DOCTORAL THESIS

Organocatalytic Enantioselective Synthesis of *N*-alkylated Indoles

Dmitri Trubitsõn

TALLINNA TEHNIKAÜLIKOOL
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TAL TECH PRESS

TALLINN UNIVERSITY OF TECHNOLOGY
School of Science
Department of Chemistry and Biotechnology
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Supervisor: Professor Tõnis Kanger
School of Science
Tallinn University of Technology
Tallinn, Estonia

Opponents: Professor Māris Turks
Faculty of Materials Science and Applied Chemistry
Riga Technical University
Riga, Latvia

Professor Lauri Vares
Faculty of Science and Technology
Institute of Technology
University of Tartu
Tartu, Estonia

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Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for a doctoral or equivalent academic degree.

Dmitri Trubitsõn

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Organokatalüütiline enantioselektiivne *N*-alküleeritud indoolide süntees

DMITRI TRUBITSÕN

TAL TECH
KIRJASTUS

Contents

List of Publications

The list of author's publications, on the basis of which the thesis has been prepared:

I Trubitsõn, D.; Kanger, T. Enantioselective Catalytic Synthesis of *N*-alkylated Indoles. *Symmetry*, **2020**, *12*, https://doi.org/10.3390/sym12071184.

II Trubitsõn, D.; Martõnova, J.; Erkman, K.; Metsala, A.; Saame, J.; Kõster, K.; Järving, I.; Leito, I.; Kanger, T. Enantioselective *N*-Alkylation of Nitroindoles under Phase-Transfer Catalysis. *Synthesis*, **2020**, *52*, 1047−1059.

III Trubitsõn, D.; Martõnova, J.; Kudrjašova, M.; Erkman, K.; Järving, I.; Kanger, T. Enantioselective Organocatalytic Michael Addition to Unsaturated Indolyl Ketones. *Org. Lett.*, **2021**, *23*, 1820−1824.

Author's Contributions to the Publications

Contributions to the papers in this thesis are:

I The author played a key role in the preparation of the review article:

- literature search;
- analysis of the literature;
- identification of important insights;
- preparation of the manuscript.

II The author developed a synthetic route to obtain chiral *N*-substituted indoles. The author carried out the synthetic experiments and characterized obtained compounds used in the study. The author wrote the manuscript with contributions from the co-authors and played a major role in the compilation of the supporting information.

III The author planned and developed a synthetic pathway for the synthesis of chiral *N*-functionalized indoles. The author prepared and characterized the compounds used in the study. The author wrote the manuscript with contributions from the co-authors and played a major role in the compilation of the supporting information.

Introduction

The development of new efficient methods for the synthesis of chiral compounds is of great importance for both synthetic and medicinal chemistry. The biological properties of the enantiomers of a racemic compound can vary and the necessity of obtaining a single enantiomer is highly important. A good example illustrating different properties of enantiomers is the well-known painkiller Ibuprofen. *(S)*-Ibuprofen offers desired pharmacological activity but the *(R)*-form is less active.[1]

Several strategies have been developed and their application has proven to be a powerful tool for achieving optically pure compounds. At the beginning of the 21st century, dramatic gains in the field of organocatalysis took place, opening up new horizons in asymmetric synthesis.[2–6] Small enantiopure organic molecules were successfully applied as catalysts, affording target compounds in high enantiomeric purities. The main features of organocatalysis are the ease of experimental procedure and usually low cost. These aspects make this type of catalysis attractive to synthetic chemists.[7–9]

The indole core, consisting of a benzene ring fused with a five-membered pyrrole ring, is the most widely distributed and important heterocyclic structure found in nature and in pharmaceuticals.[10–15] The application of an indole as a "building block" in asymmetric synthesis is well-established due to the high nucleophilicity of the indole core at the C3-position, which is 10^{13} times more reactive than a benzene ring.[16,17] In contrast to enantioselective C3 transformations,[18–22] functionalization at the *N*-position of an indole scaffold has not received sufficient attention due to the weak nucleophilicity of the nitrogen atom and low acidity of the *N*-H atom.[23,24]

Since Trost's group reported the first asymmetric transition-metal catalyzed synthesis of chiral indolocarbazole derivatives,[25] the interest in new methodologies for the synthesis of chiral *N*-functionalized indoles has grown rapidly. Several other strategies have been exploited, but difficulties in controlling chemo- and stereoselectivity continue to exist.

This doctoral thesis is focused on the development of new enantioselective organocatalytic methods for the construction of chiral *N*-alkylated indoles. In the first part of the thesis, different strategies that provide catalytic stereoselective derivatization at the *N*-atom of the indole ring will be introduced and discussed (**Publication I**). In the second part, two new synthetic routes for the preparation of target compounds will be reported and analysed (**Publication II** and **Publication III**). In addition to the development of the synthetic pathway and its implementation, computational and analytical studies were conducted (**Publication II**). The obtained results helped to clarify the mechanism of the reaction (**Publication II**). It is important to note that an organocatalytic method in which indole derivatives were used as electrophiles was developed, affording the desired *N*-functionalized indole derivatives (**Publication III**). The method provided a high level of stereocontrol and the obtained compounds could be further easily converted to precursors of biologically active compounds (**Publication III**).

The results of the present work have been presented at international conferences in Estonia, Italy and Japan.

Abbreviations

Ac	acetate
ACN	acetonitrile
aq	aqueous
Ar	aryl
aza-*p*-QM	aza-*p*-quinone methide
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINOL	[1,1'-binaphthalene]-2,2'-diol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Cbz	benzyloxycarbonyl
conv.	conversion
CPA	chiral phosphoric acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEC	dielectric constant
DFT	density-functional theory
$(DHQD)_2PHAL$	hydroquinidine-1,4-phthalazinediyl diether
$(DHQD)_2PYR$	hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DQ	3,3',5,5'-tetra-*tert*-butyl-4,4'-diphenoquinone
dr	diastereomeric ratio
ee	enantiomeric excess
En	enamine activation
equiv	equivalent
Et	ethyl
EWG	electron-withdrawing group
HPLC	high performance liquid chromatography
Im	iminium activation
*i*Pr	isopropyl
M.S.	molecular sieves
MBH	Morita–Baylis–Hillman
Mes	1,3,5-trimethylphenyl
MTBE	methyl *tert*-butyl ether
NBO	natural bond orbital

nd	not determined
NHC	*N*-heterocyclic carbene
nr	no reaction
Nu	nucleophile
PG	protecting group
pK_a	acid dissociation constant at logarithmic scale
Pr	propyl
PTC	phase-transfer catalyst
rt	room temperature
rac	racemic
SPINOL	2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
temp	temperature
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
X	halogen

1 Literature Overview

1.1 Organocatalysis *versus* Transition-Metal Catalysis

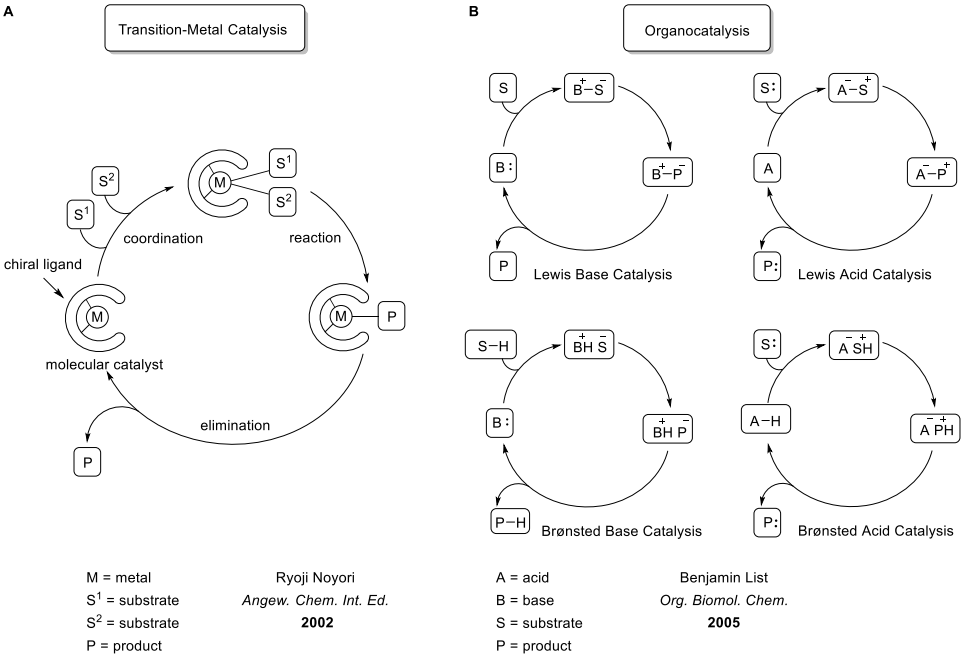
The necessity of obtaining enantioenriched molecules is as important as it has ever been.[26–28] Asymmetric catalysis is one of the promising techniques for obtaining desired chiral compounds. Enantioselective catalysis has an advantage over the other strategies applied in asymmetric synthesis. A small loading of chiral material as an external source of chirality promotes an asymmetric induction in a much larger amount of product.[29] There are three main types of catalysis that are used in asymmetric synthesis: transition-metal, enzymatic and organocatalysis. All of them have benefits and drawbacks, but we always consider these types of catalysis to be keys to the world of stereoselective transformations.

Transition-metal catalysis has been widely used in synthetic chemistry since 1960s (Scheme 1, A).[30] The incompletely filled *d*-orbitals of transition metals play a crucial role in the activation of substrates and the acceleration of reactions. Moreover, the variation of chiral ligand in a catalytic complex provides the opportunity to tune the selectivity and reactivity of the reaction.[31] Additionally, low catalyst loadings are characteristic of transition-metal-catalyzed asymmetric methods.[32] However, the most effective metals are usually the least abundant and most expensive.[33,34] Some transition-metal salts and complexes are also toxic, which makes them less attractive in terms of green chemistry.[35,36]

Organocatalysis as a new branch of asymmetric synthesis appeared at the beginning of the 2000s and has developed considerably through the last two decades, becoming an alternative to transition-metal catalysis (Scheme 1, B).[37,38] Here, small chiral organic molecules are used as workhorses in asymmetric transformations.[29,39] Organocatalysis has several advantages in contrast to transition-metal catalysis. Most organocatalysts are:

- stable to air and moisture in the reaction atmosphere;
- readily available from natural sources;
- simple to handle;
- easy to prepare;
- catalysts of both enantioseries are available.

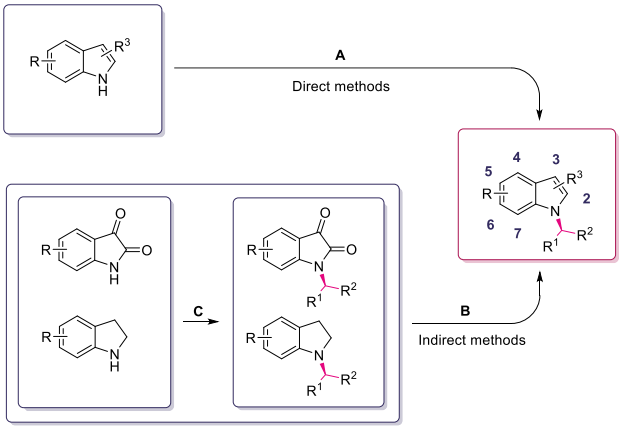
On the other hand, the organocatalytic approach has disadvantages, such as high catalyst loadings and having to carry out reactions in diluted solutions.[40]



Scheme 1. *Organocatalysis versus transition-metal catalysis. (A) Adapted from Ref. 30 with permission from John Wiley & Sons and (B) adapted from Ref. 41 with permission from The Royal Society of Chemistry.*

1.2 Strategies for the Asymmetric *N*-Functionalization of Indoles

The strategies for the catalytic stereoselective *N*-derivatization of indoles can be divided into two main categories according to the structure (Scheme 2). The first group of methods are most common and are defined as “direct methods”; here chiral *N*-functionalized products are prepared in a single step from compounds containing indole scaffold (Scheme 2, A). If the synthetic route starts from other non-indole containing heterocyclic compounds, the methods are classified as “indirect methods” (Scheme 2, B). The indirect approach is based on the sequential transformation of the heterocyclic substrates. First, stereoselective derivatization at the *N*-atom takes place, affording a chiral *N*-substituted intermediate (Scheme 2, C). Then the aromaticity of the indole core is generated through a redox reaction, which provides the corresponding *N*-alkylated indoles.

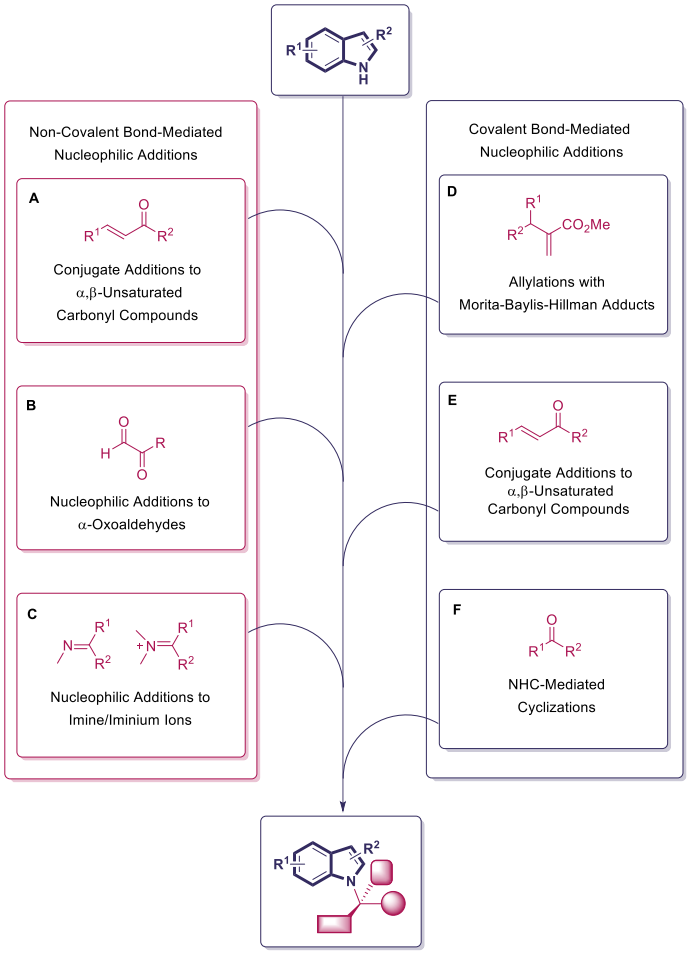


Scheme 2. *Strategies for the asymmetric N-functionalization of indoles.*

The stereoselective functionalization at the *N*-atom of the indole ring can be efficiently performed either with transition-metal based methods or organocatalysis.[42–53] Both approaches provide a facile access to a broad range of chiral *N*-substituted indoles. In this thesis, only organocatalytic strategies were studied.

1.3 Organocatalytic Direct Methods

Organocatalysis plays an essential role in catalytic asymmetric transformations at the *N*-atom of indole ring system. The reported organocatalytic methodologies can be divided into two major groups according to the type of implemented organocatalysis for the preparation of chiral *N*-functionalized indoles (Scheme 3). The first group combines methods in which a catalyst-substrate complex is formed through noncovalent bond interactions (Scheme 3, A–C), and the second group utilizes methodologies where the catalytic activation of the starting material proceeds through a covalent bond (Scheme 3, D–F). Additionally, the structure of starting material and the reaction type afford a more detailed subdivision of the organocatalytic approaches illustrated in Scheme 3, A–F.



Scheme 3. *Direct organocatalytic stereoselective N-functionalization of indole.*

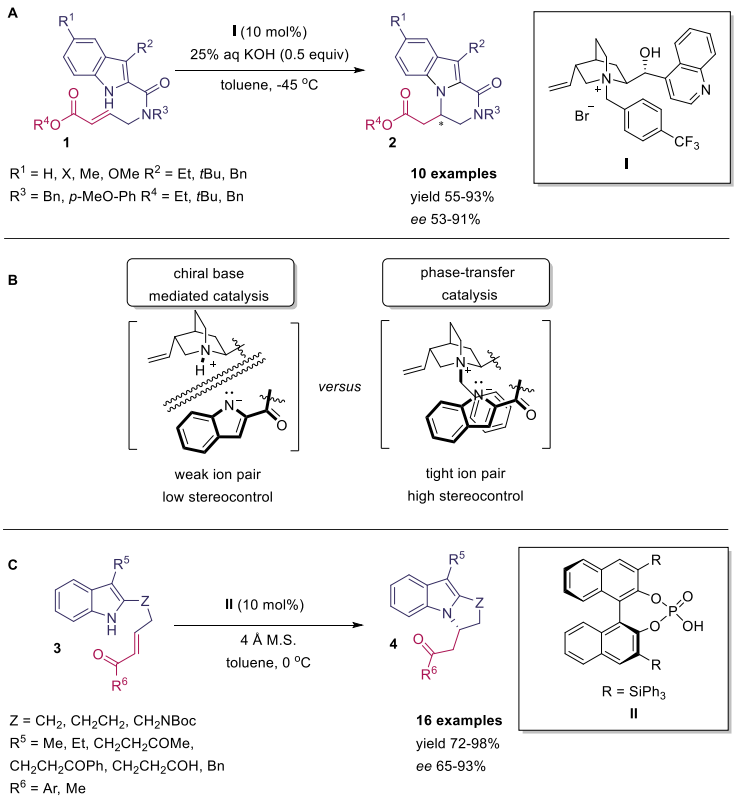
1.4 Non-Covalent Bond-Mediated Nucleophilic Additions

1.4.1 Conjugate Additions to α,β-Unsaturated Carbonyl Compounds

In 2008, the first example of the organocatalytic *N*-alkylation of an indole was described by Bandini and Umani-Ronchi (Scheme 4, A).[54] Later, a combined experimental and theoretical study of the above-mentioned method was reported.[55] The intramolecular aza-Michael cyclization of 2-substituted indoles **1** with increased acidity was smoothly catalyzed by a *Cinchona* alkaloid-based quaternary ammonium salt **I** in the presence of potassium hydroxide, affording the desired tricyclic products **2** in good to high yields and moderate to high enantiomeric excesses. The authors admitted that the chiral organic bases were inefficient in the catalysis of the reaction. The occurrence of a tight ion pair between the indolate intermediate and the quinuclidine ring of *Cinchona*-derived salt was essential in guaranteeing stereocontrol of the reaction (Scheme 4, B). Moreover, the presence of a free hydroxyl group at the C9-position of the catalyst **I** was necessary to obtain the enantioenriched products **2** in reasonable *ee* values. Additionally, the stereoselectivity of the reaction was improved with the

introduction of an electron-withdrawing trifluoromethyl group on the *para*-position of the benzyl substituent of the PTC **I**.

Another intramolecular ring-closing reaction of 2-substituted indoles **3** was explored by Shu-Li You and co-workers two years later (Scheme 4, C).[56] In comparison with the previous synthetic method (Scheme 4, A), here the indole derivatives **3** were revealed as electron-rich molecules. The asymmetric intramolecular conjugate addition was efficiently promoted by the BINOL-derived chiral phosphoric acid **II**. The substrate scope revealed that indole derivatives **3** with various functionalities at the C3-position tolerated the reaction well without affecting the reaction reactivity or selectivity. Notably, substrate **3** with an electron-withdrawing ester group at the C2-position of the indole was inactive and inhibition of the cyclization was observed.



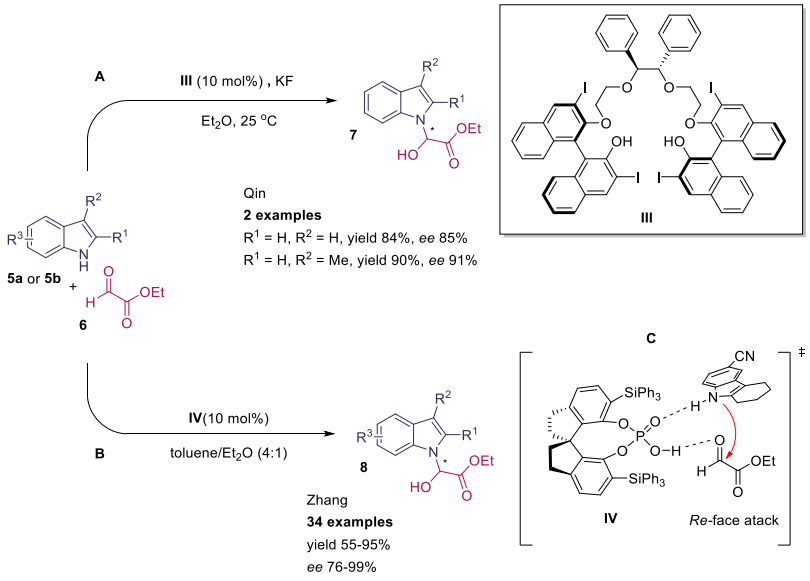
Scheme 4. *Intramolecular aza-Michael reactions of 2-substituted indoles. (B) Adapted from Ref. 54 with permission from John Wiley & Sons.*

1.4.2 Nucleophilic Additions to α-Oxoaldehydes

A number of biologically active and pharmaceutical compounds contain an *N*,*O*-substituted α-chiral carbon center at the *N*-position of indoles.[49,57] Recently, two research groups independently investigated synthetic routes for the preparation of chiral indoles with *N*,*O*-aminal structural units (Scheme 5).[57,58] In both methodologies, different types of organocatalyst were employed for the nucleophilic addition of indoles **5** to α-oxoaldehyde **6**. Qin and co-workers concentrated on an achiral Brønsted base-catalyzed version of the reaction and demonstrated the efficient application of DABCO and trimethylamine.

Then the enantioselective version of the reaction was explored in the presence of a catalytic system derived from BINOL-based polyether **III** and potassium fluoride (Scheme 5, A). Despite the fact that only two examples of the asymmetric *N*-functionalization of indoles were proposed, the approach demonstrated great potential as the reaction with a parent indole proceeded smoothly, affording product in high yield (84%) and *ee* value (85%). This aspect indicates the high level of *N*-chemoselectivity of the reaction.

A year letter, Zhang et al. reported an asymmetric addition of various substituted indoles **5b** to ethyl glyoxalates **6** in the presence of catalyst **IV** (Scheme 5, B).[57] A wide range of substituted indoles were tested and the chiral *N*-products **8** were isolated in good to excellent *ee* values and moderate to high yields. However, a reaction with a parent indole or non-substituted indole at the C3-position was not reported. In the case of a 7-fluoro-substituted indole, drastic declines in enantioselectivity and yield were observed, most probably because of steric reasons. The proposed transition state of the reaction illustrates the interaction of SPINOL-based CPA **IV** with both substrates (indole and glyoxalate) through hydrogen bonds (Scheme 5, C). According to absolute configuration of the product, the authors proposed that an attack on the aldehyde from the *Re*-face is favored (Scheme 5, C).

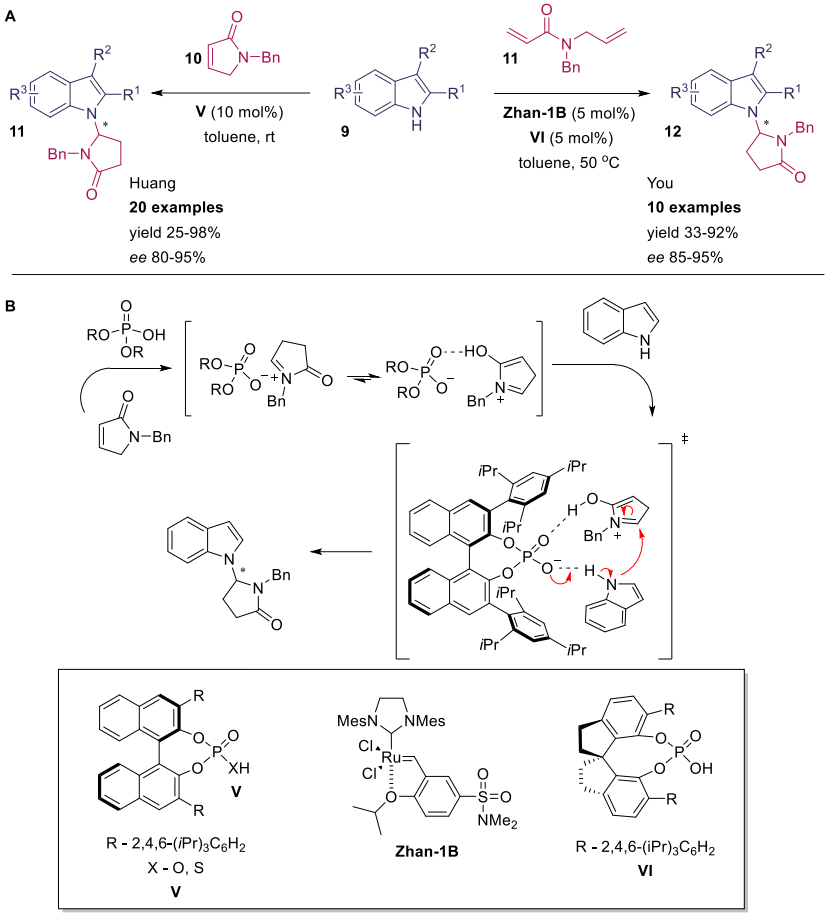


Scheme 5. *Enantioselective N-hydroxyalkylation of indoles with ethyl glyoxalates. (C) Adapted with permission from Org. Lett. 2019, 21, 2795−2799. Copyright 2019 American Chemical Society.*

1.4.3 Nucleophilic Additions to Imine/Iminium Ions

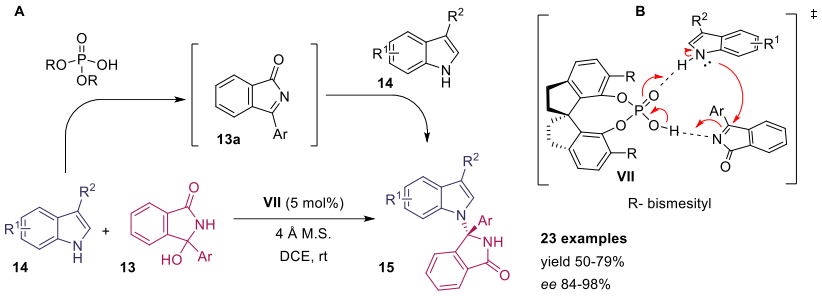
Huang and co-workers proposed to employ such highly reactive electrophiles as cyclic *N*-acyliminium ions[59] in the asymmetric *N*-functionalization of indoles **9** in the presence of BINOL-derived CPA **V** (Scheme 6, A).[60] Cyclic *N*-acyliminium ions can be easily produced in situ from corresponding α,β-unsaturated γ-lactams **10** by accepting an acidic proton from a CPA, producing a chiral conjugate base/*N*-acyliminium ion pair. The authors suggested that the acidic *N*-H proton of the indole was activated by the conjugate base of CPA through the H-bond, promoting an *N*-selective nucleophilic attack of indole on the cyclic *N*-acyliminium ion (Scheme 6, B).

