Helsinki University of Technology Department of Chemical Technology

Laboratory of Organic Chemistry

Espoo 2003

MODIFICATIONS OF CARBOXYINDOLES ON SOLID PHASE

Jan Tois

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Dissertation for the degree of Doctor of Philosophy to be presented with due permission of the Department of Chemical Technology for public examination and debate in Auditorium KE2 (Komppa Auditorium) at Helsinki University of Technology (Espoo, Finland) on the 24th of October, 2003 at 12 o'clock afternoon.

Helsinki University of Technology
Department of Chemical Technology
Laboratory of Organic Chemistry

Teknillinen korkeakoulu
Kemian tekniikan osasto
Orgaanisen kemian laboratorio

Distributor:
Helsinki University of Technology
Laboratory of Organic Chemistry
P.O. Box 6100
FIN-02015 HUT

ISBN 951-22-6751-9
ISSN 1236-2999

Otamedia Oy
Espoo 2003

Tois, Jan. ***Modifications of Carboxyindoles on Solid Phase***.
Helsinki University of Technology, Department of Chemical Technology, Laboratory of Organic Chemistry.

Keywords: carboxyindoles, solid phase synthesis, direct functionalization, Vilsmeier formylation, lithiation, bromination.

Abstract

Different solid phase modifications were studied in order to develop new and simple routes for pharmaceutically interesting highly substituted carboxyindoles. A convenient method for the preparation of 5-substituted 2-carboxyindoles and three novel direct functionalization methods for carboxyindoles were developed during this study.

5-Nitro-2-carboxyindole was synthesized easily in three steps from commercially available inexpensive 4-nitro-aniline. Through attachment of this template to solid phase followed by reduction, reductive amination, *N*-alkylation and cleavage, a small library of differently substituted carboxyindoles were obtained.

Solid phase brominations were studied followed by palladium catalyzed Suzuki-coupling. This technology offers an efficient and selective method to introduce bromine and a new C-C-bond to 3-position of polymer bound 2-carboxyindoles.

Formylation studies were also succesfull. By utilizing Vilsmeier formylation a new C-C-bond was obtained direcly and selectively at the 3-position of polymer bound 2-carboxyindoles.

In solid phase metalation studies of 5-carboxyindoles a 4-position functionalization was achieved in 80 % regioselectivity. Despite the moderate regioselectivity it is obvious that ring lithiation can be adopted to solid phase.

Acknowledgements

Research work reported in this thesis has been carried out in the Department of Pharmaceutical Chemistry at the University of Helsinki during the years 1998-2001 under the guidance of Professor Robert Franzén and in the Department of Chemistry at the Helsinki University of Technology during the years 2001-2003 under the guidance of Professor Ari Koskinen.

First I wish to thank my supervisor, Professor Ari Koskinen, for offering me the possibility to work in his group and providing his expertise in organic synthesis. His encouraging comments and helpful attitude towards my work has been extremely valuable during these years. Great thanks belongs also to my supervisor at the first years, Professor Robert Franzén. Thank you for your kind attitude and valuable hints in the early stages of this work.

Special thanks go to the people who have shared the laboratory with me. You have all encouraged me during these, not always so pleasant, years. Thank you Mikko, Antti, Mika, Petteri, Olli and Irene for standing on my side in difficult moments. Thank you all at the Helsinki University of Technology, Laboratory of Organic Chemistry and especially Markku.

I would like to thank my parents and my father-in-law for their support during my studies. You have always remined me by asking: " What is the current status of your thesis? ".

The last and the warmest thanks belong to my loving wife Eva. You are probably the only person who believed all the time that I will finally managed to do this thesis. At the moments I my self had some misbelief your belief was stronger. Thank you Eva.

Espoo, April 2003 Jan Tois

Ac	acetyl
AIBN	azobis(isobutyronitrile)
Ar	aryl
Bn	benzyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
Boc	*t*-butoxycarbonyl
Bu	butyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
dba	dibenzylideneacetone
DCA	dichloroacetic acid
DCE	dichloroethane
DCM	dichloromethane
DCC	dicyclohexylcarbodiimide
DEM	dimethoxymethyl
DIC	di-isopropylcarbodiimide
DIPEA	di-isopropylethylamine
DME	1,2-dimethoxyethane
DMA	*N*,*N*-dimethylacetamide
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
Et	ethyl
EtOAc	ethylacetate
Fmoc	fluorenylmethoxymethyl
HPLC	high-performance liquid chromatography
HOBt	1-hydroxybenzotriazole
HMB	hydroxymethylbenzoic acid
MSNT	1-(2-mesitylene-sulfonyl)-3-nitro.1,2,4-triazole
Me	methyl
NBS	*N*-bromosuccinimide
NIS	*N*-chlorosuccinimide
NMFA	*N*-methylformanilide
NMI	*N*-methylimidazole
NMP	1-methyl-2-pyrrolidine
PPA	polyphosphoric acid
PS	polystyrene
PKC	protein kinace C
PBP	pyridinium bromide perbromide
SPOS	solid phase organic chemistry
SPPS	solid phase peptide synthesis
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine
TLC	thin layer chromatography
Ts	tosyl, *p*-toluenesulfonyl
TEA	triethylamine
TFA	trifluoroacetic acid
TIPS	tri-isopropylsilyl
TMOF	trimethylorthoformate

List of Original Papers referred to in the text by Roman numerals:

I. Tois, J.; Franzén, R.; Aitio, O.; Huikko, K.; Taskinen, J., ‘ Preparation of 5-Substituted 2-Carboxyindoles on Solid Support ‘, *Tetrahedron Lett*. **2000**, *41*, 2443-2446.

II. Tois, J.; Franzén, R.; Aitio, O.; Laakso, I.; Huuskonen, J.; Taskinen, J., ‘ Solid-Phase Bromination and Suzuki Coupling of 2-Carboxyindoles ‘, *Combin. Chem. High Throughput Screen*. **2001**, *4*, 521-524.

III. Tois, J.; Franzén, R.; Aitio, O.; Laakso, I.; Kylänlahti, I., ‘ Vilsmeier Formylation 2-Carboxyindoles and Preparation of O-Benzylhydroxyureas on Solid Phase ‘, *J. Comb. Chem*. **2001**, *3*, 542-545.

IV. Tois, J.; Koskinen, A., ‘ Solid-phase Lithiation of 5-Carboxyindoles ‘, *Tetrahedron Lett*. **2003**, *44*, 2093-2095.

V. Tois, J.; Franzén, R.; Koskinen, A. ‘ Synthetic Approaches towards Indoles on Solid phase-Recent Advances and Future Directions ‘, *Tetrahedron* **2003**, *59*, 5395-5405.

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1. Introduction

1.1. Introduction to indoles

Indole **1** is a benzopyrrole in which the benzene and pyrrole rings are fused through the 2, 3-positions of the pyrrole.

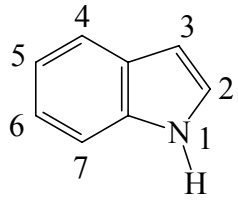

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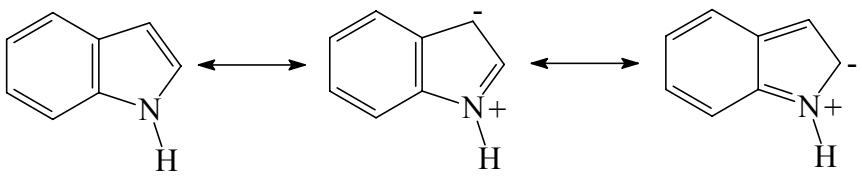
Figure 1. The basic structure and numbering system of indole compounds.

Indole is a colorless crystalline solid (mp 52-54 ^{o}C, bp 254 ^{o}C) with an unpleasant odour. It is classified as an π-excessive aromatic heterocyclic compound, with the heterocyclic nitrogen atom donating two of the ten π-electrons. Resonance structures are illustrated in Figure 2.



1 **2** **3**

Figure 2. Resonance structures of indole.

Indole derivatives occur widely in many natural products. Indole itself has been obtained in small amounts by extraction from naturally occurring materials by methods which suggest that the indole so obtained is in many cases the result of breakdown of its derivatives. Various plants have yielded indole, among them the following: *Robinia pseudacacia*,[1] the jasmines, [2, 3, 4] certain citrus plants, [5] and orange blossoms.[6] Indole is also found after putrefactive processes have taken place. It is found in the animal body wherever pus formation occurs [7] and in the liver [8] and brain.[9] Indole has also been found to be present in coal tar in the fraction boiling between 240 ^{o} - 260 ^{o}C.[10] In 1930 it was discovered that the essential amino acid, tryptophan **4** was in fact an indole derivative.

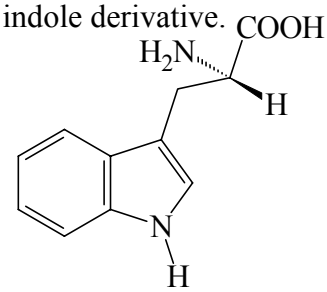


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Figure 3. Amino acid (*S*)-tryptophan.

1.2. Indole alkaloids

The alkaloids are a group of naturally occurring organic compounds containing nitrogen. The term alkaloid means simply alkalilike. The first modern definition was presented by Winterstein and Trier.[11] " True alkaloids " were defined as compounds meeting four additional qualifications:

1. The nitrogen atom is part of a heterocyclic system.
2. The compound has a complex molecular structure
3. The compound manifests significant pharmacological activity.
4. The compound is restricted to the plant kingdom.

Nowadays a more simple definition has been suggested:[12]

An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms.

The chemical classification of alkaloids is based on their carbon-nitrogen skeletons and some of the commonest skeletons are shown below.

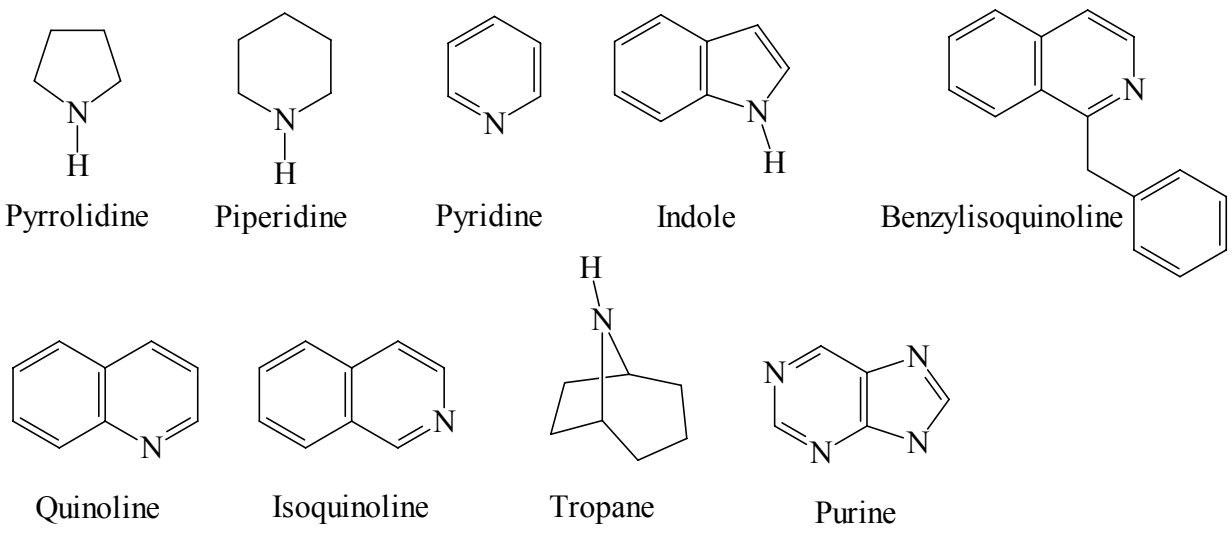


Figure 4. Some common alkaloid ring skeletons.

The alkaloids containing an indole nucleus are an extensive and complex group of compounds. It has been estimated that more than one-quarter of all known alkaloids are indole derivatives.[13] While the distribution of indole alkaloids is broad, certain plant groups are noted for containing them. Seed plant family *Apocynaceae* has been well-investigated [14] and also the fungal genus *Claviceps* (ergot) is an important source of indole alkaloids.[15]
Usually the indole alkaloids are complex molecules and optically active. Some well-known indole alkaloids are presented in Figure 5.

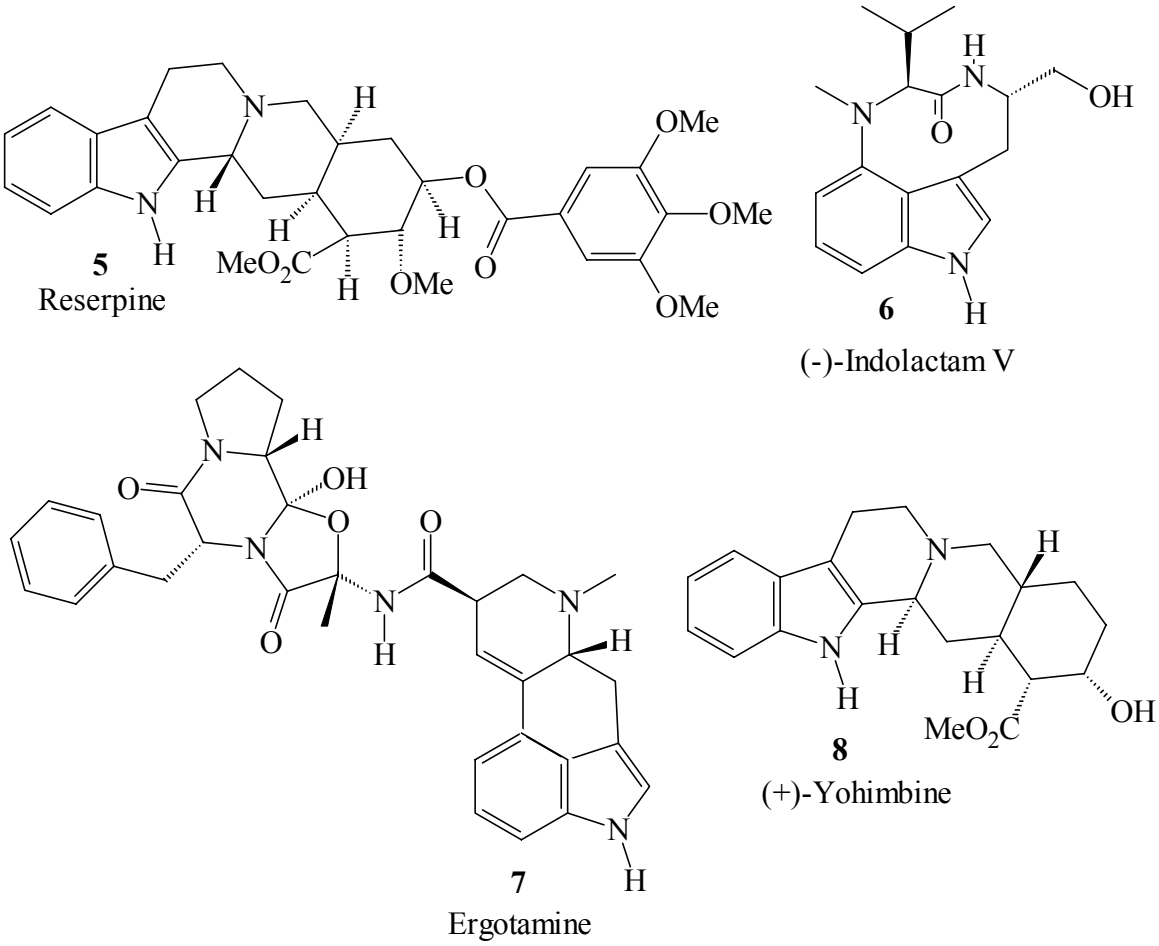
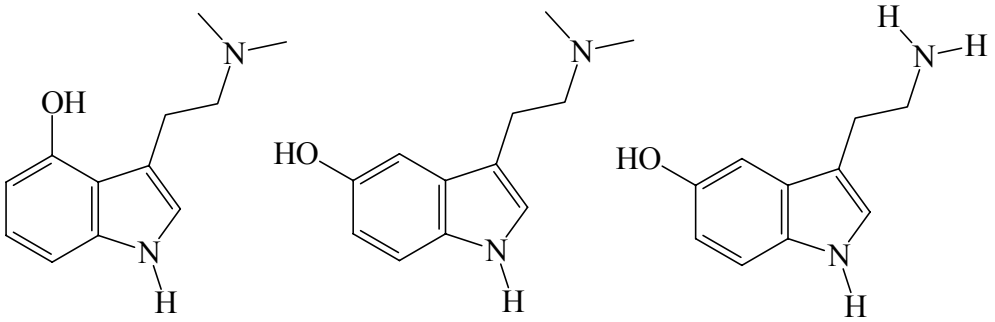


Figure 5. Some well-known indole alkaloids.

Most of the indole alkaloids are derived from the amino acid (*S*)-tryptophan **4** and the aminoethyl side chain at the 3-position is still discernible in their structures.

1.3. Physiologically active indole derivatives

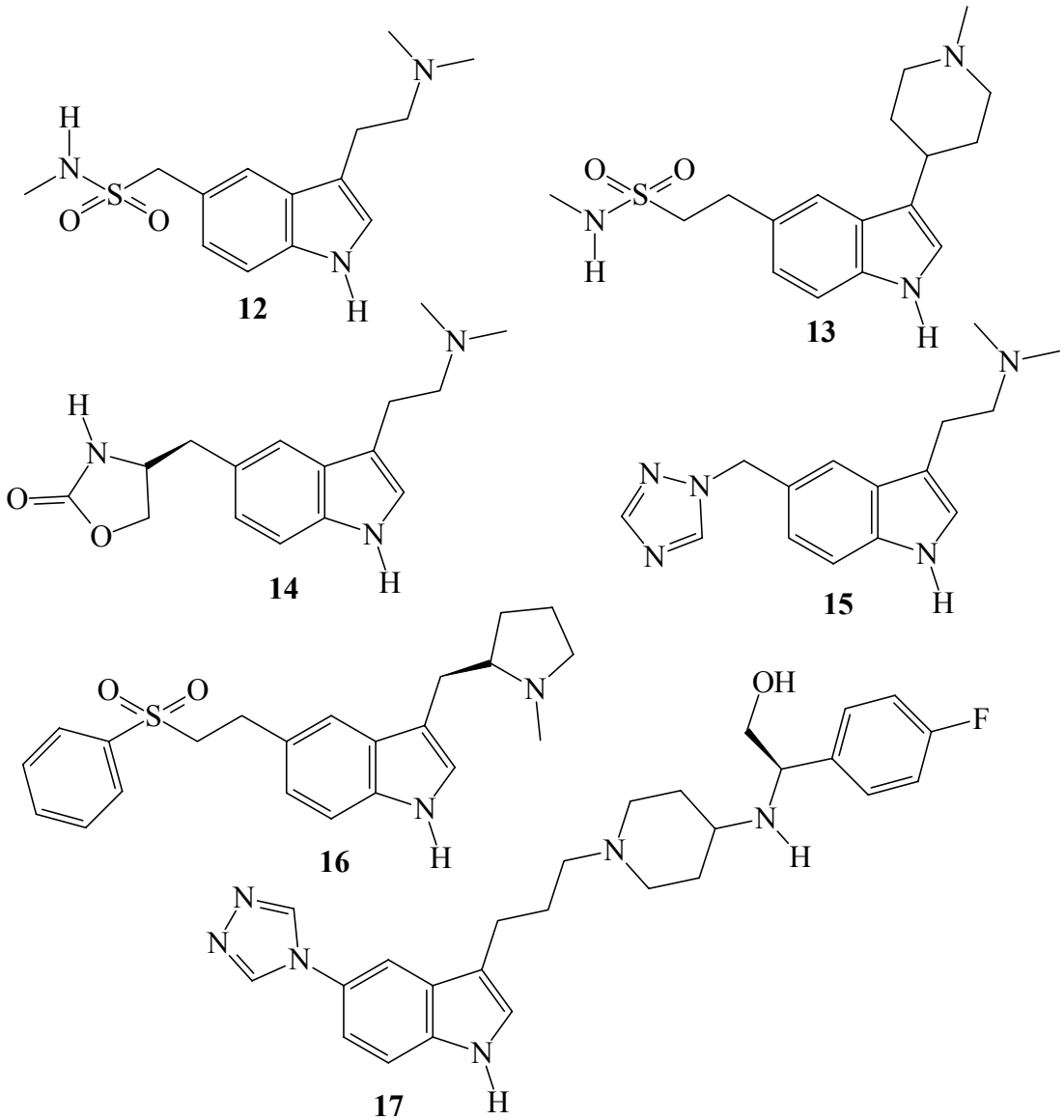
There are several thousand indole alkaloids known and many of these have important physiological activity.[16] Ergotamine **7** is a potent vasoconstrictor and is used, as its tartrate salt, to treat migraine.[17] Reserpine **5** has been used to treat hypertensive, nervous and mental disorders.[18] Even though most indole related compounds are complex structures, simple indole derivatives also exist in nature. Psilocin **9** is one of the active constituents of Mexican mushrooms which have been used as early as 1500 BC in Aztec and Mayan culture as hallucinogens.[19] Bufotenine **10** is another hallucinogen that occurs in toadstool.[20] Serotonin **11** is widely distributed in nature and it acts as a constrictor of arteries in brain and is implicated in migraine.[21]



9 **10** **11**

Figure 6. Psilocin **9**, Bufotenine **10** and serotonin **11**.

Since the discovery of sumatriptan **12** [22] (a 5-$HT_{1B/1D}$ receptor agonist, used as an effective treatment for migraine headache) intensive research in this area [23-28] has led to several related compounds such as naratriptan **13**,[29] zolmitriptan **14**,[30] rizatriptan **15** [31] and eletriptan **16** [32] entering the market and late phase clinical trials. L-772, 405 **17** [33] also shows very good selectivity over a range of other serotonin and nonserotonin receptors and has excellent bioavailability following subcutaneous administration in rats.



12 **13** **14** **15** **16** **17**

Figure 7. Indole derivatives used for treatment of migraine.

It has been suggested that affinity for 5-HT_{1D} receptors may be obtained by combining the ethylamine and indole groups. Maintenance of the hydrogen bond acceptor qualities of substituents in the 5-position should conserve affinity.[34]
Melatonin **18** is the principal hormone of the vertebrate pineal gland.[35] Recent studies on the pharmacology of **18** and on the distribution of its binding sites suggest that this neurohormone has a variety of biological effects.[36, 37] Physiological roles of melatonin are summarized in Figure 8.

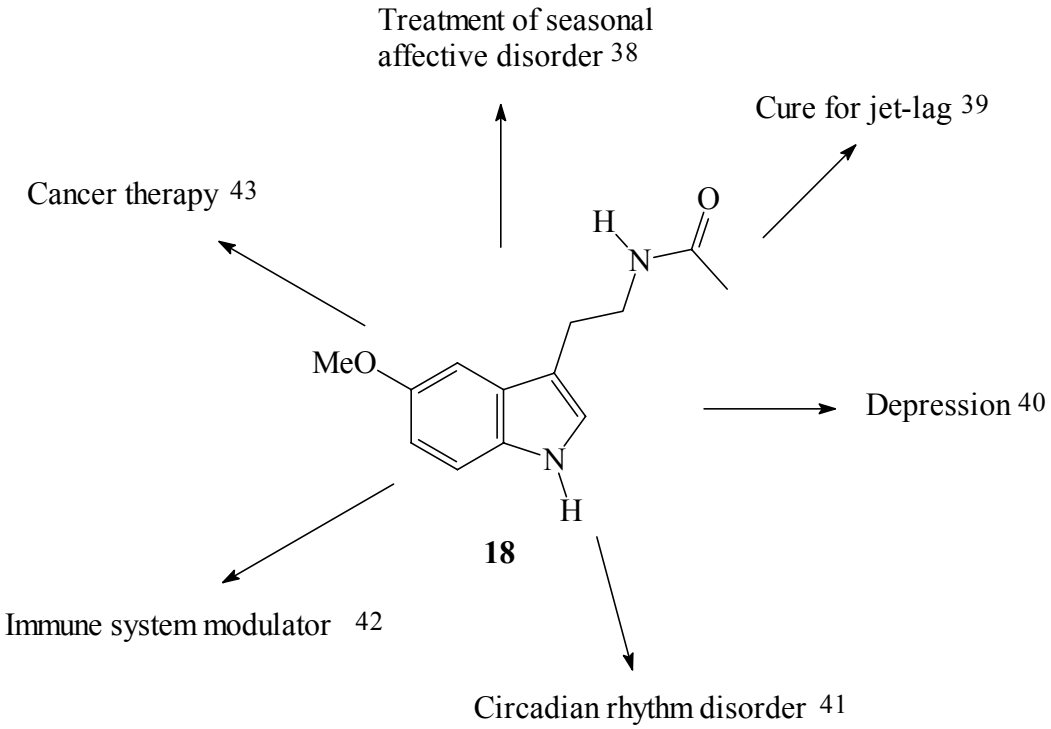


Figure 8. Pharmacological profile of melatonin **18**.

Protein kinase C (PKC) is of particular interest due to its involvement in cell differentiation, proliferation, secretory processes and gene expression [44-47] and is an actively exploited target for the treatment of diseases such as cancer, inflammatory arthritis, asthma and viral infection.[48] Several natural products such as staurosporine **19** [49] are non-specific PKC inhibitors and potent indole derivatives have been synthezised in several laboratories. Some of these structures are illustrated in Figure 9. The structural complexity has been reduced by omitting the chiral centers present in staurosporine. Also the amide group has been replaced by imide group. All these potent derivatives have similar features to staurosporine also. The indole moiety and aminopropyl chains are still discernible in their structures.

