands' Catalysis and Chemistry Conference*, Noordwijkerhout (Netherlands), 03.-05.03.2008.
2. "An Efficient Procedure for the Synthesis of Indoles via Zinc-mediated Hydrohydrazination of Alkynes" K. Alex, *3rd Symposium of Research Training Group 1213, New Methods for Sustainability in Catalysis and Technique*, Rostock (Germany), 06.-07.09.2007.
3. "Medicinal chemistry strategies to 5-HT_6 receptor ligands as target for central nervous system-mediated diseases" K. Alex, *2nd Symposium Research Training Group 1213 - New Methods for Sustainability in Catalysis and Technique*, Rostock, 17.-18.10.2006.
4. "New Method for the Synthesis of Tryptamines via Catalytic Hydrohydrazination of Alkynes" K. Alex, *Summer School Medicinal Chemistry*, Regensburg (Germany), 25.-27.9.2006.

POSTER CONTRIBUTIONS

1. "New Method for the Synthesis of Indoles via Hydrohydrazination of Alkynes" K. Alex, A. Tillack, N. Schwarz, M. Beller, *EUROPACAT VIII*, Turku (Finnland), 26.-31.08.2007.
2. "New Method for the Synthesis of Tryptamines via Catalytic Hydrohydrazination of Alkynes" K. Alex, N. Schwarz, A. Tillack, V. Khedkar, M. Beller, *Summer School Medicinal Chemistry*, Regensburg (Germany), 25.-27.9.2006.

POSTER CONTRIBUTIONS (Cont.)

3. "New Method for the Synthesis of Tryptamines via Catalytic Hydrohydrazination of Alkynes" K. Alex, N. Schwarz, A. Tillack, V. Khedkar, M. Beller, *1st European Chemistry Congress*, Budapest (Hungary), 27.-31.8.2006.

4. "Eine neue Methode für die Synthese von Tryptaminen und Tryptopholen mittels katalytischer Hydrohydrazinierung von Alkinen" N. Schwarz, K.Alex, A. Tillack, V. Khedkar, M. Beller, *39. Jahrestreffen Deutscher Katalytiker*, Weimar (Germany), 15.-17.3.2006.