A similar approach for the synthesis of chiral aminals **12** based on an "organo-metal" tandem reaction was attempted by the You group (Scheme 6).[61] First, a ruthenium complex **Zhan-1B** promoted a ring-closing metathesis of *N*-allyl-*N*-benzylacrylamide **11**, providing the corresponding α,β-unsaturated γ-lactam **10**, which was further smoothly converted into the desired *N*-alkylated product **12** in the presence of SPINOL-derived CPA **VI**. Compared with the method reported by Huang, the enantioselectivity of the sequential catalysis in general was higher. Moreover, the one-pot synthesis was a more efficient way to get chiral aminals **12** in higher yields than in the stepwise approach.



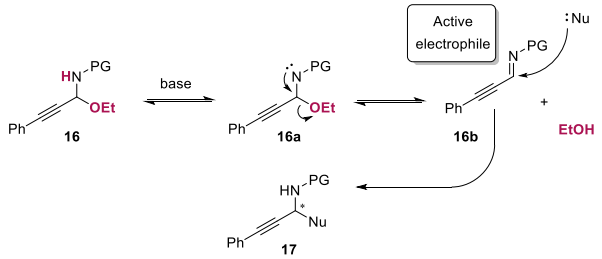
Scheme 6. *N-addition of indoles to chiral N-acyliminium generated electrophiles. (B) Adapted from Ref. 60 with permission from John Wiley & Sons.*

Alternatively to the *N*-acyl iminium-derived electrophiles, *N*-acyl imines were successfully utilized as substrates in the synthesis of chiral *N*-alkylated indoles. Zeng and Zhong described the CPA **VII** catalyzed asymmetric *N*-functionalization of indoles with in situ generated cyclic substituted *N*-acyl imines **13a** from the corresponding isoindolinone alcohols **13** (Scheme 7).[62] The current methodology made it possible to use various 3-aryl hydroxyisoindolinones **13** and different C3-substitued indoles **14** providing *N*-selective alkylation in good to excellent enantioselectivities.



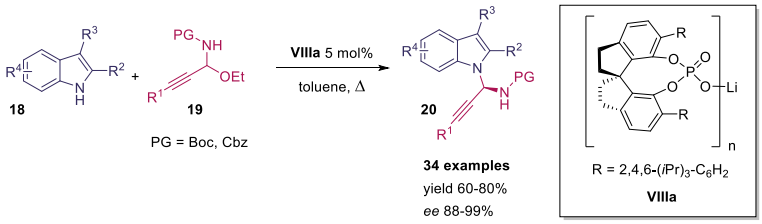
Scheme 7. *Asymmetric N-alkylation of indoles with N-acyl imines. (B) Adapted from Ref. 62 with permission from The Royal Society of Chemistry.*

Compounds bearing a propargyl moiety are useful intermediates and versatile building blocks in synthetic chemistry. These compounds can be converted into a wide variety of organic derivatives due to the rich chemistry of the triple bond.[63,64] Recently, the Shao group demonstrated the efficient application of in situ-generated imines **16b** derived from C-alkynyl *N*-protected *N*,*O*-acetals **16** as electrophiles in the asymmetric synthesis of propargylic amines **17** (Scheme 8).[65,66]



Scheme 8. *Strategy for the asymmetric synthesis of propargylamines.*

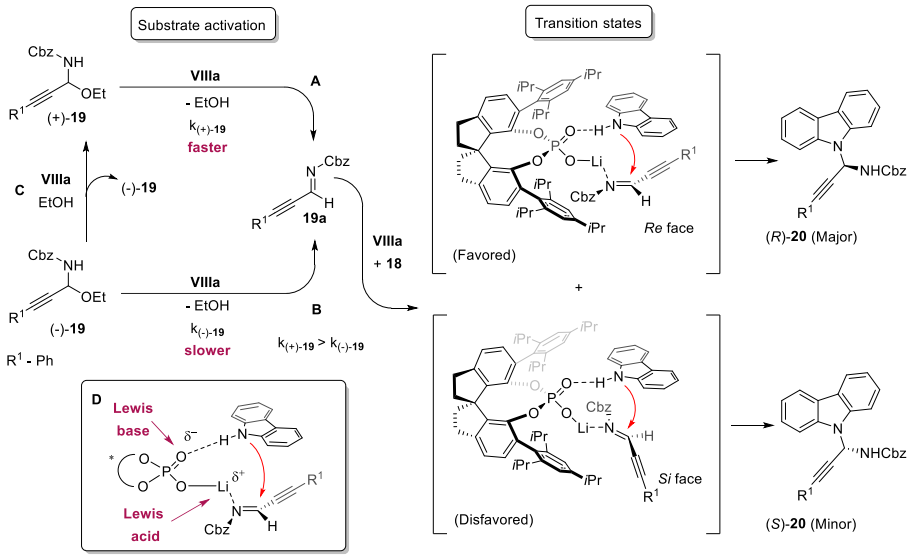
Later, C-alkynyl *N*-Boc- and *N*-Cbz-protected *N*,*O*-acetals **19** as alkylating reagents were effectively utilized in the enantioselective *N*-propargylation of 2,3-disubstituted indoles and carbazoles **18**, affording corresponding aminals **20** (Scheme 9).[67] The reaction was catalyzed by a chiral lithium SPINOL phosphate complex **VIIIa**, which had a double catalytic function in the synthesis.



Scheme 9*. Enantioselective N-propargylation of indoles.*

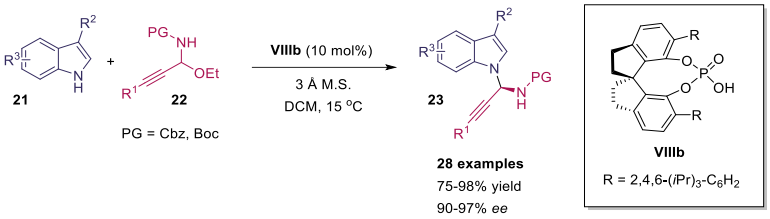
Shao et al. conducted a series of control experiments and suggested a reaction pathway, which is outlined in Scheme 10.[67] First, the racemic C-alkynyl *N*,*O*-acetal **19** was converted into imine via EtOH elimination catalyzed by lithium phosphate **VIIIa**. Notably,

the chiral catalyst **VIIIa** discriminated between the enantiomers of (±)-**19** and reacted faster with (+)-**19**, affording the imine **19a** and EtOH (Scheme 10, A). Further racemization of (-)-**19** in the presence of EtOH and the catalyst **VIIIa** took place, providing the racemic mixture of **19** (Scheme 10, C). The transition state of the reaction indicated the important role of chiral lithium phosphate complex **VIIIa** as a Lewis acid-base conjugated catalyst that guaranteed a high level of stereocontrol. The acidic *N*-H atom of indole was activated through the hydrogen bond by a P=O moiety (Lewis base) of the catalyst **VIIIa.** The nitrogen atom of the imine was coordinated by lithium (Lewis acid). This methodology afforded chiral *N*-alkylated indoles **20** bearing propargylic moiety in excellent enantioselectivities. Remarkably, the reaction proceeded with a very low catalyst loading (0.1 mol%), with high enantioselectivity and 72% yield (92% *ee*).



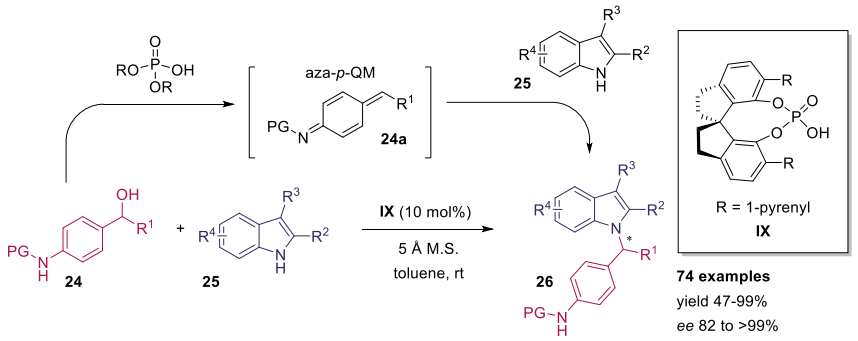
Scheme 10. *Complex* ***VIIIa*** *catalyzed reaction pathway.*

Sun and Wang reported a similar strategy for the synthesis of chiral *N*-propargyl indoles **23** (Scheme 11).[68] Compared to the above-mentioned method, the catalyst **VIIIb** with the same CPA core-structure was used, but different reaction conditions were implemented for the asymmetric *N*-alkylation of 3-substituted indoles **21**. The methodology gave a facile access to a diverse range of chiral propargyl aminals **23** with excellent levels of chemo- and stereocontrol and high yields. It should be noted that electron-donating or electron-withdrawing substituents at both indole rings tolerated the reaction well without affecting selectivity or reactivity. However, in the case of the less bulky 3-methylindole, the reaction yield and chemoselectivity were decreased. In addition, the authors demonstrated the utility of this protocol by specific modifications at the *N*-atom of tryptophan-containing peptides.



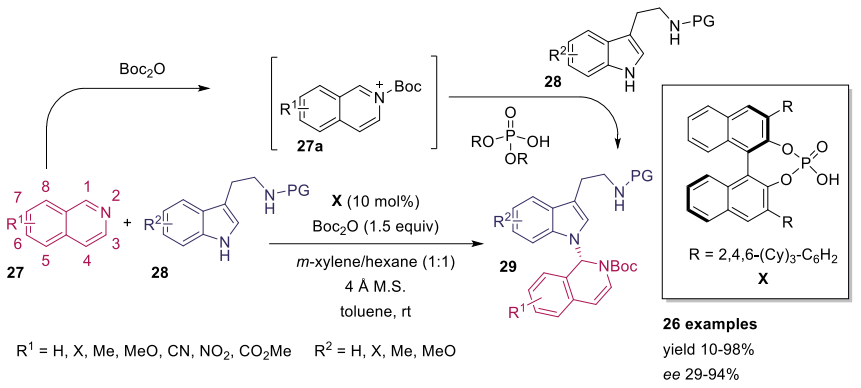
Scheme 11. *CPA* ***VIIIb*** *catalyzed enantioselective N-propargylation of indoles.*

J. Sun et al. demonstrated a successful application of aza-*p*-quinone methides **24a** derived in situ from *N*-protected *p*-aminobenzylic alcohols **24** in an asymmetric *N*-alkylation of 2,3-disubstituted indoles **25** in the presence of CPA **IX** (Scheme 12).[69] The authors emphasized that the stereoselectivity of the reaction strongly depends on the structure of the *N*-protective group of the electrophile **24**. Excellent *ee* values were obtained when bulky aliphatic acyl groups (pivaloyl and 1-adamantanecarbonyl) were used, but a decline in stereoselectivity was detected with other protective groups. Remarkably, the fact that the C3-unsubstituted indoles afforded an exclusive C3-alkylation and slightly modified reaction conditions gave access to chiral C3-alkylated indoles in excellent yields (95–99%) and in high enantiomeric excesses (82–94%).



Scheme 12. *Reaction of indoles with p-aza-quinone methides.*

An enantioselective *N*-alkylation of indole derivatives **28** via a Reissert-type reaction was disclosed by the You group (Scheme 13).[70] The authors focused on developing a strategy leading to the dearomatization of both reagents simultaneously. However, the reaction proceeded in another way, affording the enantioenriched *N*-substituted indole product **29**. A wide range of tryptamines with different protective groups and various substituents at the indole nucleus were tested, demonstrating moderate to good enantioselectivities and good yields. The scope of the isoquinoline derivatives **27** revealed the significant influence of the substitution pattern on the enantioselectivity and yield of the reaction. Sterically hindered isoquinolines with substituents at C7- or C8-positions enabled the reaction to proceed in lower yields (10–40%) and enantioselectivities (29–50% *ee*). Substituents at other positions were tolerated, leading to *N*-alkylated products with good to excellent yields (80–98%) and enantioselectivities (80–94%).



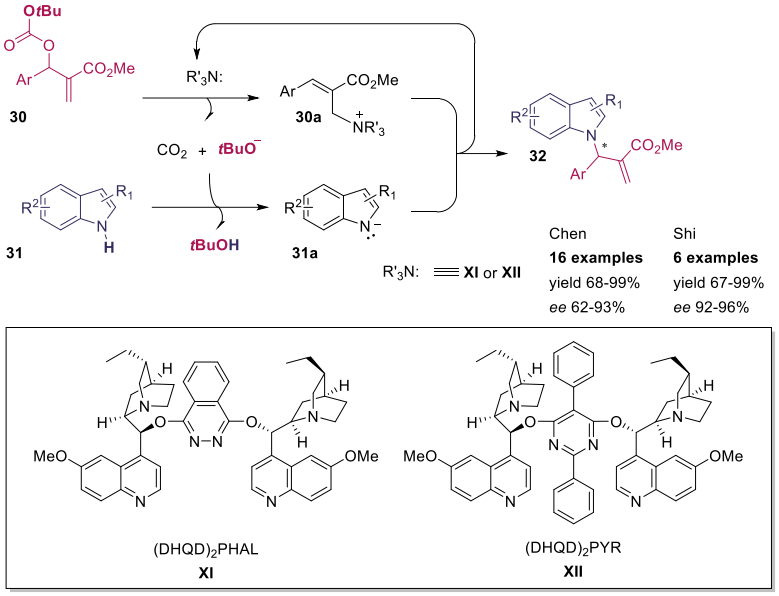
Scheme 13. *Enantioselective N-alkylation of indoles via a Reissert-type reaction.*

1.5 Covalent Bond-Mediated Nucleophilic Additions

1.5.1 Allylations with Morita-Baylis-Hilman Adducts

The first example of covalent bond-mediated organocatalytic enantioselective *N*-functionalization of indoles was demonstrated by Chen's group.[71] The authors used Morita-Baylis-Hillman *tert*-butoxy carbonates **30** as electrophiles in reactions with nucleophilic indoles **31** (Scheme 14). During the covalent bond-mediated activation of the electrophile with a chiral Lewis base catalyst **XI**, a *tert*-butoxy anion was formed and it promoted the formation of indolate intermediate **31a**. A further nucleophilic *N*-selective attack of the intermediate **31a** on the activated electrophile **30a** afforded a desired chiral product **32**. Both electron-withdrawing and electron-donating groups at various positions at the indole nucleus **31** were examined and revealed good to outstanding levels of stereocontrol. The methyl pyrrole-2-carboxylate was also tested as an *N*-nucleophile, affording the corresponding product with both good yield (80%) and *ee* value (73%).

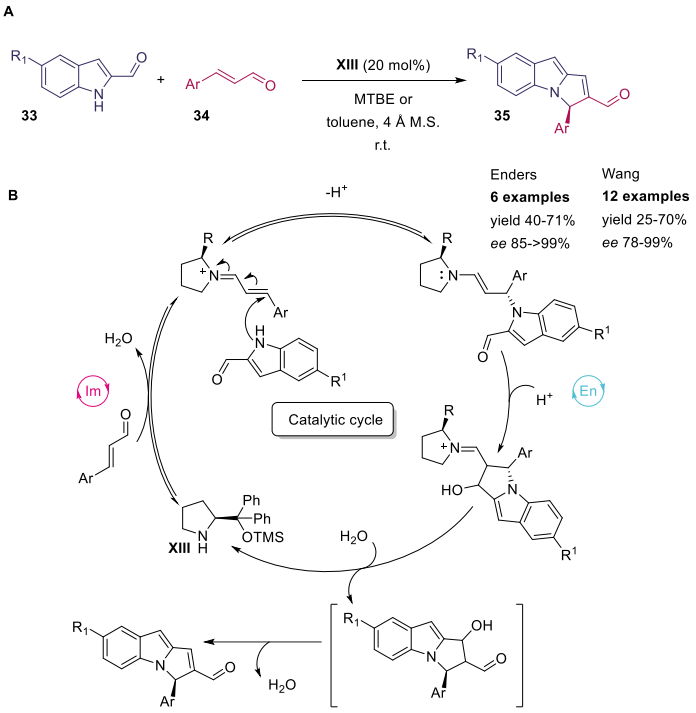
A similar approach was published three years later by Shi et al. (Scheme 14).[72] The authors concentrated more on the asymmetric *N*-alkylation of 2-cyano-substituted pyrroles, but reactions with 2-cyanoindole **31** were also carried out. The pyrroles with an electron-withdrawing cyano group at the C2-position proved to be better nucleophiles than, the methyl carboxylate-substituted pyrroles used previously by Chen's group. In general, Shi's method for the preparation of chiral *N*-alkylated indoles **32** was more efficient, but it was limited to 2-cyanoindoles, unlike Chen's work.



Scheme 14. *Asymmetric N-alkylation of indoles with MBH carbonates.*

1.5.2 Conjugate Additions to α,β-Unsaturated Carbonyl Compounds

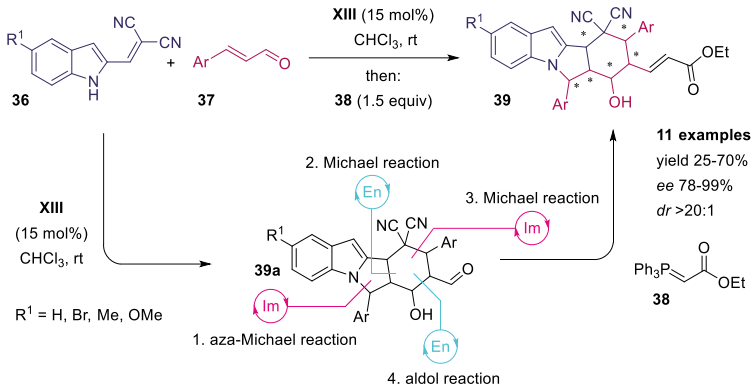
Several examples of asymmetric secondary amine-catalyzed tandem reactions for the synthesis of *N*-alkylated polycyclic indoles were reported by the Wang and Enders groups (Schemes 15 and 16).[73–75] The authors proposed using 2-substituted indoles **33** and **36** with increased acidity in reactions with α,β-unsaturated aldehydes. The introduction of an electron-withdrawing substituent at the C2-position of the indole core makes the *N*-H atom more acidic, making it possible to use the indole in *N*-alkylations as a nucleophile. Additionally, C2 substituents at the indole core lead to a wide range of domino reactions, which afford chiral *N*-functionalized polycyclic indoles in a one-step procedure.



Scheme 15. *Cascade reactions of indole-2-carbaldehyde* ***33****. (B) Adapted from Ref. 73 with permission from John Wiley & Sons.*

Both research groups independently demonstrated the efficient application of a Hayashi-Jørgensen catalyst **XIII** in a tandem reaction in which indole-2-carbaldehyde **33** was chosen as a starting material (Scheme 15). The proposed cascade reaction was based on iminium/enamine activation modes and consisted of a conjugate addition followed by aldol condensation (Scheme 15, B). The differences in reaction conditions of the two separate strategies also did not drastically affect the reaction yield nor the enantioselectivity.

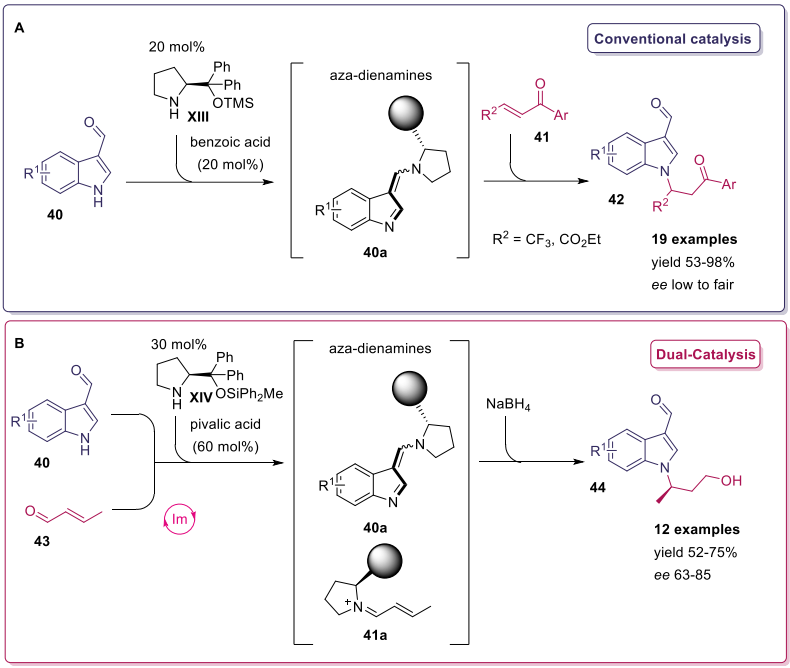
A few years later, Enders and co-workers reported a stereoselective quadruple domino reaction, where indole-2-methylene malononitriles **36** derived from indole-2-carbaldehydes **33** were utilized in reactions with α,β-unsaturated aldehydes **37** (Scheme 16). The reaction was smoothly catalyzed by the chiral secondary amine **XIII**, affording tetracyclic aldehydes **39a** that were trapped with stabilized Wittig reagent **38** in a one-pot manner. The catalytic cycle of the cascade is based on the iminium-enamine-iminium-enamine activation mode which provides a sequential aza-Michael-Michael-Michael-aldol tandem reaction. Remarkably, not only were good to excellent *ee* values (78–99%) obtained with this synthetic approach but also a high level of diastereoselectivity was achieved (*dr* >20:1).



Scheme 16. *Synthesis of polycyclic chiral N-alkylated indoles* ***39*** *via a tandem reaction. Adapted from Ref. 75 with permission from John Wiley & Sons.*

A novel activation pathway of the *N*-atom of the indole ring was recently reported by Chen and co-workers.[76] The strategy was based on an aza-Michael addition of dienamine-type intermediates **40a** generated in situ from 3-formyl-substituted indoles **40** by secondary amines (Scheme 17). The reaction of aza-fulvene intermediates **40a** generated from indole-3-carboxaldehydes **40** with trifluorinated crotonophenones **41** in most cases proceeded smoothly, affording products **42** in moderate to high yields with low to fair *ee* values (Scheme 17, A). Very low reactivity was detected when the trifluoromethyl group of substrate **41** was replaced with methyl groups or phenyl rings. The absence of enantiocontrol may have been caused by the long distance between the catalyst and *N*-atom of the indole and the formation of a *Z*/*E*-mixture of active aza-dienamine **40a** intermediates.

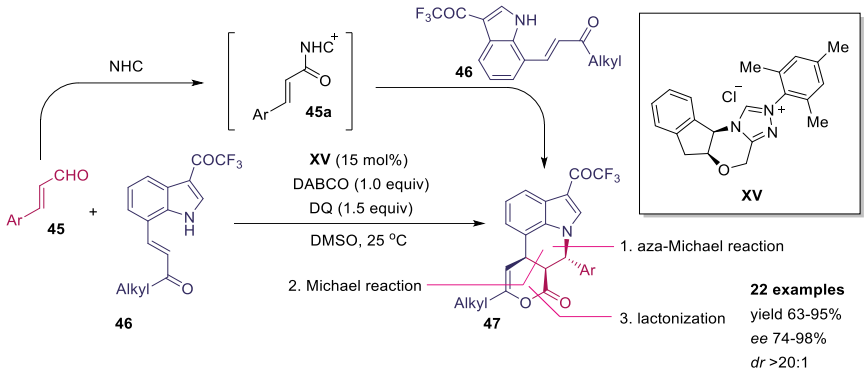
A dual activation mode of the reaction was proposed in order to improve the enantiocontrol of the reaction (Scheme 17, B). Enals were chosen as electrophilic partners because they can be easily activated by secondary amines. Among the aldehydes, only crotonaldehyde **43** tolerated the reaction well providing chiral products **44** in moderate yields with moderate to good *ee*'s. Notably, the 7-methyl-substituted indole-3-carboxaldehyde was also inactive, presumably due to steric effects.



Scheme 17. *Aza-Michael addition of 3-formylindoles.*

1.5.3 NHC-Mediated Cyclizations

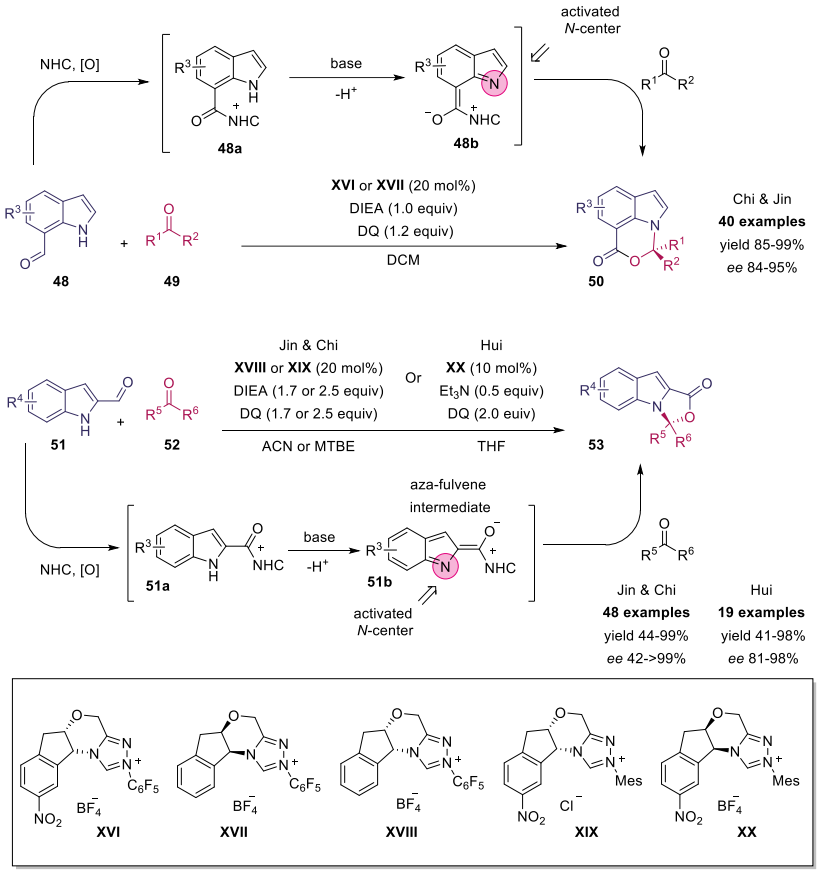
The synthesis of pyrroloquinoline derivatives **47** via an asymmetric NHC-catalyzed tandem reaction was reported by the Biju group (Scheme 18).[77] 3,7-Disubstituted indoles **46** and cinnamaldehyde derivatives **45** were used as substrates in a triple cascade aza-Michael/Michael/lactonization sequence that was efficiently catalyzed by carbene generated from the chiral aminoindanol-derived triazolium salt **XV.** A wide range of substituted indoles and various cinnamaldehyde derivatives tolerated the reaction well, providing chiral pyrroloquinolines **47** with moderate to high yields and good to high enantioselectivities. The strong electron-withdrawing group at the C3-position of the indole ring was necessary to increase the *N*-H acidity, affording an *N*-selective addition to chiral α,β-unsaturated acylazolium salts **45a**. Additionally, the cascade reaction was performed in various solvents with different dielectric constants (DEC) in order to demonstrate the dependence of the selected solvent on the stereoselectivity and reactivity of the reaction. A high *ee* value and yield were achieved when highly polar DMF (DEC: 36.7) was used; in the case of less polar THF (DEC: 7.58), a decrease in both yield and selectivity was detected, and poor results were obtained in apolar toluene (DEC: 2.38).