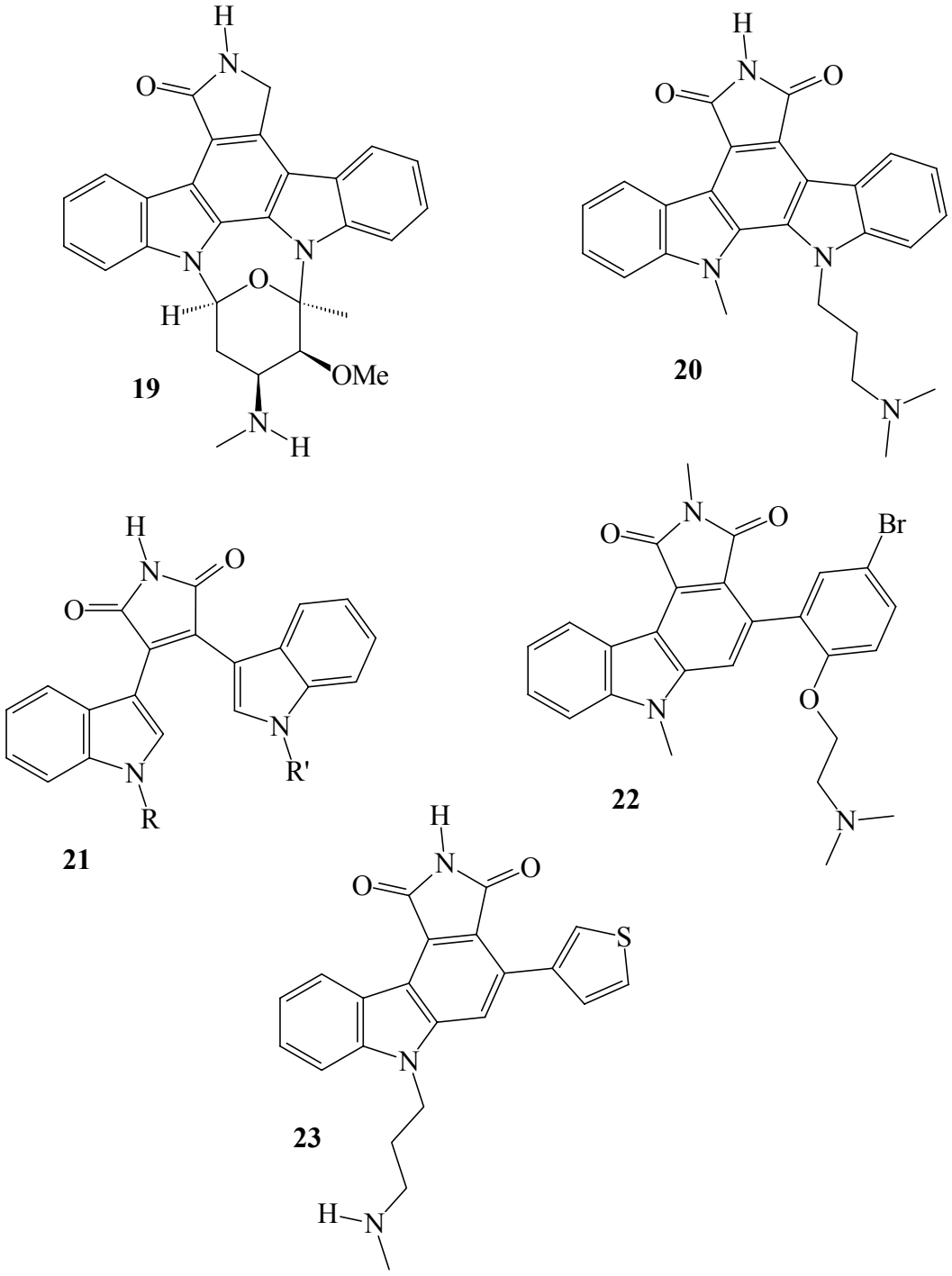
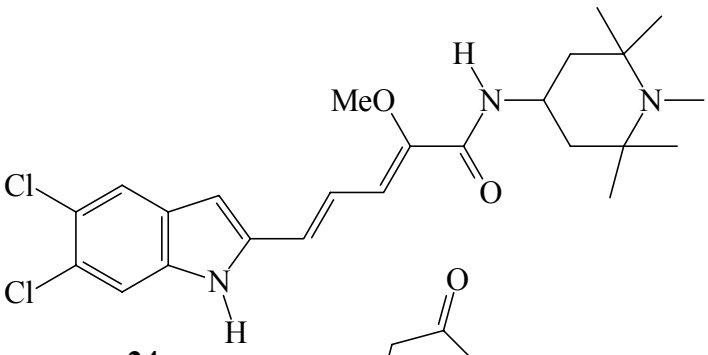


Figure 9. Potent indole based PKC inhibitors.

Thousands of indole containing pharmaceuticals exists in the literature and some of the most recent ones are collected in Figure 10. SB 242784 **24** has been developed for the treatment of osteoporosis.[50] The antiemetics Ramosetron **25** and Dolasetron **26** have potential for the treatment of chemotherapy-induced nausea and vomiting. Delavirdine mesylate **27** is a new HIV-1 reverse transcriptase inhibitor and Sertindole

28 is a neuroleptic for acute and chronic schizophrenia. Fluvastatin **29** is an HMG-CoA reductase inhibitor and Zafirlukast **30** is a new antiasthma drug.[51]



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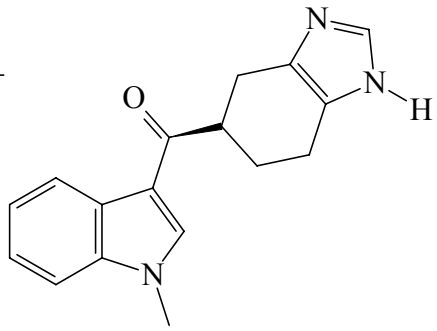

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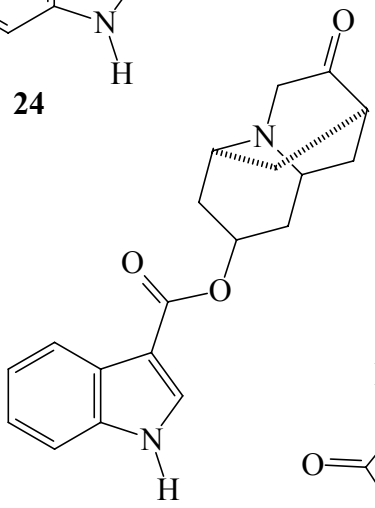

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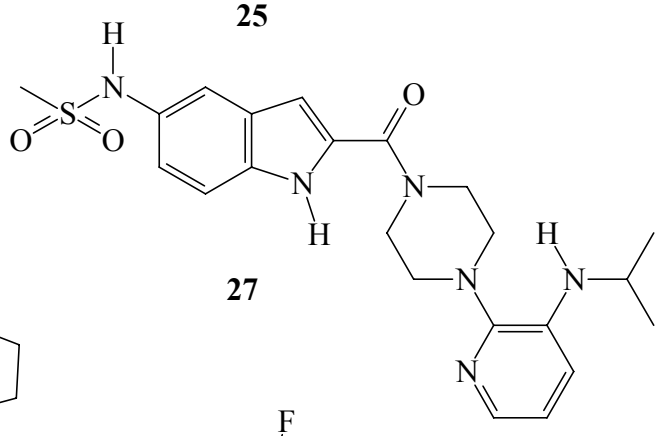

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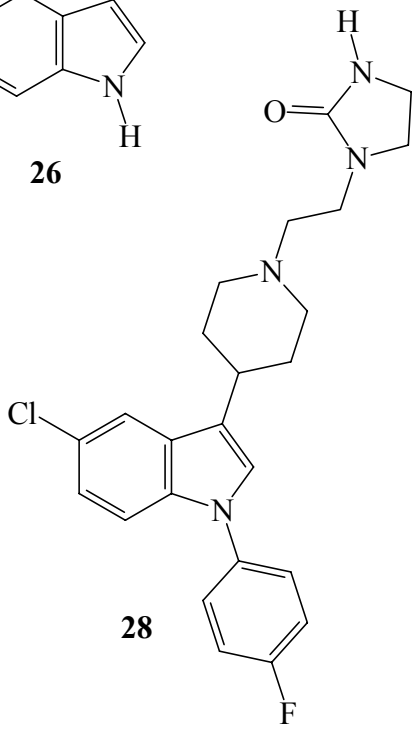

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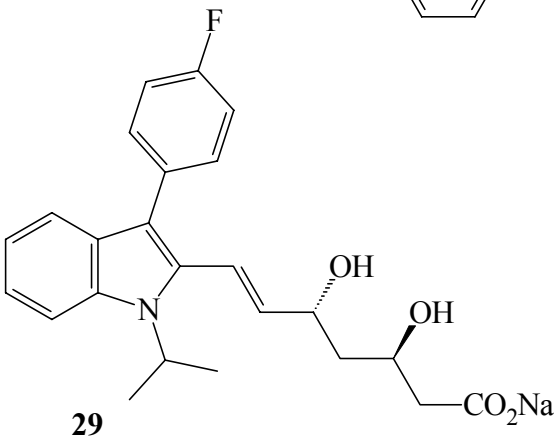

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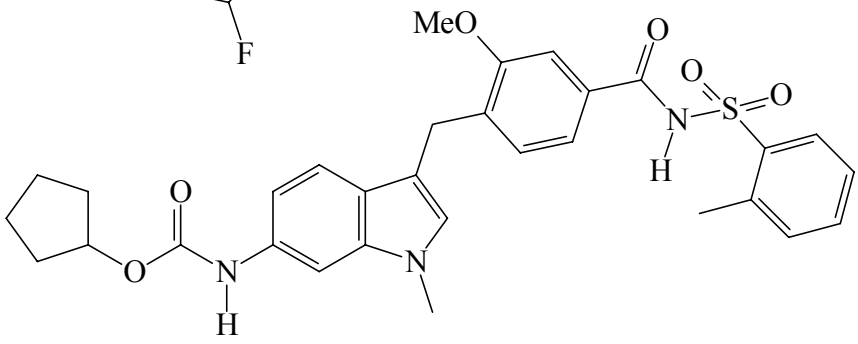

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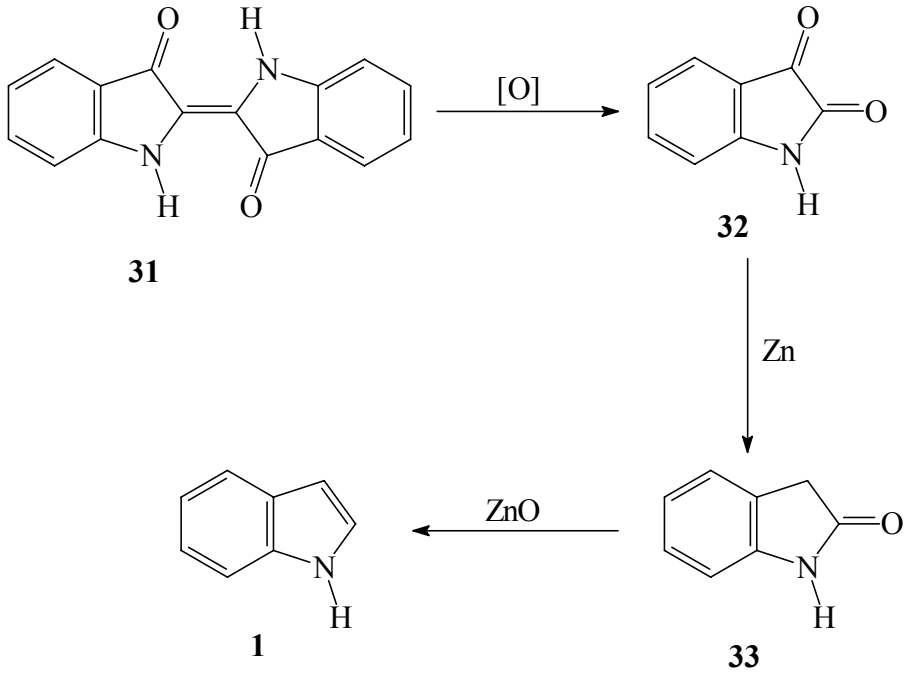
Figure 10. Some recent indole-containing drugs.

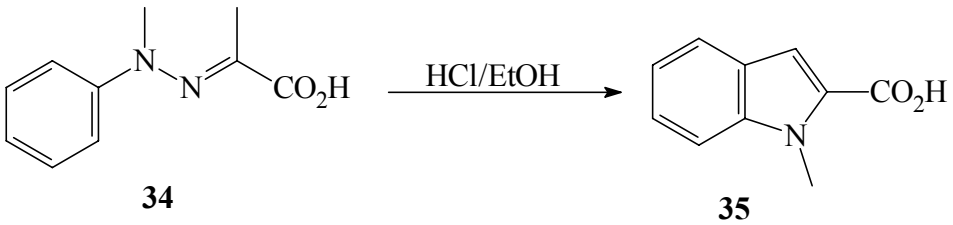
1.4. History of indole synthesis

Indole was first prepared synthetically in 1866 by von Baeyer.[52] He oxidized indigo **31** to obtain isatin **32**, reduced the isatin to oxindole **33** using zinc dust, and further reduced oxindole to indole **1** by passing its vapors over hot zinc oxide (Scheme 1).



Scheme 1. First indole synthesis.

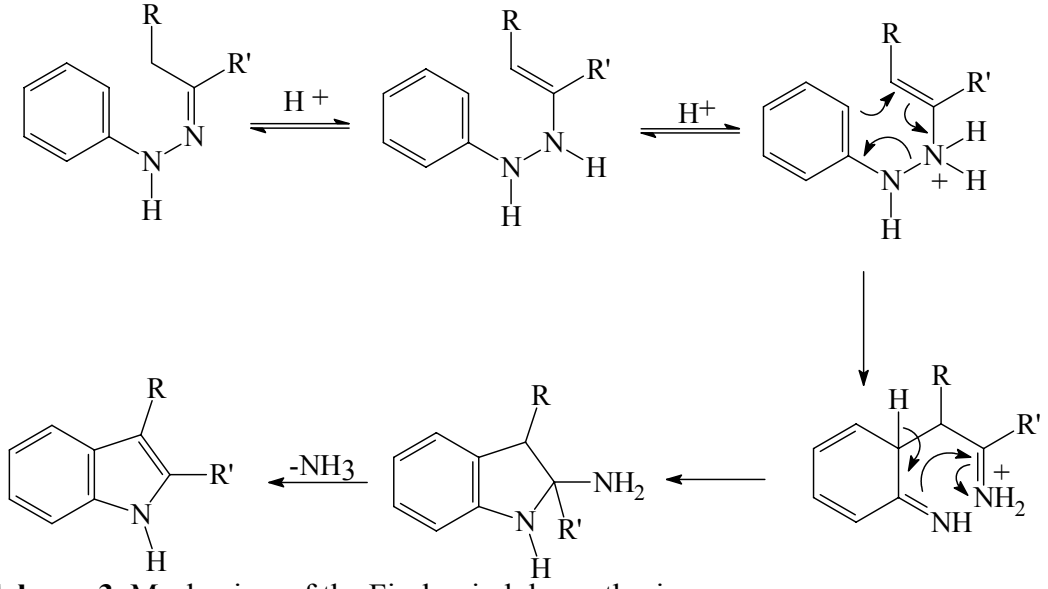
More generally applicable synthesis of indole derivatives involve ring closure to form the pyrrole ring of indole. In 1883 Fischer and Jourdan reported the first indolization of an arylhydrazone.[53] Pyruvic acid 1-methylphenylhydrazone **34** was heated in ethanolic hydrogen chloride yielding 1-methylindole-2-carboxylic acid **35**. However, it was not until the following year that Fischer and Hess identified the structure of **35**.[54]



Scheme 2. Fischer indolization.

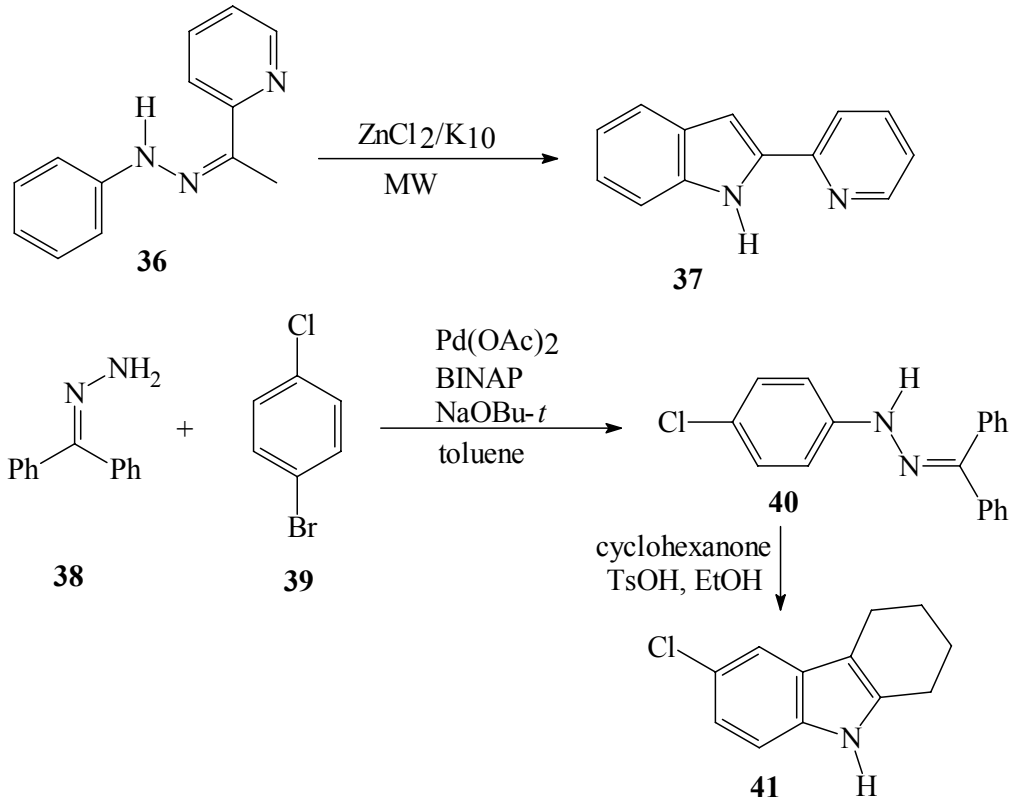
Since this discovery the reaction has been the subject of much experimental work and is still one of the most versatile methods for the preparation of indoles. For example, sumatriptan **12** and related compounds have been prepared by this method.[55] The mechanism proceeds through an initial acid-catalyzed tautomerization of an *N*-

arylhydrazone to an enehydrazine. The enehydrazine then undergoes [3, 3]-sigmatropic rearrangement to produce a bis-imine intermediate. Subsequent aromatization of the aniline ring followed by intramolecular nucleophilic attack produces an aminal, which after loss of ammonia affords the indole product.[56]



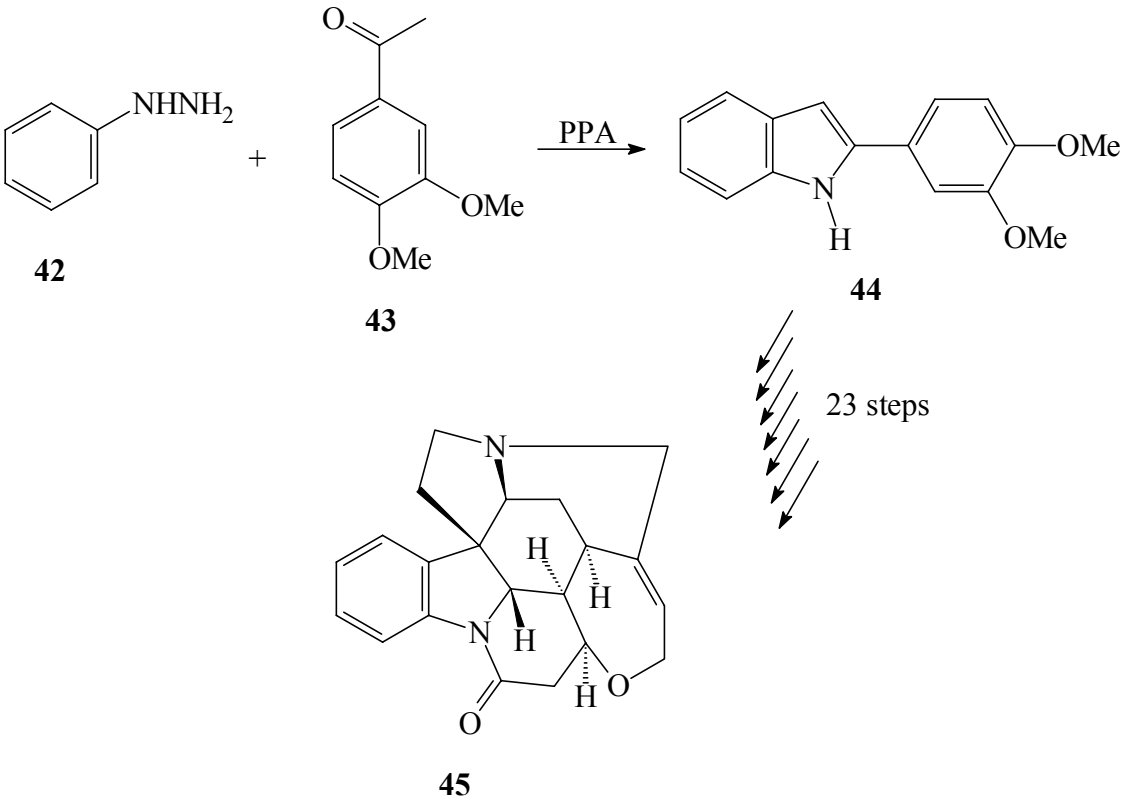
Scheme 3. Mechanism of the Fischer indole synthesis.

Some recent examples of the Fischer indole synthesis involve the use of montmorillonite clay and $ZnCl_2$ in microwave conditions [57] and the use of a "masked" hydrazine (**40**).[58] (Scheme 4)



Scheme 4. Some recent examples of the Fischer indolizations.

One of the highlights in organic synthesis is the total synthesis of strychnine **45** presented by Woodward [59] in 1954. Fischer indolization was the first step in this remarkable milestone of organic synthesis.



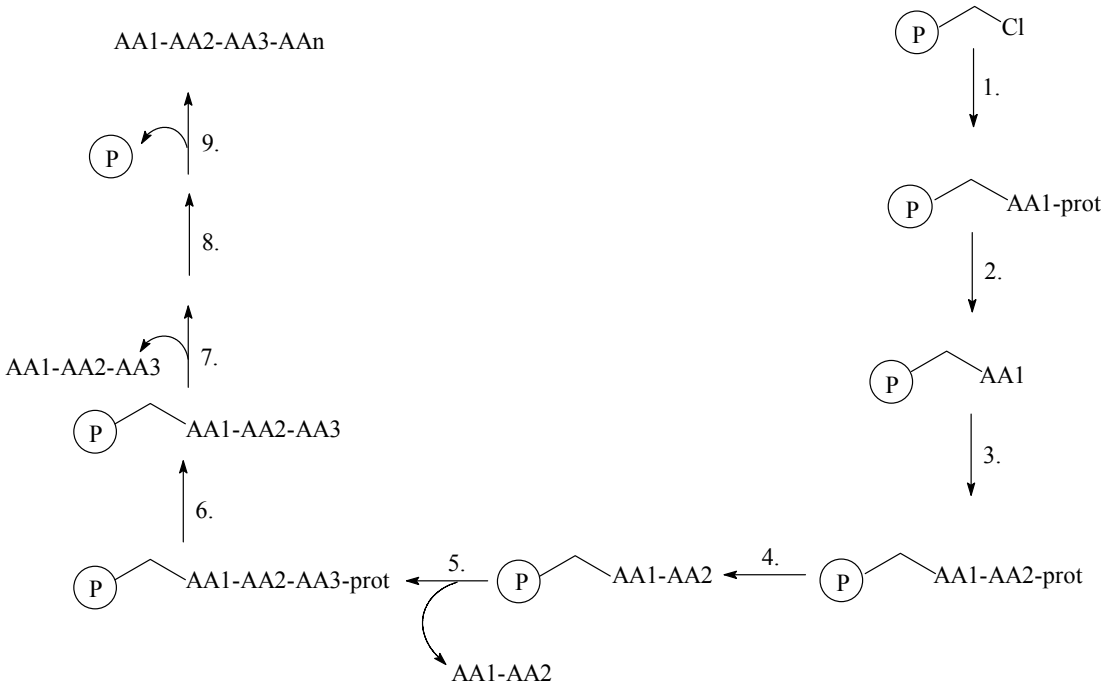
42 **43** **44** **45**

Scheme 5. Fischer indole synthesis as a part of the total synthesis of strychnine.

Even though the Fischer indole synthesis is still one of the most important routes to indoles myriad other cyclization reactions have been reported including Leimgruber-Batcho synthesis, Madelung synthesis, Bischler synthesis, Bartoli synthesis, Gassman synthesis and palladium-catalyzed cyclizations. These and other indole cyclization reactions have been reviewed elsewhere.[60-62] Only those reactions, which have been adopted to solid phase, will be discussed later in chapter 2. The Fischer indole synthesis has been discussed in detailed because it was the only used cyclization reaction in this thesis.