Scheme 18. *N-heterocyclic carbene-mediated synthesis of pyrroloquinolines.*

Robin Chi and Zhichao Jin used 7-formyl- and 2-formyl-substituted indoles (**48** and **51**) in an enantioselective NHC-catalysis for the construction of cyclic *N*,*O*-aminal indole derivatives **50** and **53** (Scheme 19). [78,79] In both strategies, the nitrogen atom of indole was activated by an NHC catalyst via a carbaldehyde moiety at the corresponding position of the indole ring. Reactions were smoothly catalyzed by the NHC catalysts derived from aminoindanol skeletons, affording an asymmetric aza-nucleophilic addition of activated indole intermediate **48b** or **51b** to carbonyl compounds followed by intramolecular ester formation. A wide range of electrophilic substrates such as trifluoromethyl ketones, isatins and ketoesters were used for the synthesis of indole based polycyclic chiral compounds.

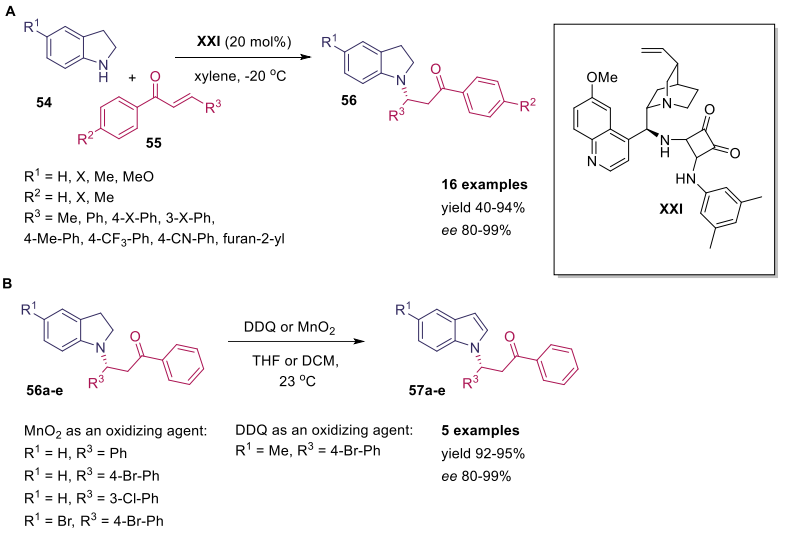
A similar NHC-based approach for the enantioselective *N*-alkylation of 2-formyl-substituted indoles was demonstrated by Xinping Hui and co-workers.[80] Despite differences in reaction conditions, both Jin's and Hui's methodologies gave efficient asymmetric *N*-alkylation of indole-2-carboxaldehydes with isatins, affording chiral products **53** in comparable yields and *ee* values.



Scheme 19. *Cyclization reactions of 2- and 7-formylindoles.*

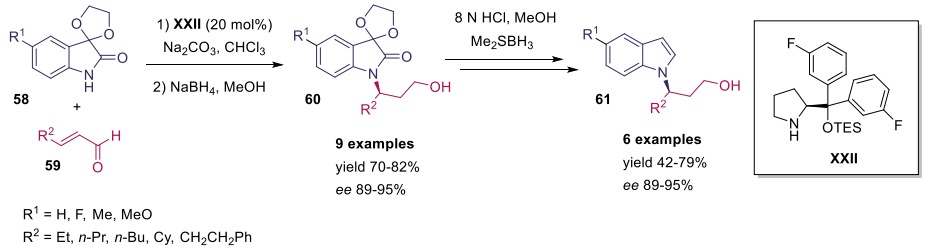
1.6 Organocatalytic Indirect Methods

The synthesis of optically enriched *N*-alkylated indoles can be performed indirectly in two steps starting from other *N*-containing heterocyclic core structures (Scheme 20 and 21). A synthetic route based on the *N*-alkylation of indolines followed by oxidation was proposed by Ghosh et al. (Scheme 20).[81] The conjugate addition of indolines **54** to α,β-unsaturated ketones **55** was efficiently catalyzed by squaramide based bifunctional organocatalyst **XXI**, which afforded corresponding *N*-functionalized indolines **56** in moderate to high yields and good to excellent *ee*'s (Scheme 20, A). The oxidation of a set of chiral indoline derivatives **56a-e** in the presence of DDQ or MnO_2 led to the desired *N*-alkylated indoles **57a-e** (Scheme 20, B). Notably, the oxidation proceeded in high yields without affecting the *ee* values of the products.



Scheme 20. *Indoline N-alkylation/aromatization sequence.*

Alternatively to the *N*-alkylation/oxidation sequence of indolines (Scheme 20), the reduction of *N*-functionalized protected isatins **58** was proposed as a synthetic strategy for the synthesis of *N*-alkylated indoles with α-branched alkyl substituents **61** (Scheme 21).[82] The aza-Michael reaction of C3-protected isatin derivatives **58** with aldehydes **59** was achieved via the iminium activation of enals **59** by a chiral secondary amine **XXII**. A broad scope of different aliphatic and aromatic aldehydes was tested, demonstrating good yields and high *ee*'s of the products. Chiral *N*-alkylated protected isatins **60** were converted to the corresponding *N*-substituted indoles **61** after deprotection and reduction with borane.



Scheme 21. *Preparation of N-functionalized indoles starting from protected isatins.*

1.7 Summary of Literature Overview

Recent achievements in transition-metal catalysis and a significant rise in organocatalysis during the last two decades have led to the development of various strategies for the stereoselective *N*-derivatization of indoles. However, most methodologies have limitations caused by the aromatic nature of indole and low reactivity of the *N*-H atom. The main drawback is the influence of a substitution pattern on the stereoselective *N*-functionalization and the necessity of using C3-substituted indoles as starting materials.

In some cases, the *N*-derivatization of the parent indole may be accompanied by a background reaction occurring at the C3-position, which affords a mixture of C3/*N*-substituted products. For this reason, the C3-substituent was often introduced to prevent competitive C3-functionalization. On the other hand, some methodologies suggest using a C3-substituent as a powerful tool for increasing *N*-H reactivity.[76,77] Similarly, C2- or C7-positions should be substituted to promote *N*-alkylation. [54,56,73–75,78–80] Not all methods can provide access to chiral products when sterically hindered C2- or C7-substituted indoles are used as starting materials. Several methods are limited regarding the choice of coupling partners for *N*-functionalization due to the low reactivity of the *N*-H site. To overcome this obstacle, the generation of strong electrophiles is required that could be viewed as a disadvantage of the method.

2 Aims of the Present Work

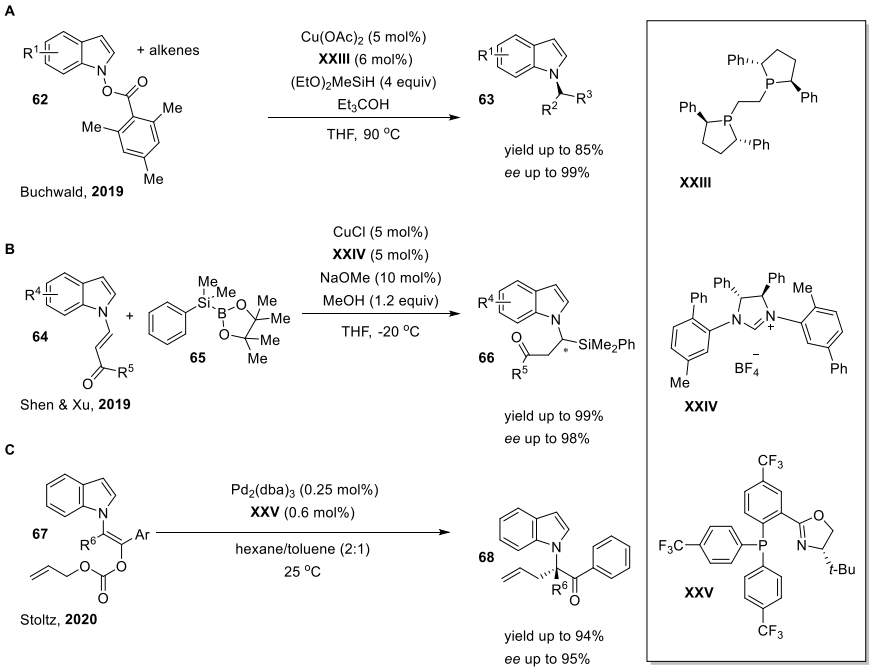
The stereoselective derivatization of the *N*-atom of the indole core has been extensively studied in recent years. However, the synthesis of chiral *N*-alkylated indoles remains challenging, as most methods have limits in terms of reaction scope.

The main goal of the present thesis is to work out novel synthetic routes for the preparation of *N*-substituted indoles based on asymmetric organocatalysis. The proposed methods should be easily implementable, demonstrating the efficacy and synthetic utility of these approaches. Moreover, common obstacles, such as the lack of chemoselectivity and problems with the activation of the *N*-atom of the indole, must be overcome. In addition to the main aim, we have defined more specific aims of the current work:

- to elaborate new organocatalytic approach and explore suitable starting compounds for the asymmetric *N*-derivatization of indoles;
- to achieve *N*-selective transformation;
- to examine the influence of the substituents at the indole core on the process of the formation of *N*-alkylated products;
- to determine the relative and absolute stereochemistry of all new synthesized compounds;
- to show the synthetic utility of the developed method of the synthesis of *N*-alkylated indoles.

3 Results and Discussion

Despite the numerous publications on the catalytic synthesis of chiral *N*-alkylated indoles that have been published recently, there are few strategies based on *Cinchona*-alkaloid-derived catalysts.[54,71,72,81] With the ongoing interest of our group in developing novel and promising organocatalytic approaches for the preparation of chiral compounds,[83–86] we decided to investigate the stereoselective functionalization of the *N*-atom of the indole ring. To the best of our knowledge, only one asymmetric phase-transfer-catalyzed approach has been reported for the intramolecular *N*-cyclization of C2-substituted indoles where *Cinchona* alkaloid based PTCs were used (Scheme 4, A).[54] However, phase-transfer catalysis is one of the most well-known and efficient catalytic approaches used in asymmetric synthesis.[87–92] First, we concentrated on the application of phase-transfer catalysis in the asymmetric intermolecular *N*-alkylation of indoles with increased *N*-H acidity. The conventional synthetic route was implemented in which indoles act as *N*-nucleophiles in reactions with electrophilic partners.

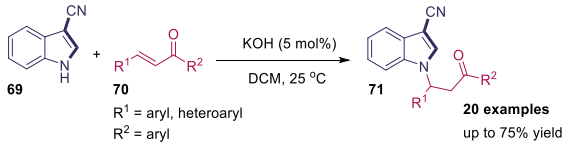


Scheme 22. *Transition-metal-catalyzed polarity reversal strategies for the formal N-alkylation of indole.*

Further interest in stereoselective *N*-derivatization of indoles was stimulated by two polarity reversal strategies demonstrated by Buchwald[93] and Shen & Xu[94] (Scheme 22, A and B). In both transition-metal-catalyzed methodologies, an indole derivative (**62** or **64**) was used as an electrophile, which was the distinctive feature of these approaches. Moreover, our curiosity regarding the application of non-conventional approaches was further piqued by Stolz's work in which enantioselective palladium-catalyzed allylic alkylation of indolyl ketones **67** was disclosed (Scheme 22, C).[95] Inspired by the above-described strategies, we decided to develop an organocatalytic method where the electrophilic activation mode of indolyl substrates would take place in the presence of bifunctional *Cinchona* alkaloid-derived catalysts.

3.1 Enantioselective *N*-Alkylation of Nitroindoles under Phase-Transfer Catalysis (Publication II and Unpublished Results)

The introduction of EWG into indole core activates the *N*-atom for the nucleophilic addition. 3-Cyanoindole **69** was chosen as a model compound because its application as an *N*-nucleophile was recently successfully demonstrated in non-asymmetric *N*-alkylation with unsaturated aromatic ketones **70** catalyzed by potassium hydroxide (Scheme 23).[96] The 3-cyano substituent as a strong electron-withdrawing group affects π-electron delocalization in the indole ring. Thus, the electron density on the *N*-atom of the indole is reduced through a resonance withdrawing effect and the acidity of the *N*-H atom is increased. Moreover, a C3-substituent prevents the C3-alkylation that usually occurs as a side reaction, and 3-cyanoindole **69** is a commercially available substrate.



Scheme 23. *Non-asymmetric reaction of 3-cyanoindole with various enones.*

The asymmetric version of the *N*-alkylation of 3-cyanoindole **69** was investigated in the presence of *Cinchona* alkaloid-derived phase-transfer catalysts (Table 1). The screening of a model reaction was performed with electrophilic *trans*-crotonophenone **72a** in toluene at room temperature with varying different PTCs (Figure 1). C*inchonidine*-based ammonium salts with different substituents at quinuclidine were tested (Table 1, entry 1–3). The first three catalysts (**XXVI**, **XXVII** and **XXVIII**) illustrated the clear dependence of the steric effect of the PTC on stereoselectivity. In the case of catalysts **XXVI** and **XXVII**, almost full conversion was obtained, but the reaction proceeded with poor enantioselectivity (*ee* 18% and 26%). The *ee* value was improved up to 42% when the more sterically demanding anthracenyl-substituted catalyst **XXVIII** was used. The phase-transfer catalyst with *para*-nitrobenzyl-substituent **XXIX** afforded results similar to the catalyst **XXVIII**. The phase-transfer catalyst **XXX** was inefficient for the catalysis of the reaction, most likely because of the low solubility of the PTC **XXX** in toluene (Table 1, entry 5). Next, the model reaction was studied with a ammonium salt **XXXI** where the bromide anion was replaced by a BARF anion. Both conversion and *ee* value declined dramatically (Table 1, entry 6). The pivotal role of a hydrogen bond donor in the stereocontrol of the reaction was determined with the catalysts **XXXII** and **XXXIII** (Table 1, entries 7 and 8). Full conversion was achieved with the allyl-protected catalyst **XXXII**, despite the fact that a complete absence of enantioselectivity was observed. The phase-transfer catalyst derived from thiourea **XXXIII** demonstrated an *ee* value comparable to results obtained with catalyst **XXVII**, though the conversion was lower.

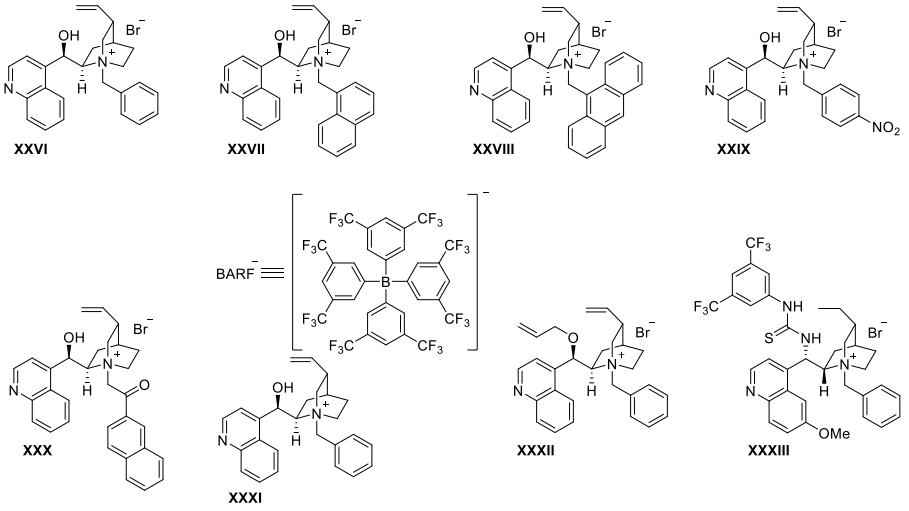
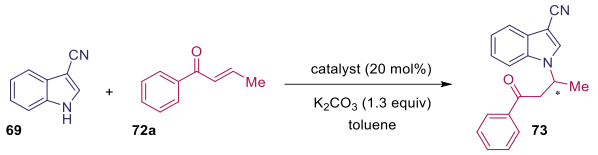


Figure 1. *PTC catalysts screened for the synthesis of N-alkylated indole* ***73****.*

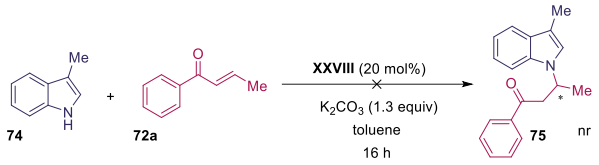
Table 1. *Screening of the catalyst.*[a]



entry	catalyst	time (h)	conv. (%)[b]	*ee* (%)[c]
1	**XXVI**	18	98	18
2	**XXVII**	18	99	26
3	**XXVIII**	16	83	42
4	**XXIX**	16	80	36
5	**XXX**	16	26	4
6	**XXXI**	18	5	6
7	**XXXII**	16	99	rac
8	**XXXIII**	20	29	-28

[a] Reaction conditions: 0.1 mmol scale, 1.2 equiv of **69**, 1 equiv of **72a**, 20 mol% of catalyst and 1.3 equiv of K_2CO_3 in 1 mL of toluene (0.1 M) at rt. [b] Conversion was determined by ^{1}H NMR from the crude mixture. [c] Determined by chiral HPLC analysis of the sample obtained by preparative TLC.

The significance of the *N*-H acidity of the indole substrate was demonstrated by a control experiment where less acidic 3-methyl-substituted indole **74** was subjected to a reaction with *trans*-crotonophenone **72a** in the presence of catalyst **XXVIII** under the same reaction conditions that were previously applied in a reaction with 3-cyanoindole (Table 1). However, no reaction was observed within 16 hours (Scheme 24). Thus, the crucial role of the electron-withdrawing group in the activation of the *N*-atom was clearly illustrated.



Scheme 24. *Michael reaction between 3-methylindole and trans-crotonophenone.*

Disappointed with the obtained results (Table 1), we decided to conduct a more precise study of substituted indole derivatives. In addition to 3-cyanoindole **69**, a series of mono nitro-substituted indoles were investigated as potential nucleophiles **76** for asymmetric intermolecular *N*-alkylation. We selected nitroindoles because nitro compounds are well-known for their possible interactions with phase-transfer catalysts.[97–100]

First, the acidity of indoles was determined in cooperation with Professor Ivo Leito from Tartu University (Figure 2).[101] According to the measurements performed in acetonitrile, 3-cyanoindole **69** and nitroindoles **76** behaved as weak acids and their pK_a values were in the range of 22–30. The increased acidity of indole derivatives could be explained by the delocalization of π-electrons in the aromatic indole system caused by the introduction of an electron-withdrawing group. Notably, the acidity of *N*-H atom can be controlled by varying the position of the nitro group in the indole ring. The resonance stabilization by the π electron pair of the indolate anion and the vicinity of the nitro group to the *N*-H site were the main features that affected the pK_a values. The acidity of the *N*-H proton is higher when the nitro group is located in a five-membered ring (pK_a between 22 and 24), thus the indoles with the nitro group in a six-membered ring are less acidic (pK_a between 27 and 30). Among the nitro-substituted indoles, the most acidic was 3-nitroindole due to the highly efficient resonance form of indolate anion and the vicinity of the electron withdrawing group to the *N*-H atom.

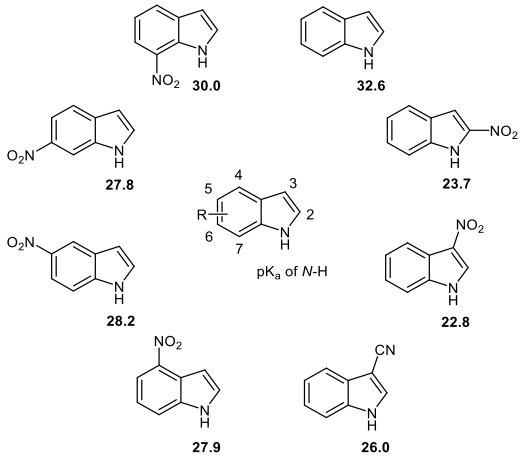
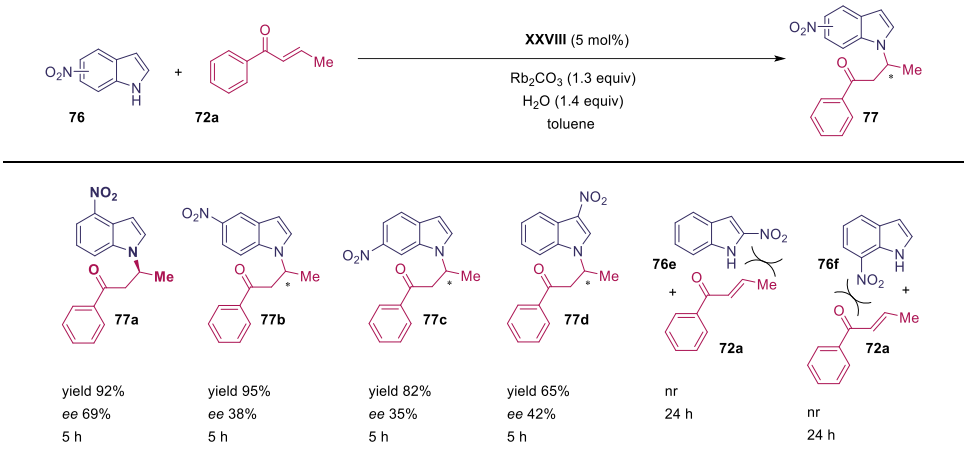


Figure 2. *Strengths of indoles as N-H acids in acetonitrile.*

Next, a reaction with commercially available 4-nitroindole **76a** as a starting material was studied.[i] In contrast to 3-cyanoindole **69**, the reaction of 4-nitroindole **76a** under similar conditions proceeded in a more enantioselective manner and the desired *N*-alkylated indole was obtained in high yield (92%) and good *ee*-value (69%). Encouraged by this result, other mono nitro-substituted indoles were tested in an asymmetric phase-transfer-catalyzed Michael addition (Scheme 25).

The most acidic 3-nitroindole **76d** was less reactive than 4-nitroindole **76a** and only a moderate level of stereocontrol was achieved. The indoles with nitro substituent in the fifth or sixth positions provided products in lower *ee* values than 4-nitroindole (Scheme 25). However, a high yield was gained with 5-nitroindole **76b**. No reaction was observed with 2-nitroindole **76e** or 7-nitroindole **76f**, even with increased reaction time. Obviously, steric hindrance in close proximity to the reactive *N*-H site caused by the nitro group was the main reason. The results clearly indicate the key role of the position of the nitro group in imposing effective stereocontrol of the aza-Michael reaction. Unfortunately, no correlation was observed between *N*-H acidity and reactivity of nitroindoles in the conjugate addition. However, the dependence of reactivity and steric hindrance provided by the nitro group was determined. The most active substrates were 4-nitro- and 5-nitroindoles. The reactivity was decreased with 3-nitro- and 6-nitro-substituted substrates and no reaction took place when 2-nitro- and 7-nitroindoles were used as nucleophiles. On the basis of the above-mentioned results, 4-nitroindole **76a** was clearly the best Michael donor in terms of enantioselectivity and reaction yield.



[a] Reaction conditions: 0.1 mmol scale, 1 equiv of **76**, 2.1 equiv of **72a**, 5 mol% of catalyst **XXVIII**, 1.3 equiv of Rb_2CO_3 and 1.4 equiv of H_2O in 1 mL of toluene (0.1 M) under inert atmosphere at rt. Enantiomeric excess was determined by chiral HPLC analysis of the isolated product.

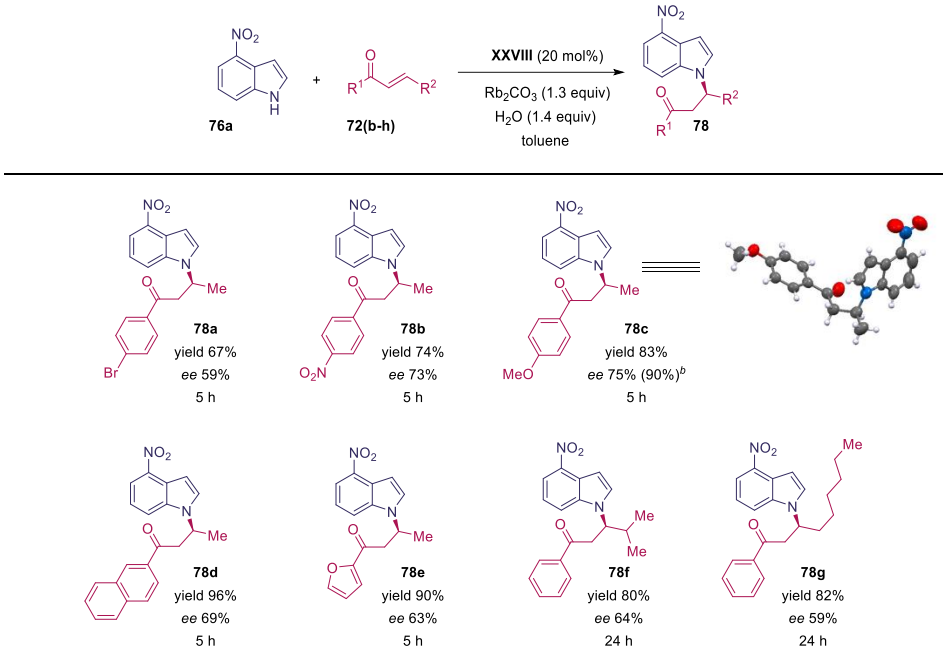
Scheme 25. *The effect of the position of the NO_2-group on an aza-Michael reaction.*[a]

The scope of Michael acceptors with the most selective 4-nitroindole **76a** was investigated (Scheme 26). Among the electrophiles, the most suitable reactants in this catalytic transformation were aromatic and heteroaromatic enones **72**, providing the desired products **78** within a reasonable time (5 hours) in moderate to high yields

[i] For more details see, Table 3 in **Publication II**.