1.5. Solid phase chemistry

Solid phase techniques have become a routine in modern organic chemistry.[63] These techniques often employ polymeric supports to immobilize either the substrate or the reagent in order to simplify compound manipulation and purification. Insoluble polymer resins are most commonly used for such applications,[64] but soluble polymers have also proven useful.[65] The insoluble polymer resin was originally introduced by Merrifield in 1963,[66] and that revolutionized the peptide synthesis for which he received the 1984 Nobel prize in chemistry. The solid-phase peptide synthesis (SPPS) developed by Merrifield is illustrated in Scheme 6.



Scheme 6. Solid-phase peptide synthesis.

Reaction sequences are as follows. 1. Protected amino acid (AA1) is attached to an insoluble polymer via an ester bond. The polymer is filtered from solution and excess reagents are washed. 2. Deprotection of the first amino acid. 3. Coupling of the second protected amino acid (AA2-prot) via an amide bond. 4. Deprotection of the second amino acid. 5. Coupling of the third amino acid or cleavage of peptide AA1-AA2. 6. Deprotection of the third amino acid. 7. Coupling of protected amino acid Aan-prot. or cleavage of peptide AA1-AA2-AA3. 8. Deprotection of amino acid Aan. 9. Cleavage of the peptide AA1-AA2-AA3-Aan.

In the original Merrifields peptide synthesis a polystyrene-based polymer was used as the solid support in which some of the benzene rings were substituted by chloromethyl-groups (Figure 11).

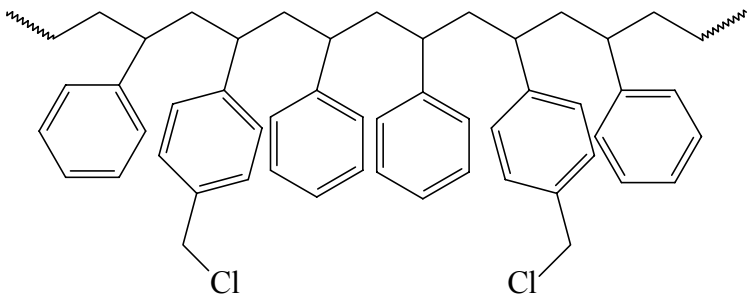
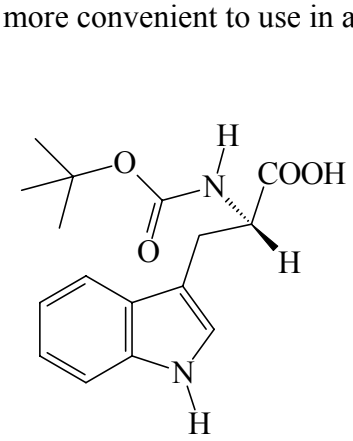


Figure 11. Chloromethylated polystyrene.

The protecting group utilized in the synthesis was *t*-butoxycarbonyl group referred to as *Boc*. Deprotection was achieved with trifluoroacetic acid. This kind of peptide synthesis could be referred to as *Boc*-peptide synthesis. At present time the most common protecting group is fluorenylmethoxycarbonyl group (*Fmoc*). Nowadays the peptide synthesis is carried on by automated robots and this base sensitive group is more convenient to use in automated systems.



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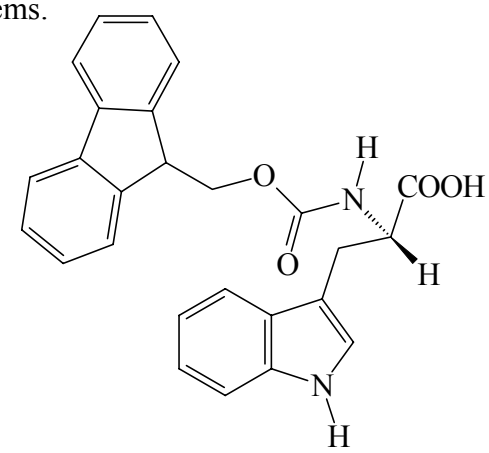


47

Figure 12. Boc-protected- and Fmoc-protected (*S*)-tryptophan.

Solid phase chemistry was initially almost exclusively devoted to peptide synthesis. However, in 1970s solid phase techniques were adopted towards small organic molecule synthesis by pioneering works of Leznoff, Camps, Frèchet and Rapoport,[67] and more challenging chemistry is now being carried out routinely on solid phase.[68] Much research has been directed toward optimization of tailored linker groups for different functional group attachment.[69, 70] Also the flexibility of the resins have been improved by incorporation of flexible cross-inkers.[71] The hydrophobic nature of polystyrene was initially a problem, but new materials have solved this drawback and at present it is possible to carry out solid phase reactions even in water.[72, 73]
2-Chlorotrityl-Cl-resin **48** is an acid labile resin and it has been used to immobilize alcohols,[74] carboxylic acids,[75] amines [76] and hydroxylamines.[77] Carboxypolystyrene **49** is a base labile resin and suitable to immobilize amines [78] and alcohols.[79] DL-α, β-isopropylideneglycerol resin **50** has been used to immobilize aldehydes after hydrolysis of the acetal.[80] *O*- (2-Hydroxyethyl) penta (oxyethylene) polymer **51** (HypoGel®) is a hydrophilic polystyrene gel-type resin and can be used in aqueous solvents.[81] Silica based hydroxypropyl resin **52** has also been developed for use with a variety of solvents, thereby countering the problem posed by swelling.[82] Rink amine resin **53** is one of the most widely used resins in solid phase chemistry. The resin is most often used in the construction of carboxyamides.[83] 3-Hydroxymethyl-4-nitrophenoxymethylpolystyrene **54** is an example of a photolabile resin. The acids could be cleaved from the resin with exposure of light. The linker is stable towards strong acids (Figure 13).[84]
An example of more exotic resin is the traceless silicon linker resin **55**. Most linkers leave a residue attached to the cleaved molecule; that is the functional group or a derivative thereof used to attach the molecule to the linker. Linkers that leave no obvious residue on the cleaved molecule are called traceless linkers. Shortly traceless linker could be defined as one where a new carbon-hydrogen bond is formed at the

linkage site of the cleaved molecule. Lithiated aromatic species can be attached to the resin affording **56**. After synthetic modifications the pyridine based tricyclics could be cleaved with TBAF in a traceless manner (Scheme 7).[85]

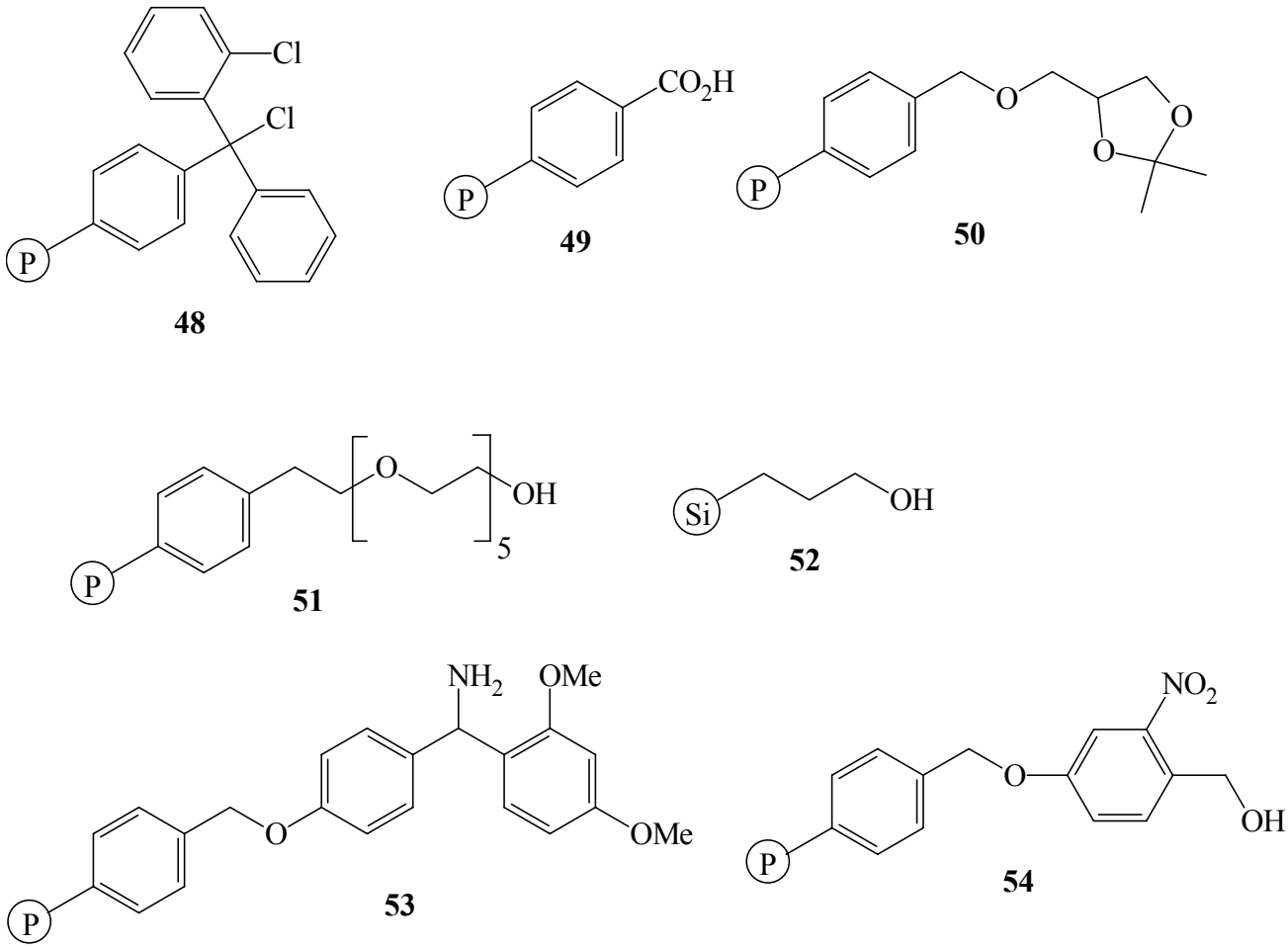
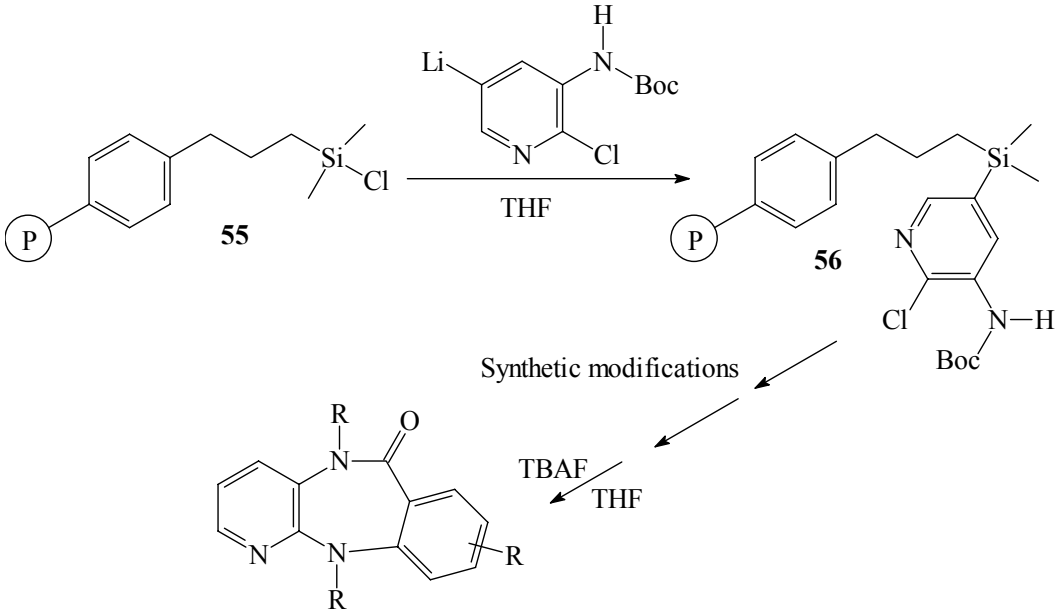


Figure 13. Resins used in solid phase chemistry.



Scheme 7. Traceless silicon linker attachment and cleavage.

2. Modification of indole structure on solid phase

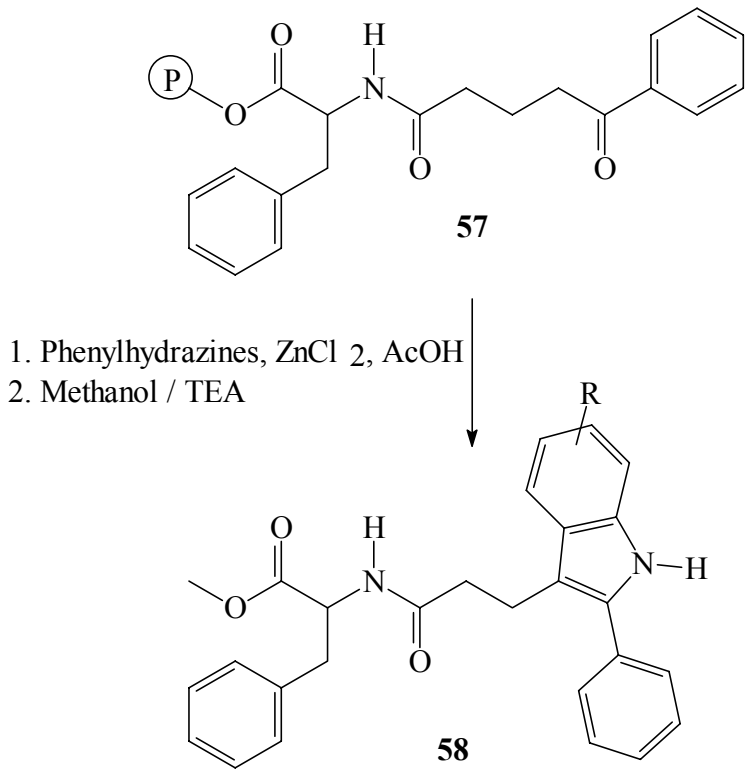
This chapter is a review of the synthetic solid phase approaches toward indoles and their analogues to be found in the literature. The first part describes the methods for the preparation of the indole core on solid phase. The second part covers the circumstances where the readily available indole core has been attached to a solid phase and the ring substituents have been modified. The latter part describes also methods for direct functionalization of polymer bound indole skeleton.

2.1. Preparation of the indole core on solid phase

2.2.1. Fischer cyclization on solid phase

On solid phase, the Fischer indole synthesis was first adapted by Hutchins and Chapman.[86] The synthetic route involved the use of support bound 4-benzoylbutyric acid **57** and a variety of substituted phenylhydrazine hydrochlorides as starting materials. Since the indole cyclization required acid catalysis, a base labile linker was chosen for the preparation of 2-arylindoles **58** (Scheme 8). Although the purity of the cleaved indoles was high, the overall yields remained moderate. This group has also adopted this method to dendrimer supports.[87] Later, Cheng and Chapman [88] described a method for the solid phase synthesis of spiro indolines using the Fischer indole reaction.

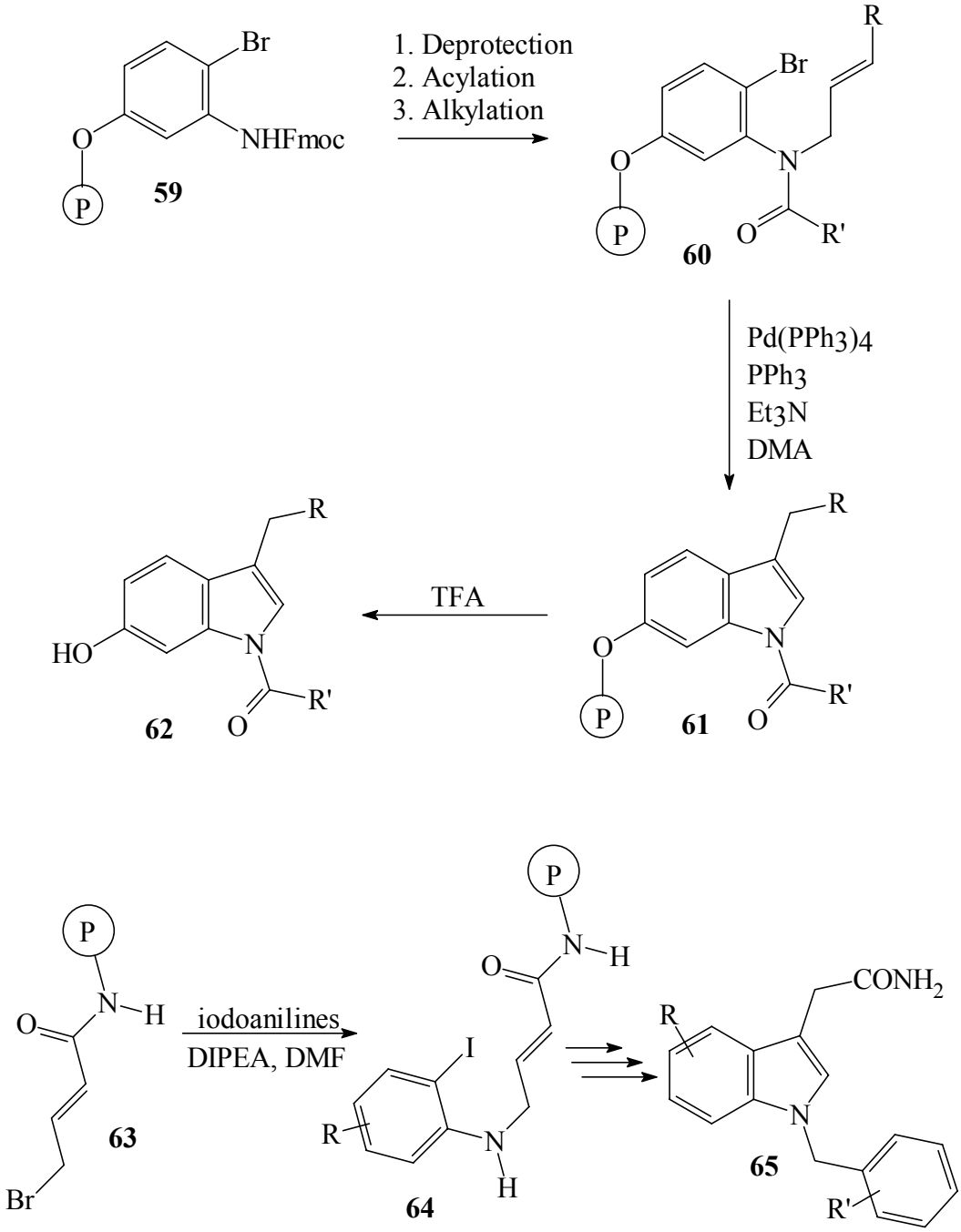
Only a few methods have been developed for the utilization of the Fischer indole synthesis on solid phase. It is therefore anticipated that the method will be further developed and more efficiently transferred to the polymer matrix within the next few years making it more suitable for combinatorial chemistry purposes.



Scheme 8. Fischer indolization on solid phase.

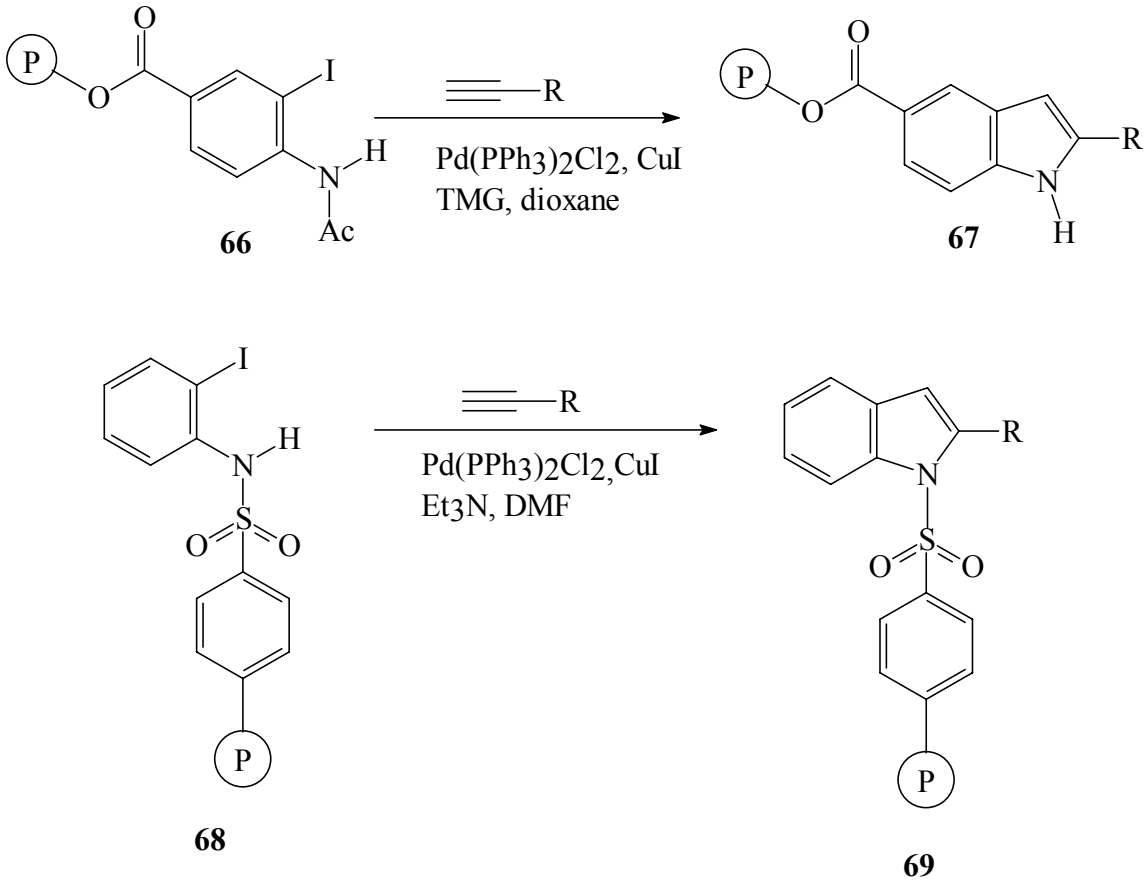
2.1.2. Palladium-catalyzed cyclization on solid phase

Methods for the aromatic substitution based on catalysis by transition metals, mainly palladium, have proven to be efficient approaches towards indoles on solid phase. In the intramolecular Heck reaction an *o*-halo-N-allylaniline is efficiently cyclized to yield the indole in good yield and high purity. This versatile method has been reported in several papers. Yun and Mohan [89] described the intramolecular Heck reaction of polymer-bound aryl halides **59** and similar approach was later published by Balasubramaniam *et al.* [90] for 2-oxindoles. Instead of coupling the aryl moiety to the solid phase Zhang *et al*.[91] immobilized the γ-bromocrotonic acid and thus obtained the amide **63** (Scheme 9).

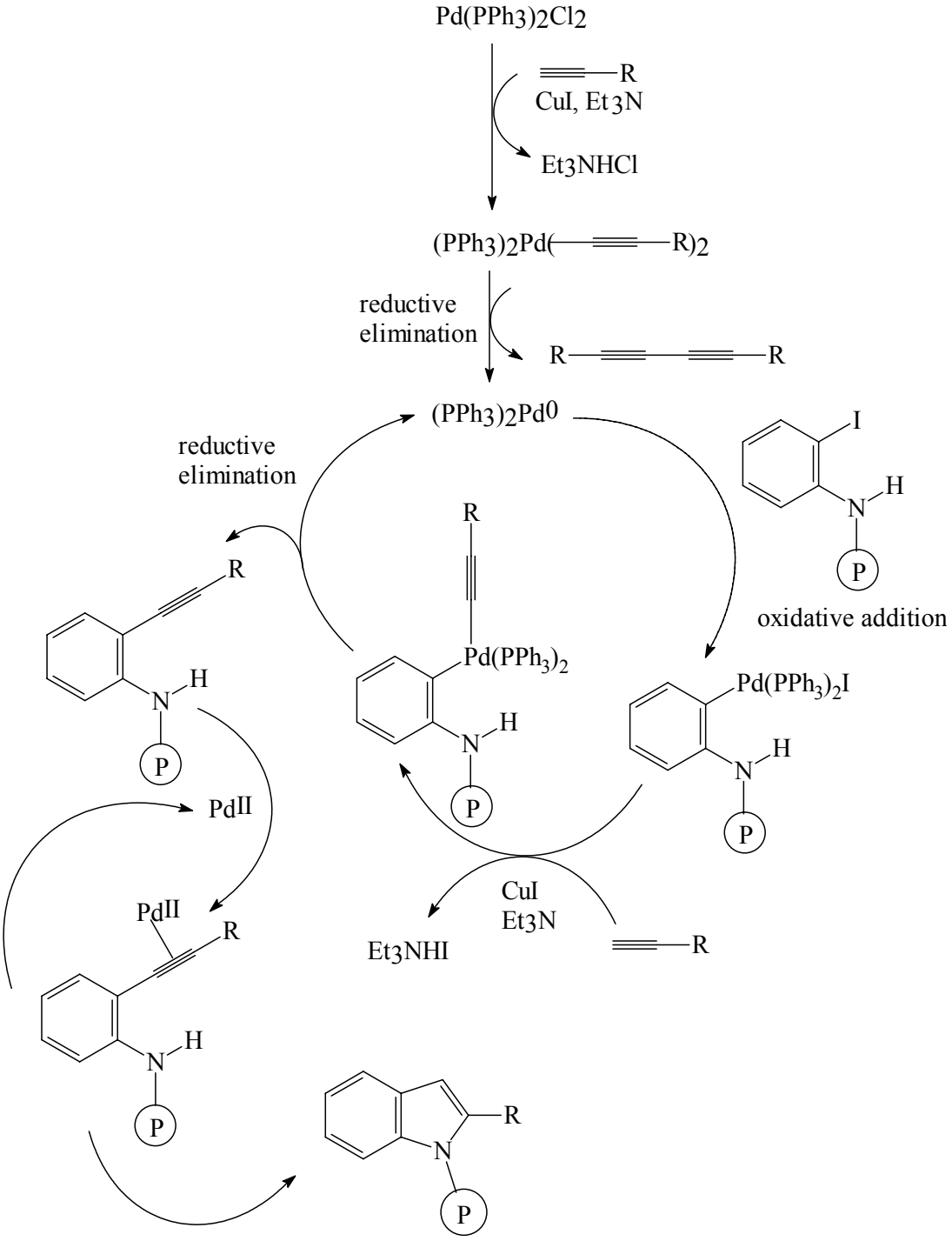


Scheme 9. Heck reactions on solid phase.