(67–90%) and moderate enantioselectivities (59–75%). The substitution at the *para*-position of the phenyl ring did not significantly affect the stereoselectivity or yield of the reaction. To our pleasure, the enantiomeric purity of the product **78c** was improved by a single recrystallization. The bulky 2-naphthyl substituent of enone **72d** tolerated the reaction well and the corresponding product **78d** was isolated in excellent yield (90%) and good *ee* value (69%). The heteroaromatic 2-furyl substrate **72e** also provided reasonable enantioselectivity (63%) and high yield (90%). It should be noted that a slower reaction rate was observed with more sterically hindered enones **72f** and **72g**.

The absolute stereochemistry of *N*-alkylated products was assigned by a single crystal *X-ray* diffraction of indole derivative **78c** and configurations of other products in the series were assigned by analogy (Scheme 26).

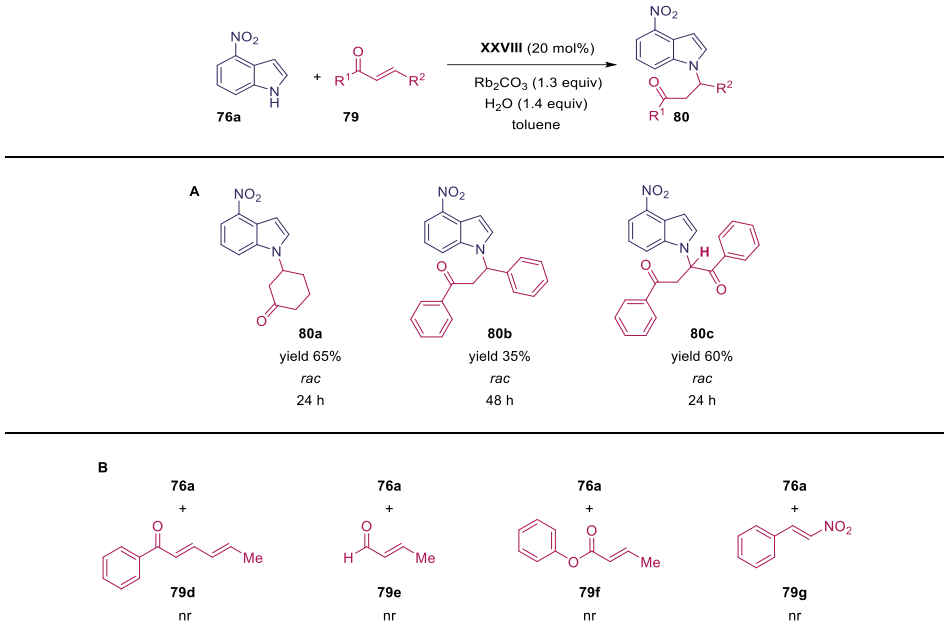


[a] Reaction conditions: 0.1 mmol scale, 1 equiv of **76a**, 2.1 equiv of **72**, 5 mol% of catalyst **XXVIII**, 1.3 equiv of Rb_2CO_3 and 1.4 equiv of H_2O in 1 mL of toluene (0.1 M) under inert atmosphere at rt. Enantiomeric excess was determined by chiral HPLC analysis of the isolated product. [b] *ee* value obtained after single recrystallization.

Scheme 26. *Scope of aza-Michael addition of 4-nitroindole* ***76a****.*[a]

We were faced with reaction limitations that fell into two distinct categories according to the reactivity of the substrates (Scheme 27, A and B). Group **A** combined substrates that provided the reaction in a non-asymmetric fashion; in group **B** no reaction took place. We considered that the steric environment of a Michael acceptor could drastically affect the stereochemical outcome of the reaction. Thus, the reaction of 4-nitroindole **76a** with aliphatic 2-cyclohexene-1-one **79a** afforded a racemic product. The sterically more demanding *trans*-chalcone **79b** also afforded a non-enantioselective reaction with prolonged reaction time. Obviously, the steric hindrance provided by the phenyl group at the β-position of the enone suppressed the asymmetric Michael addition and the

product was formed due to a background reaction catalyzed by the basic additive. The reaction with 1,4-diketone **79c** proceeded within 24 h in moderate yield, but the isolated product was optically inactive. Probably, the loss of enantioselectivity was induced by the racemization of the stereocenter through the enolization of the carbonyl group. In addition, a series of different Michael acceptors were tested and each of them was inactive in asymmetric *N*-alkylation, resulting in no reaction (Scheme 27, B).



[a] Reaction conditions: 0.1 mmol scale, 1 equiv of **76a**, 2.1 equiv of **79**, 5 mol% of catalyst **XXVIII**, 1.3 equiv of Rb_2CO_3 and 1.4 equiv of H_2O in 1 mL of toluene (0.1 M) under inert atmosphere at rt. Enantiomeric excess was determined by chiral HPLC analysis of the isolated product.

Scheme 27. *Scope limitations.*

To get an understanding of the *N*-alkylation mechanism and the origin of the enantioselectivity, computational studies were performed by Dr. Andrus Metsala (from the Department of Chemistry and Biotechnology in TalTech).

According to the NBO calculations, an H-bond was observed between the hydroxyl group of the catalyst **XXVIII** and the nitrogen atom of indole in the intermediate **INT-1** (Figure 3, A). Moreover, π-π stacking took place between the aromatic quinolone ring of the catalyst **XXVIII** and the indolate in the same ternary complex **INT-1**. A reorganization of the geometry caused by a distortion of the complex **INT-1** led to the formation of a new intermediate **INT-2** in which a strong H-bond occurred between the hydroxyl group of the catalyst and the nitro group of the indolate (Figure 3, B). The complex **INT-2** led to the formation of the desired product through a C–N bond forming step. π-Stacking was essential over the whole *N*-alkylation process (Figure 3, A–C). The absolute *S*-configuration of the product obtained by a single crystal *X-ray* diffraction analysis confirmed the calculated results achieved with DFT calculations.

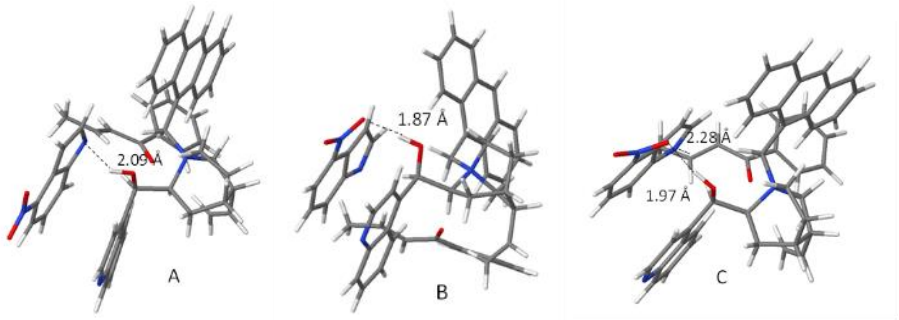
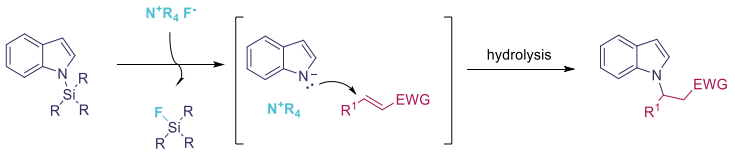


Figure 3. *Optimized geometries of transition states: A:* ***INT-1****; B:* ***INT-2****; C:* ***TS-1****.*

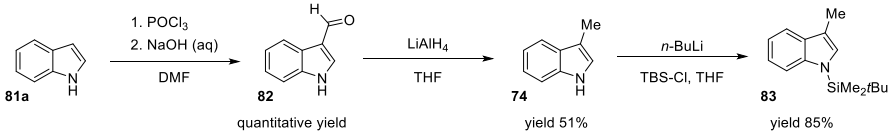
3.2 *N*-Alkylation of TBS-3-Methylindole (Unpublished Results)

As an alternative strategy, we used an *N*-silyl-protected indole as a Michael donor in conjugate additions. We assumed that an *N*-silylated indole could be easily activated in situ, affording a strong nucleophile (indolate) by selective silyl-deprotection in the presence of ammonium fluoride. The following addition of indolate to a Michael acceptor could occur and provide access to *N*-functionalized indoles (Scheme 28).



Scheme 28. *N-alkylation of a silyl-protected indole via desilylation.*

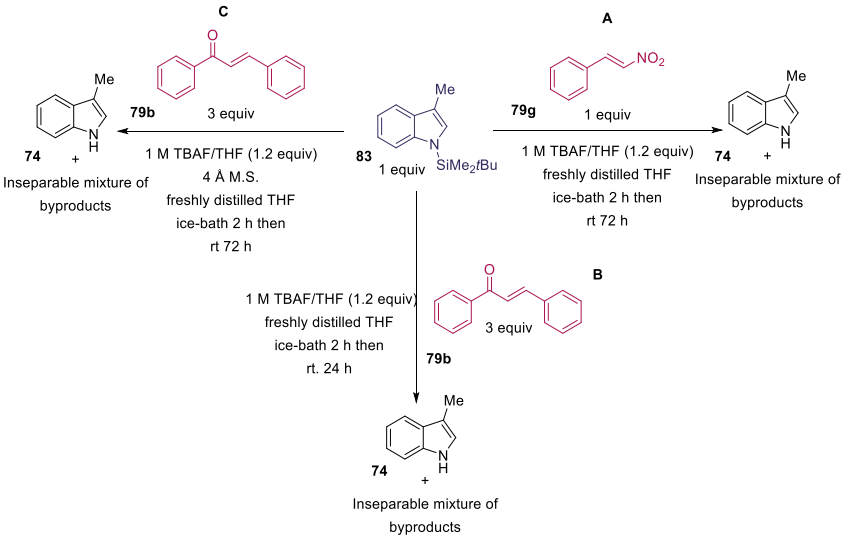
To test our hypothesis, we chose TBS-3-methylindole **83** as a starting material, which was synthesized in three steps starting from the parent indole **81a** (Scheme 29). A 3-methyl-substituted indole was used in order to prevent possible side reactions that could take place at the C3-position. The preparation of an indole-3-carboxaldehyde **82** proceeded efficiently via a Vilsmeier-Haack reaction and the followed reduction of the corresponding aldehyde **82** in the presence of $LiAlH_4$ afforded the desired 3-methylindole **74** in moderate yield (51%).[102] The *N*-silylation of the corresponding indole **74** provided the desired product **83** in good yield (85%).[103]



Scheme 29. *Synthesis of TBS-3-methylindole* ***83****.*

Next, the non-asymmetric reaction of TBS-3-methylindole **83** promoted by tetra-*n*-butylammonium fluoride was first performed with β-nitrostyrene **79g** in freshly distilled THF (Scheme 30, A). Unfortunately, the desired product did not form within two hours. An inseparable mixture of 3-methylindole **74** and polar by-products were observed in the crude mixture. We assumed that the polymerization of β-nitrostyrene **79g** as a side

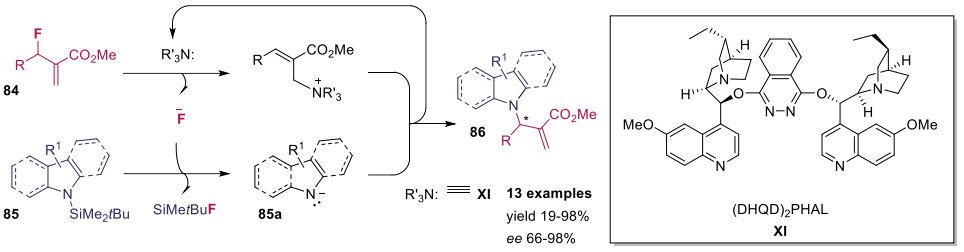
reaction could be the reason for that and switched our attention to *trans*-chalcone **79b** as a Michael acceptor (Scheme 30, B). However, the change of the electrophile and increasing its amount from 1.2 equivalents to 3 equivalents provided results similar to those achieved with β-nitrostyrene **79g**. The reaction was repeated in the presence of 4 Å molecular sieves in order to minimize the effect of water in the reaction, but the reaction was sluggish and gave an inseparable mixture of 3-methylindole **74** and by-products (Scheme 30, C).



Scheme 30. *Unsuccessful attempts with TBS-3-methylindole* ***83****.*

Our proof of concept attempts to synthesize *N*-alkylated indoles by using *N*-silyl-protected indole as a starting material were unsuccessful (Scheme 30).

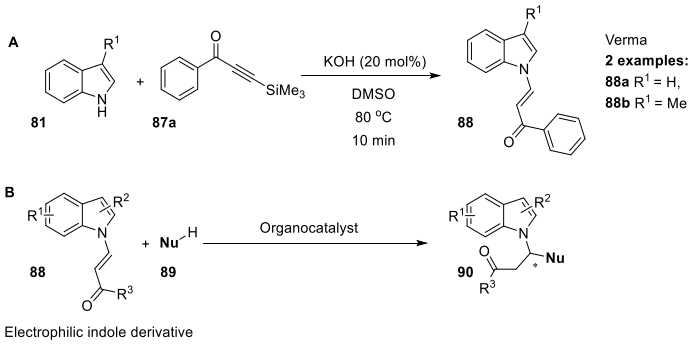
However, a similar approach was later reported by the Vilotijević group (Scheme 31).[104] They efficiently applied *N*-silylated heterocycles **85** as latent nucleophiles in reactions with fluorides derived from Morita–Baylis–Hillman adducts **84** in the presence of a *Cinchona* alkaloid-based ether **XI** (Scheme 31). Latent nucleophiles are a class of non-nucleophilic compounds that can be activated to serve as strong nucleophiles.[105] The covalent bond-mediated activation of fluorinated Morita–Baylis–Hillman adducts **84** promoted the release of fluoride anions, which were responsible for the desilylation of the indole and the formation of indolate intermediate **85a**. The simultaneous activation of an electrophile/nucleophile pair afforded the stereoselective *N*-alkylation of silyl-protected heterocycles **85** in moderate to high *ee* values (up to 98%) with a yield up to 98%.



Scheme 31. *Reaction of latent nucleophiles and MBH-fluorides.*[104]

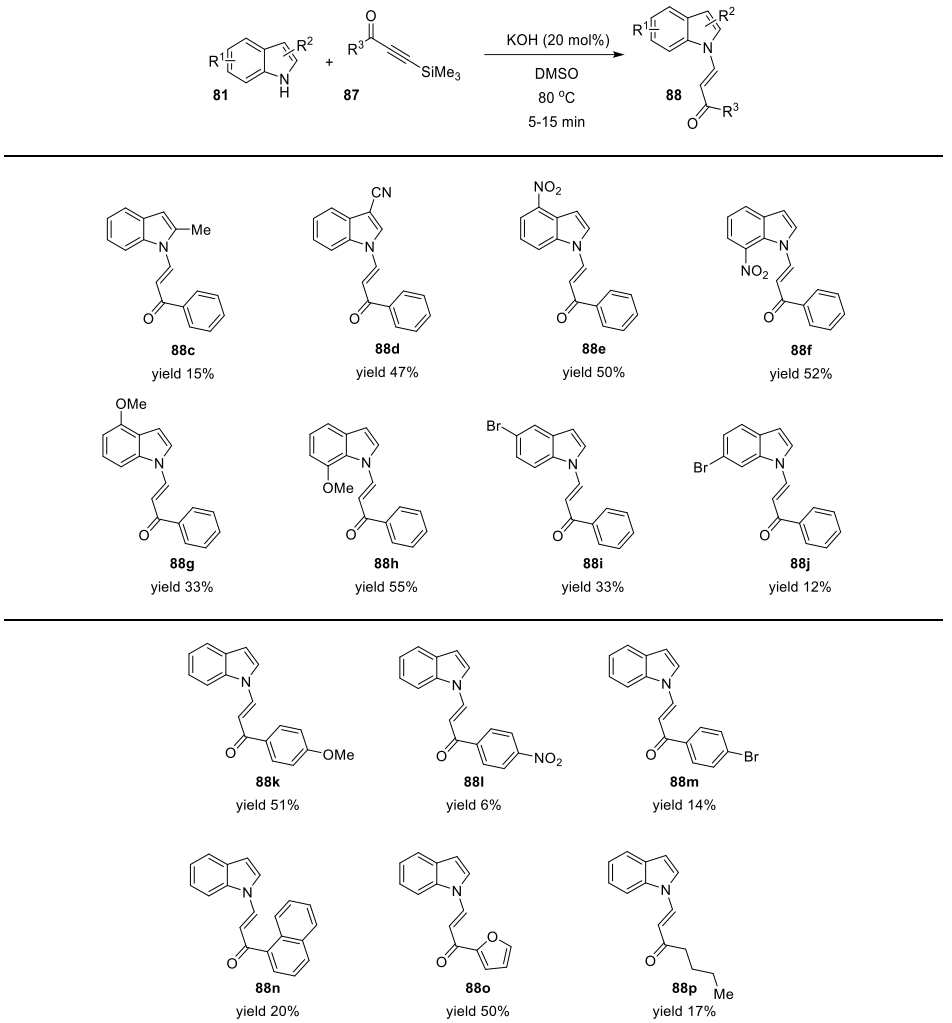
3.3 Enantioselective Organocatalytic Michael Addition to Unsaturated *N*-Indolyl Ketones (Publication III)

The Michael addition is one of the most famous reactions applied in asymmetric organocatalysis. A wide range of available Michael acceptors and donors makes this transformation a powerful tool in the synthesis of different chiral compounds in a selective and effective manner.[106–110] Recently, Verma et al. reported a synthetic protocol in which the preparation of enaminones **8** via the hydroamination of alkynones **87a** was accomplished (Scheme 32, A).[111] We recognized these *N*-indolyl ketones **88** as Michael acceptors that could be utilized in the synthesis of chiral *N*-alkylated indoles **90** (Scheme 32, B). The proposed approach to use an indole derivative as an electrophile is different from conventional organocatalytic strategies in which the indole is considered as a nucleophile.



Scheme 32. *Hydroamination of an indole (A) and a proposed approach to the enantioselective synthesis of N-substituted indoles (B).*

First, a set of Michael acceptors were synthesized according to Verma's procedure (Scheme 33). Generally, the desired enaminones **88** were isolated in poor to moderate yields (6–55%). However, the high availability of starting materials, a cheap catalyst (potassium hydroxide) and the simplicity of the synthetic procedure made it attractive and practical. The low reaction yields in some cases were probably caused by the need for additional purification steps in order to improve the chemical purity of products.

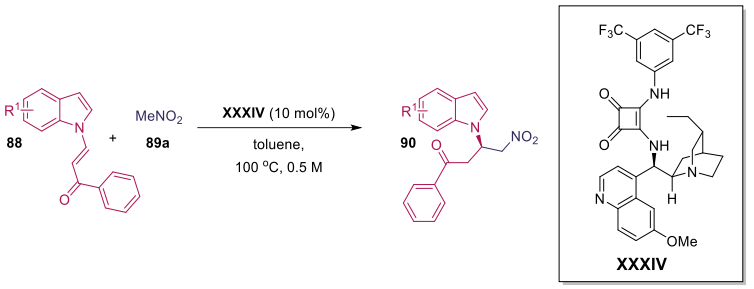


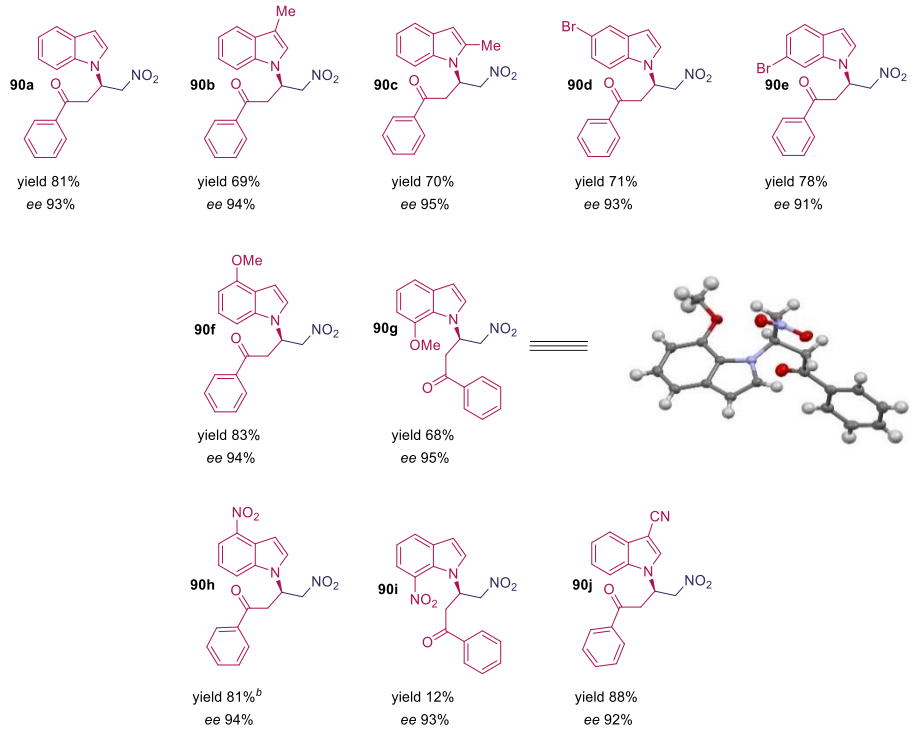
Scheme 33. *Synthesis of N-indolyl ketones* ***88****.*

To evaluate our assumption, an *N*-indolyl ketone **88a** and nitromethane **89a** were chosen as model substrates for the conjugate organocatalyzed 1,4-addition. It is well known that nitroalkanes can be successfully utilized as excellent Michael donors in stereoselective reactions accelerated by various organocatalytic systems.[112–117] With the model compounds in hand, we performed a screening of the reaction conditions.[ii]

Having established the optimal conditions [**88** (1 equiv), $MeNO_2$ (10 equiv), **XXXIV** (10 mol%) in toluene (0.5 M) at 100 °C, 24 hours], we next examined the generality of this reaction with a broad range of indole derivatives, and the results are summarized in Schemes 34, 35 and 36.

[ii] For more details, see Table 1 and Figure S1 in **Publication III**.





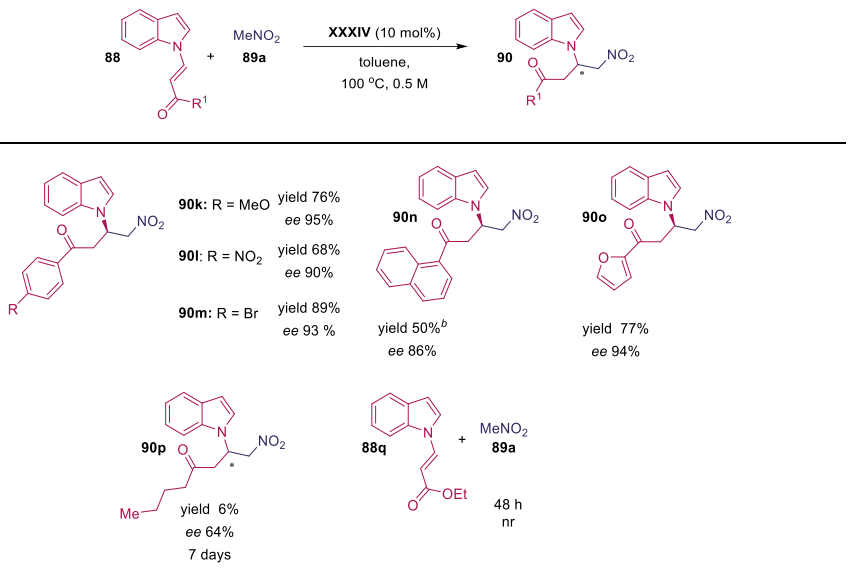
[a] Reaction conditions: 0.2 mmol scale, 1 equiv of **88**, 10 equiv of nitromethane **89a**, 10 mol% of catalyst **XXXIV**, in 0.4 mL of toluene (0.5 M), 24 h. Enantiomeric excess was determined by chiral HPLC analysis of the isolated product. [b] 0.2 M.

Scheme 34. *Scope of monosubstituted indole derivatives.*[a]

To explore the influence of the substitution pattern of the indole core on the reaction outcome, a variety of indole derivatives that differed from each other in the position and nature of the monosubstituent were investigated (Scheme 34). The reaction of C2- or C3-methyl-substituted *N*-indolyl ketones proceeded well, affording the desired chiral *N*-alkylated products **90b** and **90c** in good yields (69% and 70%) with excellent levels of enantioselectivities (94% and 95%). The variation of groups with opposite electronic natures at C4- and C7-positions had no significant influence on the enantioselectivity (93–95%) of the Michael addition. However, yields of the corresponding products decreased when C7-substituted substrates were used, especially, with a 7-nitro-substituted indole derivative. We assumed that such a drastic decline in yield (12%) was most

probably caused by a retro-Michael reaction. Additionally, 3-cyano-substituted substrate was tested, providing the product **90j** with increased yield (88%) and *ee* value (92%), comparable with the model compound **90a**. The incorporation of halogen-substituent either to the C5- or C6-position did not have a substantial impact on the reactivity, and the corresponding products **90d** and **90e** were isolated in good yields (71% and 78%) and high enantioselectivities (93% and 91%). It can be concluded that the substitution pattern of the indole core is not crucial, and the method is applicable to monosubstituted *N*-indolyl ketones possessing substituents in any position.

The structural assignment of **90g** was established by *X-ray* crystallographic analysis and configurations of other products in the series were determined by analogy (Scheme 34 and 35).



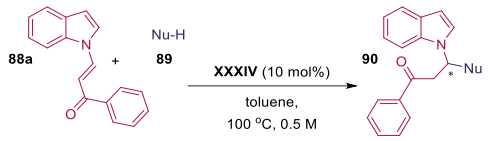
[a] Reaction conditions: 0.2 mmol scale, 1 equiv of **88**, 10 equiv of nitromethane **89a**, 10 mol% of catalyst **XXXIV**, in 0.4 mL of toluene (0.5 M), 24 h. Enantiomeric excess was determined by chiral HPLC analysis of the isolated product. [b] 0.1 mmol scale.

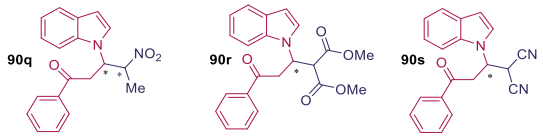
Scheme 35. *Scope of Michael acceptors with parent indolyl scaffold.*[a]

Next, we investigated the scope of Michael acceptors with parent indolyl scaffolds (Scheme 35). Tolerance toward both electron-withdrawing and electron-donating groups at the *para*-position of a phenyl ring was highlighted by substrates **88k** and **88l** (Scheme 34), providing chiral *N*-substituted indoles **90k** and **90l** in good yields (76% and 68%) in a highly enantioselective fashion (95% and 90%). Also, the *para*-bromo-substituted product **90m** was obtained in high yield and *ee* (89% and 93%, respectively). A significant drop in yield (50%) and a slight decline in enantioselectivity (85%) were observed when the sterically more hindered substrate bearing bulky 1-naphthyl substituent was used. Heteroaromatic 2-furyl-substituted product **90o** was successfully isolated in good yield (77%), and the achieved *ee* value (94%) was comparable to the model compound **90a**. Remarkably, the substitution of the phenyl ring with an aliphatic butyl chain led to a considerable decrease in the reactivity and enantioselectivity (64%), and the product **90p** was obtained in only 6% yield. The reaction was sluggish, indicating the substantial role

of π−π interactions between substrate and catalyst. Furthermore, no reaction took place within two days when the substrate containing an ethoxy group **88q** was subjected to a reaction with nitromethane.

The scope of the reaction was further extended to include other Michael donors **89**, such as nitroethane **89b**, malonic ester **89c**, malononitrile **89d** and 2,4-pentanedione (Scheme 36). The use of nitroethane **89b** instead of nitromethane resulted in the formation of a 1:1 mixture of diastereoisomers, which were chromatographically separable, and the enantioselectivities were high for both isomers (92%/92%). The high level of enantiocontrol remained when dimethyl malonate **89c** was used as a Michael donor and the corresponding product was isolated in good yield (67%). However, the reaction with 2,4-pentanedione under the same reaction conditions gave a mixture of inseparable products. Malononitrile **89d** reacted smoothly, providing the desired product **90c** within one hour in high yield (88%), but the *ee* value of the product dropped dramatically (45%).





yield 32%/37%
1:1 *dr*
ee 92%/92%

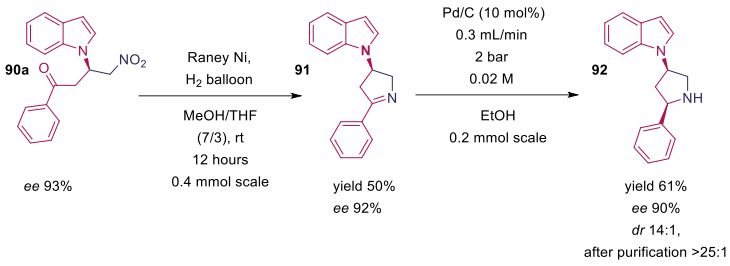
yield 67%
ee 93%

yield 88%[b]
ee 45%

[a] Reaction conditions: 0.2 mmol scale, 1 equiv of **88a**, 10 equiv of **89**, 10 mol% of catalyst **XXXIV**, in 0.4 mL of toluene (0.5 M), 24 h. Enantiomeric excess was determined by chiral HPLC analysis of the isolated product. [b] Reaction time 1 hour.

Scheme 36. *Scope of Michael donors.*[a]

Finally, the synthetic utility of this methodology was evaluated by a gram-scale experiment with model substrate **88a** and the subsequent modification of the chiral *N*-alkylated indole **90a** was performed (Scheme 37). To our delight, the scale-up of the reaction did not adversely affect the efficiency and enantioselectivity (78% yield, 92% *ee*). Moreover, compound **90a** was efficiently converted in two steps to a 5-HT_6 receptor modulator analogue precursor **92**.[118] A reductive cyclization of *N*-alkylated product **90a** was carried out in the presence of Raney-Ni and the corresponding chiral imine **91** was isolated in moderate yield (50%) without the loss of enantioselectivity. Hydrogenation of the imine **91** was successfully conducted in a continuous-flow reactor with a Pd/C catalyst cartridge, affording chiral pyrrolidine derivative **92** in high *ee* value (90%), *dr* ratio (14:1), and good yield (62%). The diastereomeric ratio of the product **92** was improved after the purification of the reaction mixture (*dr* >25:1) and the *cis*-configuration of the substituents in the pyrrolidine ring was assigned by a selective NOESY experiment.



Scheme 37. *Synthetic transformation of compound* ***90a****.*

4 Conclusions

In the course of the present study, two organocatalytic methods for the asymmetric synthesis of *N*-alkylated indoles were developed. Both approaches exclusively provided enantiomerically enriched *N*-alkylated products.

The specific results of the first method, in which indole derivatives were applied as nucleophiles:

- The comprehensive study of the *N*-alkylation of nitroindoles **76** under phase-transfer catalysis revealed that the acidity of the *N*-H proton of the indole was not the decisive factor in determining the reactivity and selectivity of the reaction. The position of the nitro group is essential in determining both the reactivity and enantioselectivity of the reaction.
- The reaction proceeded selectively in the presence of *Cinchona* alkaloid-derived PTC **XXVIII** and the most suitable substrates were found to be 4-nitroindole **76a** and *trans*-crotonophenone derivatives **72**, affording products in moderate *ee* values (up to 75%) and good to high yields (up to 96%).
- Computational studies revealed the importance of a hydrogen bond in the transition state between the hydroxyl group of catalyst **XXVIII** and the nitro group of indole **76a**. The π-π interactions between the quinolone ring of the catalyst **XXXVIII** and indole **76a** remained important throughout the reaction.

The specific results of the second method, in which indole derivatives were applied as electrophiles:

- We worked out the first organocatalytic enantioselective formal *N*-alkylation of indoles using indolyl ketones **88** as Michael acceptors.
- The common problems with *N*-selectivity were totally avoided due to the electrophilic activation mode of indole substrates **88**.
- A wide range of electrophilic indole *N*-derivatives **88** and various nucleophiles **89** afforded *N*-alkylated indoles **90** with branched substituents in good yields (up to 89%) and high to excellent *ee* values (up to 95%).
- The substitution pattern of the indole core did not affect the enantioselectivity of the reaction.
- The synthetic utility of the method was demonstrated by the synthesis of a 5-HT_6 receptor modulator analogue precursor.

5 Experimental

General Information

All commercially available reagents were used without further purification. The reactions were monitored by thin layer chromatography (TLC) with silica gel-coated aluminium plates (Merck 60 F254) and visualized with a $KMnO_4$, anisaldehyde or vanillin stain. Yields refer to chromatographically purified products. ^{1}H NMR spectra were recorded on a Bruker Avance III instrument at 400 MHz and are reported in parts per million (δ) referenced to the residual solvent signal ($CDCl_3$ δ = 7.26 ppm, TMS δ = 0.00 ppm). Data for the ^{1}H NMR spectra are as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad signal), coupling constant *J* Hz, and relative integration. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40−63 µm. EtOAc was distilled over phosphorous pentoxide. Petroleum ether has a boiling point of 40−60 °C.

3-(3-Methyl-1*H*-indol-1-yl)-1-phenylbutan-1-one

3-Methyl-1*H*-indole (15.8 mg, 0.12 mmol), phase-transfer catalyst **XXVIII** (11.3 mg, 0.02 mmol) and K_2CO_3 (18 mg, 0.13 mmol) were loaded in a 1 mL vial. Toluene (1 mL) and *trans*-crotonophenone (14.6 mg, 0.1 mmol) were added and the reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by TLC and NMR spectroscopy. No reaction was detected.

Compounds **82**, **74** and **83** were prepared by corresponding literature procedures.[102,103]

1*H*-Indole-3-carbaldehyde 82

A three-necked flask was charged with an indole (2.343 g, 20 mmol) and DMF (7.7 mL) under an inert atmosphere. The mixture was stirred and cooled to 0 °C, and then the freshly distilled $POCl_3$ (3.68 g, 2.24 mL, 24 mmol) was added dropwise over 30 min by syringe pump. The solution was heated at 45 °C for 2 h, 2 M NaOH aqueous solution (120 mL) was added and the reaction mixture was heated at 90 °C for another 1 h. EtOAc (180 mL) was added to dissolve the red/yellow solid, and the aqueous layer was extracted with the EtOAc (3 × 60 mL). The combined organic phases were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The corresponding 1*H*-indole-3-carbaldehyde **82** (colourless crystals) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.77 (br, 1H), 8.35 – 8.25 (m, 1H), 7.86 (d, *J* = 2.8 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.36 – 7.32 (m, 2H). NMR data were in agreement with the literature data.[119]

3-Methyl-1*H*-indole 74

In a dry flask, freshly distilled $LiAlH_4$ (1.140 g, 30 mmol) in THF (60 mL) was cooled at 0 °C, and a solution of 1*H*-indole-3-carbaldehyde (3.02 g, 20 mmol) in THF (45 mL) was added dropwise over 40 min by syringe pump. The mixture was stirred overnight at rt. After completion of the reaction, 1.2 mL of ice water was added carefully, followed by the addition of aqueous 15% NaOH (2.5 mL) and H_2O (6.0 mL). The mixture was stirred for 20 min, the solid was removed by filtration and was washed with diethyl ether (3 × 40 mL). The combined organic phase was dried over $MgSO_4$ (10 min), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography

on silica gel (7–15% EtOAc in petroleum ether) to provide the corresponding 3-methyl-1*H*-indole **74** as a white solid (1.327 g, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 7.05 – 6.86 (m, 1H), 2.37 (s, 3H). NMR data were in agreement with the literature data.[120]

1-(*tert*-Butyldimethylsilyl)-3-methyl-1*H*-indole 83

n-BuLi (2.5 M in hexane, 1.5 mL) was added dropwise over 5 min to a solution of 3-methyl-1*H*-indole (0.321 g, 2.45 mmol) in anhydrous THF (8 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and *tert*-butyl-dimethylchlorosilane (0.555 g, 3.68 mmol) in anhydrous THF (4.9 mL) was added dropwise before allowing the solution to warm to rt and stirring overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, and the aqueous phase was washed with Et_2O (3 x 20 mL), followed by washing the combined organic phases with brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) to provide the corresponding 1-(*tert*-butyldimethylsilyl)-3-methyl-1*H*-indole **83** as a colourless oil (0.512 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 1H), 7.57 – 7.51 (m, 1H), 7.26 – 7.15 (m, 2H), 7.04 – 6.98 (m, 1H), 2.51 – 2.20 (m, 3H), 1.00 (s, 9H), 0.65 (s, 6H). NMR data were in agreement with the literature data.[121]

Experiments for the *N*-Alkylation of TBS-3-Methylindole

3-Methyl-1-(2-nitro-1-phenylethyl)-1*H*-indole

In a dry Schlenk tube, TBAF (1 M in THF, 0.24 mL, 0.24 mmol) was added dropwise to a solution of 1-(*tert*-butyldimethylsilyl)-3-methyl-1*H*-indole (49 mg, 0.2 mmol) in anhydrous THF (1.4 mL) at 0 °C. The mixture was stirred for 10 min. β-Nitrostyrene (29 mg, 0.2 mmol) dissolved in THF (0.4 mL) was added dropwise and the mixture was stirred for 2 hours at 0 °C. The reaction produced an inseparable mixture consisting of 3-methylindole and other polar byproducts. The reaction mixture was allowed to warm to rt and stirred for 72 h. No changes were observed.

3-(3-Methyl-1*H*-indol-1-yl)-1,3-diphenylpropan-1-one

Procedure I

In a dry Schlenk tube, TBAF (1 M in THF, 0.24 mL, 0.24 mmol) was added dropwise to a solution of 1-(*tert*-butyldimethylsilyl)-3-methyl-1*H*-indole (49 mg, 0.2 mmol) in anhydrous THF (1.4 mL) at 0 °C. The mixture was stirred for 10 min. *trans*-Chalcone (125 mg, 0.6 mmol) dissolved in THF (0.4 mL) was added dropwise and the mixture was stirred for 2 hours at 0 °C. The reaction produced an inseparable mixture consisting of 3-methylindole and other polar by-products. The reaction mixture was allowed to warm to rt and stirred for 24 h. No changes were observed.

Procedure II

In a dry Schlenk tube, TBAF (1 M in THF, 0.24 mL, 0.24 mmol) was added dropwise to a mixture of 1-(*tert*-butyldimethylsilyl)-3-methyl-1*H*-indole (49 mg, 0.2 mmol) and 4 Å molecular sieves (360 mg, powder) in anhydrous THF (1.4 mL) at 0 °C. The mixture was stirred for 10 min. *trans*-Chalcone (125 mg, 0.6 mmol) dissolved in THF (0.4 mL) was added dropwise and the mixture was stirred for 2 hours at 0 °C. The reaction produced

an inseparable mixture consisting of 3-methylindole and other polar by-products. The reaction mixture was allowed to warm to rt and stirred for 72 h. No changes were observed.

Table 2. *Supporting information concerning compounds discussed in the thesis but not presented in the Experimental section can be found in the corresponding publications.*

Entry	Compound Number in thesis	Compound number in publication	
		II	III
1	**XXVI**	**I**	
2	**XXVII**	**II**	
3	**XXVIII**	**III**	
4	**XXIX**	**IV**	
5	**XXX**	**V**	
6	**XXXI**	**VI**	
7	**XXXII**	**VII**	
8	**XXXIII**	**VIII**	
9	**XXXIV**		**I**
10	**72a**	**2**	
11	**72b**	**2a**	
12	**72c**	**2b**	
13	**72d**	**2c**	
14	**72e**	**2g**	
15	**72f**	**2d**	
16	**72g**	**2e**	
17	**72h**	**2f**	
18	**76d**	**4b**	
19	**76e**	**4e**	
20	**77a**	**5a**	
21	**77b**	**5c**	
22	**77c**	**5d**	
23	**77d**	**5b**	
24	**78a**	**6a**	
25	**78b**	**6b**	
26	**78c**	**6c**	
27	**78d**	**6g**	
28	**78e**	**6d**	
29	**78f**	**6e**	
30	**78g**	**6f**	
31	**79d**	**2k**	
32	**79f**	**2m**	
33	**80a**	**6h**	
34	**80b**	**6i**	
35	**80c**	**6j**	
36	**87a**		**a**
37	**87b**		**d**
38	**87c**		**c**

39	**87d**		**b**
40	**87e**		**e**
41	**87f**		**f**
42	**87g**		**g**
43	**88a**		**1**
44	**88b**		**1a**
45	**88c**		**1b**
46	**88d**		**1c**
47	**88e**		**1d**
48	**88f**		**1e**
49	**88g**		**1f**
50	**88h**		**1g**
51	**88i**		**1h**
52	**88j**		**1i**
53	**88k**		**1j**
54	**88l**		**1k**
55	**88m**		**1l**
56	**88n**		**1m**
57	**88o**		**1n**
58	**88p**		**1o**
59	**90a**		**3**
60	**90b**		**3a**
61	**90c**		**3b**
62	**90d**		**3h**
63	**90e**		**3i**
64	**90f**		**3f**
65	**90g**		**3g**
66	**90h**		**3d**
67	**90i**		**3e**
68	**90j**		**3c**
69	**90k**		**3j**
70	**90l**		**3k**
71	**90m**		**3l**
72	**90n**		**3m**
73	**90o**		**3n**
74	**90p**		**3o**
75	**90q**		**3t**
76	**90r**		**3q**
77	**90s**		**3p**
78	**91**		**4**
79	**92**		**5**

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Abstract

Organocatalytic Enantioselective Synthesis of *N*-Alkylated Indoles

During the last two decades, explosive growth in the field of organocatalysis and substantial progress in transition-metal catalysis have promoted the development of novel strategies for the stereoselective *N*-functionalization of indoles. Nevertheless, a catalytic asymmetric derivatization of the *N*-atom of the indole ring system has remained challenging due to a wide range of limitations caused by the poor nucleophilicity of the *N*-atom and the competing background reaction at the C3-position.

Herein, we present two different organocatalytic approaches to the synthesis of chiral *N*-substituted indoles. In both cases *Cinchona* alkaloid-derived organocatalysts were efficiently used and complete *N*-selectivity was gained.

First, the asymmetric intermolecular phase-transfer-catalyzed *N*-addition of indoles with increased acidity to different Michael acceptors was investigated. 3-Cyano- and mono nitro-substituted indoles were chosen as Michael donors and evaluated in an aza-Michael reaction, demonstrating the absence of correlation between *N*-H acidity and reactivity. However, the position of the nitro group on the indole core was crucial to control both the reactivity and enantioselectivity of the reaction. Various Michael acceptors were tested in the reaction, with the most selective 4-nitroindole affording the desired *N*-alkylated products in high yields (up to 96%) and moderate enantioselectivities (up to 75%). In addition to the reaction scope and limitations, the geometries of the transition states of the reaction were calculated.

The initial proof of concept experiments with an *N*-silyl-protected indole as the pronucleophile in reactions with Michael acceptors were unsuccessful. We decided to reject this idea and concentrated our attention on an organocatalytic polarity-reversed approach where indole derivatives were used as electrophiles.

The enantioselective synthesis of *N*-substituted indoles with α-branched alkyl substituents was realized through an asymmetric Michael addition of different nucleophiles to the corresponding unsaturated *N*-indolyl ketones. High levels of stereocontrol (*ee* up to 95%) and good yields (up to 89%) were obtained in the presence of the bifunctional squaramide organocatalyst. The significant feature of this approach is the exploiting of an indole derivative as an electrophile, fully avoiding the chemoselectivity problems common with other *N*-functionalization strategies. Various nucleophiles, such as nitroalkanes, malonic ester and malononitrile can be utilized. The substitution pattern of the indole ring did not affect the reaction outcome. Substituents with different electronic natures in any position of the indole ring system tolerated the reaction well. Moreover, we demonstrated the successful scale-up of the model reaction and performed the efficient synthetic transformation of the model compound without the loss of enantioselectivity.

Lühikokkuvõte
Organokatalüütiline enantioselektiivne *N*-alküleeritud indoolide süntees

Viimase kahe aastakümne jooksul on toimunud nii organokatalüüsi kui ka siirdemetallide katalüüsi kiire areng. See on otseselt mõjutanud ka indoolide stereoselektiivse N-funktsionaliseerimise meetodite arengut. Vaatamata sellele jääb indooli lämmastikuaatomi katalüütiline asümmeetriline derivatiseerimine ikkagi väljakutseks, kuna enamus meetoditest on reeglina piiratud lämmastikuaatomi madala nukleofiilsuse ja asendis C3 toimuvate kõrvalreaktsioonide tõttu.

Käesoleva töö raames töötati välja kaks erinevat organokatalüütilist sünteesimeetodit kiraalsete *N*-asendatud indoolide saamiseks. Mõlemal juhul kasutati *Cinchona* alkaloididel põhinevaid katalüsaatoreid ning saavutati täielik *N*-selektiivsus.

Esiteks uuriti asümmeetrilist intermolekulaarset faasiülekande katalüüsitud *N*-liitumist erinevatele Michaeli aktseptoritele, kus nukleofiilidena kasutati suurendatud happelisusega indooli derivaate. Asa-Michaeli reaktsioonis kasutati doonoritena 3-tsüano- ja mono nitro-asendatud indoole. Saadud tulemused näitasid korrelatsiooni puudumist *N*-H happelisuse ja reaktsiooni kiiruse vahel, kuid samal ajal leiti nitrorühma asendi tugev mõju reaktiivsusele ning enantioselektiivsusele. Reaktsiooni ulatuse uurimine viidi läbi kõige selektiivsema indooli derivaadi (4-nitroindooli) ja erinevate Michaeli aktseptoritega. Produktid saadi kõrge saagise (kuni 96%) kuid mõõduka enantiomeerse puhtusega (*ee* kuni 75%). Lisaks reaktsiooni ulatuse ja piirangute uurimisele arvutati ka siirdeoleku optimaalne geomeetria.

Esialgsed katsed *N*-silüül kaitstud indooliga kui pronukleofiiliga reaktsioonides Michaeli aktseptoritega ei andnud positiivseid tulemusi. Seetõttu otsustati sellest ideest loobuda ja keskenduda organokatalüütilisele lähenemisviisile, kus indooli derivaate kasutatakse elektrofiilidena.

Enantioselektiivne *N*-asendatud indoolide süntees lähtudes küllastumata *N*-indolüülketoonidest kulges bifunktsionaalse skvaaramiidi kui katalüsaatori manulusel kõrge stereoselektiivsuse (*ee* kuni 95%) ja saagisega (kuni 89%). Antud lähenemisviisi oluliseks tunnuseks on indooli derivaadi kasutamine elektrofiilina, mis välistab täielikult kemoselektiivsuse probleemi, mis on omane teistele *N*-funktsionaliseerimise strateegiatele. Reaktsiooni ulatus oli lai, mis võimaldas kasutada erinevaid nukleofiile (nitroalkaanid, maloonester ja malononitriil). Indooli tuuma asendusmuster ei mõjutanud oluliselt reaktsiooni tulemust ning samuti oli võimalik kasutada erinevate elektroonsete omadustega asendajatega indoole. Reaktsiooni skaleerimisel gramm-skaalasse kasutades põhisubstraati ja vastava produkti sünteetilisel modifitseerimisel bioaktiivse ühendi sünteetiliseks eellaseks säilis produkti kõrge enantiomeerne puhtus.

Appendix 1

Publication I

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Review

Enantioselective Catalytic Synthesis of *N*-alkylated Indoles

Dmitri Trubitsõn and Tõnis Kanger *

Department of Chemistry and Biotechnology, School of Science, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia; dmitri.trubitson@taltech.ee

* Correspondence: tonis.kanger@taltech.ee; Tel.: +372-620-4371

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Abstract: During the past two decades, the interest in new methodologies for the synthesis of chiral *N*-functionalized indoles has grown rapidly. The review illustrates efficient applications of organocatalytic and organometallic strategies for the construction of chiral α-*N*-branched indoles. Both the direct functionalization of the indole core and indirect methods based on asymmetric *N*-alkylation of indolines, isatins and 4,7-dihydroindoles are discussed.

Keywords: indole; asymmetric synthesis; organocatalysis; transition-metal catalysis; C-N bond formation; enantioselective; heterocycles

1. Introduction

Heterocyclic compounds are of great interest in medicinal chemistry. According to the U.S. Food and Drug Administration database, approximately 60% of unique small-molecule drugs contain a nitrogen heterocyclic motif [1]. The indole core is the most common nitrogen-based heterocyclic fragment applied for the synthesis of pharmaceutical compounds and agrochemicals [2]. The indole moiety can be found in a wide range of natural products [3]. Therefore, some biologically active indoles contain a substituted α-chiral carbon center on the *N*1-position (Figure 1) [4–7].

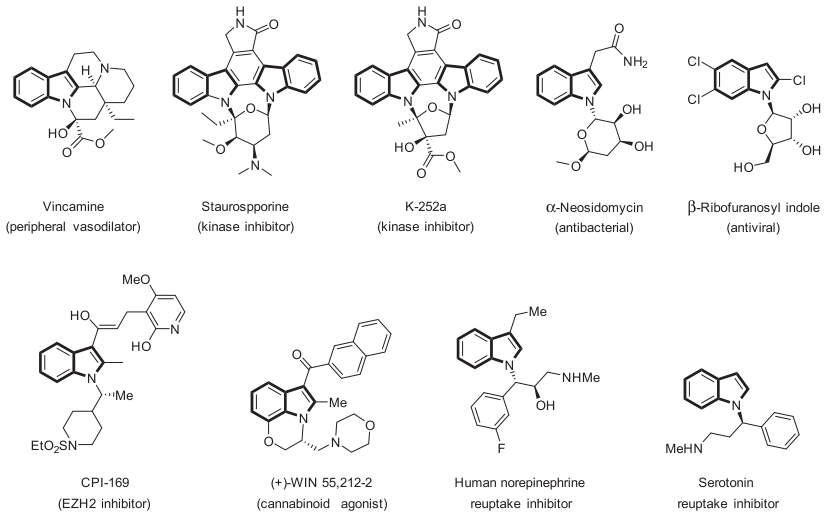
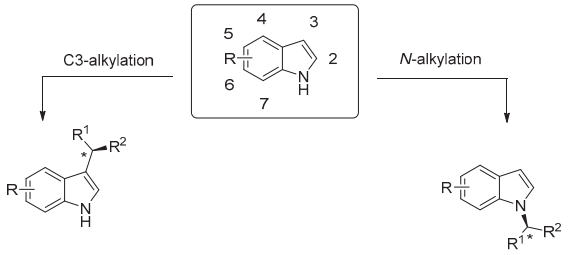


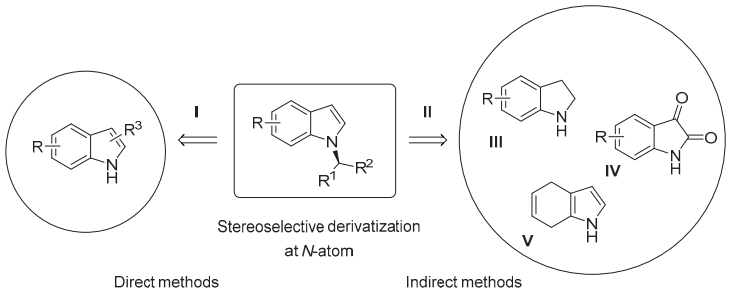
Figure 1. Biologically active chiral α-*N*-branched indoles.

The synthesis of enantioenriched indole derivatives is of great importance in organic chemistry. During the past two decades, different strategies have been proposed for the construction of chiral indole derivatives [8–11]. The most typical synthetic modifications of indoles take place at the C3 position (Scheme 1). The enantioselective electrophilic substitution at C3 is common due to the high nucleophilicity of this position, which is 10^{13} times more reactive than benzene [12,13]. In contrast to enantioselective C3 transformations, the stereoselective *N*-alkylation of indole is still a challenge due to the weak nucleophilicity of the nitrogen atom (Scheme 1). Despite this, a number of publications have been published recently that demonstrate new synthetic routes affording chiral *N*-substituted indole derivatives. In this review, we will introduce and discuss methodologies that provide catalytic stereoselective derivatization at the *N*-atom of indole.



Scheme 1. Regioselectivity of the asymmetric functionalization of indoles.