In all these papers, the efficiency of the cyclization was demonstrated by the use of different starting materials. The palladium-mediated intramolecular heteroannulation has also proved to be a valuable method for the synthesis of the indole moiety on solid phase. New carbon-carbon bonds are created through a palladium-catalyzed addition of acetylenes to *o*-iodoanilines. Recent examples include the work by Bedeschi *et al.*[92] where 2-substituted indoles could be obtained in the reaction between resin attached *o*-iodoaniline **66** and a terminal alkyne. Zhang *et al.* [93] and Smith *et al.* [94] developed this methodology suitable for internal alkynes and also Collini and Ellingboe [95] reported a solid phase synthesis of indoles with three independently variable components. Zhang *et al.* [96] and Schultz *et al.* [97] have also demonstrated that a palladium-mediated heteroannulation of terminal alkynes can be performed using a traceless sulfonamide linker (Scheme 10). The catalytic cycle of this reaction is presented in Scheme 11.

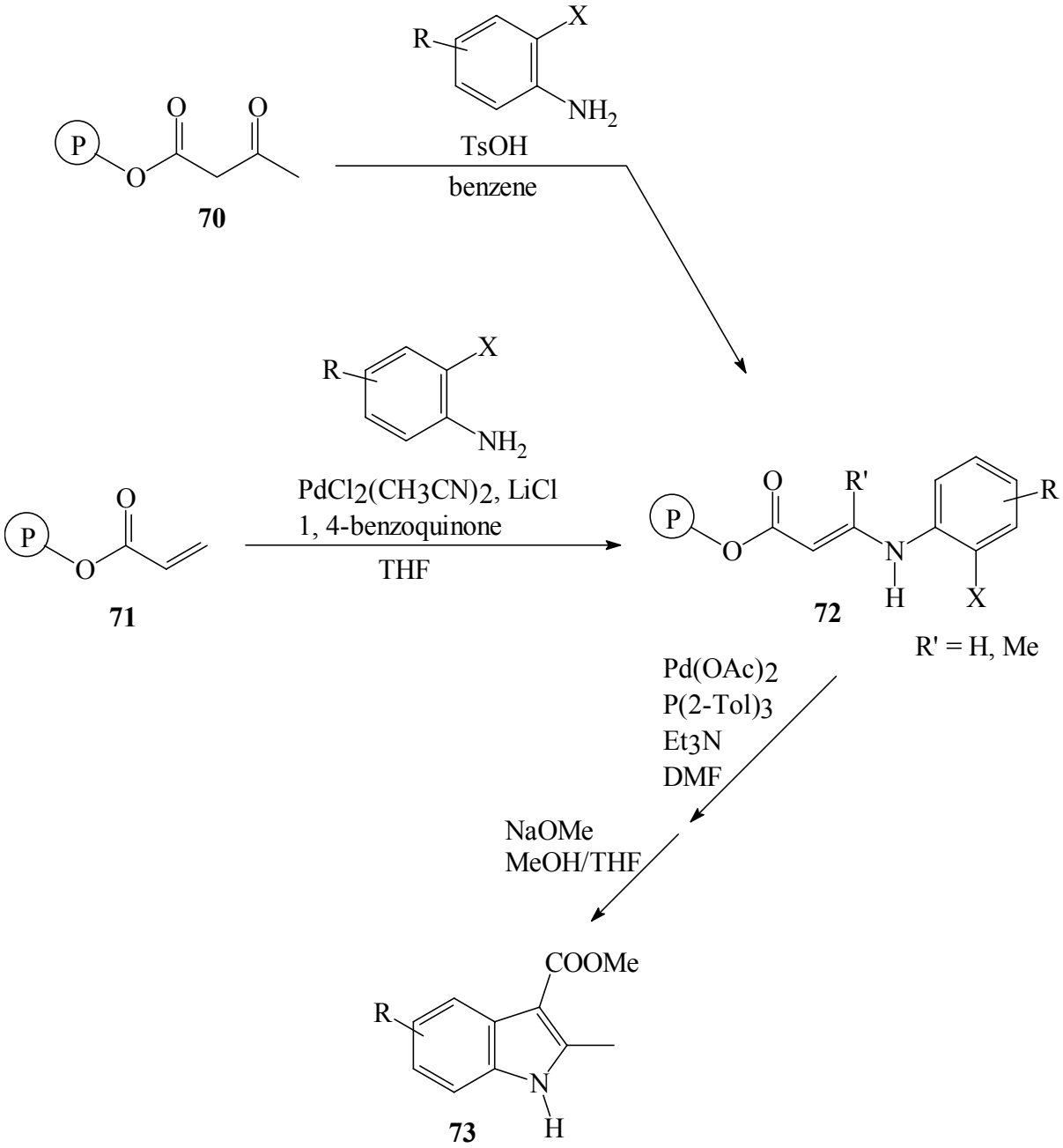


Scheme 10. Indoles from resin-bound *o*-iodoanilines.



Scheme 11. Catalytic cycle of palladium-catalyzed addition of acetylenes *o*-iodoanilines.

Recently, a palladium catalyzed cyclization of a β-(2-halophenyl) amino-substituted α, β-unsaturated ester **72** was found to be effective for the solid phase synthesis of indole 3-carboxylates **73**.[98] The polymer-bound enaminoester was synthesized by acid catalyzed condensation or by palladium(II) chloride catalyzed oxidative amination (Scheme 12).



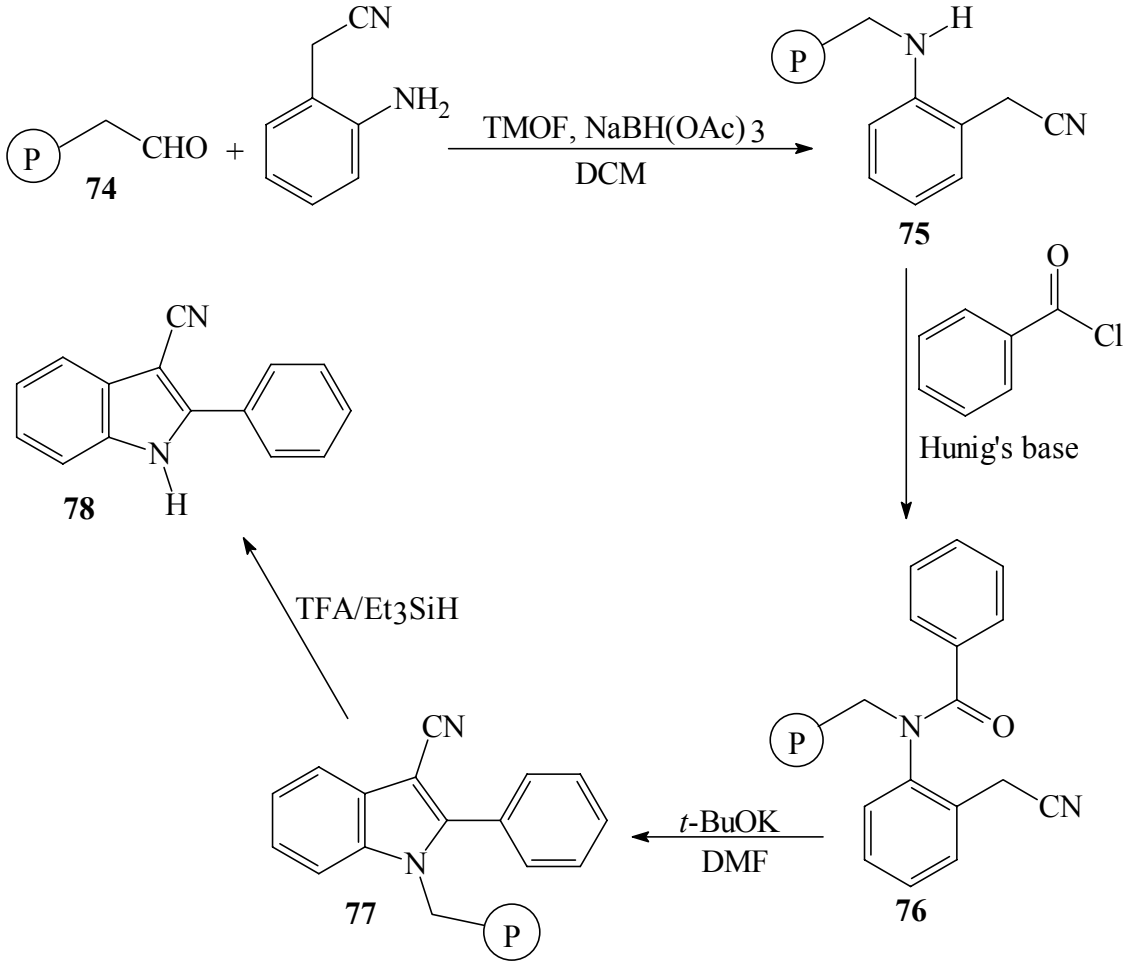
Scheme 12. Solid-phase synthesis of indole 3-carboxylates.

While these methods are of great importance, a drawback is the requirement of a bifunctional precursor for the formation of a new C-C and C-N bond. This means that, in order to prepare an indole with one substituent on the aromatic ring, one must employ an aromatic precursor with three substituents. There are only a limited number

of commercially available highly functionalized aromatic compounds and time consuming extra work is often needed to prepare the benzenoid starting materials.

2.1.3. Madelung cyclization and intramolecular Wittig reaction

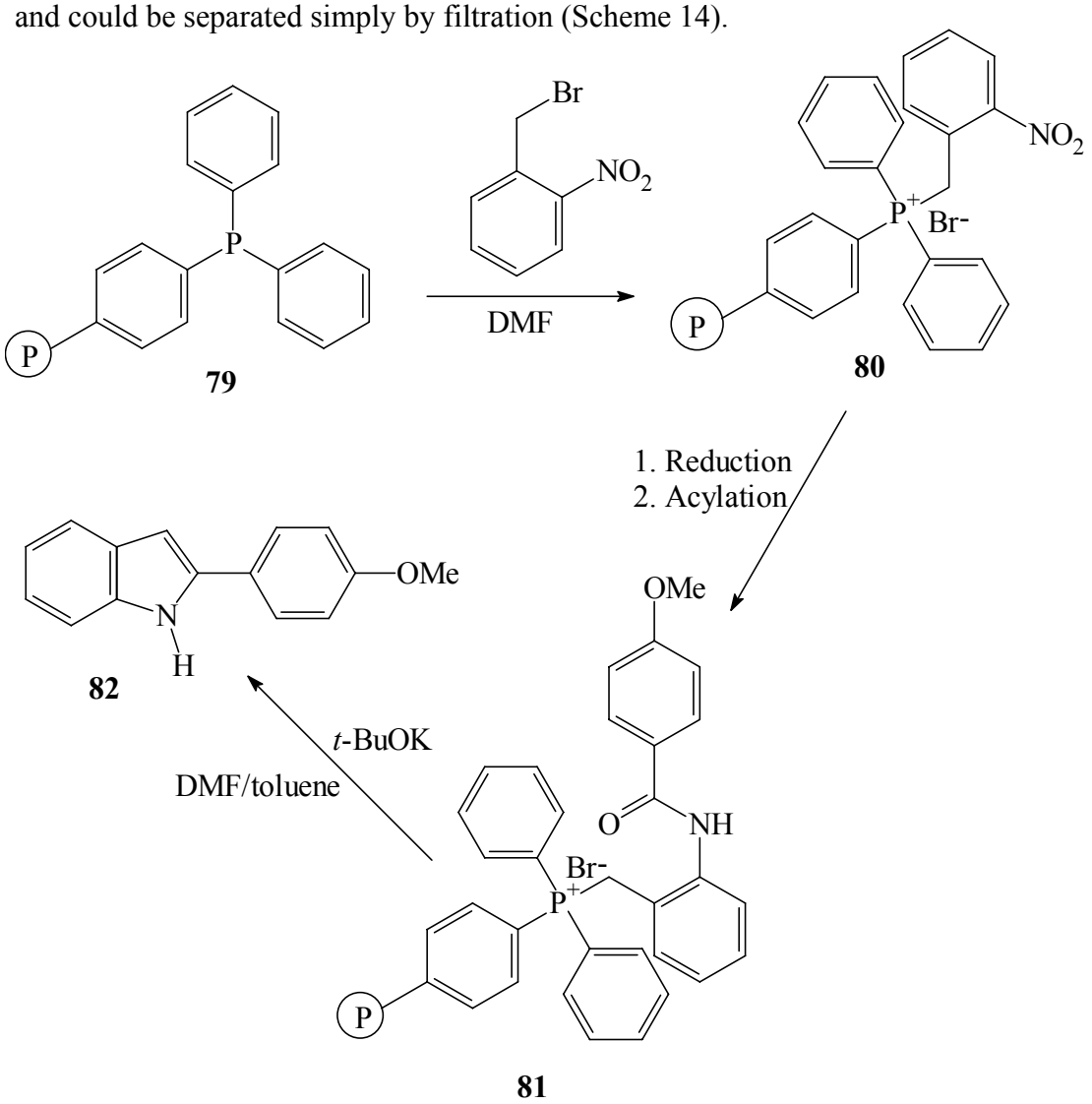
Wacker and Kasireddy [99] have utilized the modified Madelung indole synthesis successfully on solid phase. 2, 3-Disubstituted indoles were obtained in excellent yields and purities. Bal-resin **74** was functionalised by reductive amination followed by acylation, cyclization and acid promoted cleavage (Scheme 13).



Scheme 13. Madelung synthesis.

A variation of the Madelung cyclization involves installing a functional group in the benzenoid precursor, which can facilitate the cyclization. Such a group is for example a triphenylphosphonium substituent that converts the reaction into an intramolecular

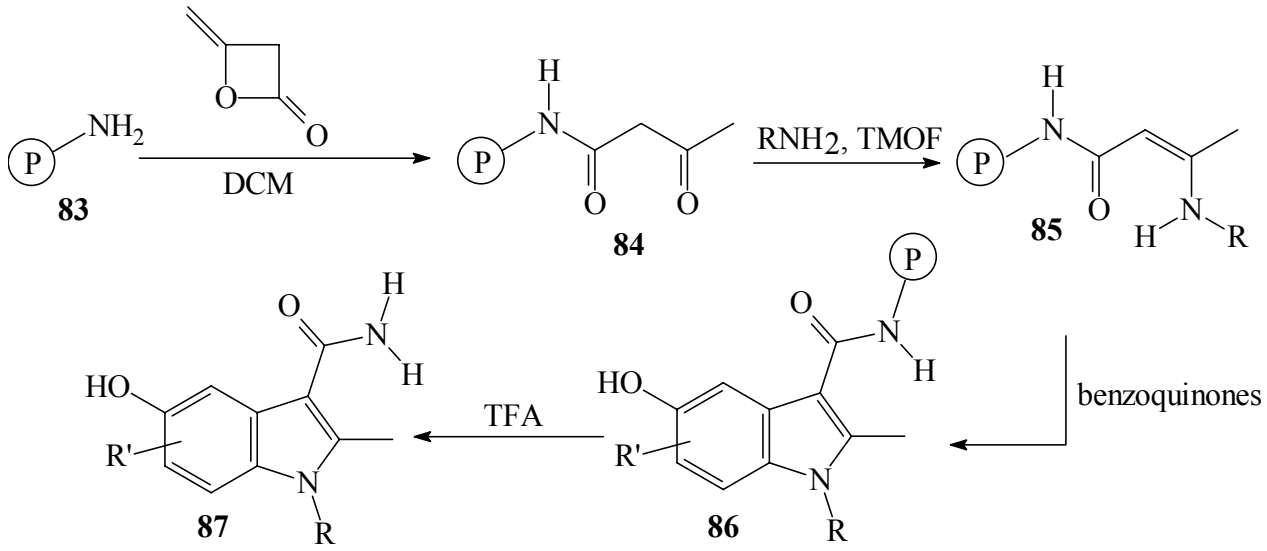
Wittig condensation. The required phosphonium salts **81** can be prepared from an *o*-nitrobenzyl chloride or bromide. Hughes [100] utilized the phosphonium group as a traceless linker for the solid-phase synthesis of indole **82** on solid phase in 78% yield. An advantage is that the phosphine oxide by-product remains bound to the polymer and could be separated simply by filtration (Scheme 14).



Scheme 14. Intramolecular Wittig reaction in synthesis of indoles.

2.1.4. Solid phase Nenitzescu indole synthesis

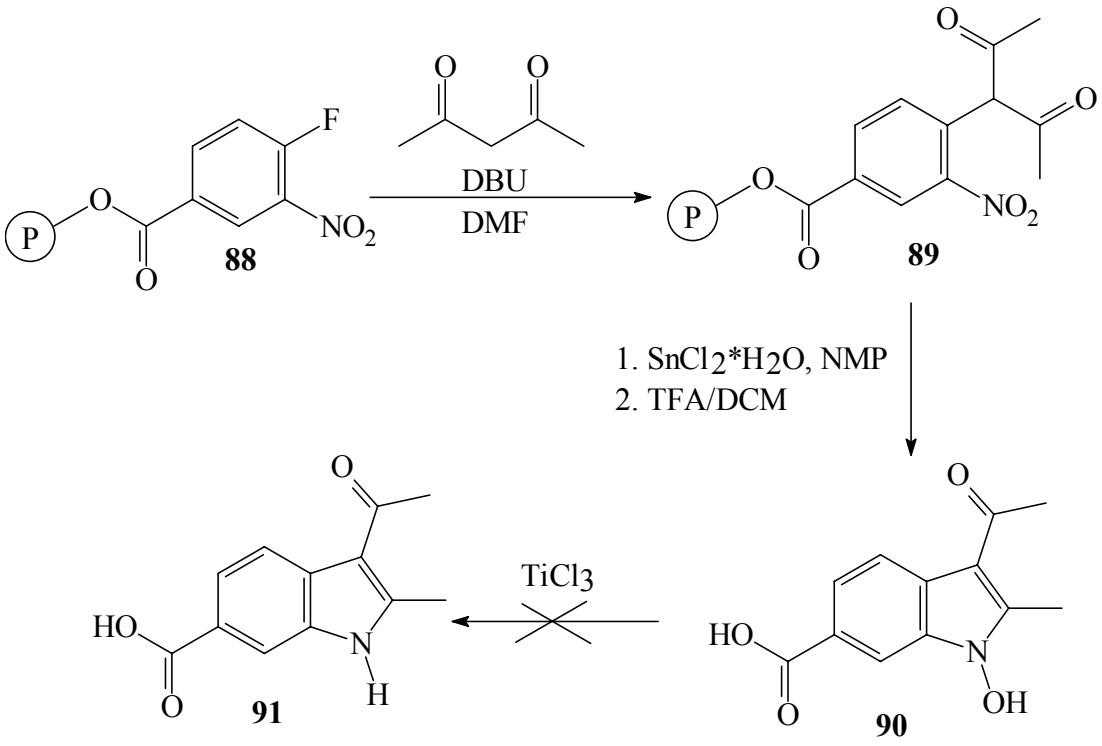
5-hydroxyindole derivatives can be synthesized by condensation of *p*-benzoquinone with β-aminocrotonic esters. Since many important natural products and molecules possess the 5-hydroxyindole-skeleton, the recent discovery of the solid-phase version by Ketcha *et al*. [101] gave a new tool to be used in the combinatorial preparation of 5-hydroxyindole-3-carboxamides. The solid phase process involved sequential acetoacylation, condensation with primary amines, addition of 1,4-benzoquinones and cleavage by TFA (Scheme 15).



Scheme 15. Nenitzescu reaction on solid phase.

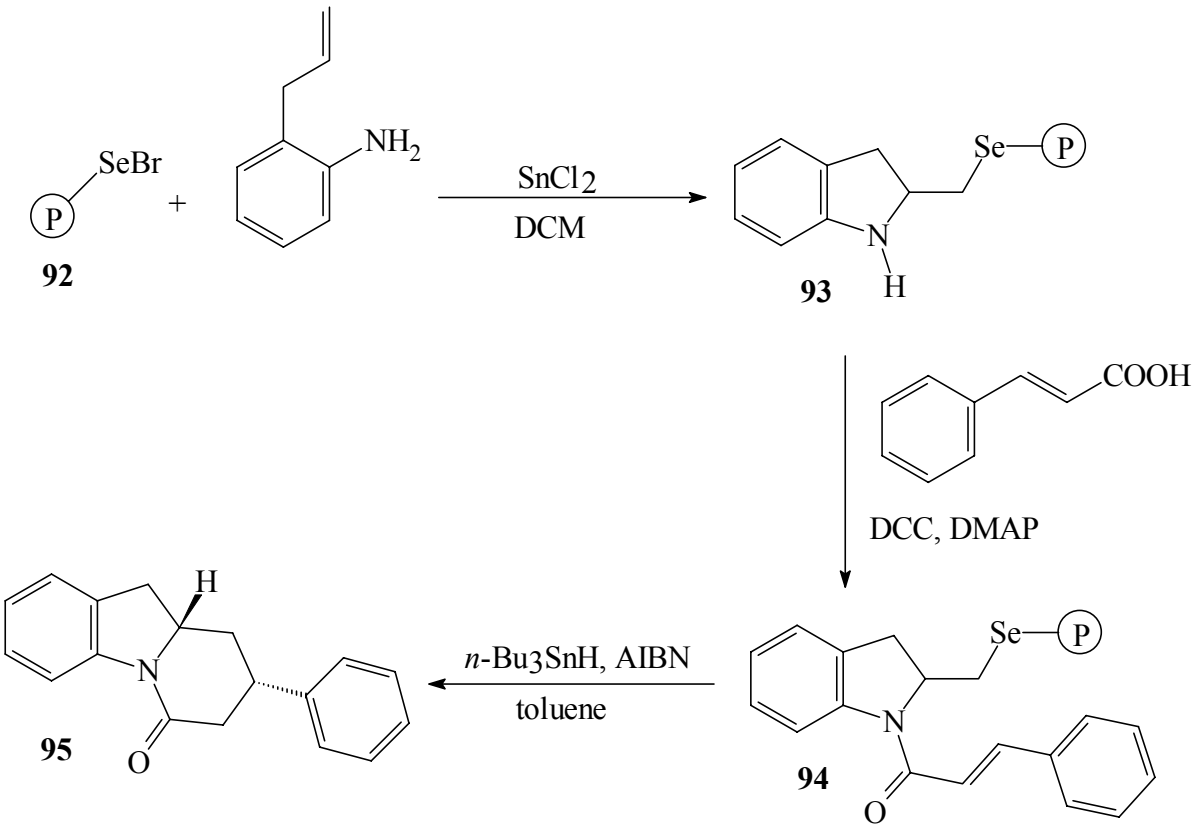
2.1.5. Other intramolecular cyclizations giving the indole or structurally closely related core

Other methods for the preparation of indoles and indole-analogues include the preparation of 1-hydroxy-6-indolecarboxylic acids **90.**[102] The compounds were obtained by treatment of Wang resin bound 4-fluoro-3-nitrobenzoic acid **88** with 1,3-dicarbonyl compounds, followed by reduction and cleavage. Reductive cleavage of the N-O bond was attempted but was not successful (Scheme 16).



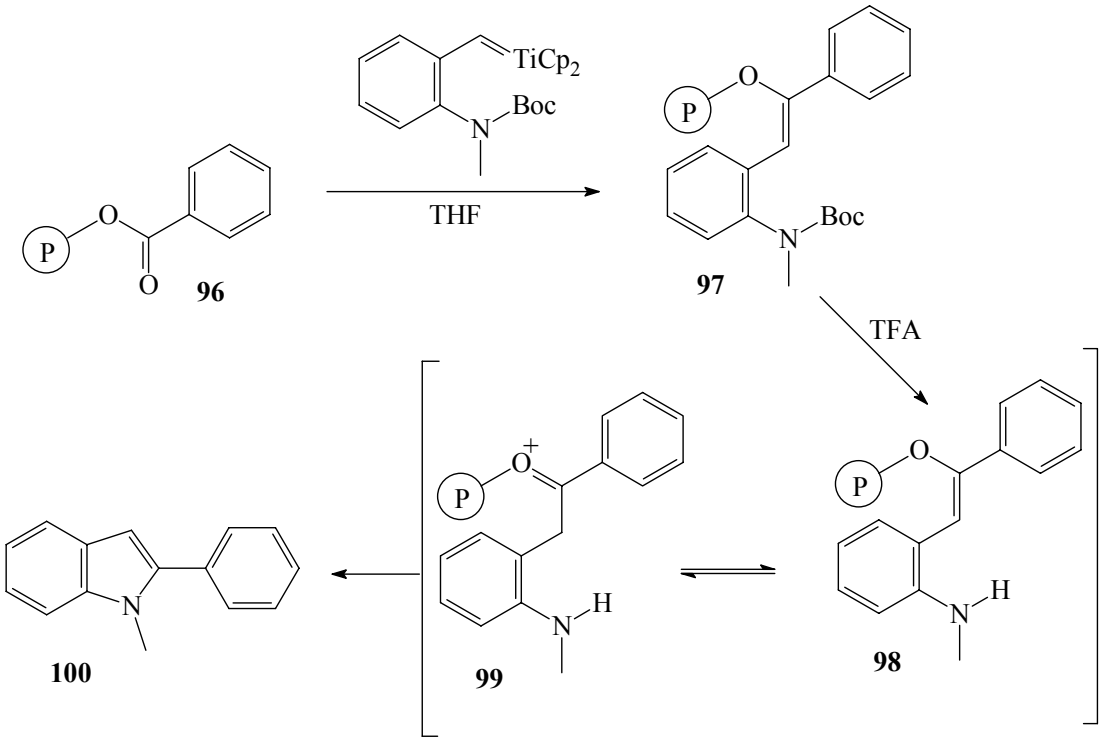
Scheme 16. Preparation of 1-hydroxy-indole analogues.

Nicolaou *et al*. [103] have described a highly efficient method for the solid phase synthesis of substituted indoline scaffolds. Substituted *o*-allyl anilines were cycloadded onto selenenyl bromide resin **92**. Resin-bound indoline scaffold **93** was further elaborated and cleaved tracelessly (Scheme 17).



Scheme 17. Traceless indoline synthesis.

Recently, Hartley utilized titanium(IV)benzylidene reagents that allow traceless solid-phase synthesis of indoles.[104] Resin-bound esters **96** were reacted with titanium benzylidene, and thus converted to acid labile enol ether **97**. Deprotection of the nucleophile leads to the formation of oxonium ion **99** and release of the indole from the resin **100**.



Scheme 18. Indoles from titanium benzylidenes.

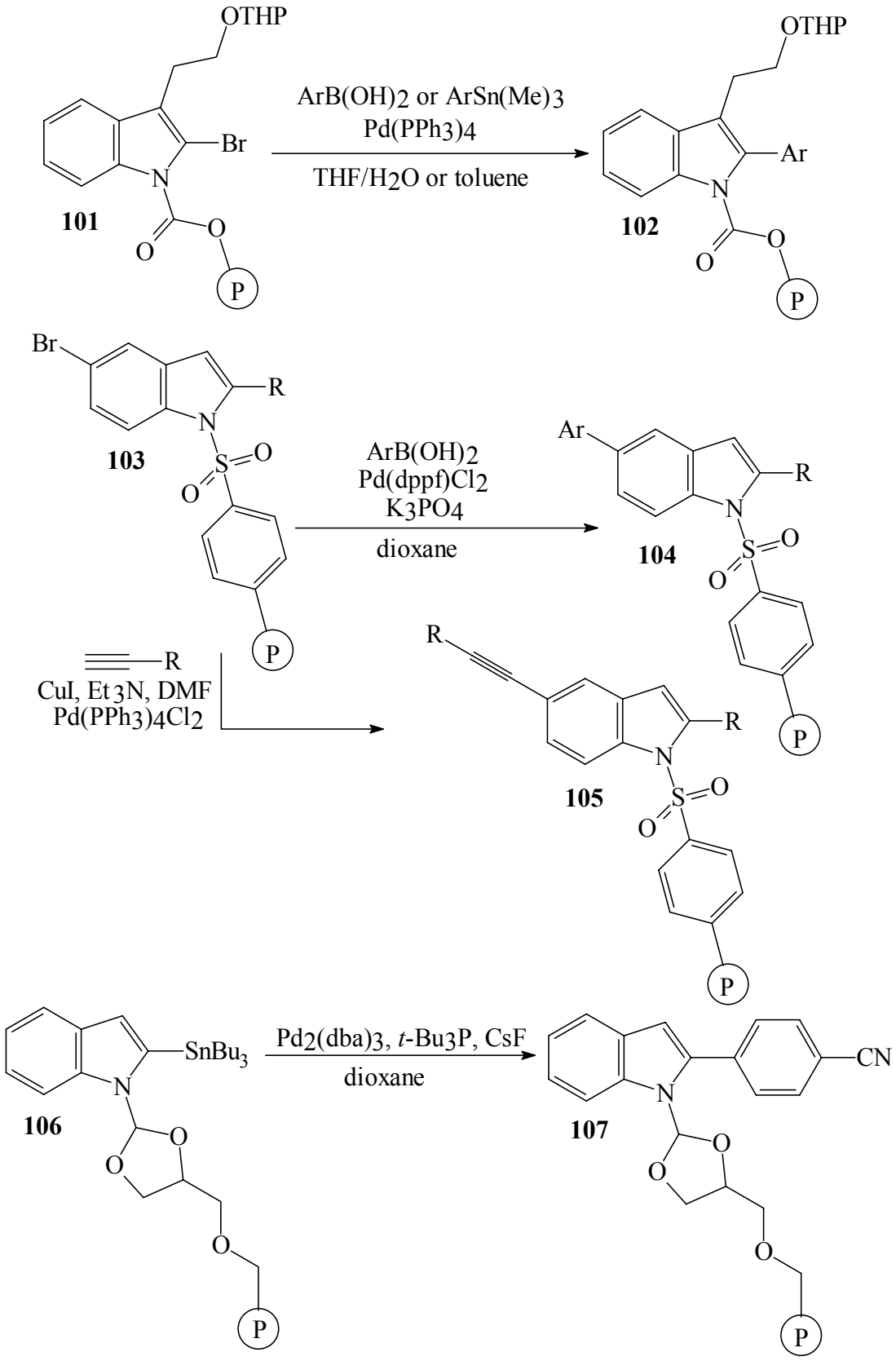
2.2. Modification of substituents on the indole ring

This part of the thesis covers circumstances where indole moieties are already adorned with suitable substituents before attachment to the solid phase.

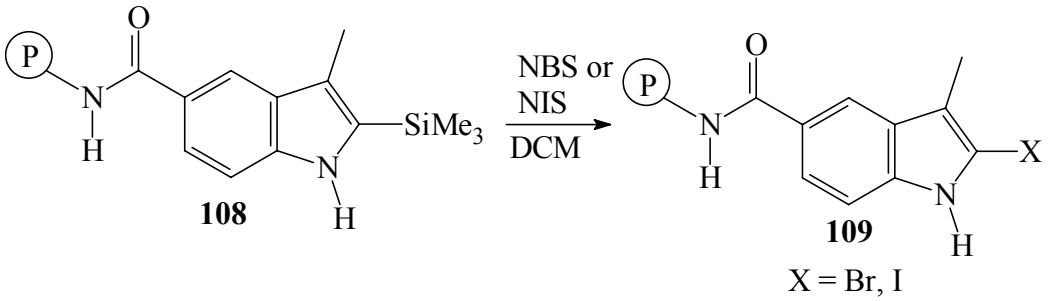
2.2.1. Palladium-catalyzed modifications of the indole ring

As in the case of cyclizations, also in the case of the ring modifications palladium plays an important role. Organoboronic acids, stannanes, halides and palladium reagents are commercially available and the coupling reactions are among the most studied reactions on solid phase. Also the indole structure has been modified by these reactions. Smith *et al.* [105] successfully utilized Suzuki- and Stille-couplings in their discovery of a novel, high-affinity h5-HT_{2A} antagonist. In this small series of 2-aryl tryptamines **102**, the starting indole **101** was tethered to a Wang-carbamate linker. Traceless PS-TsCl (polystyrene sulfonyl chloride) linkage was used by Schultz *et al.*[97] when they modified the indole C-5 position by Sonogashira-, and Suzuki-couplings. Both above methods are based on the couplings where the electrophilic component (halide) is attached to solid phase. The only example where nucleophilic species **106** (stannane) is polymer bound has been reported by Gmeiner *et al.*[106] Their linking strategy was also traceless and based on transacetalization of diethoxymethyl (DEM) protected indoles (Scheme 19).

Zhang *et al.* [93] introduced a halo substituent to the indole core by conversion of a trimethylsilyl-group to bromo or iodo groups and they also mentioned organometallic coupling reactions. However no description of these reactions were mentioned (Scheme 20).



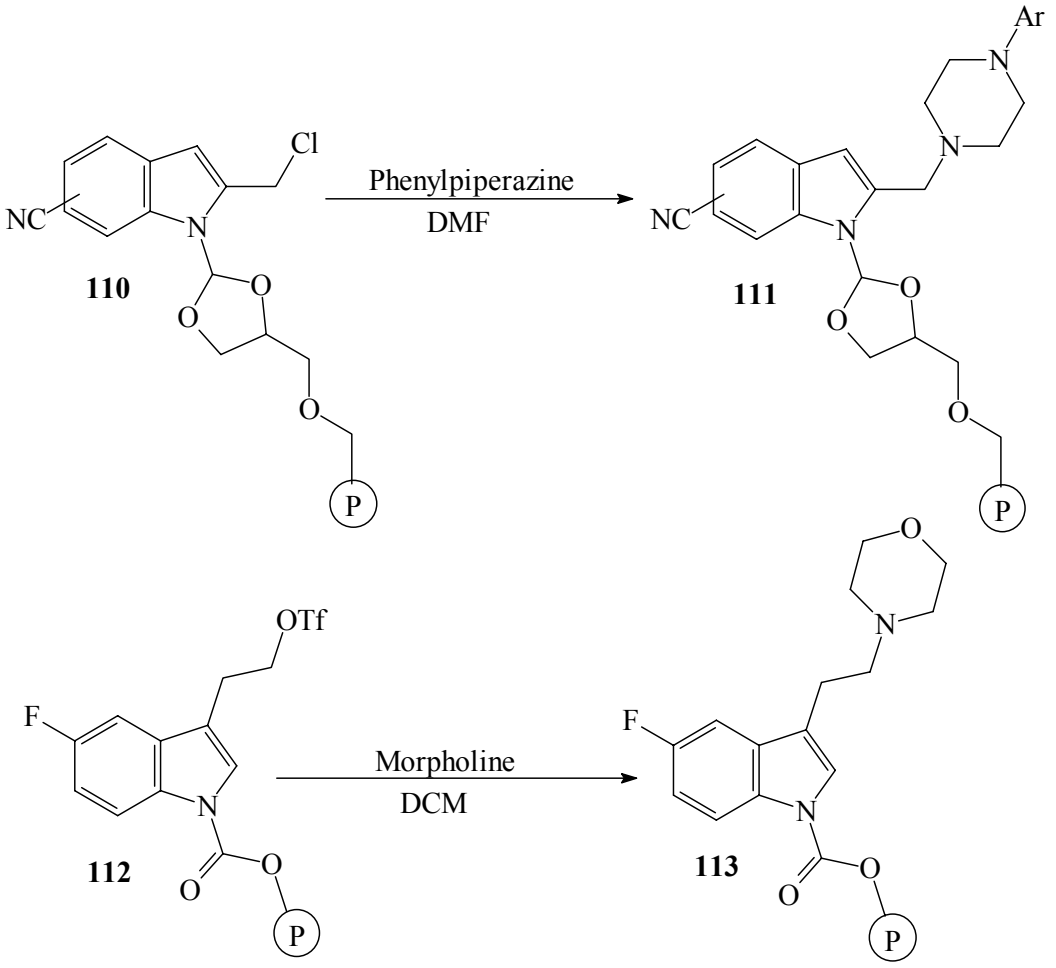
Scheme 19. Palladium-catalyzed modifications.



Scheme 20. Conversion of trimethylsilyl-group to halo-groups.

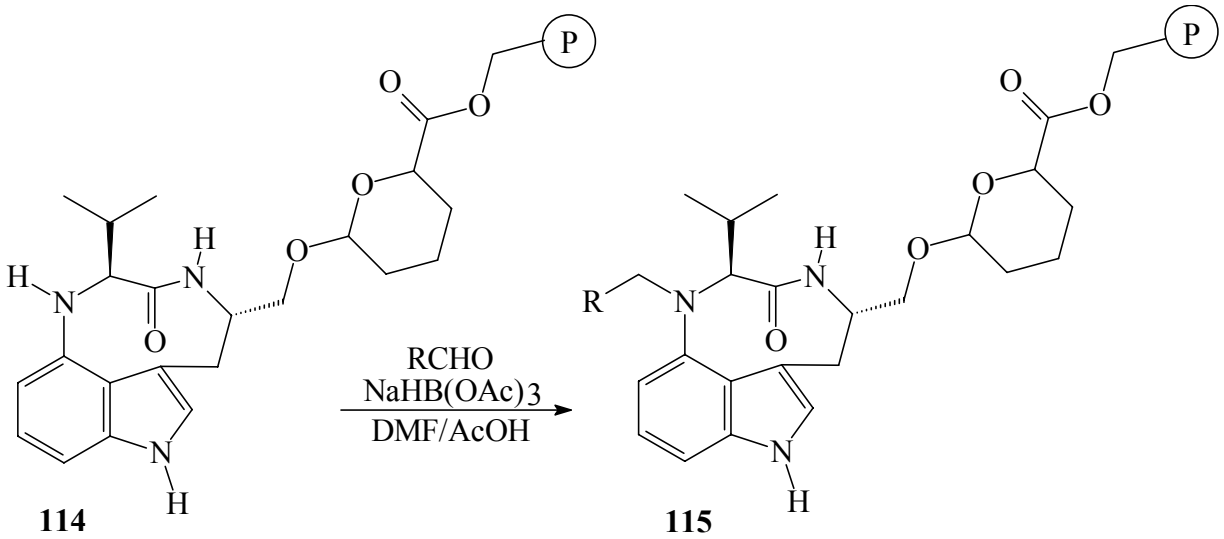
2.2.2. Modifications leading to tertiary amines

Gmeiner *et al.* [107] modified the indole 2-position by treating the polymer bound 2-chloromethylindoles **110** with arylpiperazines (Scheme 21). The compounds obtained were highly selective dopamine D_4 receptor partial agonists. Smith *et al.* reported the use of polymer bound triflates **112** in the preparation of tertiary amines (Scheme 21).[105]



Scheme 21. Preparation of tertiary amines.

Herget *et al.* [108] utilized the reductive amination in the preparation of a Teleocidin library. In this case only aliphatic aldehydes were used (Scheme 22).

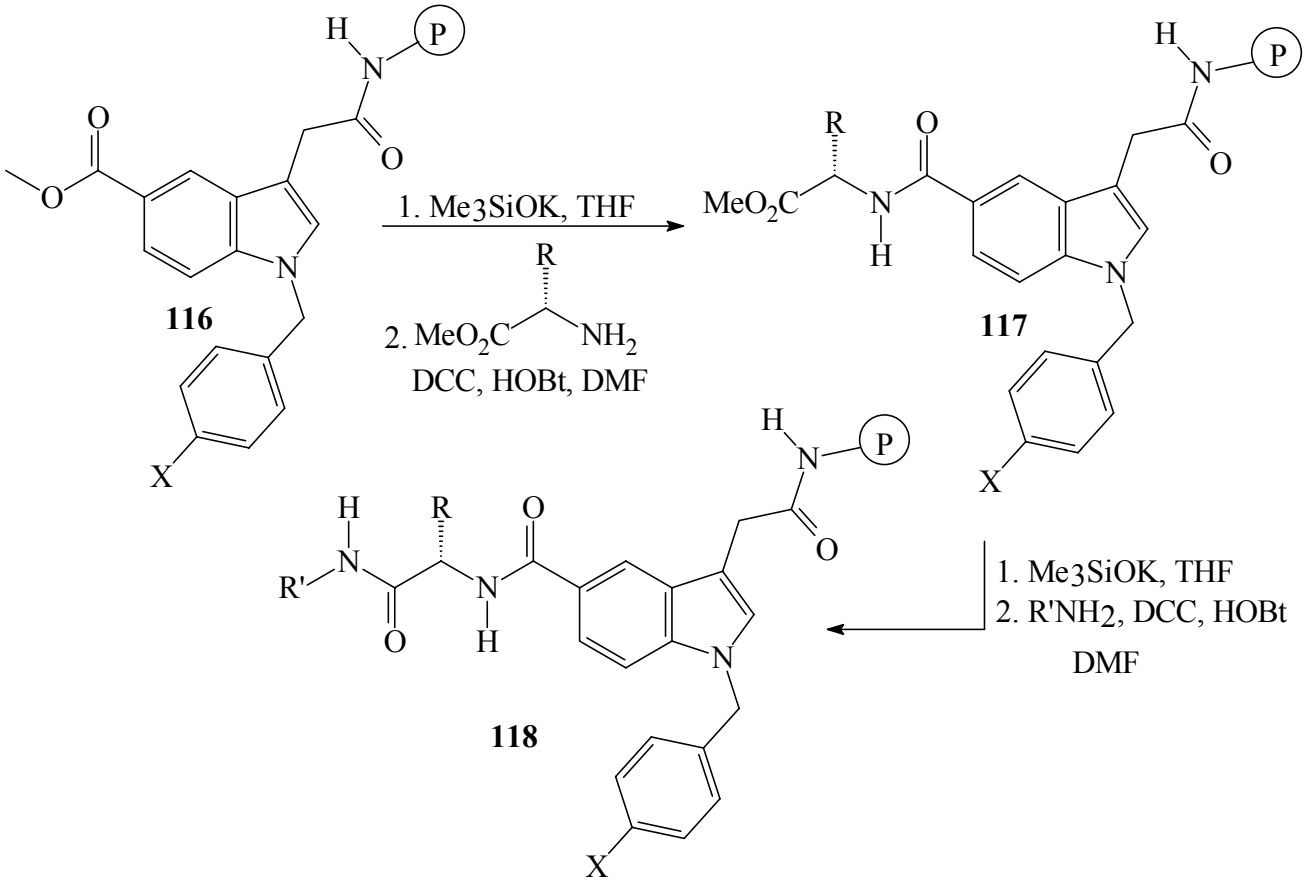


114 **115**

Scheme 22. Reductive amination on solid phase.

2.2.3. Modification leading to amides

Despite the fact that solid phase peptide synthesis has appeared in the literature over four decades only one example where the indole nucleus has been modified by amino acids exists. Zhang *et al.* [91] modified the 5-position of the resin bound carboxyindole **116**. A minilibrary of 18 compounds was prepared and an uncommon methyl ester hydrolysis was utilized in this solid supported library synthesis (Scheme 23).



116 **117** **118**

Scheme 23. Modification of 5-carboxyindole derivative.

2.3. Direct functionalization of the indole ring

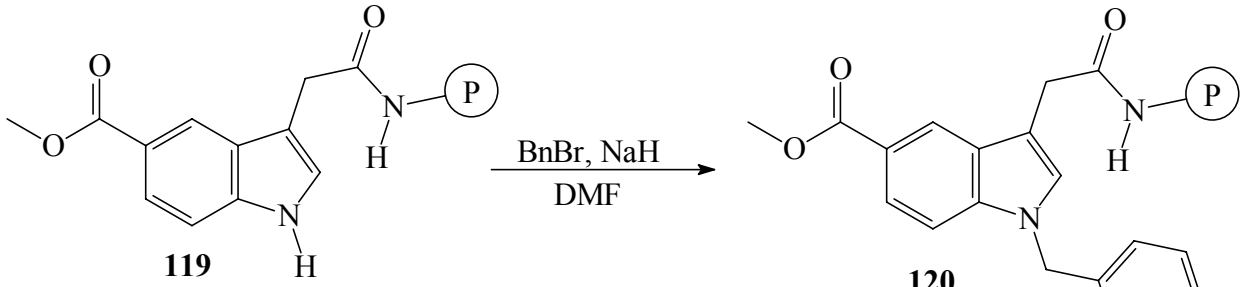
This chapter describes methods for direct ring substitution when the indole skeleton has already been attached to a polymer. Methods are introduced in numerical order of the substituents.

2.3.1. Modification of indoles by substitution at nitrogen

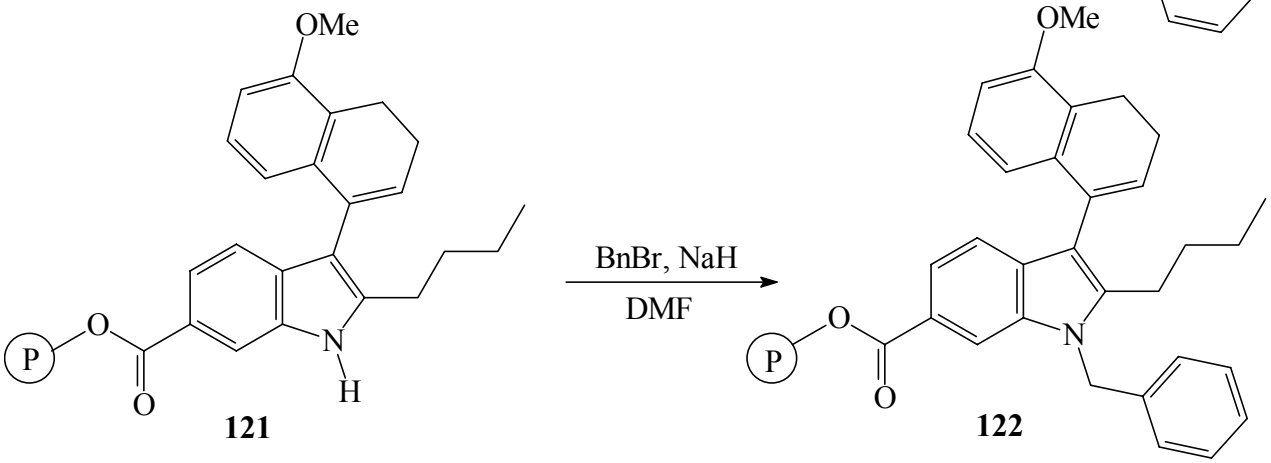
Procedures for *N*-1 substitution involve normally a base-catalyzed nucleophilic substitution. The strong bases usually needed for deprotonation create some difficulties in solid-phase chemistry. Substituents should be tolerant under highly basic conditions and also the linker must be compatible. In fact, the only reported modifications on solid-phase are alkylations.[91, 95, 109] Deprotonation has been performed by NaH or *t*-BuOK and alkyl bromides have been used as electrophiles. One post-cleavage methylation has also been reported (Scheme 24).[97]
On the other hand, palladium-catalyzed [110, 111] or copper-catalyzed [112] *N*-arylations reported in solution phase have not been reported on solid phase so far. Maybe in the future these reactions will be adopted to solid phase chemistry and also alkylations or acylations with groups that have a directing effect toward C-2 lithiation.

2.3.2. Modification of the 2-position by Pictet-Spengler reaction

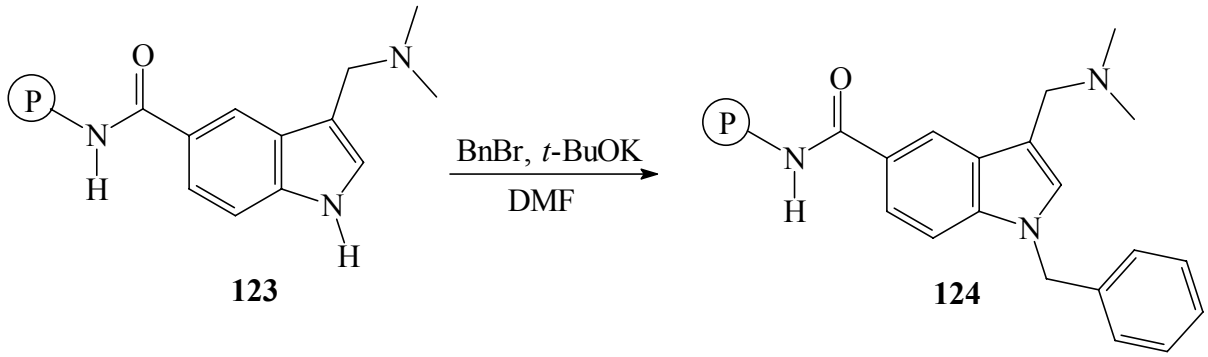
The β-carboline skeleton is a key structural motif common to a large number of tryptophan derived alkaloids. Pictet-Spengler cyclization gives access to this class of compounds and this reaction has been well studied in solid phase chemistry. [113-116] Both acid-[113, 114] and base-labile [115, 116] linkers have been used to obtain the desired products. A variety of commercially available substituted aryl aldehydes, aliphatic aldehydes and ketones are viable substrates and thus allow the preparation of large β-carboline compound libraries (Scheme 25). Recently Grigg *et al.* [117] reported a five component solid supported procedure where they utilized cycloaddition attachment, Pictet-Spengler reaction and finally Pd(0)-catalyzed reactions (**131 ➜ 134**) (Scheme 26).