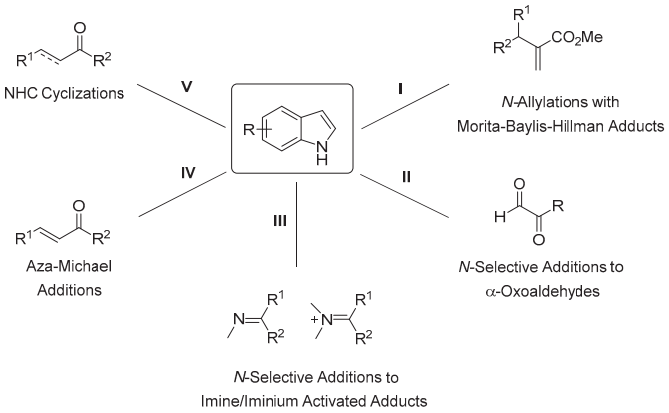
On a structural basis, the strategies for the construction of α-*N*-branched indoles can be classified into two groups: "direct methods" and "indirect methods" (Scheme 2). In the former case, indole derivatives are transformed by transition-metal catalysis or by organocatalysis into chiral compounds (Scheme 2, **I**). If the structure of the starting compound does not contain an indole moiety, the methods are defined as indirect methods (Scheme 2, **II**). The indirect methods are subdivided according to the structure of the starting compound and the modifications occurring during the synthesis of α-*N*-branched indoles (Scheme 2, **II**). There are several ways to prepare *N*-functionalized indoles indirectly. This review covers the asymmetric *N*-alkylation of indolines, isatins and 4,7-dihydroindoles, followed by a redox reaction, which provides the corresponding *N*-alkylated indoles (Scheme 2, **III**, **IV** and **V** respectively).



Scheme 2. Strategies for the enantioselective *N*-functionalization of indoles.

2. Direct Organocatalytic Methods

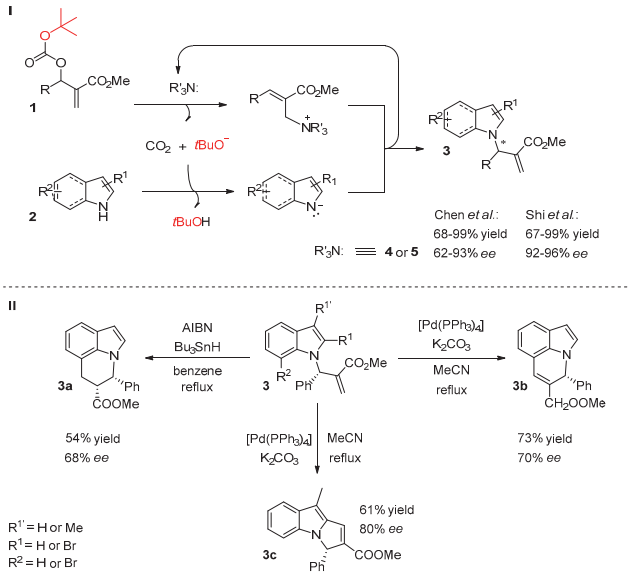
During the past two decades, organocatalysis has become a powerful methodology in enantioselective synthesis [14–17]. In the first part of this review, the direct methods of the stereoselective *N*-alkylation of indoles based on organocatalysis are discussed. Various electrophiles and different types of organocatalysts have been used to achieve targets with high enantiomeric purities (Scheme 3).



Scheme 3. Direct organocatalytic derivatization of indole.

2.1. *N*-Allylations with Morita-Baylis-Hillman Adducts

Chen and co-workers proposed applying Morita-Baylis-Hillman (MBH) *tert*-butoxy carbonates **1** as electrophiles in a reaction with indole derivatives **2** (Scheme 4, **I**) [18]. The activation of MBH adducts with a chiral tertiary amine generates in situ *tert*-butoxy anion which is responsible for the deprotonation of the indole at the *N*-position. The screening of the reaction revealed that the reaction could be smoothly catalyzed by cinchona alkaloid derived ether **4** (Figure 2) in mesitylene. The substrate scope was performed with either electron-rich or electron-deficient indoles, providing products with moderate to excellent enantiomeric excesses (62–93%). Moreover, the methyl pyrrole-2-carboxylate was examined as a nucleophile, providing the *N*-substituted product with a good yield (80%) and moderate *ee* (73%). The C2- and C7-brominated *N*-allylated indoles can be further converted into fused, cyclic indole systems (Scheme 4, **II**).



Scheme 4. The reaction of indole derivatives and Morita–Baylis–Hillman (MBH) carbonates.

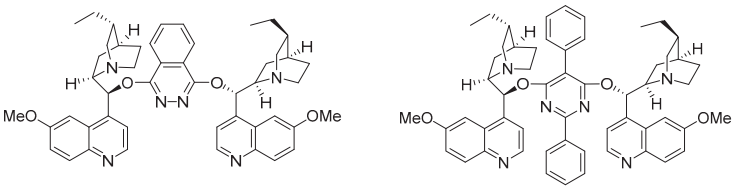
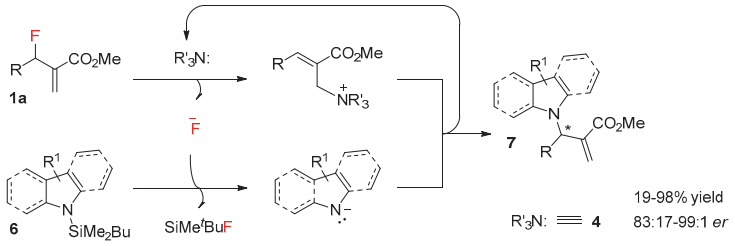


Figure 2. Chiral Lewis base catalysts.

Shi et al. reported an effective method in which C2-cyano-substituted pyrroles and indoles **2** were subjected to a reaction with O-Boc-protected MBH adducts **1** in the presence of a catalyst **5** [19]. They obtained corresponding *N*-allylated products **3** under optimal conditions with good to high yields (up to 99%) and moderate to high *ee* values (up to 96%). Compared with Chen's work, the introduction of a cyano group at the C2-position of pyrrole instead of a methyl carboxylate group had a positive impact on the reaction stereoselectivty (73% *ee* vs. 92% *ee*) and yield (80% vs. 92%). In the case of indoles, only 2-cyanoindole was examined. The *ee*s and yields of the reactions were slightly improved. It should be noted that Chen's group applied indoles with both electron-withdrawing and electron-donating groups, but Shi's method was limited to 2-cyanoindoles.

A new method for the activation of pyrroles, indoles and carbazoles was proposed by Vilotijević et al. in 2019 [20]. The silyl-protected indole derivatives **6** can act as latent nucleophiles in the presence of a chiral Lewis base catalyst **4**. Latent nucleophiles are compounds that are not nucleophilic, but can be converted into strong nucleophiles when activated. The modification of MBH carbonates by replacing the O-Boc group with a fluoro group affords a new type of fluorinated MBH adducts **1a**, which are the source of fluoride ions needed for the desilylation of the indole derivative. The authors performed a mechanistic study and their proposed mechanism is outlined in Scheme 5. The elimination of fluoride ions occurs during the activation of the MBH adduct with catalyst **4**. At the same time, fluoride ions deprotect *N*-silylindole derivatives. As a result, simultaneous activated pairs of electrophiles/nucleophiles occur and the enantioselective *N*-alkylation of an indole proceeds with excellent regioselectivity and moderate to high enantioselectivity (up to 98%) with a yield up to 98%.

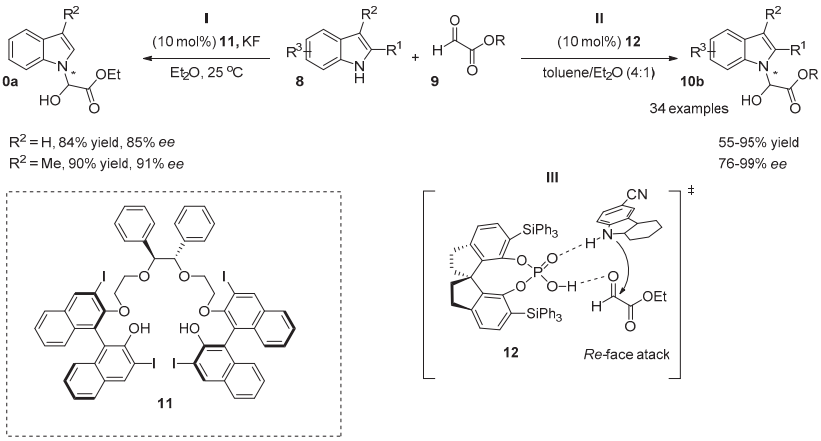


Scheme 5. The use of a latent nucleophile.

2.2. *N*-Selective Additions to α-Oxoaldehydes

The chiral *N*,*O*-aminal indole structural motif can be found in natural products and pharmaceutical compounds [4,5]. Recently, two organocatalytic approaches to the synthesis of *N*,*O*-aminals with indole skeletons were reported (Scheme 6) [4,21]. In both methods, ethyl glyoxylate derivatives **9** were used as electrophiles, but different types of organocatalysts were used. Activation with both a chiral Lewis base and a Lewis acid was exploited efficiently for the same reaction (Scheme 6). Based on the achiral method for the preparation of *N*,*O*-aminals of indole derivatives in the presence of a Brønsted base (DABCO), Qin elaborated an asymmetric version of the reaction [21]. The catalytic

system derived from BINOL-derived polyether **11** and potassium fluoride provides *N*,*O*-aminals with high *ee* (up to 91%) and with high yields (up to 90%) (Scheme 6, **I**). Only two examples of an asymmetric reaction were demonstrated. The second approach illustrates the application of a SPINOL-based chiral phosphoric acid **12** in the *N*-selective alkylation of indole derivatives **8** (Scheme 6, **II**) [4]. Differently substituted indole derivatives (substitution at both rings) were applied as nucleophiles, affording products with good to excellent enantiomeric excess (up to 99%) and with moderate to high yields (up to 96%). The exception was the product of a 7-fluorosubstituted indole obtained with a 55% yield and 76% *ee*. The authors concluded that the decrease in stereoselectivity and in the yield of the reaction can be explained by the steric hindrance of the substituent at the C7 position. The transition state of the reaction is outlined in Scheme 6, **III**. The ethyl glyoxalate and the indole are both activated by chiral phosphoric acid **12**. The attack on the aldehyde from the *Re*-face is favored, affording an (*R*)-isomer of the product. Remarkably, BINOL-derived chiral phosphoric acid was not as efficient as SPINOL-derived and provided the product with a low level of stereocontrol (*ee* 5–7%).



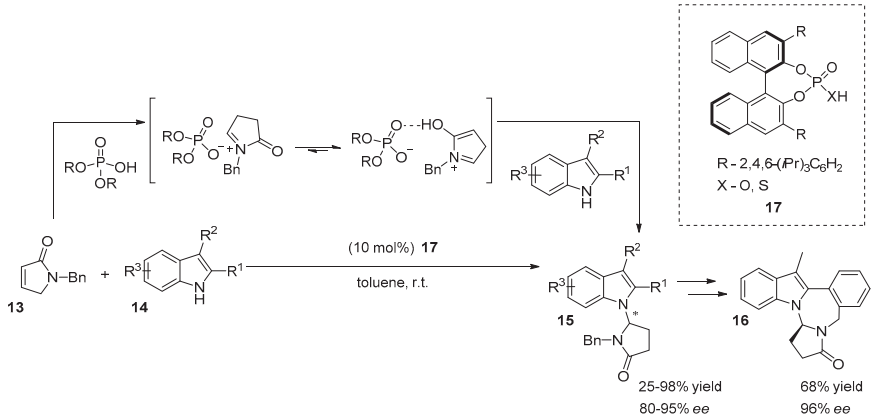
Scheme 6. Reactions of indoles with glyoxylate derivatives.

2.3. N-Selective Additions of Indoles to Imine/Iminium Activated Adducts

In situ, generating electrophiles such as imines or iminium ions can provide wide access for the construction of chiral indoles. They not only bear substituents at the C3 position, but they are also powerful tools for the synthesis of *N*-substituted indoles. The activation of electrophiles can be promoted by chiral Brønsted acids such as phosphoric acids. There are a large number of different BINOL- and SPINOL-derived chiral acids and their ability to act as bifunctional catalysts provides unique opportunities for the enantioselective functionalization of the C-N bond.

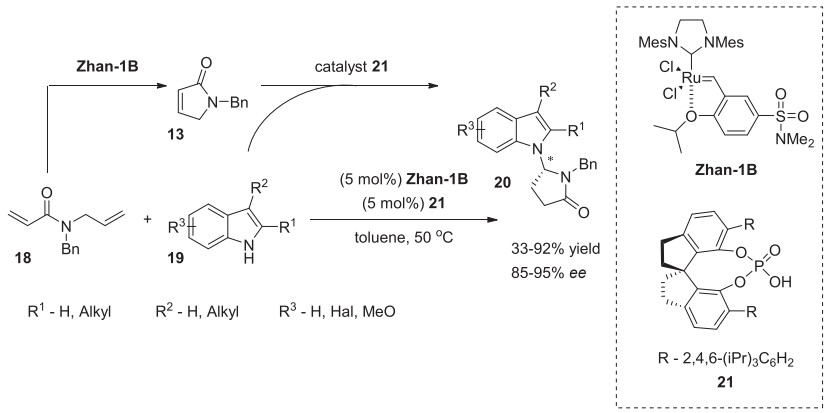
The first synthesis of chiral α-*N*-branched indoles **15** via their addition to the acyliminium ion catalyzed by chiral phosphoric acid **17** was proposed by Huang et al. (Scheme 7) [22]. Cyclic *N*-acyliminium ions are highly reactive electrophiles [23]. They are easily generated from α,β-unsaturated γ-lactams (such as compound **13**) by accepting an acidic proton from a chiral phosphoric acid, affording a chiral conjugate base/*N*-acyliminium ion pair. Huang proposed that the acidic N-H atom of the indole is activated by the conjugate base of chiral phosphoric acid through the hydrogen bond, favoring an attack of the nitrogen atom on the cyclic *N*-acyliminium ion. The authors conducted a series of labeling and FTIR experiments that explained the formation of the *N*-acyliminium ion and the indole alkylation step. The reaction was catalyzed by catalyst **17**, providing a high level of stereocontrol (*ee* up to 95%) and high yields of the reaction (up to 98%). The synthetic method afforded chiral indole derivatives **15** with different substituents in both ring systems. The product **15** (R^1 = Br, R^2 = Me, R^3 = H) was further converted into an *N*-fused polycyclic compound **16** in two additional

steps. Interestingly, Boc and phenyl *N*-protected α,β-unsaturated γ-lactams afforded only C3 alkylated products with low *ee* values.



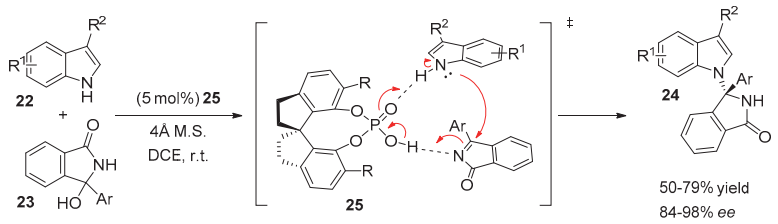
Scheme 7. *N*-Acyliminium activated *N*-alkylation of indoles.

You and co-workers later reported a modified route of Huang's enantioselective indole *N*-alkylation with *N*-acyliminium ions [24]. The new method is based on the cascade reaction, involving a ring-closing metathesis catalyzed by a Ru complex and chiral SPINOL-derived phosphoric acid-catalyzed **21** indole *N*-alkylation (Scheme 8). The starting *N*-allyl-*N*-benzylacrylamide **18** was first converted into α,β-unsaturated γ-lactam **13** by a Ru complex (**Zhan-1B**) followed by the selective *N*-alkylation of the indole in the presence of catalyst **21**. The authors compared their method with stepwise reactions and found that the sequential catalysis allowed for a more efficient synthesis.



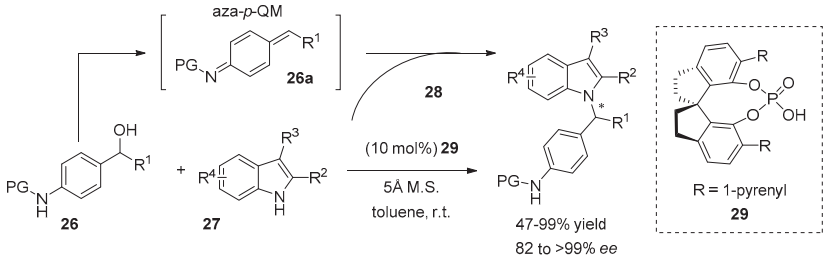
Scheme 8. Sequential ring-closing/*N*-alkylation of indoles.

Another example of the application of SPINOL-derived phosphoric acid in the *N*-alkylation of indoles was demonstrated by Zeng and Zhong [25]. An enantioselective *N*-addition of indoles to in situ generated cyclic *N*-acyl imines from hydroxy isoindolinones **23** was efficiently catalyzed by hindered bismesityl-substituted chiral phosphoric acid **25** (Scheme 9). The reaction proceeded smoothly with a broad range of indoles and isoindolinone alcohols affording chiral *N*-alkylated tetrasubstituted aminals **24** with moderate to good yields (up to 77%) and good to excellent enantioselectivities (up to 98%). The proposed transition state indicates the dual activation mode of the catalyst **25** (Scheme 9).



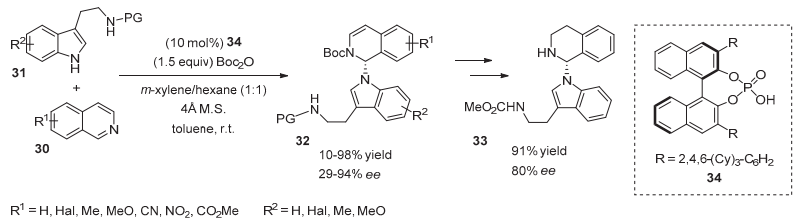
Scheme 9. Enantioselective addition of indoles to *N*-acyl imines.

A new class of in situ activated electrophiles for the enantioselective *N*-alkylation of indoles from the *N*-protected *p*-aminobenzylic alcohol **26** was reported by Sun [26]. These alcohols were easily converted to aza-*p*-quinone methides **26a** in the presence of the chiral phosphoric acid **29** and used as alkylating reagents in reactions with 2,3-disubstituted indoles **27** (Scheme 10). The protective group on the nitrogen atom of the electrophile drastically affects the stereoselectivity of the reaction. In the case of bulky aliphatic acyl groups, such as pivaloyl and 1-adamantanecarbonyl groups, excellent enantioselectivities were achieved (*ee* up to 95%). Other protective groups afforded products with moderate *ee* values. It is important to mention that C3 unsubstituted indoles gave an exclusive reaction at the C3 position with good *ee* (74%). The slight modification of the reaction conditions improved the enantioselectivity of the reaction and chiral C3 alkylated indoles were obtained with excellent yields (up to 99%) and high *ee*s (up to 94%). The control experiments proved that the reaction proceeds due to the generation of an aza-*p*-QM intermediate **26a** and, without a nucleophile, the dimerization of the aza-*p*-QM intermediate occurred. The authors proposed a transition state that demonstrates the bifunctional role of the chiral phosphoric acid in the activation of both an electrophile and a nucleophile.



Scheme 10. Enantioselective *N*-alkylation of indoles with *para*-aza-quinone methides.

Recently, an asymmetric *N*-alkylation of indole derivatives via a Reissert-type reaction catalyzed by a chiral phosphoric acid **34** was reported by You's group [27]. The authors expected the dearomatization of both reagents, but the reaction proceeded in another manner, providing the *N*-alkylated adduct **32** (Scheme 11). The method tolerates various protective groups on the amine of tryptamine **31**, affording products with good yields (72–98%) and moderate to good enantioselectivities (*ee* 64–82%). Substituents in the phenyl ring of the tryptamine **31** did not have a negative impact on the *ee* values (63–73%) or yield (78–89%) of the reaction. Various substituents on the isoquinoline core **30** were tested and their influence on the reaction was studied. Sterically hindered isoquinolines (7- or 8-substituted isoquinolines) afforded lower yields (10–40%) and *ee* values (29–50% *ee*). Substituents at other positions were tolerated, leading to *N*-alkylated products with good to excellent yields (80–98%) and enantioselectivities (80–94%). It is notable that the indole ring bearing a 3-methyl substituent was also tolerated, affording *N*-alkylated product with excellent yield (98%) and high *ee* (85%). The chiral *N*-alkylated product **32** (R^1 = R^2 = H) was easily modified by the reduction in 1,2-dihydroisoquinoline moiety and the deprotection of the Boc group, leading to free amine **33**.

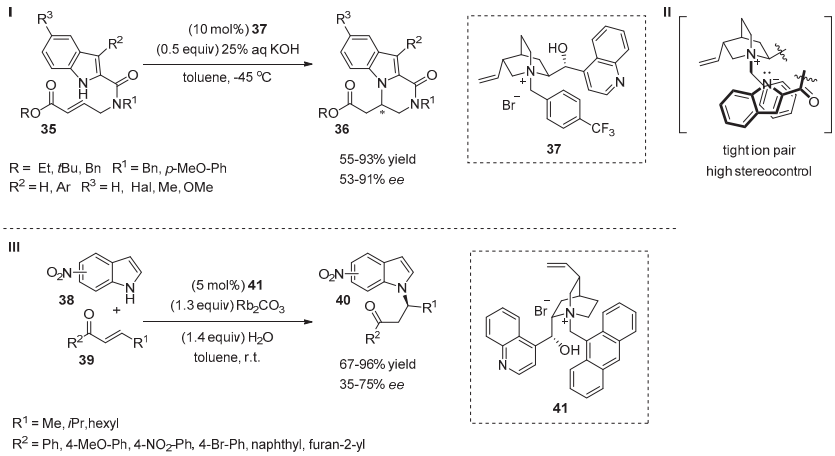


Scheme 11. Enantioselective *N*-alkylation of indoles via Reissert-type reaction.

2.4. Aza-Michael Additions

The application of efficient organocatalytic strategies for the synthesis of chiral α-*N*-branched indoles is limited by the low acidity of the N-H atom and low nucleophilicity of the nitrogen of the indole. Electron-withdrawing groups at C2 or C3 positions increase the acidity of the N-H atom of the indole [28], thus improving its reactivity. Another way to activate the nitrogen atom is the introduction of an electron-donating group at the C3 position, which increases the nucleophilicity of the indole. Sometimes, the functionalization at the C2 and C3 positions of the indole are used to prevent side reactions.

The enantioselective intramolecular ring-closing reaction of 2-substituted indoles **35** with increased acidity under phase transfer catalysis was reported by Bandini and Umani-Ronchi et al. (Scheme 12, **I**) [29,30]. The authors emphasized the importance of the tight ion pair that occurs between the cinchona-based salt of the quinuclidine ring and the nucleophilic indolate intermediate (Scheme 12, **II**). The stereocontrol of the reaction was increased by the introduction of electron-withdrawing substituents on the *para*-position of the benzyl group of the catalyst **37**. The substituents at C5 positions of the indole ring did not influence stereoselectivity as indole derivatives **35** with electron-withdrawing or electron-donating groups gave high yields (85–93%) and high *ee* values (82–89%), which could be increased further by recrystallization.

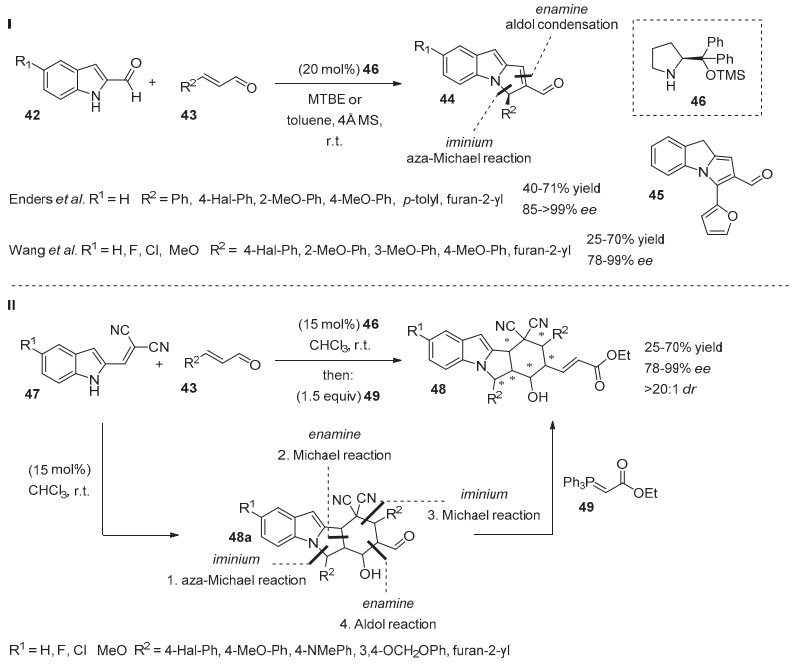


Scheme 12. Phase transfer-catalyzed *N*-alkylation of indoles.

The phase transfer-catalyzed asymmetric aza-Michael addition of nitroindoles **38** to α,β-unsaturated carbonyl compounds **39** was investigated by Kanger and co-workers (Scheme 12, **III**) [31]. The authors determined that the position of the nitro group on the indole core was crucial to control the enantioselectivity of the reaction. The reaction did not proceed with 2- and 7-substituted nitroindoles. The indoles bearing a nitro group at the C5, C6 or C3 positions were non-selective

substrates for the reaction as the enantioselectivity was too low (35–42% *ee*). The reaction between various *trans*-crotonophenone derivatives and 4-nitroindole afforded products with good to high yields (67–96%) and moderate to good enantioselectivities (59–75%) in the presence of a cinchona alkaloid-based phase transfer catalyst **41**. It is important to mention that there was essentially no correlation between the acidity of the indole and its reactivity in the aza-Michael reaction.

The introduction of an electron-withdrawing substituent at the C2-position of the indole ring not only increases the acidity of the N-H atom, but this substitution pattern also opens wide access to cascade reactions that provide chiral *N*-alkylated polycyclic indoles in a single step. Wang and Ender's groups separately reported a method where tricyclic chiral indole derivatives were obtained from indole-2-carbaldehyde **42** and various α,β-unsaturated aldehydes **43** in the presence of a Hayashi-Jørgensen catalyst **46** (Scheme 13, **I**) [32,33]. The cascade reaction is possible due to an iminium/enamine activation mode and consists of an aza-Michael reaction followed by aldol condensation. Despite differences in reaction conditions, both synthetic methods demonstrated moderate to good yields (40–71% and 57–81%) and good to excellent *ee* values of products (85 to >99% and 71–96%). In the case of 2-furyl enal, the isomeric achiral product **45** was formed.