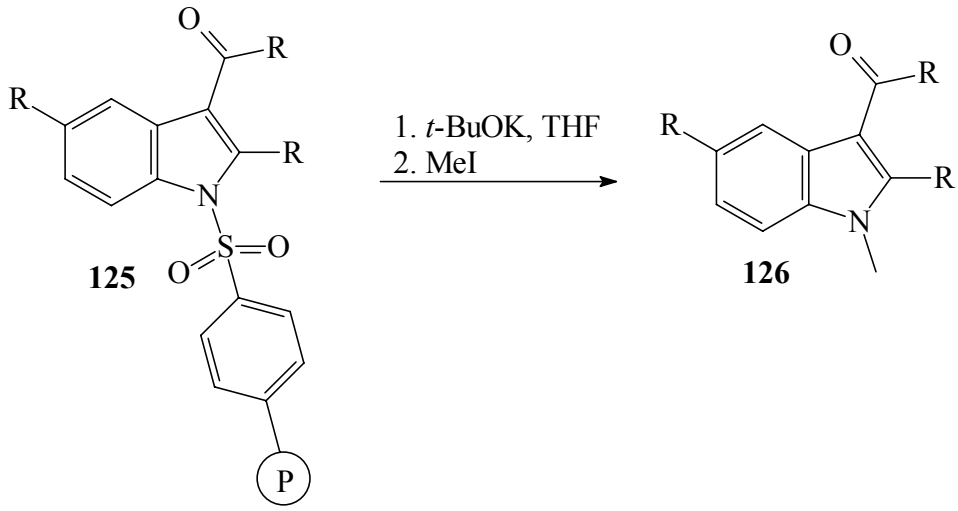
119 **120**



121 **122**

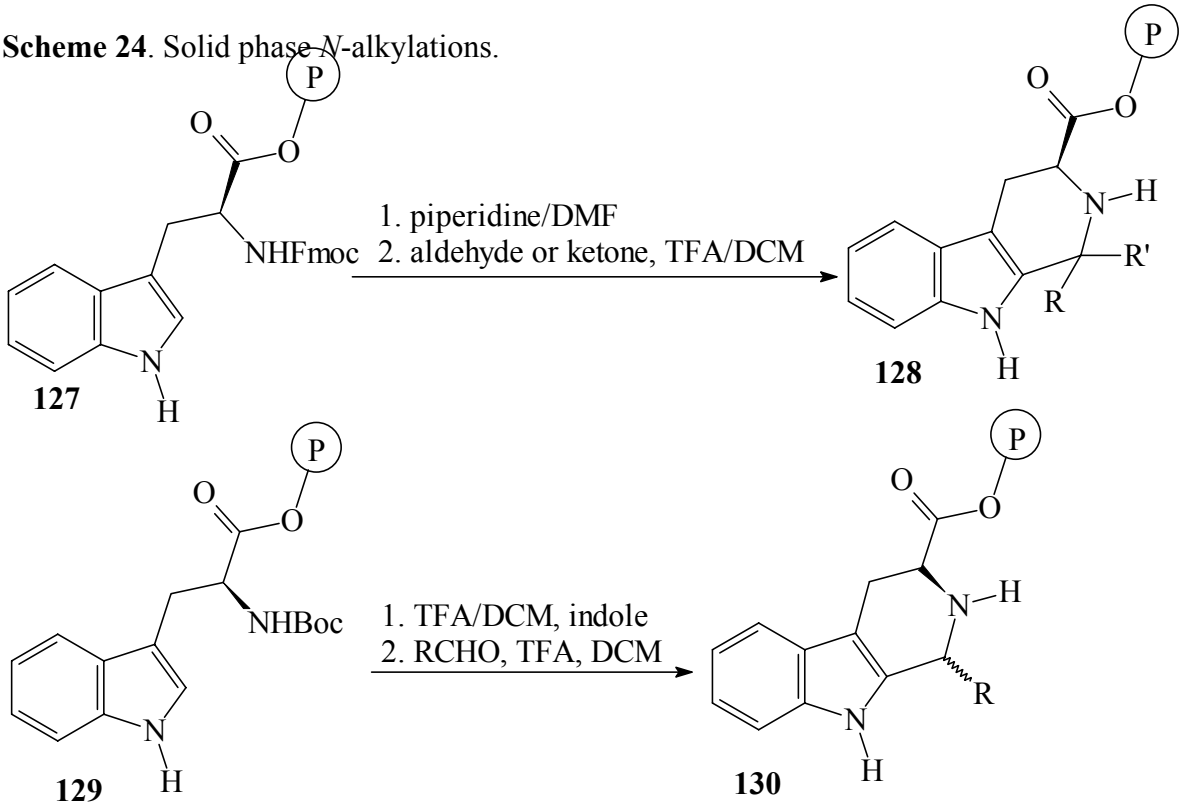


123 **124**

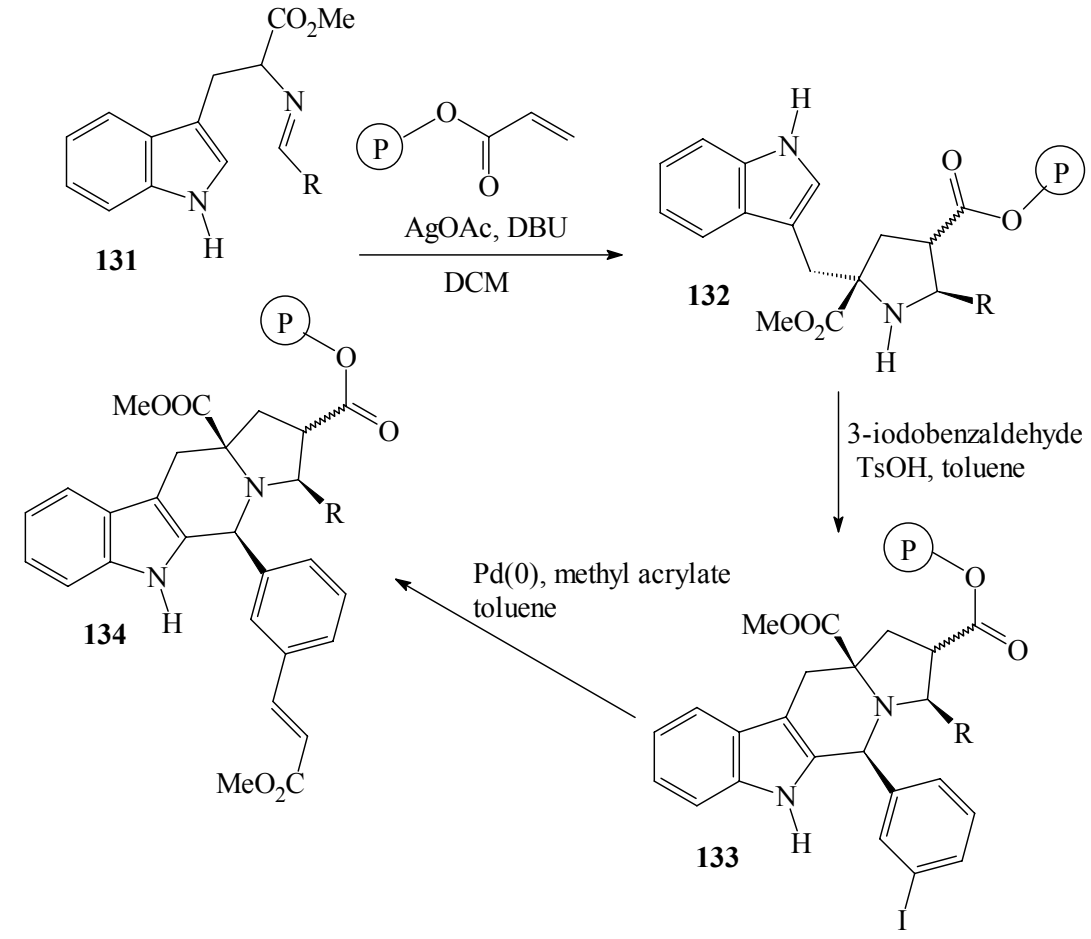


125 **126**

Scheme 24. Solid phase *N*-alkylations.



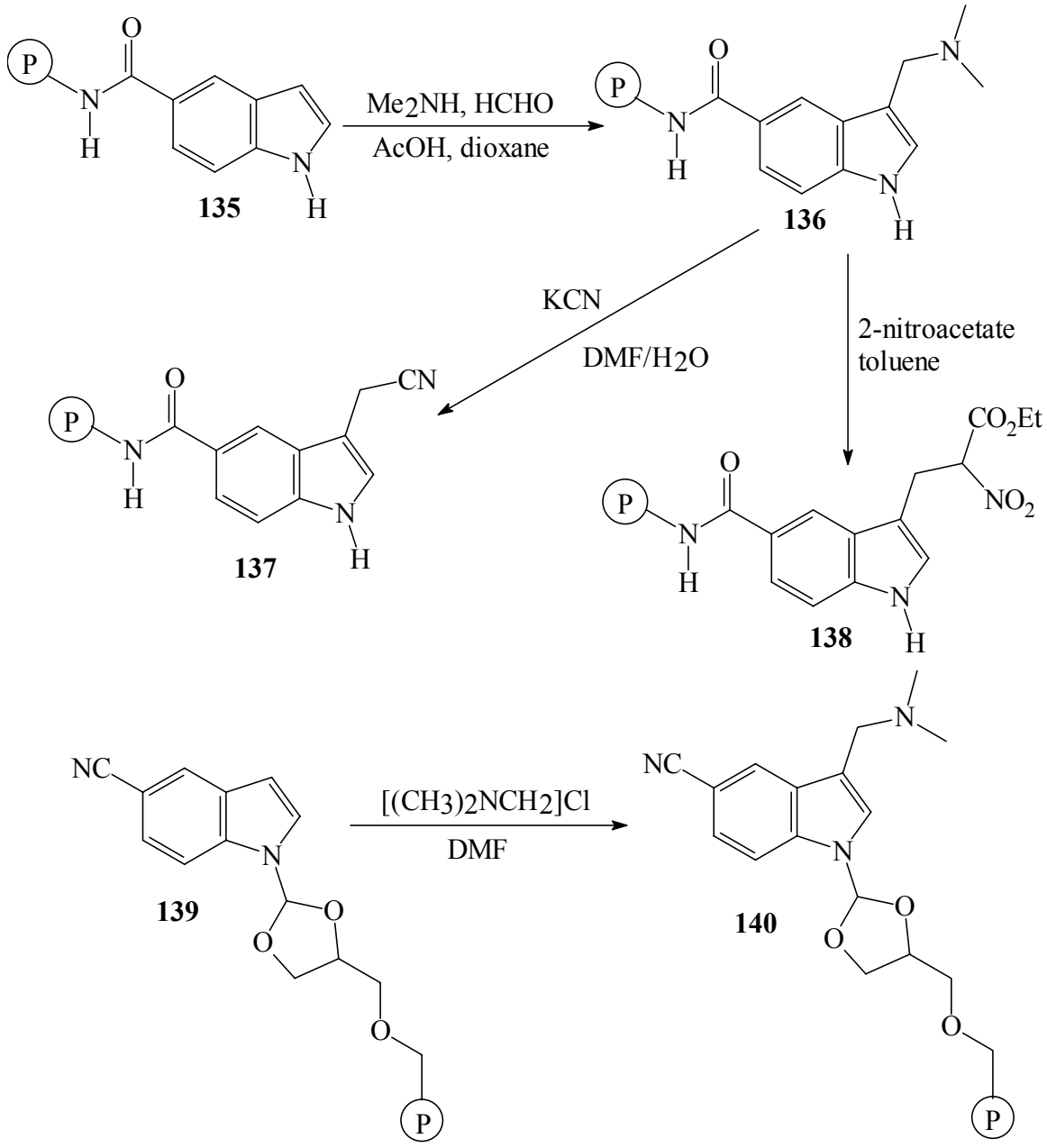
Scheme 25. Pictet-Spengler reaction on solid phase.



Scheme 26. Pictet-Spengler reaction on solid phase.

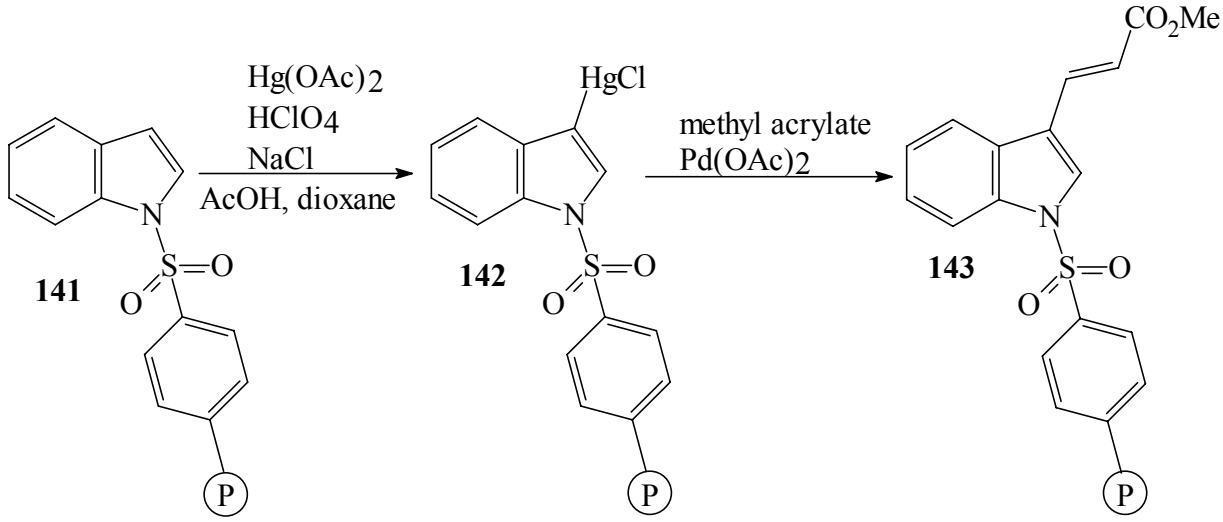
2.3.3. Indole 3-position modifications

There are a number of methods for introducing substituents at the C-3 since this is the preferred site for electrophilic substitution. Most of the direct functionalizations on solid phase chemistry have focused on that position. The first published functionalization utilized the Mannich reaction as presented by Zhang *et al.*[109] Resin bound (Rink amide resin) 5- and 6-carboxyindoles **135** were subjected to Mannich reaction with formaldehyde and a secondary amine in the presence of acetic acid. The obtained gramines **136** were further modified by nucleophilic substitutions with KCN and 2-nitroacetate. Different reaction conditions for solid phase Mannich reaction have been reported by Gmeiner *et al.*[106] Dimethylmethyleneimmonium chloride (Böhme's salt) was used in order to avoid acidic aqueous conditions (Scheme 27).

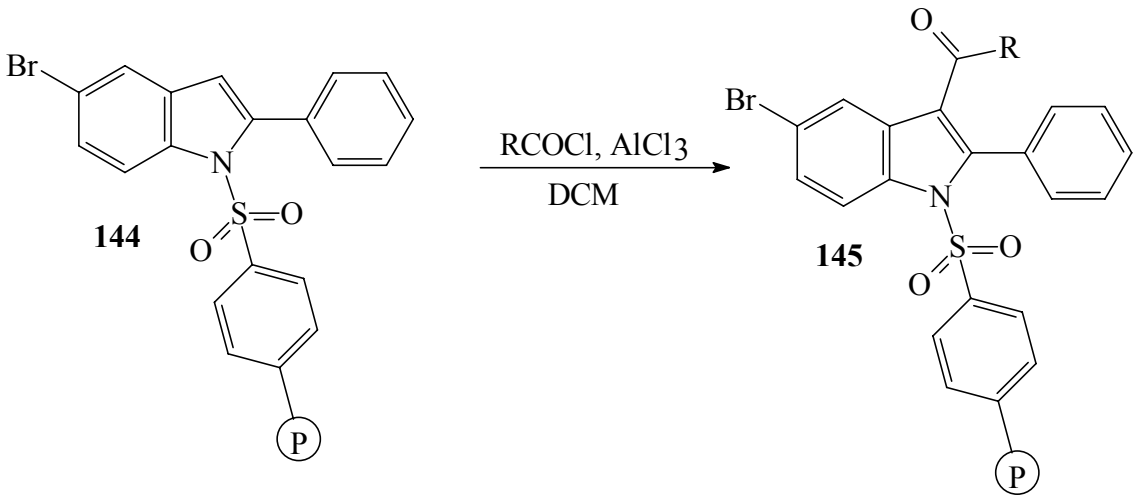


Scheme 27. Mannich reaction.

Synthetically versatile resin-bound 3-indolylmercury specie **142** was recently reported by Zhang *et al.*[96] Solid supported indole was treated with mercury(II)acetate, catalytic amount of $HClO_4$ and NaCl in AcOH/dioxane followed by palladium mediated coupling with methyl acrylate (Scheme 28).
Solid phase acylation of indoles at C-3 by Friedel-Crafts reaction has been demonstrated by Schultz *et al.* [97] in their synthesis of 2,3,5-trisubstituted indoles. Aromatic acid chlorides were found to be most reactive in this $AlCl_3$ catalyzed reaction (Scheme 29).



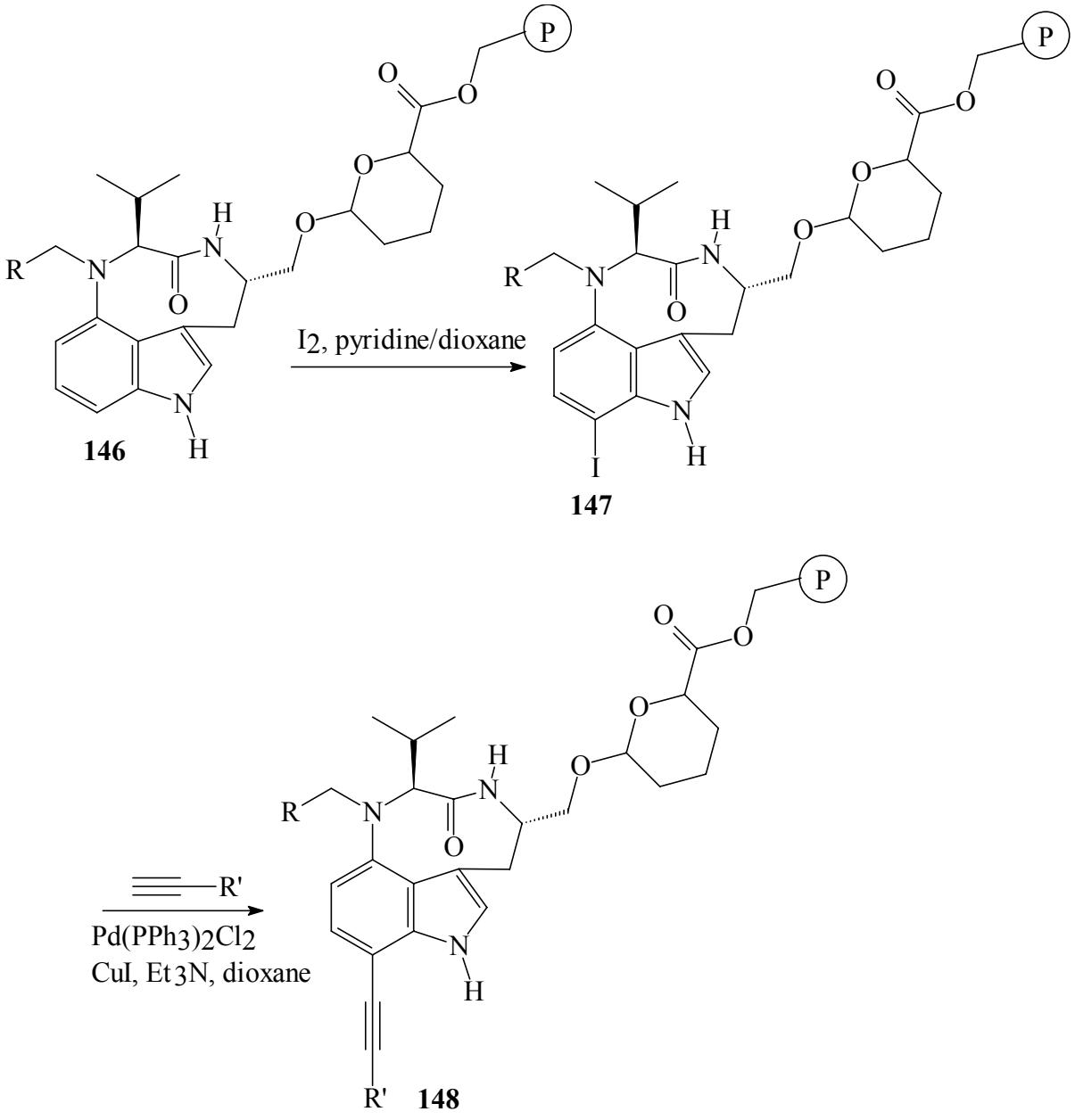
Scheme 28. Solid phase mercuration.



Scheme 29. Friedel-Crafts acylation.

2.3.4. Functionalization of other positions

The only published method for direct functionalization of the benzenoid ring on solid phase has been reported by Herget *et al*.[108] In their solid phase synthesis of teleocidin analogues a functionality at C-7 was needed. A regioselective iodination was performed with iodine in pyridine/dioxane at 0°C. The resulting iodides were subjected to Sonogashira coupling with acetylenes on the polymeric support (Scheme 30).



Scheme 30. Modification of 4-position by halogenation.

3. Aims of the study

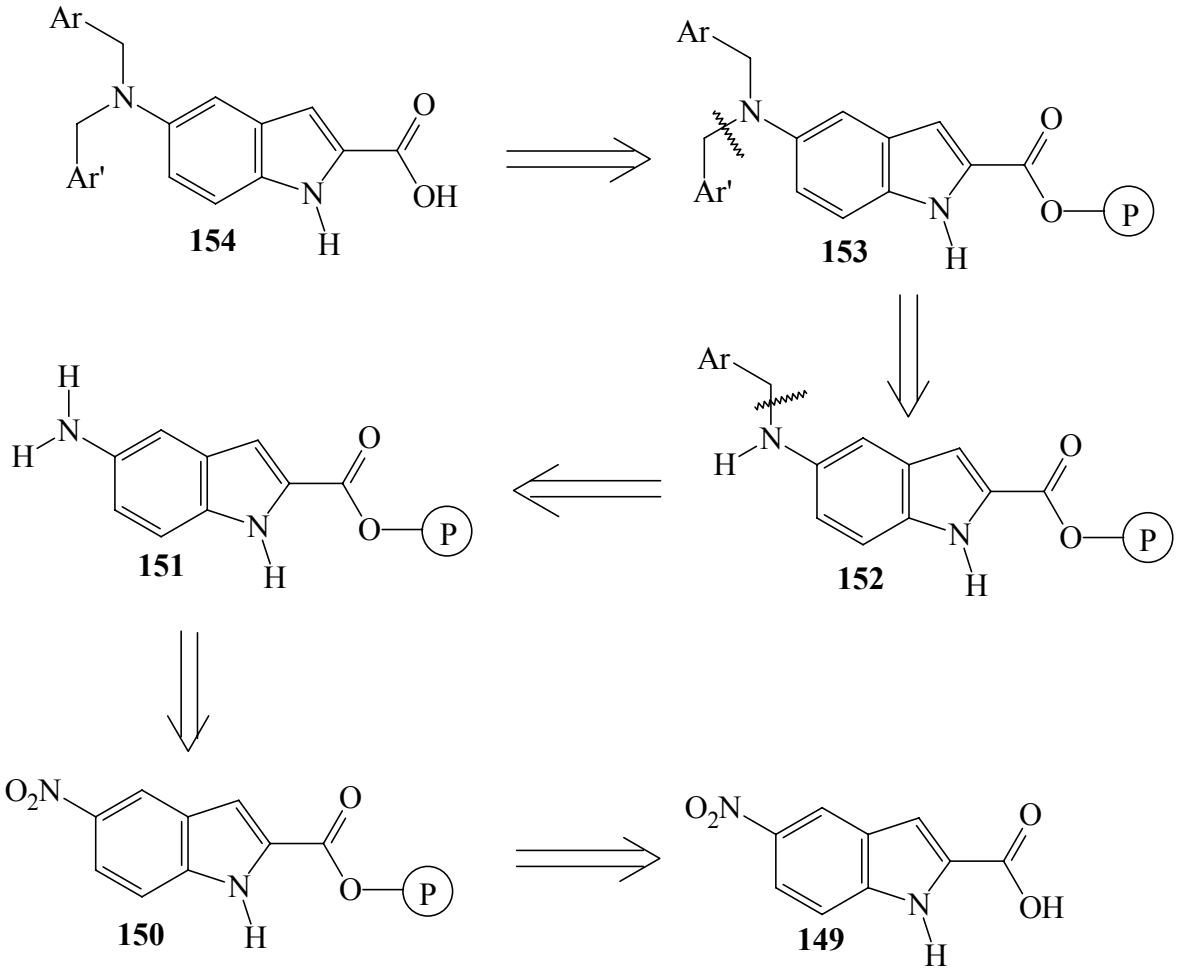
Despite the fact that pharmaceutical industry worldwide is utilizing solid-phase chemistry routinely, in Finland this technology is quite new. Although some small pharmaceutical companies are using solid supported techniques, in academia the research has been focused mainly on solid phase peptide synthesis. The aim of this study was therefore to develop solid phase chemistry techniques suitable for the preparation of small-molecule libraries. The fact that indole moiety is present in many pharmaceutical substances, gave me the reason to choose carboxyindoles as target molecules for my investigations in the field. I decided to modify the carboxyindoles by functional group transformations and by direct functionalizations.
The specific aims of the work described here are as following:

1. Preparation of 5-substituted 2-carboxyindoles on solid support (I).
2. Bromination of different 2-carboxyindoles on solid phase (II).
3. Vilsmeier formylation of 2-carboxyindoles on solid phase (III).
4. Directed lithiation of polymer-bound carboxyindoles (IV).

4. Results and Discussion

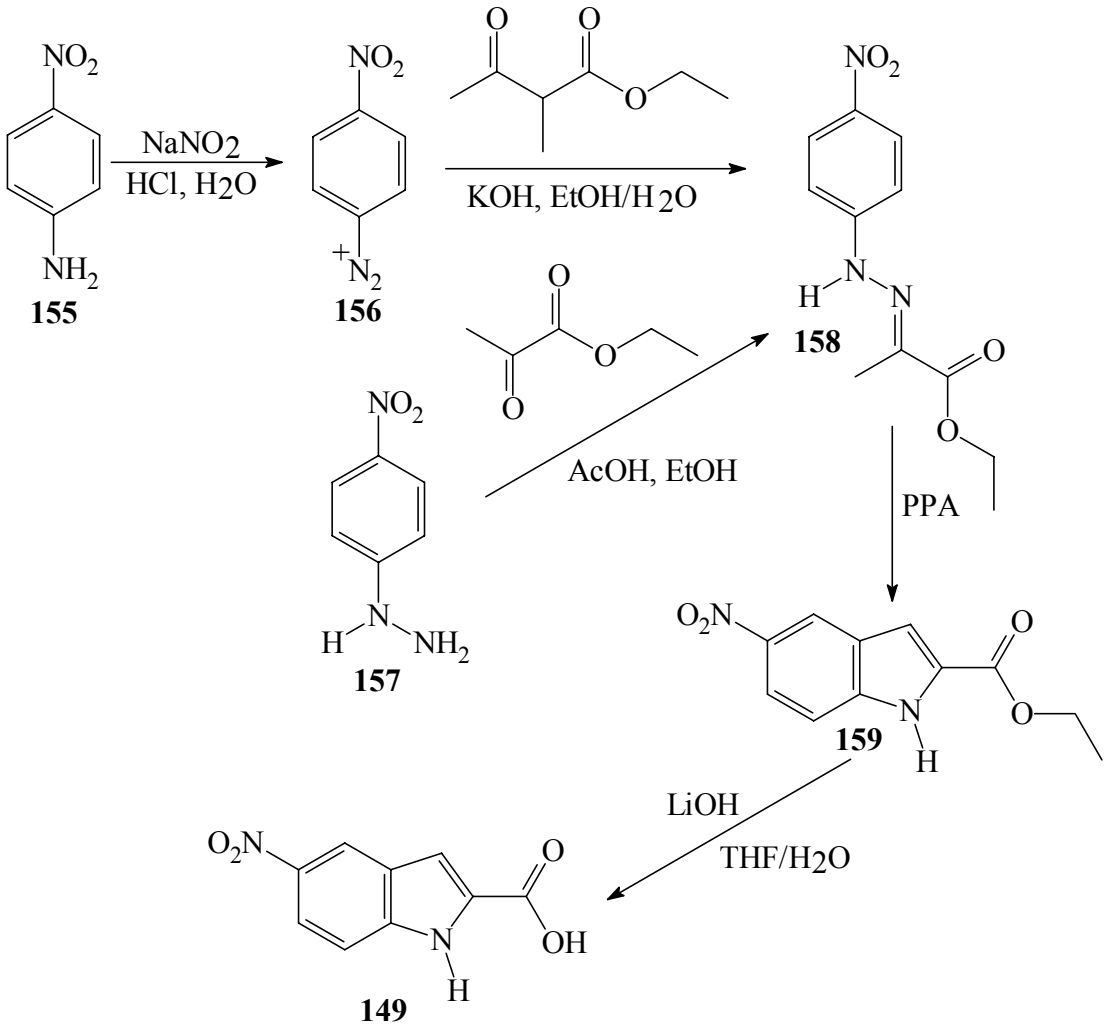
4.1. Synthesis of 5-substituted 2-carboxyindoles (I)

The basic structure of the target molecule **154** and retrosynthetic analysis is shown in Scheme 31.



Scheme 31. Retrosynthetic analysis of the target molecule **154**.

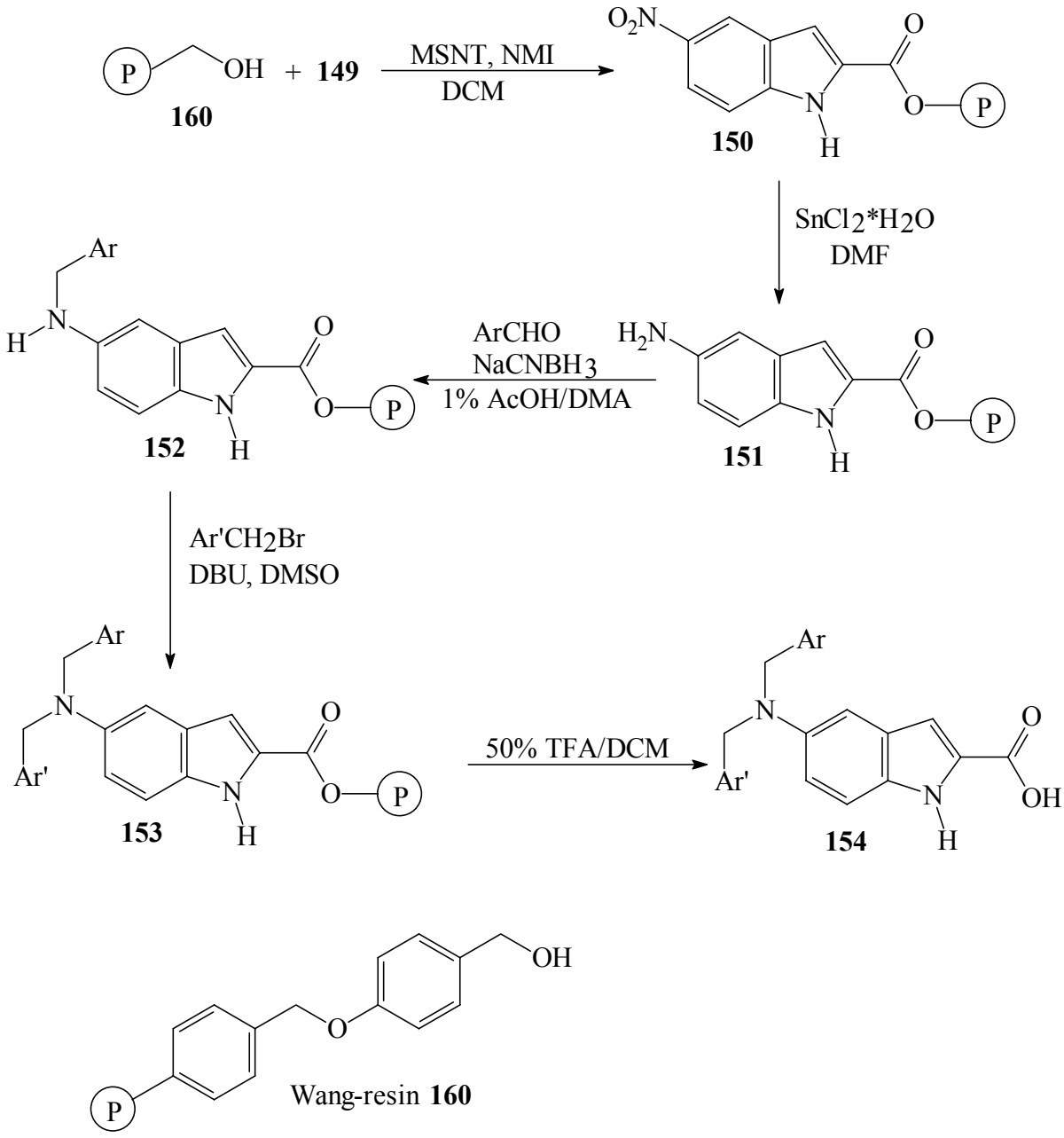
5-nitro-2-carboxyindole **149** was synthezised either from 4-nitroaniline **155** by a Japp-Klingemann reaction [118] followed by Fischer indolization [119] or from commercially available 4-nitrophenylhydrazine **157**. In the former case the hydrazone **158** was obtained in 75 % yield and in the latter case in 80 % yield after recrystallization from EtOH. Polyphosphoric acid (PPA) was found to be efficient reaction medium for cyclization to the indole **159**. Indolization occurred smoothly at 80 ^{o}C and there was no need to heat the reaction mixture to 130 ^{o}C as reported earlier.[119] The yield of ethyl-5-nitro-2-indolecarboxylate **159** was 83 %. Hydrolysis of **159** with LiOH in THF/H_2O gave **149** in quantitative yield.



Scheme 32. Synthetic routes to **149**.

Our initial idea was to reduce the nitro group and protect the amine with a Fmoc group. However, hydrogenation at atmospheric pressure in the presence of Pd/C-catalyst was very slow probably due to the poor solubility of **149**. The 5-amino-2-

carboxyindole was also found to be quite unstable. So we decided to perform the reduction on solid phase. Because we needed the acid functionality to the 2-position at the end we chose an acid-labile Wang resin **160** as a solid support. The solid phase procedure is described in Scheme 33.

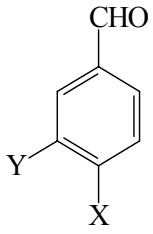
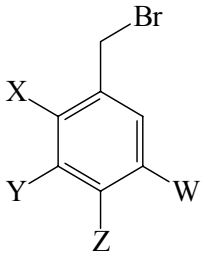
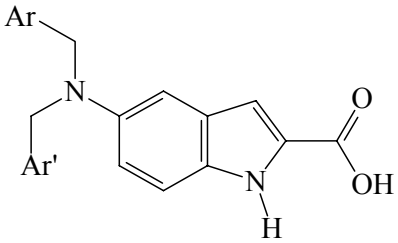
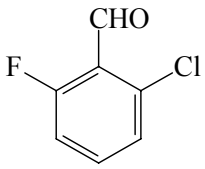
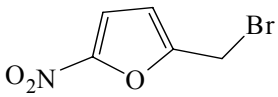
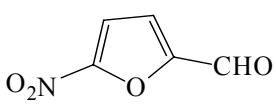
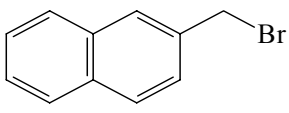


Scheme 33. Solid phase synthesis of compounds type **154**.

Indole **149** was attached to the polymer **160** using 1-(2-mesitylene-sulfonyl)-3-nitro-1, 2, 4-triazole (MSNT) and *N*-methylimidazole (NMI) in dichloromethane.[120] The attachment was monitored by IR and characteristic bands at 1350 cm^{-1} (NO_2) and 1700 cm^{-1} were observed. The nitro-group was reduced with $SnCl_2*2H_2O$ in DMF.[121] The conversion was checked by IR (disappearence of band at 1350 cm^{-1}) and by the Kaiser test.[122] In the first diversity step a reductive amination with aromatic aldehydes

in the presence of sodium cyanoborohydride in AcOH/DMA was performed.[123] A further alkylation with benzylic bromides in the precence of DBU was performed thus providing the second diversity step.[123] Cleavage using the standard TFA/DCM method produced the final products, which were purified by preparative TLC ($CHCl_3$/EtOAc 1:1+1% AcOH). The used monomers, (aldehydes and benzylbromides) products and yields are summarized in Table 1.

Table 1. Starting materials, products and yields summarized.

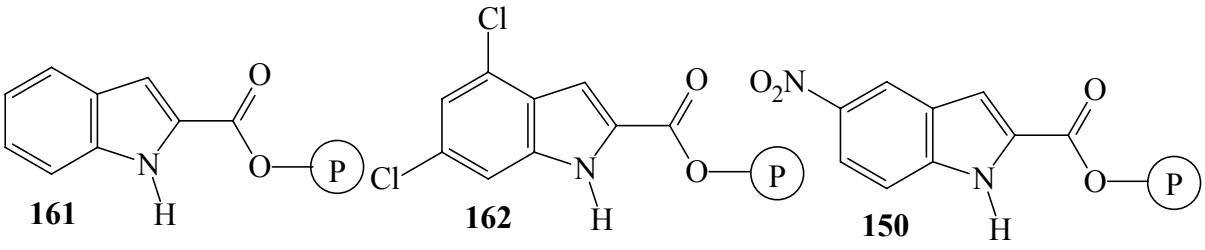
Aldehydes Ar	Benzylbromides Ar'	Product	Yield (%) [a]
			
$X = CF_3$, Y = H	$X = OMe$, $W = NO_2$ Y = Z = H	**154a**	51 %
$X = NO_2$, Y = H	$W = NO_2$ X = Y = Z = H	**154b**	73 %
X = H, Y = Me	X = Y = Z = W = H	**154c**	55 %
X = OMe, Y = H	$W = NO_2$ X = Y = Z = H	**154d**	69 %
X = Cl, Y = H	$W = NO_2$ X = Y = Z = H	**154e**	74 %
X = H, $Y = NO_2$	$X = NO_2$, Y = H Z = W = OMe	**154f**	40 %
		**154g**	60 %
		**154h**	45 %

[a] Isolated purified yield (calculated based on the commercially announced loading).

This procedure was also performed on Merrifield resin. Attachment and cleavage were performed according to Frenette and Friesen.[124] The cesium salt of **149** was attached to chloromethylated polystyrene, reaction steps were performed in similar manner and cleavage was effected by transesterification. We noticed also that $NaCNBH_3$ could be replaced by sodium acetoxyborohydride, which was also more convenient to use.
In summary, we demonstrated that starting from a simple precursor **149** a diverse set of compounds could be synthezised in an easy manner.

4.2. Bromination of 2-carboxyindoles on solid phase (II)

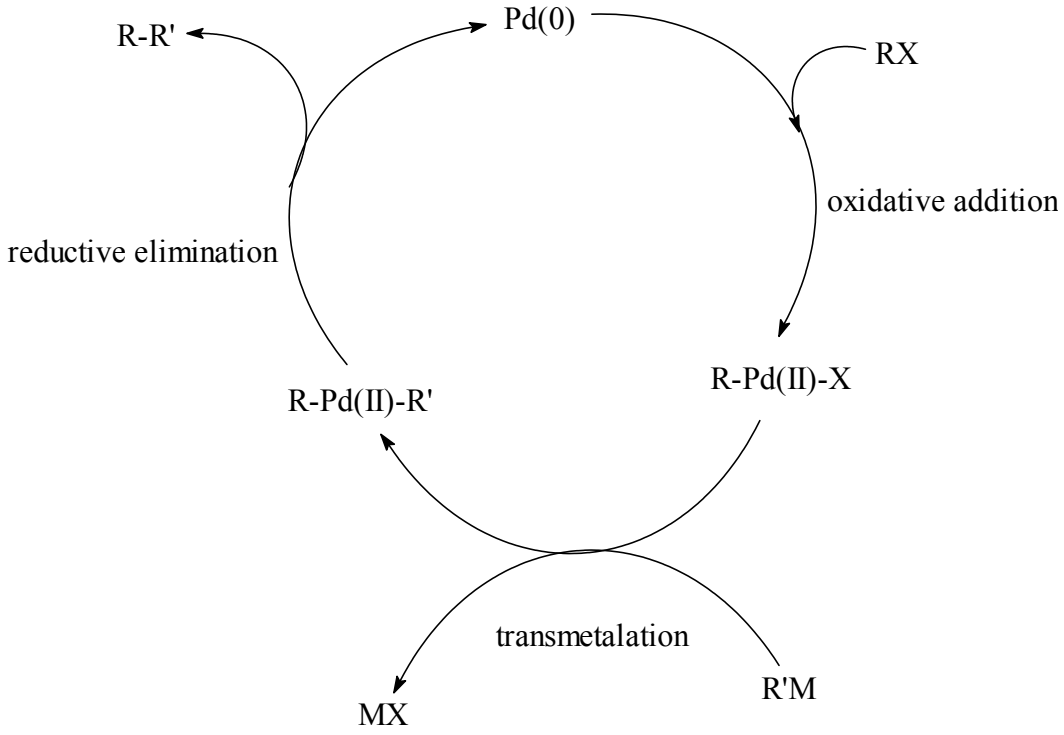
Reactions performed on solid support usually involve quite simple reactions. Usually the reactions involve readily installed functional group transformations similar to our route from **150** to **154**. However, solid phase reactions where some new functionality is installed selectively to resin-bound aromatic molecule are rare. Reactions where this kind of transformation is performed can be named as " direct functionalization " according to Ganesan *et al*.[125] Ganesan *et al*. modified resin-bound tiophene- and furan derivatives by directed lithiation. Recently, Han *et al*. presented the introduction of bromine onto polymer supported thiophene.[126] Solid phase iodination of phenols has been reported by Arsequell *et al*. [127, 128]
We decided to attempt selective 3-position solid-phase bromination of resin-bound 2-carboxyindoles. The bromination targets are presented in Scheme 34.



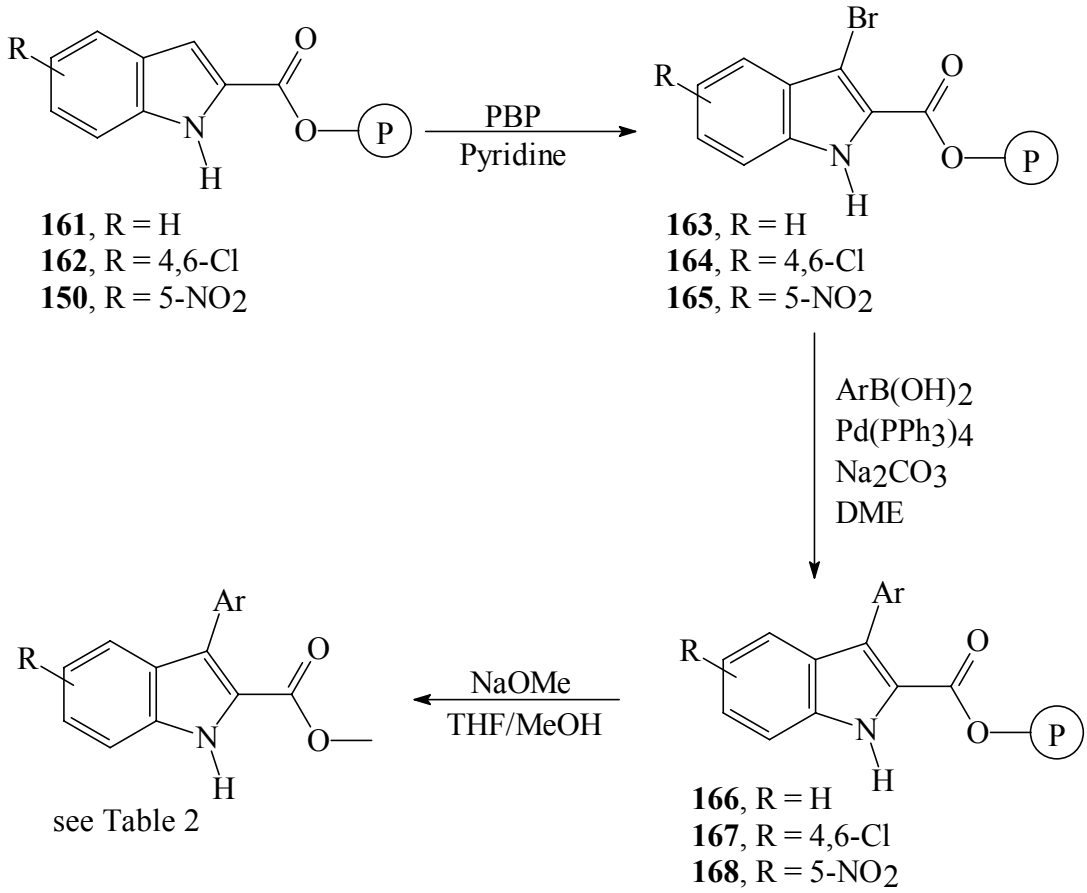
Scheme 34. Selected indole-resins.

Indole-2-carboxylic acid was commercially available and 4, 6-dichloro-2-carboxyindole was prepared similarly to **149**. In solution pyridinium bromide perbromide (PBP) has been used successfully as a brominating agent.[129] In fact, we tested all brominations first in solution phase before transferring them to solid phase. To avoid the functionalization of the resin itself we chose the simple Merrifield-resin as the support. In a typical procedure the starting resin was suspenced in dry pyridine under nitrogen and the mixture was cooled to 0 ^{o}C. PBP was dissolved in pyridine and added dropwise to the slurry with syringe. The mixture was stirred for 4 h at 0 ^{o}C before resin filtration and washing. Cleavage and analysis showed quantitative conversion. The brominated resin-bound indoles **163**-**165** where thereafter subjected to Suzuki coupling reaction [124] summarized in Scheme 36 and Table 2. The Suzuki

reaction is a palladium-catalyzed cross-coupling reaction between an organoboron reagent and an organohalide or triflate.[132] A Growing number of organoboron reagents, mainly arylboronic acids, are commercially available and these compounds are stable and easy to handle. Those reagents are not toxic and therefore, for a large scale setting, a Suzuki coupling is an attractive choice. The general catalytic cycle for cross-coupling is presented in Scheme 35.

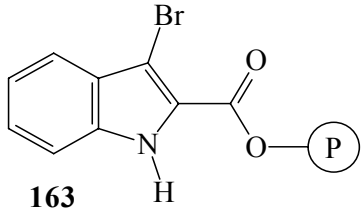
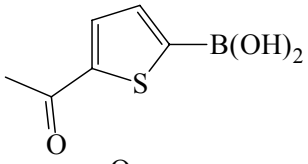
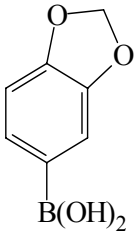
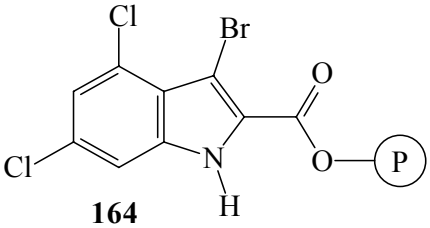
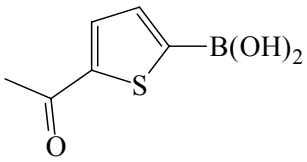
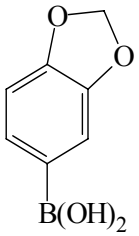
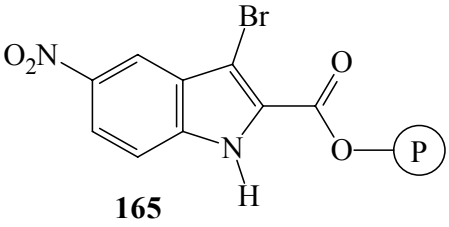
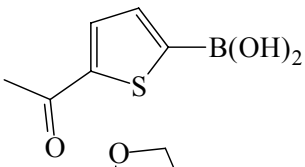
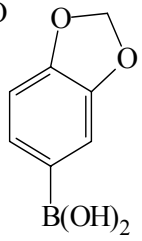
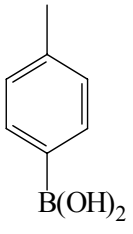


Scheme 35. Catalytic cycle of Pd-catalyzed coupling reactions.



Scheme 36. Synthetic route.

Table 2. Starting materials, products and yields summarized.

Starting polymer	$ArB(OH)_2$	Product	Yield [a]
 **163**		**166a**	42 %
		**166b**	47 %
 **164**		**167a**	95 %
		**167b**	97 %
 **165**		**168a**	96 %
		**168b**	98 %
		**168c**	97 %

[a] Isolated yields after column chromatography.

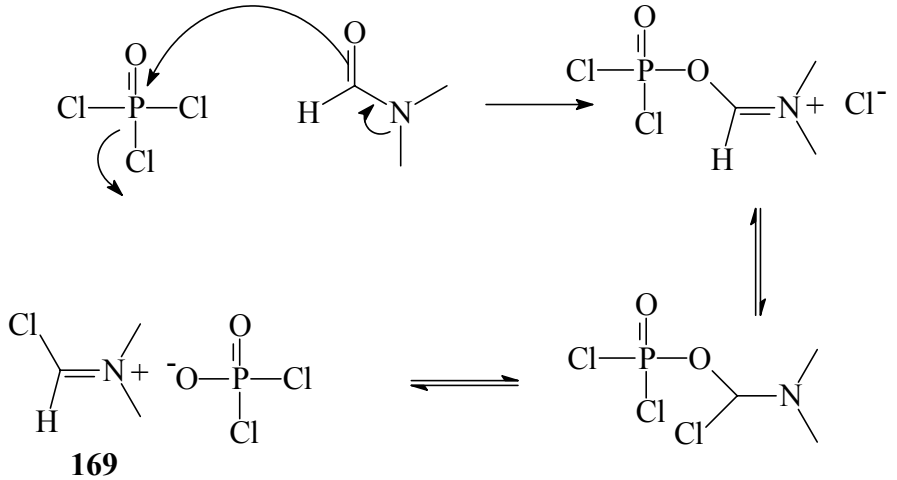
The catalyst used in our experiments was tetrakis(triphenylphosphine)palladium, which is represented as Pd(0). In the first step polymer-bound haloindole (RX) undergoes an oxidative addition to Pd(0) affording intermediate R-Pd(II)-X. The next step is a transmetallation step with arylboronic acid (R'M). Intermediate R-Pd(II)-R' undergoes reductive elimination step yielding the coupling products R-R'. Oxidative addition is often the rate-determining step in the catalytic cycle.[130] Arylhalides activated by electron-withdrawing groups are known to be more reactive to the oxidative addition. This could be the reason for higher yields when the resin-bound electrophile had substituents (see Table 2). For resins **164** and **165** the reaction went to completion in 16 h, but for the resin **163** even the prolonged reaction time 48 h did not increase the yields. We didn't try to optimize the yields in other ways because we had achieved our main purpose, the selective bromination on solid-phase. In fact, Mederski *et al*. [112] have reported quite comparable yields in their coupling studies in solution.

In summary, we have shown that bromination could be done selectively on solid phase. Of course the same limitations for selectivity exist on solid phase as in solution, but choosing a simple polymer with no special linkers, which could make the polymer itself prone to functionalizations, the aromatic functionalizations could be done on solid support.