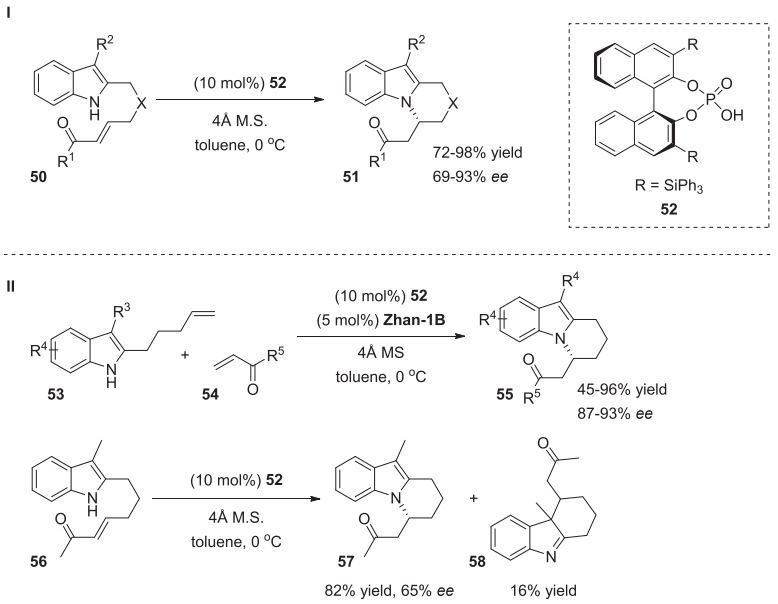


Scheme 13. Secondary amine catalyzed cascade reactions.

Enders et al. continued to investigate the reactions of 2-substituted indoles with unsaturated aldehydes and reported an asymmetric quadruple cascade reaction (Scheme 13, **II**) [34]. Indole-2-methylene malononitriles **47** derived from indole-2-carbaldehydes **42** were subjected to reactions with various α,β-unsaturated aldehydes **43** in the presence of the chiral secondary amine **46**, providing tetracyclic aldehydes **48a**. The domino reaction consists of a tandem aza-Michael-Michael-Michael-aldol reaction, which exploits the iminium-enamine-iminium-enamine activation approach. Because of the enolization during the purification of aldehydes **48a**, they were trapped with stabilized Wittig reagent **49**. The cascade reaction and olefination were easily completed in a one-pot manner with no impact on the reaction outcome. The reaction scope was performed with both electron rich and electron poor aromatic α,β-unsaturated aldehydes **43** and chiral products **48**

were obtained as single diastereoisomers (>20:1 *dr*) with moderate to good yields (25–70%) and good to excellent enantioselectivities (91–99%). A decrease in enantioselectivity and yield was detected in the case of the heteroaromatic furyl group (33% yield, 78% *ee*). Indoles with electron-withdrawing and electron-donating substituents at the C5 position tolerated the reaction without affecting yields or stereoselectivities.

An intramolecular reaction of appropriately C2 substituted indole **50** provided selectively *N*-alkylated tricyclic indole derivatives **51** via an aza-Michael reaction in the presence of a phosphoric acid catalyst **52** (Scheme 14, **I**) [35]. Under optimal conditions, the reaction scope was broadened with various substituted aromatic enones with electron-donating or electron-withdrawing groups. The authors demonstrated the tolerance of various functionalities such as carbonyl, hydroxyl groups and aromatic rings at the C3 side chain without any impact on the reaction yields (82–96%) or enantioselectivities (88–93%). However, the introduction of an electron-withdrawing group at the C2-position of the indole totally inhibited the reaction. Further investigations of the reaction were concentrated on the combination of mechanistically distinct organocatalysis and transition-metal catalysis (Scheme 14, **II**). The indolyl olefins **53** and enones **54** reacted smoothly in the presence of the chiral phosphoric acid **52** and ruthenium catalyst **Zhan-1B** affording the desired products with moderate to excellent yields (45–96%) with 87–93% *ee*s (Scheme 14, **II**). Notably, if indole **56** was applied as the substrate, both the *N*-alkylated product **57** and the C3-alkylation product **58** were obtained (Scheme 14, **II**).



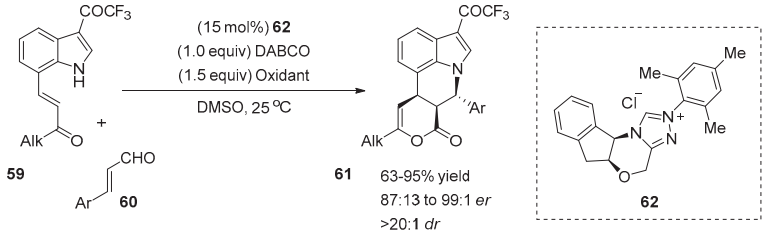
Scheme 14. Cyclization of electron rich 2-substituted indoles.

2.5. N-Heterocyclic Carbene-Mediated Cyclizations

In recent years, there has been growing interest in the field of *N*-heterocyclic carbene (NHC) catalysis. The functionalization of the indole core via various NHC-intermediates has been reported by several research groups [36–40]. There are only two articles dedicated to the *N*-functionalization of indoles [41,42]. Both synthetic methodologies were applied to 7-substituted indole derivatives as a starting material and obtained *N*-fused tricyclic structures were characteristic.

Biju and co-workers demonstrated an asymmetric NHC-catalyzed domino reaction for the synthesis of pyrroloquinolines (Scheme 15) [41]. The indole substrates **59** used in this reaction had a

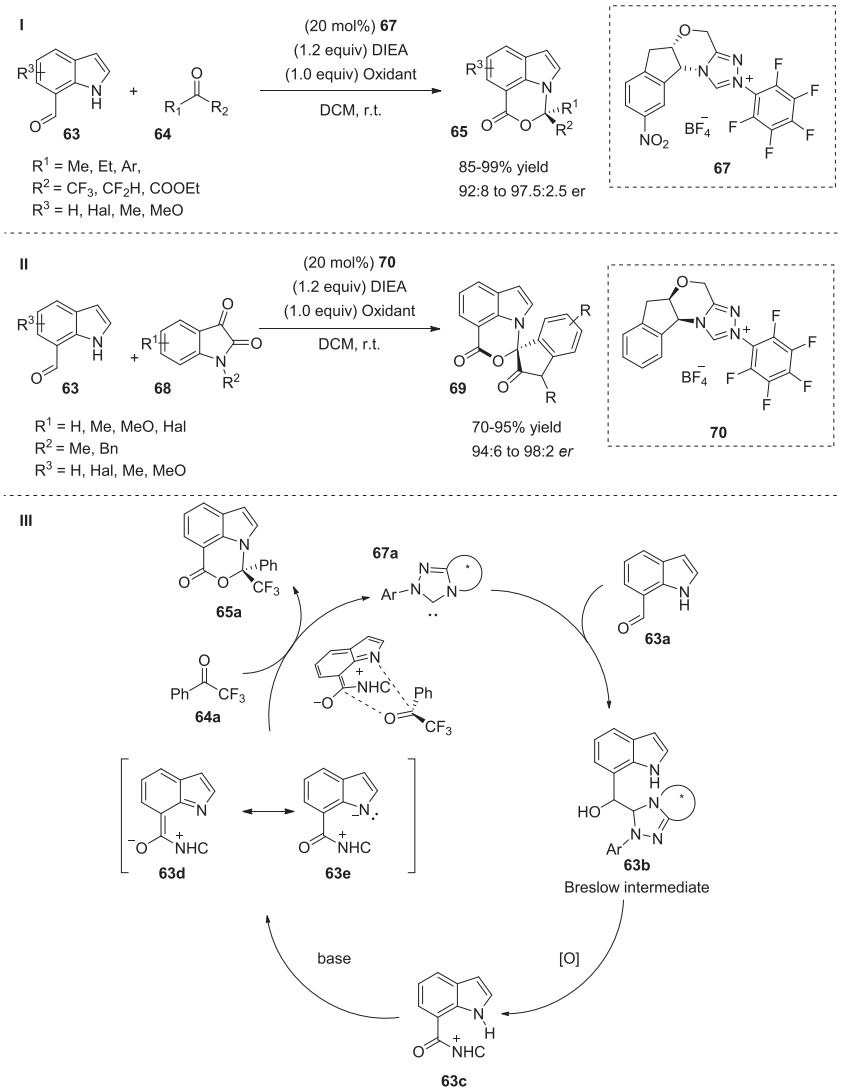
Michael acceptor moiety at the C7-position and a strong electron-withdrawing group at the C3-position to increase the acidity of the N-H atom of indoles. The cascade reaction was catalyzed by carbene generated from the chiral aminoindanol-derived triazolium salt **62** and proceeded smoothly with various substituted indoles **59** and cinnamaldehyde derivatives **60**. The substrate scope revealed that α,β-unsaturated aldehydes bearing electron-withdrawing and electron-donating substituents at the 4-, 3- and 2-positions of the β-aryl ring of enals had no impact on the reaction outcome, affording pyrroloquinoline derivatives with good to high yields (63–95%), good to excellent enantiomeric ratios (87:13 to 99:1) and excellent diastereoselectivities (>20:1). Additionally, heterocyclic enals and disubstitued β-aryl ring enals reacted smoothly with indole derivatives and products were obtained with good yields (67–82%) and high *er* values (90:10 to 97:3). Cyclic and acyclic alkyl groups at the Michael acceptor moiety of compound **59** could be used without affecting the reactivity/selectivity. In addition, the influence of solvents with different dielectric constants (DEC) on the reaction selectivity and yield was studied. The authors demonstrated that the aprotic solvents with higher dielectric constants afforded better *ee* and yield. For instance, a poor yield and *ee* value were obtained in toluene (DEC: 2.38), moderate in THF (DEC: 7.58) and high in DMF (36.7). Therefore, the solvent with higher polarity not only provided good solubility of reactants but it could stabilize zwitterionic intermediates.



Scheme 15. *N*-heterocyclic carbene (NHC)-catalyzed cascade reaction of 7-substituted indoles.

Chi et al. reported the enantioselective functionalization of an indole carbaldehyde N-H group through NHC catalysis (Scheme 16) [42]. The indole derivative **63** was activated by NHC via a carbaldehyde moiety at the C7-position of the indole. The reaction of indole-7-carbaldehyde adducts with derivatives of various carbonyl compounds **64** demonstrated high *er* values and yields in the presence of a carbene catalyst generated from a triazolium salt **67**. The differences in structure and electronic properties of the starting compounds did not affect the reaction selectivity or yield. Both trifluoroacetophenone derivatives and aliphatic trifluoromethyl ketones tolerated the reaction well affording the desired products with high yields and *er* values (89–98% yield, 94:6 to 96:4). Substitutions on the indole 5- and 6-positions gave the desired products with excellent yields (90–99%) and optical purities (92:8 to 97.5:2.5), regardless of the electronic properties of the substituents. The reaction scope was broadened with the application of isatins **68** as electrophiles (Scheme 16, **II**). In the case of the isatin derivatives, another precatalyst **70** was used to maintain high yields (up to 95%) and *er* values (up to 98:2).

The authors proposed the mechanism of the NHC-catalyzed reaction, which is outlined in Scheme 16, **III**. The nucleophilic attack of NHC **67a** on aldehyde **63a** forms a Breslow intermediate **63b**, which undergoes an oxidation reaction to generate an acylazolium intermediate **63c**, followed by its deprotonation, providing the intermediate **63d**. Finally, a formal [4 + 2] annulation reaction between intermediate **63d** and trifluoroacetophenone **64a** affords the desired product **65a** and regenerates the NHC catalyst.



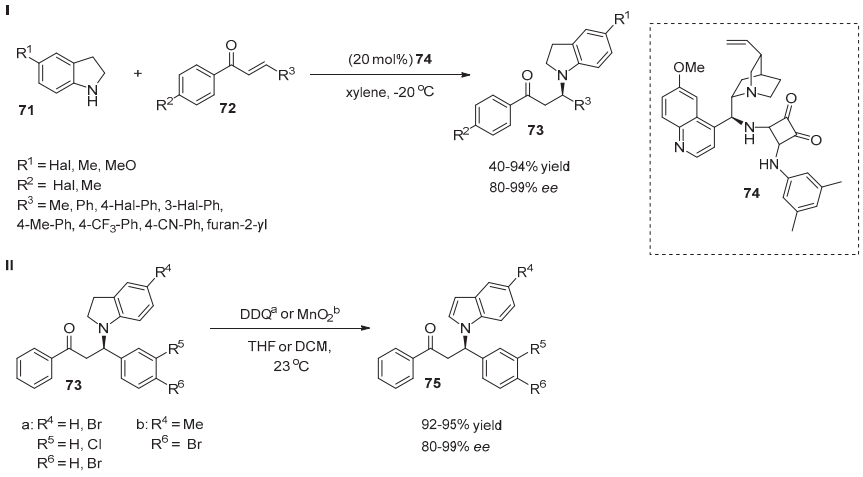
Scheme 16. NHC mediated *N*-alkylation of indoles.

3. Organocatalytic Indirect Methods

There are several examples of organocatalytic methods in which the synthesis of chiral *N*-alkylated indoles was performed indirectly. Three routes for the preparation of *N*-functionalized indoles are proposed. The first two methods are based on the enantioselective *N*-alkylation of indoline or isatin and further redox transformation of *N*-alkylated intermediates into chiral *N*-functionalized indoles. In the last method, 4,7-dihydroindole was used as the starting material for the C2 Friedel-Crafts alkylation followed the oxidative cyclization, affording *N*-alkylated indole.

The enantioselective aza-Michael reaction between indoline derivatives **71** and α,β-unsaturated ketones **72** was reported by Ghosh et al. (Scheme 17, **I**) [43]. A set of *N*-alkylated indoline adducts **73** were further oxidized to corresponding *N*-functionalized indole derivatives **75** (Scheme 17, **II**). The *N*-alkylation of indolines was investigated and various thiourea and squaramide based bifunctional

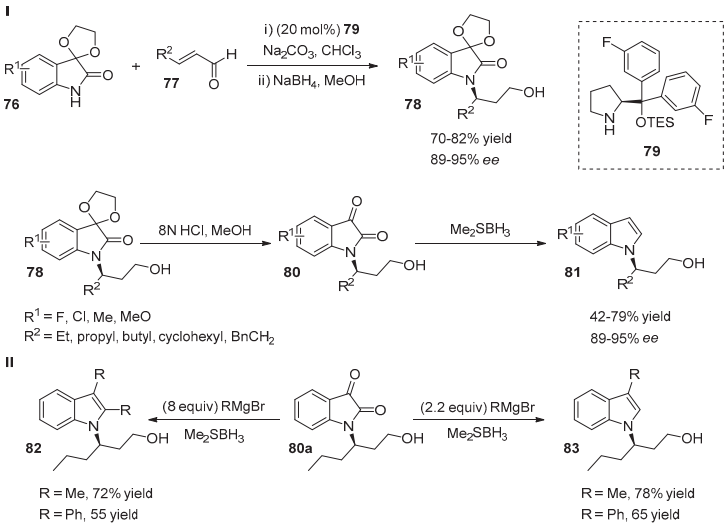
organocatalysts were tested. The best results were obtained with quinine-derived catalyst **74** in xylene at −20 °C. The influence of substituents in the aromatic rings of α,β-unsaturated ketones **72** was also studied. The authors demonstrated that in the case of electron-withdrawing substituents in the phenyl ring (R^3), both the enantioselectivity and yield increased (83–86% yield, 90-96% *ee*). At the same time, the introduction of an electron-donating group (R^3 = 4-Me-Ph) did not affect the selectivity or yield (55% yield, 86% *ee*). The incorporation of a cyano group on the phenyl ring (R^3) afforded a product with a low yield (40%) and high *ee* (90%). Notably, the heterocyclic furan-2-yl and methyl substituents tolerated the reaction well, providing good yields and stereoselectivities (55–57% yield, 80–84% *ee*). Indolines with electron-donating substituents at the C5 position afforded products with high yields with high levels of stereocontrol (93–94% yield, 95–99% *ee*). Electron-withdrawing groups at the C5 position of the indoline decreased the reaction yield and *ee* value (53–54% yield, 80% *ee*). The oxidation of chiral *N*-functionalized indolines **73** to the corresponding *N*-substituted indoles **75** with DDQ (1.05 equivalent) in THF or MnO_2 (10 equivalent) in dichloromethane led to products without any loss in enantioselectivity and with high yields (Scheme 17, **II**).



Scheme 17. Synthesis of *N*-functionalized indoles via alkylation/oxidation of indolines.

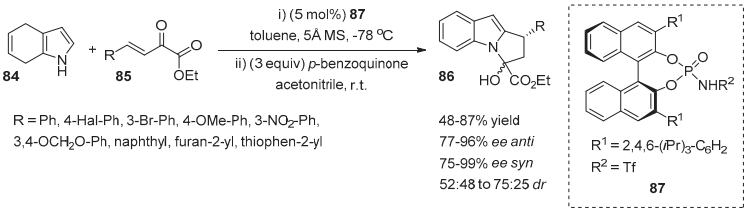
An interesting route for the preparation of chiral *N*-functionalized indoles **81** from *N*-alkylated isatin derivatives **80** was proposed by Lu and co-workers (Scheme 18, **I**) [44]. The method is based on the enantioselective conjugated addition of protected isatin derivatives **76** to α,β-unsaturated enals **77** via the iminium activation of aldehydes by a prolinol-derived catalyst **79**. A wide range of various aliphatic, aromatic linear and branched enals **77** tolerated the reaction, providing products with good yields (70–82%) and high enantioselectivities (89–95%). Corresponding *N*-functionalized indoles **81** were obtained after deprotection and reduction with borane.

The unprotected *N*-alkylated isatins **80a** were further transformed into C2/C3-substituted *N*-functionalized indoles **82** or **83** (Scheme 18, **II**).



Scheme 18. Isatin based synthetic route for the preparation of α-*N*-branched indoles.

The application of electron-deficient 4,7-dihydroindole **84** for the construction of *N*-functionalized indoles **86** was investigated by You et al. (Scheme 19) [45]. Chiral *N*-functionalized indoles were obtained in a one-pot synthesis. First, the Friedel-Crafts C2-alkylation between the 4,7-dihydroindole **84** and β,γ-unsaturated α-keto ester **85** was catalyzed by chiral *N*-triflyl phosphoramide **87** at −78 °C in toluene. The authors determined the importance of 4Å molecular sieves in the reaction mixture. Moreover, the stereoselectivty of the reaction was improved when the ester **85** was added by syringe pump to the reaction mixture over 15 min.

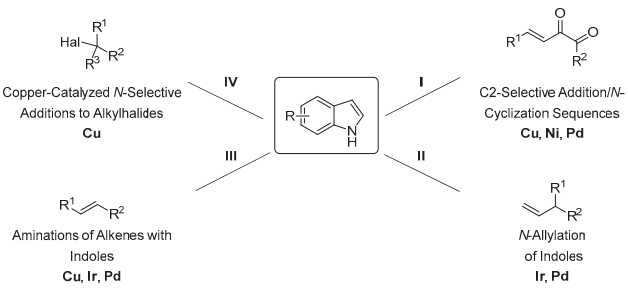


Scheme 19. C2-alkylation of 4,7-dihydroindoles, followed by oxidative intramolecular cyclization.

The simple work-up with *p*-benzoquinone after the completion of the first step afforded the oxidative intramolecular cyclization of 2-substituted chiral intermediates. Various *N*-functionalized products **86** were obtained with moderate to good yields (48–87%), good to excellent enantioselectivities (75–99%) and poor to moderate diastereoselectivities (52:48 to 75:25).

4. Direct Organometallic Methods

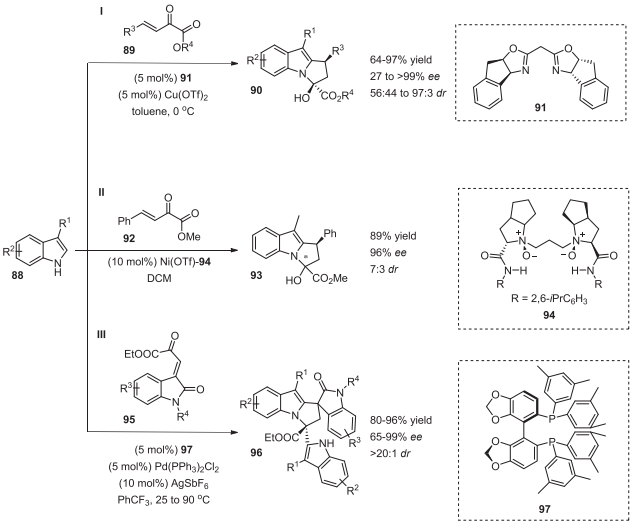
Transition metal catalysis is often applied in asymmetric synthesis as a highly efficient method for the construction of chiral compounds [46]. Small loadings of transition metal complexes and the excellent stereocontrol of the reaction make organometallic methods attractive for the stereoselective *N*-functionalization of indoles. In this part of the review, direct methods of the stereoselective *N*-alkylation of indoles based on transition metal catalysis are discussed. Various alkylating agents and different types of transition metal complexes were applied to gain a high level of stereocontrol (Scheme 20).



Scheme 20. Direct transition-metal based stereoselective derivatization of indole.

4.1. C2-Selective Addition/N-Cyclization Sequences

Chen and Xiao applied 3-substituted indoles **88** as N1/C2 dinucleophiles in enantioselective reactions with various β,γ-unsaturated α-ketoesters **89** (Scheme 21, **I**) [47]. A highly enantioselective cascade reaction consisting of sequential C2 Friedel-Crafts alkylation followed by *N*-hemiacetalization, providing tricyclic chiral *N*-functionalized indoles **90**, was described. The domino reaction was smoothly catalyzed by copper(II)triflate in the presence of chiral bis(oxazoline) ligand **91** in toluene at 0 °C. The investigation of the substrate scope revealed that the cascade reaction tolerated various esters well, electron-withdrawing and electron-donating groups in the γ-aryl ring of ester, heteroaromatic and vinyl-substituents at the γ-position. γ-Alkyl-substituted β,γ-unsaturated α-ketoesters also reacted smoothly, but in the case of the straight-chain aliphatic substrate (R^3 = propyl, R^4 = Et) a decrease in the stereoselectivity of the cascade reaction was detected (67% yield, 27% *ee*, 67:33 *dr*). Various substituents with different electron and steric properties at the indole core did not affect either the reaction yield or the stereoselectivity of the reaction. The only exception was the reaction with 3-phenylindole, where slight decreases in *ee* and *dr* were observed (80% *ee*, 86:14 *dr*).



Scheme 21. C2-alkylation of indoles followed by intramolecular *N*-cyclization.

Feng et al. investigated the enantioselective intermolecular Friedel-Crafts alkylation reaction at the C2-position of *N*-methylated indoles with β,γ-unsaturated α-ketoesters [48]. The cascade reaction of the C2-alkylation/*N*-hemiacetalization of skatole (3-methyl indole) was catalyzed by a chiral *N*,*N*′-dioxide **94** Ni(II) complex affording the corresponding product **93** with high yield (89%), excellent

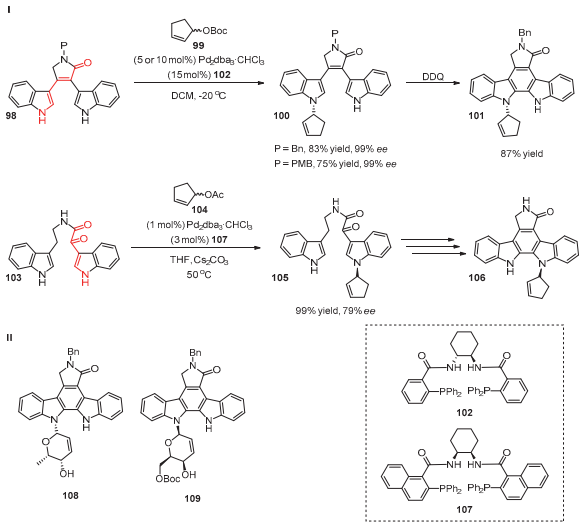
ee (96%) and moderate *dr* (7:3) values (Scheme 21, **II**). The results were slightly worse than with the chiral Box–copper(II)-catalyzed method discussed above (95 yield, >99% *ee*, 95:5 *dr*).

An efficient stereoselective triple cascade reaction of 3-alkylindoles with oxindolyl β,γ-unsaturated α-ketoesters **95** in the presence of a chiral diphosphine **97** palladium(II) catalyst was reported by the Wang group (Scheme 21, **III**) [49]. The domino reaction consists of asymmetric Friedel-Crafts/*N*-cyclization/Friedel-Crafts sequential alkylation and provides a wide range of spiro-polycyclic N1/C2 functionalized enantioenriched indoles **96**. The various substituents at the phenyl ring and *N*-atom of oxindolyl β,γ-unsaturated α-ketoesters **95** were well tolerated, affording the spiro-polycyclic products **96** with good to excellent yields (80–96%), high to excellent *ee* values (86–99%) and excellent diastereoselectivities (>20:1). The indole scope demonstrated some limitations of the reaction: electron-withdrawing or electron-donating substituents at the C5 or C6 positions provided products with high yields (87–94), enantioselectivities and diastereoselectivities (91–98% *ee*, >20:1 *dr*) but in the case of the 4-bromo substituted indole a decline in enantioselectivity (65% *ee*) was detected. Sterically hindered indoles at the C3 position were not the best starting compounds for this cascade reaction. For instance, an *n*-hexyl substituent negatively affected the *ee* value of the reaction (81% *ee*) and the reaction with a bulkier *i*-Pr substituted indole afforded a product with a low yield (<30%).

Compared with Xiao's highly enantioselective method based on chiral Box-copper(II) catalysis, Wang's route, based on a chiral diphosphine **97** palladium(II) catalyst, has its advantages in the use of isatin-derived electrophiles **95**, but is not particularly effective for simple γ-aryl substrates **89**.