4.3. Vilsmeier formylation on solid-phase (III)

Vilsmeier is a classical organic name reaction invented by Anton Vilsmeier in 1927.[131] The reaction is a useful variant of the Friedel-Crafts acylation and introduces an aldehyde functionality to aromatic molecules. Although the reaction was first used only for activated aromatics and heteroaromatics, it has recently also shown its compatibility for aliphatic substrates.[132] The Vilsmeier reaction is an important industrial process but large quantities of phosphorus byproducts are an environmental problem.

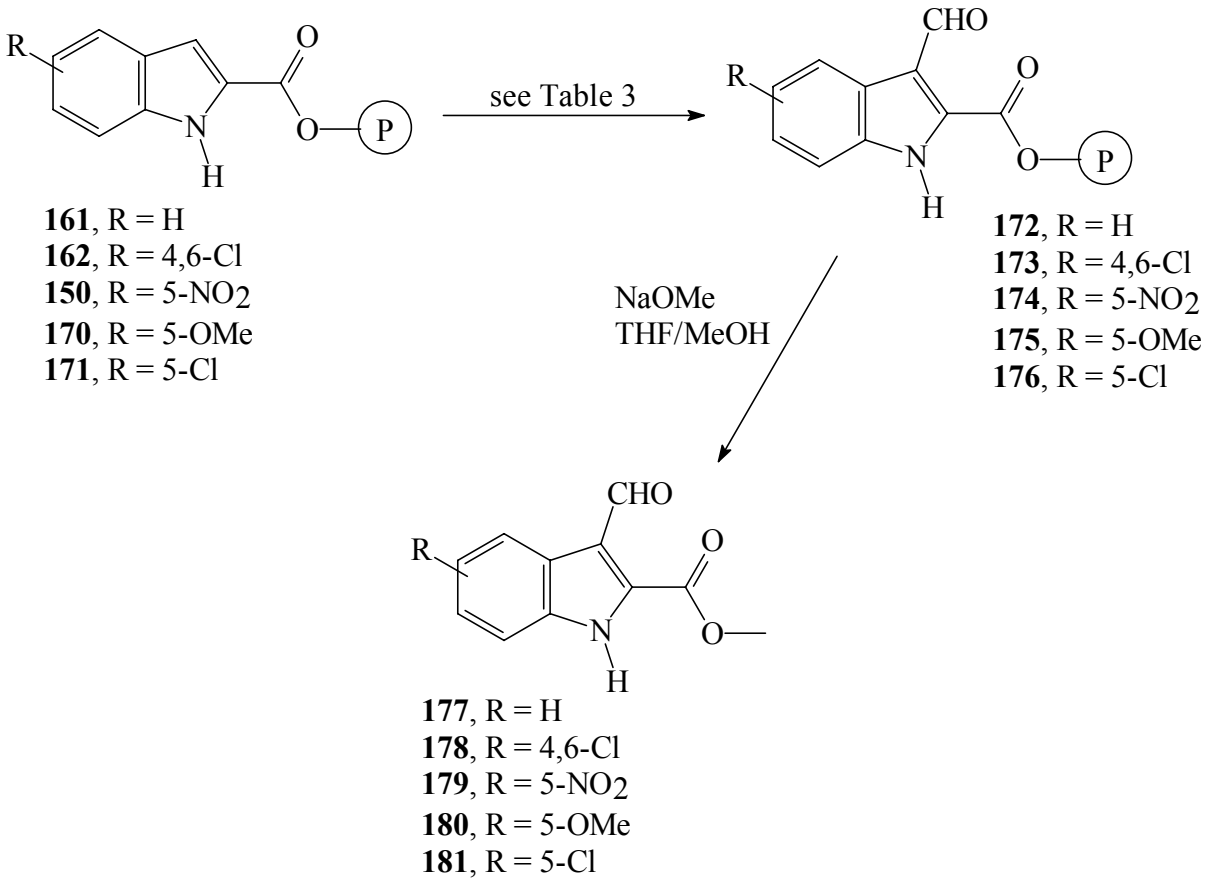
The electrophilic reagent in the Vilsmeier formylation is a chloroiminium ion **169**, which is formed from phosphorus oxychloride and dimethylformamide as shown in Scheme 37.



169

Scheme 37. Formation of Vilsmeier reagent.

The Friedel-Crafts reaction has been utilized in construction of different linker systems starting from polystyrene,[133, 134] but only Schultz *et al*. [97] have used this acylation as direct functionalization method. We decided to try the related Vilsmeier reaction to provide a facile way for introducing an aldehyde group to 2-carboxyindoles on solid phase. As in the case of the bromination studies, Merrifield resin was chosen as a support. The synthetic route is illustrated in Scheme 38 and the results are collected on Table 3.



161, R = H
162, R = 4,6-Cl
150, R = 5-NO_2
170, R = 5-OMe
171, R = 5-Cl

172, R = H
173, R = 4,6-Cl
174, R = 5-NO_2
175, R = 5-OMe
176, R = 5-Cl

177, R = H
178, R = 4,6-Cl
179, R = 5-NO_2
180, R = 5-OMe
181, R = 5-Cl

Scheme 38. Vilsmeier reaction.

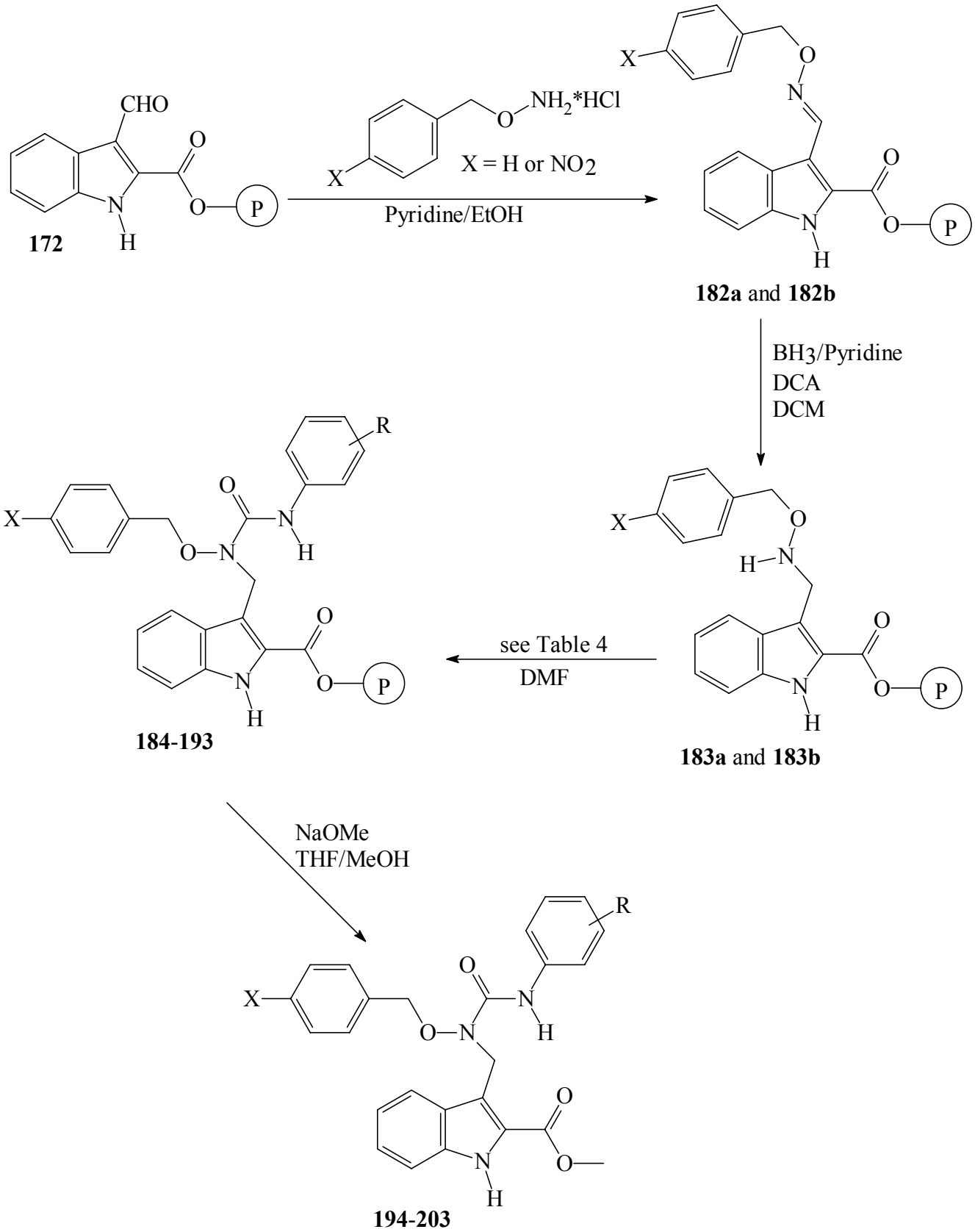
Three different formylating salts were tested; $POCl_3$/DMF, $POCl_3$/NMFA and $SOCl_2$/DMF. In all experiments the reaction time and equivalents of the formylating agent were kept constant (16 h and 10 equiv.). All reactions were run in 1, 2-dichloroethane. Reaction worked smoothly for resins **161**, **170** and **171** (quantitative conversion at room temperature), but for resins **150** and **162** full conversion were not achieved. The best conversion was achieved with $POCl_3$/NMFA in these these circumstances. The results were expected because electrophilic substitutions are known to be more difficult in the presence of the electron withdrawing groups. In the case of resin **161**, we also found out that two hours was enough to bring the reaction to completion.

Table 3. Attempted reaction conditions in our experiments.

Resin	Formylating agent [a]	Conversion (%) [b]	T (^{o}C) [c]
161	$POCl_3$/NMFA	100	rt
161	$POCl_3$/DMF	100	60
161	$POCl_3$/NMFA	100	60
162	$POCl_3$/DMF	15	60
162	$POCl_3$/NMFA	30	60
162	$POCl_3$/NMFA	90	reflux
162	$SOCl_2$/DMF	10	60
150	$POCl_3$/DMF	15	60
150	$POCl_3$/NMFA	40	60
150	$POCl_3$/NMFA	85	reflux
150	$SOCl_2$/DMF	10	60
170	$POCl_3$/NMFA	100	rt
170	$POCl_3$/DMF	100	rt
171	$POCl_3$/NMFA	100	rt
171	$POCl_3$/DMF	100	rt

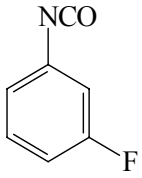
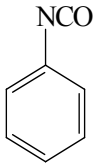
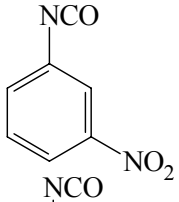
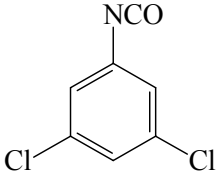
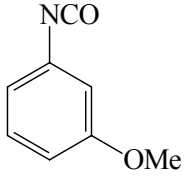
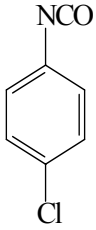
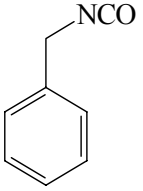
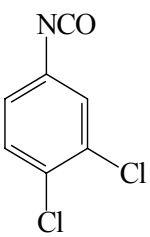
[a]NMFA: *N*-methylformanilide
[b]Determined by mass percentages of isolated column-purified yields.
[c]Boiling-point of 1, 2-dichloroethane (DCE) is 85 ^{o}C.

To demonstrate the versatility of the obtained aldehyde functionality we prepared a small series of *O*-benzylhydroxyureas. **172** was treated with *O*-benzylhydroxyamine hydrochloride (or 4-NO_2-*O*-benzylhydroxyamine hydrochloride) affording oxime-ether **182a** or **182b**, respectively. Reduction of **182a** and **182b** with borane-pyridine complex in the presence of dichloroacetic acid [135] gave **183a** and **183b**. O-benzylhydroxylamines **183a** and **183b** were reacted with aromatic isocyanates and cleaved from the resin providing *O*-benzylhydroxyureas **194-203**. The synthesis is shown in Scheme 39 and yields and structures are summarized in Table 4. After each reaction step a small sample of resin was treated with NaOMe and the completion of the reactions was checked by thin-layer chromatography. The reaction times were not optimized. Although the overall yields of the six steps were only moderate (30-70 %, calculated on the basis of the commercially announced loading), the purities of the compounds were high (> 90 %, determined by HPLC). All products showed a single spot on TLC and there was no need for chromatographic purification after cleavage.



Scheme 39. Synthesis of *O*-benzylhydroxyureas.

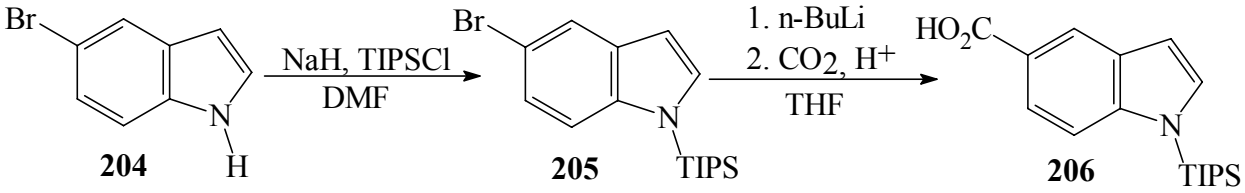
Table 4. Starting materials and yields summarized.

Polymer	Isocyanate	Product	Yield (%)
183a		**194**	67
183a		**195**	71
183a		**196**	30
183a		**197**	53
183a		**198**	70
183a		**199**	52
183a and **183b**		**200** and **201**	73 and 75
183a and **183b**		**202** and **203**	67 and 33

In summary we have demonstrated that Vilsmeier formylation is an efficient and simple method for direct functionalization on solid phase. In the past combinatorial chemistry has largely focused on simple synthetic sequences, whereas the natural product route tends to be more complicated and creative. Combination of the solid phase techniques and natural product synthesis is called *diversity-oriented synthesis*.[136] By using direct functionalization methods to vary the structure of scaffolds the diversity will go a lot further and will give an access to natural-product-like libraries.

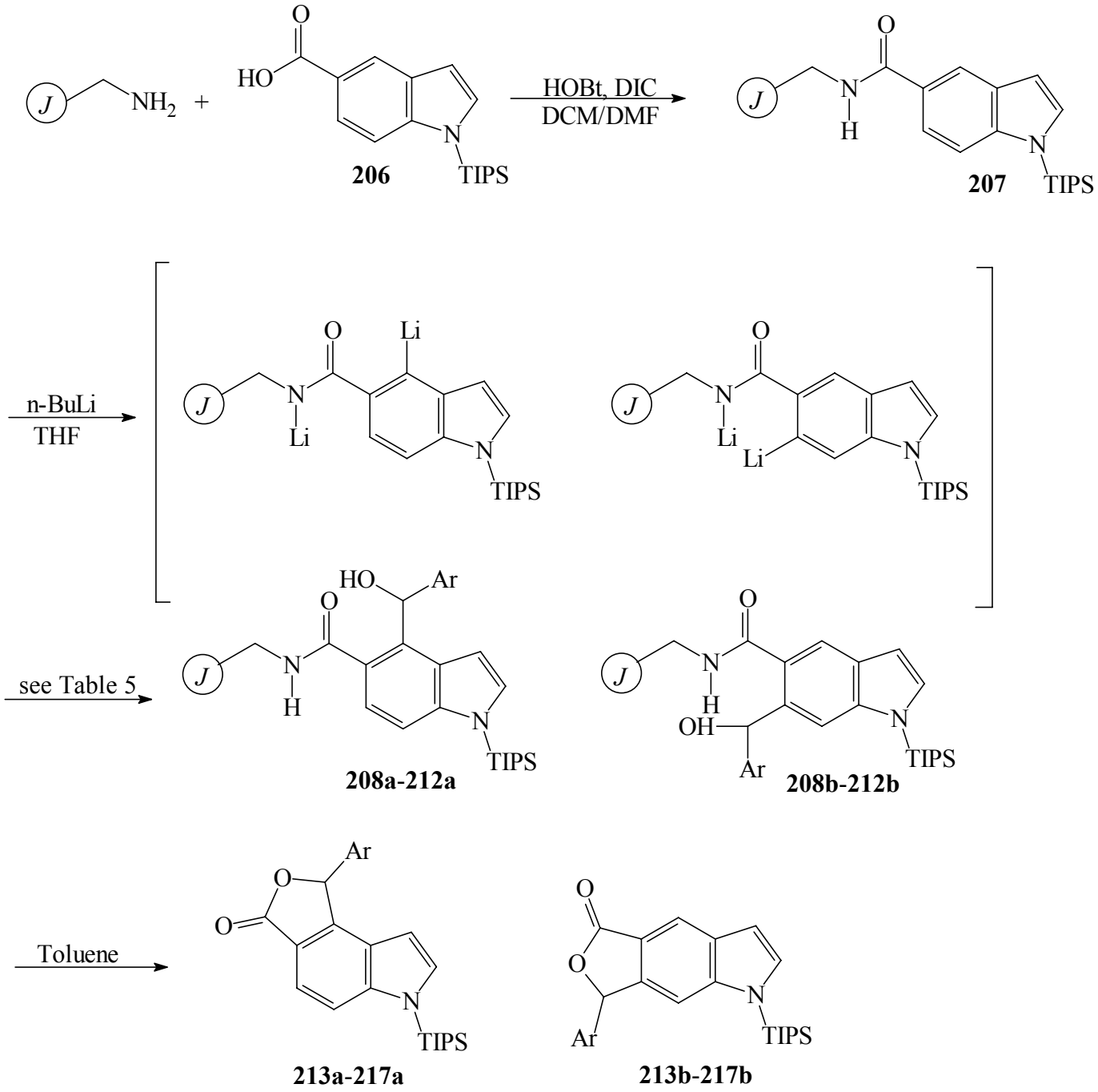
4.4. Directed lithiation of polymer-bound carboxyindoles (IV)

Usually the formation of 4-substituted indoles relies on the formation of the pyrrole ring from a suitably adorned benzenoid precursor.[137] Very seldom direct functionalization of the 4-position can be achieved without a substituent at the 3-position and according to our knowledge there are only two previously reported methods in solution.[138, 139] Garibay *et al*. have recently published their studies on the directed *ortho*-lithiation on solid phase [140, 141] and we decided to explore this method in our solid phase experiments. We tried to lithiate polymer bound protected 5-carboxyindole regioselectively at the 4-position. The precursor **206** was prepared as described in Scheme 40 (yield from **204** to **206** was 44 %).



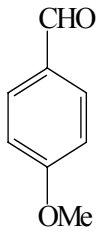
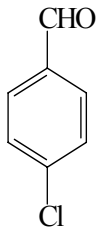
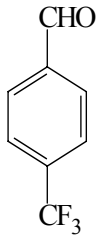
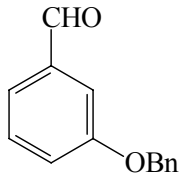
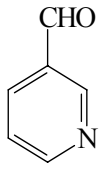
Scheme 40. Preparation of lithiation target.

Indole **206** was tethered to aminomethylated polytetrahydrofuran cross-linked polystyrene (*J*anda*J*el™-NH_2 resin), forming a secondary amide **207**, which functioned as a directing metalation group. Polymer-bound indole **207** was lithiated with n-BuLi and quenched with benzaldehydes (see Table 5) yielding alcohols **208a-212a** and **208b-212b**. After cyclative cleavage phthalides **213a-217a** and **213b-217b** were obtained in ratio 80 : 20 determined by NMR. The solid phase procedure is illustrated in Scheme 41. We tried to improve the regioselectivity by reducing the amount of n-BuLi and cooling the reaction mixture but no improvement was achieved. Five different aldehydes were examined and in all cases the product ratio was the same.



Scheme 41. Solid phase lithiation.

Table 5. Starting materials, products and yields summarized.

Aldehydes	Products	Yield [a] (%)
	**213a** and **213b**	25
	**214a** and **214b**	23
	**215a** and **215b**	31
	**216a** and **216b**	36
	**217a** and **217b**	27

[a] Isolated yield of two regioisomers based on the commercially announced loading.

In summary we have demonstrated that direct functionalization, by lithiation, of 5-carboxyindoles is possible on solid phase. Although only moderate regioselectivities were obtained it is obvious that directed *ortho*-metalation is a powerful tool for direct functionalization on solid phase.

5. Conclusions

During this study, I have developed three direct functionalization methods and a simple method for the preparation of 5-substituted 2-carboxyindoles. These methods give an alternative to solid phase indole cyclizations. The brominations worked smoothly for all studied resin bound carboxyindoles and Suzuki-coupling could successfully be utilized thereafter. Combining this reaction and the 5-position modifications of the nitro group an additional combinatorial step could be achieved. The Vilsmeier formylation worked smoothly on solid phase and the obtained aldehyde functionality should also give many possibilities to further modify resin attached templates. In solid phase metalation studies of 5-carboxyindole 4-position functionalization was achieved in 80 % regioselectivity. Despite the moderate regioselectivity it is obvious that ring lithiation reactions can be adopted to solid phase. A wide variety of new supports with better solvent compatibility and thermal stability are being developed and will allow new possibilities to directly add functionalities to resin attached templates. Development of new functionalization techniques is of great importance when more complex and diverse molecule libraries are planned to be built on solid phase. In summary, I have shown that direct functionalizations are fast and simple ways to modify the indole core. In the future the fascinating indole core will give new challenges for both solution phase and solid phase organic chemists.

6. Experimental

^{1}H NMR data and mass spectra data for compounds **154b**-**154h**.
Compound **154b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4. 66 (s, 2H); 4.68 (s, 2H); 6,93 (d, *J*= 2.4 Hz, 1H); 6.97 (dd, *J* = 9 Hz and 2.4 Hz, 1H); 7.02 (dd, *J* = 2.1 Hz and 0.9 Hz, 1H); 7.30 (d, *J* = 8.9 Hz, 1H); 7.50 (m, 3H); 7.63 (d, *J* = 7.3 Hz, 1H); 8.12 (d, *J* = 7 Hz, 1H); 8.18 (m, 3H); 8.70 (br, 1H). MS (ESI) *m/z* 445 (M-H^+).
Compound **154c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H); 4.60 (s, 2H); 4.63 (s, 2H); 6.93 (d, *J* = 2.4 Hz, 1H); 7.00 (m, 2H); 7.08 (m, 3H); 7.23 (m, 3H); 7.31 (m, 4H); 8.70 (br, 1H). MS (ESI) *m/z* 369 (M-H^+).
Compound **154d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H); 4.55 (s, 2H); 4.60 (s, 2H); 6.86 (d, *J* = 8.7 Hz, 2H); 6.95 (d, *J* = 2.4 Hz, 1H); 7.03 (m, 2H); 7.20 (d, *J* = 8.7 Hz, 2H); 7.29 (d, *J* = 10 Hz, 1H); 7.46 (t, *J* = 7.5 Hz, 1H); 7.61 (d, *J* = 8.1 Hz, 1H), 8.1 (*dt*, J = 8.1 Hz and 1.2 Hz, 1H); 8.16 (s, 1H); 8.70 (br, 1H). MS (ESI) *m/z* 430 (M-H^+).
Compound **154e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 2H); 4.61 (s, 2H); 6.94 (d, *J*= 2.4 Hz, 1H); 6.99 (dd, *J* = 9 Hz and 2.4 Hz, 1H); 7.02 (dd, *J* = 2.1 Hz and 0.9 Hz, 1H); 7.22 (d, *J* = 8.6 Hz, 2H); 7.29 (m, 3H); 7.47 (t, *J* = 7.9 Hz, 1H); 7.61 (dd, *J* = 7.7 Hz and 0.5 Hz, 1H); 8.10 (dt, *J* = 8.1 Hz and 1.2 Hz, 1H); 8.15 (s, 1H); 8.70 (br, 1H). MS (ESI) *m/z* 435 (M-H^+).
Compound **154f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H); 3.96 (s, 3H); 4.73 (s, 2H); 5.04 (s, 2H); 6.90 (m, 2H); 7.01 (dd, *J* = 2.1 Hz and 0.9 Hz, 1H); 7.07 (s, 1H); 7.28 (dd, *J* = 10 Hz and 0.8 Hz, 1H); 7.51 (t, *J* = 7.9 Hz, 1H); 7.65 (d, *J* = 8 Hz, 1H);

7.76 (s, 1H); 8.13 (dt, *J* = 8.1 Hz and 1.2 Hz, 1H); 8.23 (s, 1H); 8.70 (br, 1H). MS (ESI) *m/z* 505 ($M\text{-}H^+$).
Compound **154g**: ^1H NMR (400 MHz, $CDCl_3$): δ 4.47 (s, 2H); 4.63 (d, *J* = 1.6 Hz, 2H); 6.27 (d, *J* = 3.7 Hz, 1H); 6.98 (m, 1H); 7.11 (dd, *J* = 2.1 Hz and 0.9 Hz, 1H); 7.13 (d, *J* = 3.7 Hz, 1H); 7.20 (m, 4H); 7.33 (d, *J* = 8.9 Hz, 1H); 8.70 (br, 1H). MS (ESI) *m/z* 443 ($M\text{-}H^+$).
Compound **154h**: ^1H NMR (400 MHz, $CDCl_3$): δ 4.61 (s, 2H); 4.74 (s, 2H); 6.34 (d, *J*= 3.7 Hz, 1H); 7.08 (dd, *J* = 2.1 Hz and 0.8 Hz, 1H); 7.11 (m, 2H); 7.20 (d, *J* = 3.6 Hz, 1H); 7.33 (dd, *J* = 9.7 Hz and J = 0.9 Hz, 1H); 7.48 (m, 3H); 7.84 (m, 4H); 8.70 (br, 1H). MS (ESI) *m/z* 440 ($M\text{-}H^+$).

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