4.2. N-Allylation of Indoles

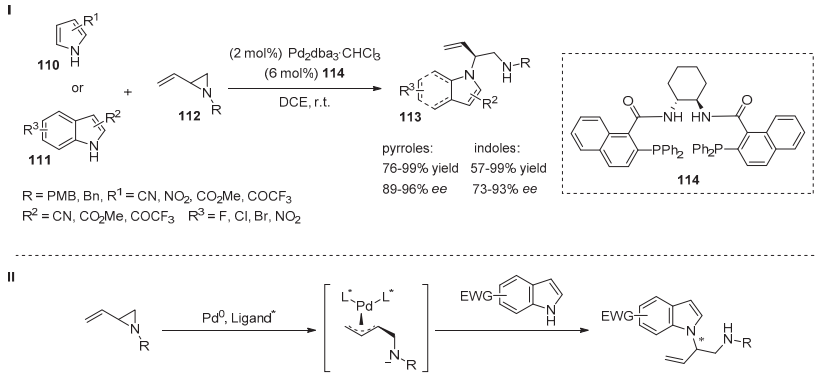
The enantioselective version of a Tsuji-Trost reaction was applied for the synthesis of chiral indolocarbazole derivatives (Scheme 22, **I**) [50]. The reaction of protected bis(indole) **98** with cyclopentyl carbonate **99** in the presence of a chiral ligand **102** and palladium catalyst proceeded smoothly, providing products **100** with excellent *ee* values (99%) and good yields (83% and 75%, depending on the protective group used). The authors conducted a series of NMR experiments and conformational analyses and found that the preferred site of the alkylation was the nitrogen atom of the indole moiety, which was linearly conjugated to the carbonyl function of lactam. Catalytic allylations of (bis)indoles with sugar-derived electrophiles were performed and cyclic products **108** and **109** were successfully obtained (Scheme 22, **II**).



Scheme 22. Pd-catalyzed *N*-allylation of (bis)indoles.

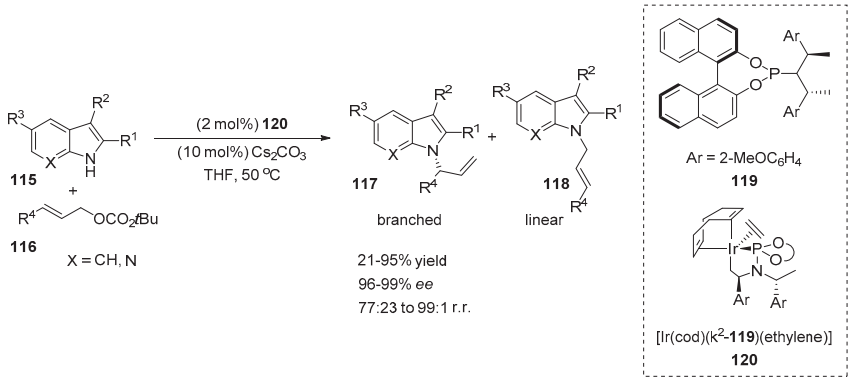
The preferred site of the allylation of bis(indole) depends on the acidity of the N-H atom of the indole derivative. When the bis(indole)-bearing conjugated dione moiety **103** at the C3 position was subjected to a reaction, a cyclopentenyl acetate **104** product **105** was formed. The authors also proposed a strategy for the construction of the chiral indolocarbazole **106** from the (bis)indole adduct **105**.

Later, Trost et al. demonstrated a general method for the enantioselective *N*-allylation of electron deficient pyrroles **110** and indoles **111** with vinyl aziridines **112** as electrophiles (Scheme 23, **I**) [51]. The Pd-catalyzed asymmetric allylic alkylation provided a wide range of the heterocycle-containing chiral 1,2-diamines **113**. The desired branched *N*-alkylated products were obtained with a similar catalytic system that was previously applied for allylation of bis(indole) adducts **98** (Scheme 22, **I**). The alkylation of indoles and pyrroles was catalyzed by a palladium complex in the presence of a chiral ligand **114** in dichloroethane at room temperature. The authors determined the positive impact of a naphthyl moiety of the chiral ligand on the enantioselectivity of the reaction. The scope of electron-deficient indoles demonstrated exclusively *N*-alkylation with moderate to high enantioselectivity (73–93%) and moderate to high yields (57–99%). Weak electron-withdrawing groups (such as bromo or chloro) negatively affected the reaction yield and *ee*. 2-Phenylindole afforded only trace quantities of the desired product. It should be noted that the amide anion of the vinyl aziridine in the π-allyl Pd intermediate was sufficiently basic to deprotonate the indole N-H and facilitate the reaction in most of the cases (Scheme 23, **II**).



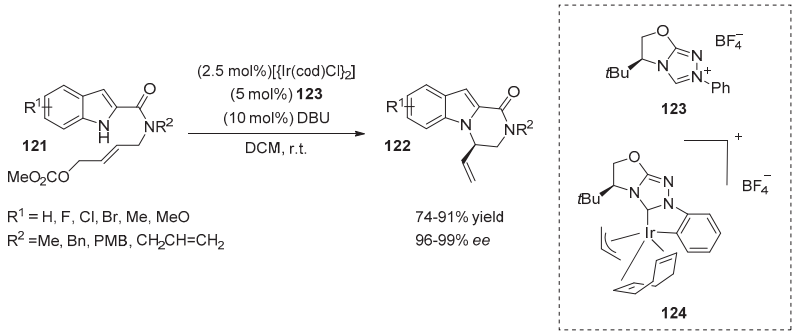
Scheme 23. Pd-catalyzed *N*-allylation of electron-deficient pyrroles and indoles.

A highly enantioselective iridium-catalyzed *N*-allylation of electron-deficient or C3-substituted indoles was reported by Hartwig et al. (Scheme 24) [52]. The authors used a chiral phosphoramidite ligand **119**, which was previously studied in *N*-allylation reactions with more acidic and nucleophilic benzimidazoles, imidazoles and purines. The initial results showed that the reaction proceeded in the presence of metallacycle **120** and cesium carbonate, affording an exclusively *N*-substituted product **117** with excellent branched-to-linear selectivity (**117**/**118** = 97:3). The reaction scope of the ethyl indole-2-carboxylate **115** with various allylic carbonates **116** revealed that allylation proceeded smoothly at the *N*-position, providing corresponding products **117** with moderate to excellent regioselectivities (77:23 to 99:1), excellent enantioselectivities (96–99%) and moderate to high yields (54–95%). Indoles bearing various substituents at the C2, C3 and C5 positions were also tested with *tert*-butyl cinnamyl carbonate, providing excellent branched-to-linear selectivities (94:6 to 99:1), enantioselectivities (96–99%) and yields (21–95%). It should be noted that the parent indoles, 2-methylindole and 2-phenylindole, were allylated selectively at the C3 position. At the same time, 7-azaindole successfully underwent *N*-allylation in a high *N* to C3 ratio (9:1) and branched-to-linear selectivity (91:9). The chiral *N*-substituted 7-azaindole product was isolated with a 79% yield and 99% *ee*.



Scheme 24. Ir-catalyzed *N*-allylation of indoles.

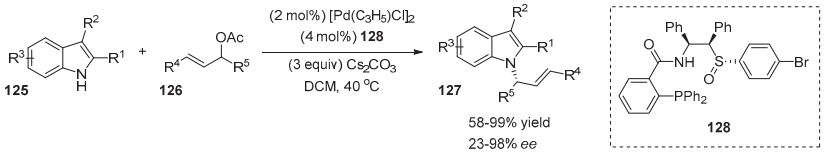
An efficient route for the synthesis of chiral indolopiperazinones was proposed by You and coworkers (Scheme 25) [53]. The intramolecular allylic amination of indole derivatives **121** was catalyzed by an iridium(I) NHC complex generated from the salt **123** and $[Ir(cod)Cl]_2$ in the presence of DBU in dichloromethane at room temperature. The model reaction provided *N*-selective products with high yields (82%) and excellent *ee* values (99%). The amount of Ir complex could be reduced to 1.25 mol% without affecting the reaction outcome (80% yield, 96% ee). Indole derivatives containing electron-donating and electron-withdrawing groups at the C5 or C6 positions were examined in allylation reactions, affording the desired products **122** with good yields (77–91%) and excellent enantioselectivities (97–99% *ee*). Substrates with various substituents R^2 (Bn, Me, allyl and PMB) on the amide nitrogen atom were well tolerated (77–89% yields and 96–99% *ee*, respectively). The authors also separately synthesized an Ir complex **124** and demonstrated its catalytic efficiency in asymmetric intramolecular cyclization (93% yield, 99% *ee*). These results were comparable to the results obtained with an in situ formed catalyst (82% yield, 99% *ee*).



Scheme 25. Ir-catalyzed synthesis of chiral indolo- and pyrrolopiperazinones.

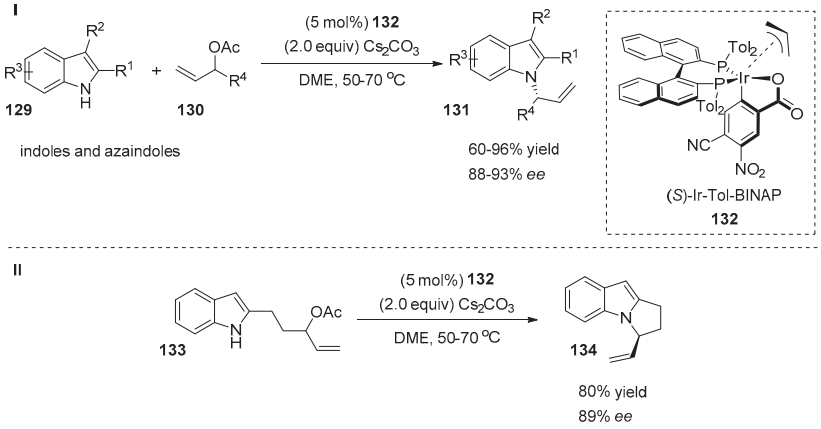
Xiao et al. reported a highly stereoselective Pd-catalyzed *N*-functionalization of indoles in the presence of chiral sulfoxide-phosphines (Scheme 26) [54]. The reaction of methyl indole-2-carboxylate with racemic (*E*)-1,3-diphenylallyl acetate was efficient and stereoselective in the presence of a catalytic system derived from $[Pd(C_3H_5)Cl]_2$, sulfoxide-phosphine ligand **128** and cesium carbonate in dichloromethane at 40 °C (99% yield, 97% *ee*). The scope of the reaction was performed with various substituted indoles **125** and allyl acetates **126**. Both C2- and C3-substituted indoles tolerated the reaction, demonstrating good to excellent enantioselectivities (75–97%) and moderate to high yields (58–95%) of the corresponding *N*-alkylated indoles **127**. Interestingly, 2-vinyl indole afforded an

N/C-dialkylated product as a single diastereomer with good yields (74%) and high enantioselectivity (93%). At the same time, 2-vinyl 7-chloroindole gave an exclusively C3-alkylated product. The scope of allyl acetates revealed that acetates containing phenyl rings afforded products with high yields (89–95%) and excellent *ee* values (94–96%). The reaction with a sterically less hindered 1-methyl-3-phenylallyl acetate was regioselective and had a high yield (98%), but a decrease in enantioselectivity was detected (65%). The cyclic acetate afforded the desired product with a low *ee* value (23%).



Scheme 26. Pd-catalyzed *N*-functionalization of indoles.

Recently, Krische and co-workers demonstrated an efficient asymmetric intermolecular Tsuji–Trost-type indole *N*-allylation, where complete *N*-regioselectivity and regioselectivity towards branched products were achieved (Scheme 27, **I**) [6]. The reaction was smoothly catalyzed by cyclometallated *p*-allyliridium *C*,*O*-benzoates modified with (S)-tol-BINAP **132** under basic conditions. A wide range of various substituted indoles **129** reacted with high levels of enantiomeric enrichment (88–93%), affording products **131** with moderate to excellent yields (60–96%). The parent indole was successfully alkylated with diverse α-substituted allyl acetates **130** containing alkyl groups, phenyl, benzyl ether and methyl sulfide moieties (65–79% yield, 91–93% *ee*). Furthermore, α-cycloalkyl substituted allyl acetates **130** tolerated the reaction well, affording *N*-functionalized indoles with good yields (60–76%) and high *ee* values (90–92%). The authors also demonstrated the intramolecular cyclization of the racemic indole adduct **133** under optimized conditions (Scheme 27, **II**). The desired chiral tricyclic *N*-allylated indole **134** was isolated with high yields and high enantioselectivity (80% yield, 89% *ee*).

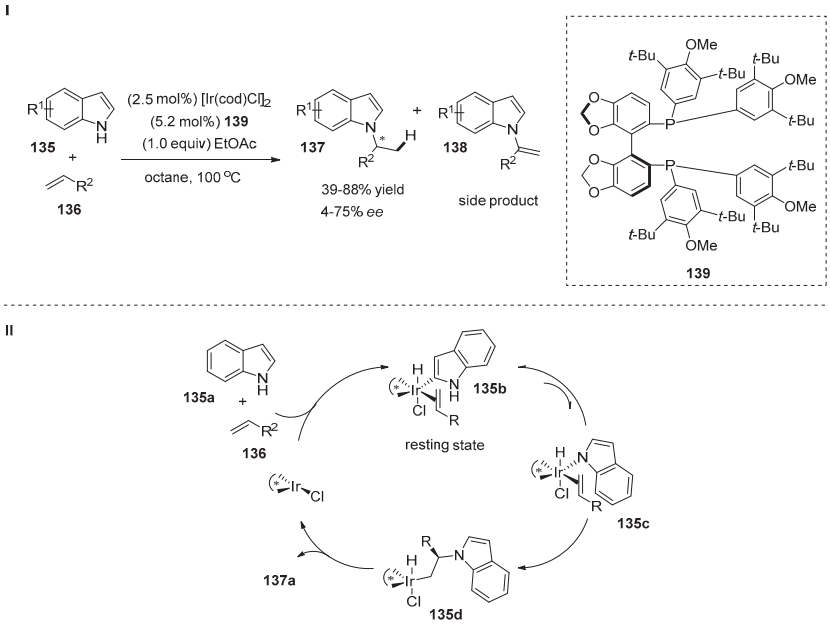


Scheme 27. Highly selective Ir-catalyzed allylation of indoles.

4.3. Aminations of Alkenes with Indoles

An iridium-catalyzed highly selective intermolecular N-H addition of indoles **135** to inactivated terminal olefins **136** was investigated by Hartwig's group [55]. The reaction proceeded according to Markovnikov's selectivity in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and a chiral bulky DTMB-SEGPHOS ligand **139** (Scheme 28, **I**). The authors found that the addition of ethyl acetate to the

reaction mixture increased the rate and yield of the reaction. Various substituted indoles and α-olefins substrates were examined in an enantioselective hydroamination reaction. The study of the scope of the indoles with 1-octene revealed that C3-, C5- and C6-substituted indoles tolerated the reaction successfully affording products with moderate to good enantioselectivities (45–75% *ee*) and yields (58–88%). There were no reactions in the case of 2- or 7-substituted indoles. The electron density of the indole core did not noticeably affect the reaction outcome. The scope of α-olefins demonstrated the influence of the β-substituent on the reaction rate, yield and enantioselectivity (39–70%, 4–67% *ee*, respectively). For instance, yields of products derived from bulky substituted olefins were lower than with 1-octene based products. Moreover, significant amounts of vinylindoles **138** as side products were determined (20–30%). In some cases, the reaction conditions were modified in order to get better results. A drastic decline in *ee* value (4–5%) was detected when *tert*-butylpropene was used as a starting compound.

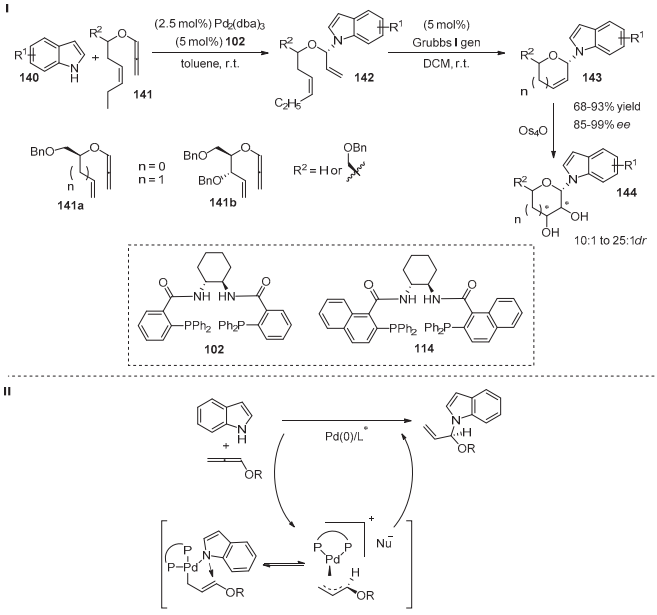


Scheme 28. Ir-catalyzed hydroamination of alkenes with indoles.

According to mechanistic and computational studies, the authors proposed the mechanism of the reaction that is outlined in Scheme 28, **II**. The olefin insertion into the Ir−N bond of an *N*-indolyl complex **135c** is faster than the insertion of olefin into the Ir−C bond of the isomeric C-2-indolyl complex **135b** (resting state). This feature determines the *N*-selectivity of the addition of olefin. The formation of vinylindole as a side product and the racemization of the product were also explained and discussed based on mechanistic studies.

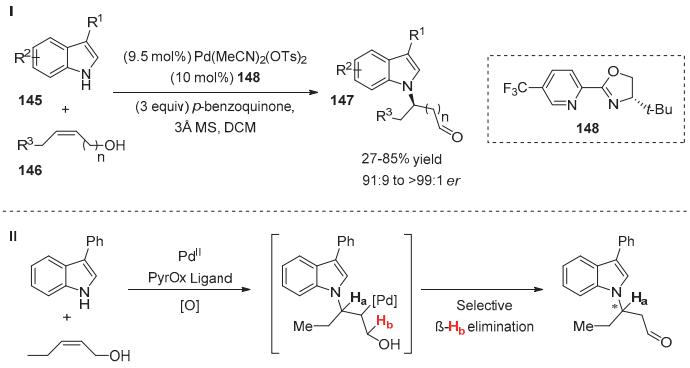
Chiral *N*,*O*-aminals **143** were obtained by the stepwise metal-catalyzed synthesis from alkoxyallenes **141** and indoles **140** (Scheme 29, **I**) [5]. The addition of indole **140** to allene proceeded exclusively at the *N*-position affording unsaturated adducts **142**. The obtained *N*,*O*-aminals **142** were subjected to a ring-closing metathesis reaction catalyzed by Grubbs 1st generation catalyst. The cyclic products **143** were isolated with a nearly quantitative yield. The authors determined the critical impact of the chiral ligand **102** on the Pd-catalyzed reaction. In the case of ligand **114** the conversion of the reaction nearly stopped. The scope of the reaction demonstrated that indoles with electron-donating or electron-withdrawing groups tolerated the reaction well, providing products with high yields

(87–98%) and *ee* values (85–93%). It is important to mention that the ester group at the C7 position of the indole decreased the rate of the reaction but the product was still isolated with good yields and excellent enantiomeric excess (70%, >99%, respectively). Indoles bearing substituents at C2-position afforded chiral products with good yields (74–93%) and excellent *ee*s (95–98%). The obtained products were successfully converted into various pyranosylated and furanosylated glycosides **144** through stereoselective dihydroxylation by osmium tetraoxide. According to their DFT calculations, the authors proposed the mechanism of the Pd-catalyzed reaction that is outlined in Scheme 29, **II**.



Scheme 29. Pd-catalyzed synthesis of chiral *N*,*O*-aminals.

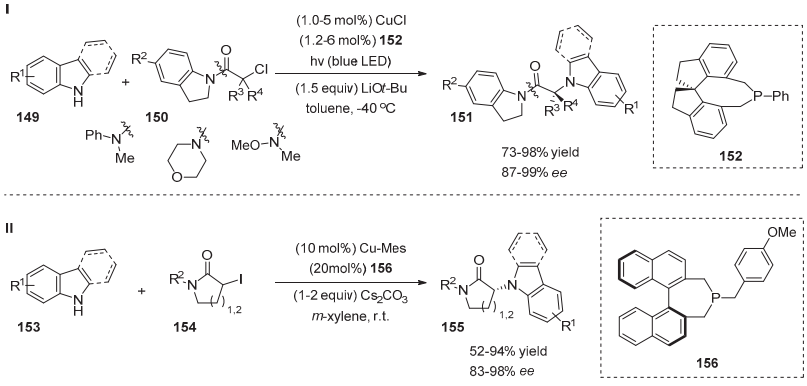
The enantioselective *N*-alkylation of indoles via an intermolecular aza-Wacker-type reaction was reported by Sigman et al. (Scheme 30, **I**) [56]. The formation of the desired product **147** was possible only if selective β-H_b elimination of the unsaturated compound was guaranteed (Scheme 30, **II**). Otherwise, the classic enamine product was formed. The Pd-catalyzed reaction proceeded between 3-substituted indoles **145** and 1,2-disubstituted alkene **146** in the aprotic solvent (dichloromethane) in the presence of a chiral ligand **148**, base (DTBMP) and oxidant (*p*-benzoquinone). It is important that C2 products were not detected; the alkylation proceeded exclusively at the *N*-position. The reaction scope was performed with a wide range of substituted alkenols, demonstrating low to good yields (27–78%) and good to high *er* values (91:1 to 98:2). An excellent functional group tolerance was achieved and highly reactive tosyl- or halide-containing alkenols were compatible with the reaction. The indole scope revealed that the electronic nature of 3-phenylindole did not significantly affect the reaction outcome (69–82% yields, 95:5 to 96:4 *er*). The authors conducted a series of deuterium-labeled experiments that proved a syn-aminopalladation pathway for this reaction.



Scheme 30. *N*-alkylation of indoles via an aza-Wacker-type reaction.

4.4. Copper-Catalyzed N-Selective Additions of Indoles to Alkylhalides

In recent years, stereoselective visible-light photocatalysis has received considerable attention from the synthetic community due to the unique activation mode of the substrates [57,58]. The photoinduced Cu-catalyzed enantioconvergent *N*-selective cross-coupling of 3-substituted indoles and carbazoles with racemic tertiary alkyl halides was described by Fu et al. (Scheme 31, **I**) [59]. The strategy of the reaction is based on the activation of an electrophile via the formation of the stable tertiary radical that is involved in the enantioselective process. A copper salt serves as the photocatalyst and, together with the chiral ligand **152**, is responsible for the enantioselective bond-forming process. The reaction was studied with a wide range of carbazole derivatives, 3-substituded indoles **149** and various α-halocarbonyl compounds **150**. The scope of the *N*-coupling partner demonstrated high levels of stereocontrol despite its electronic and steric nature (88–94% *ee*); the products were obtained with good to excellent yields (79–89%). The electronic effects of the indoline amide group and variations of the amide groups tolerated the reaction well, providing products **151** with excellent enantioselectivities (90–96% *ee*) and moderate to high yields (73–92%).



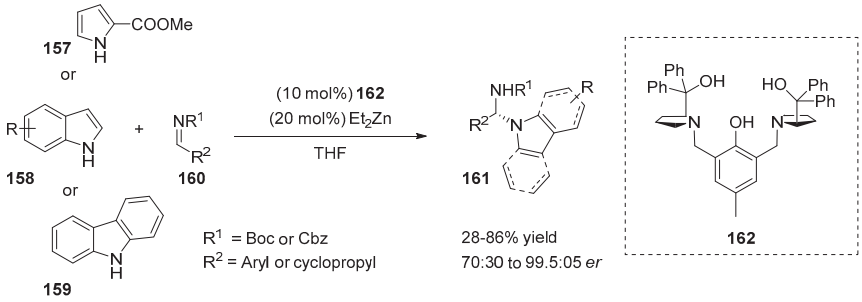
Scheme 31. Cu-catalyzed *N*-functionalization of indole derivatives.

Fu and co-workers continued to study the enantioselective Cu-catalyzed *N*-alkylation of indole derivatives with α-halocarbonyl compounds (Scheme 31, **II**) [60]. Secondary alkyl iodides **154** were used as coupling partners in a photocatalytic reaction for the preparation of chiral 3-indolyl lactams **155** but the results were unsatisfactory (<1% *ee*, 24% yield). The screening of the reaction conditions revealed that the reaction occurred under nonphotocatalytic conditions in the absence of light and

in the presence of Cu-Mes, a chiral monodentate phosphine ligand **156** and cesium carbonate at room temperature in *m*-xylene. The catalytic method was not air- or moisture-sensitive. The scope of the electrophiles showed that various *N*-substituted aromatic and alkyl lactams **154** tolerated the reaction well despite the electronic properties of the substituents. When alkyl bromide was used instead of iodide as an electrophile, a slight decrease in yield (60% vs. 73%) and a comparable value of *ee* were determined (*ee* 88%). The yield was improved up to 85% by an increase in the amount of electrophile from 1.5 equivalent to 2.0 equivalent. The authors conducted a series of experiments where the *ee* of the unreacted electrophile and the yield of the product were monitored during the reaction. These experiments revealed that the asymmetric *N*-alkylation of an indole with racemic alkyl bromide proceeded via a simple kinetic resolution but, in the case of alkyl iodide, a dynamic kinetic resolution occurred.

5. Other Direct Methods

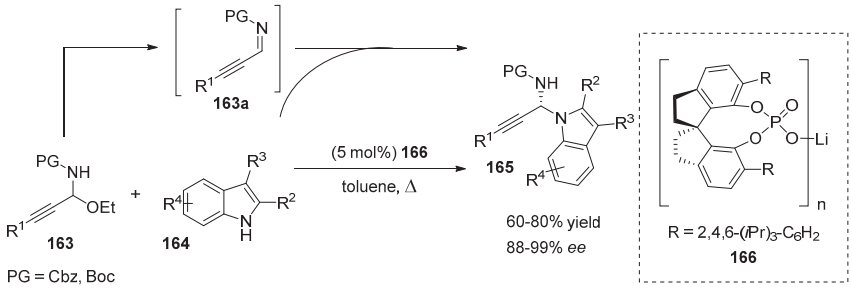
Chiral *N*,*N*′-acyl aminals were prepared from indoles and *N*-Boc or *N*-Cbz imines in the presence of a dinuclear zinc–prophenol complex (Scheme 32) [61]. The method was characterized by high N/C3 regioselectivity, which was maintained due to the application of carbamate-protected imines **160**. The choice of the solvent also drastically affected the regioselectivity of the reaction. For example, the *N*-substituted product was formed with a 61% yield if THF was used as a solvent and with a 14% yield with toluene. Although the complete *N*-selectivity of the alkylation was not achieved, *N*-alkylated products **161** were easily separable from C3-alkylated products. The study of the substrate scope was performed with a wide range of substituted indoles. Higher yields were obtained when 3-substituted indoles were applied. Moreover, the sterical hindrance of the protection group of the imine affected the reaction yield. Substrates with the Cbz group were more reactive than the Boc-substrates. The reactions of Cbz-imines with indoles proceeded at a lower temperature (4 °C) without any loss of yield and with improved enantioselectivity. To demonstrate the generality of the proposed method, the authors extended the reaction scope to other nitrogen-containing heterocycles, such as carbazole **159** and methyl pyrrole-2-carboxylate **157**. The reactions proceeded smoothly affording *N*-alkylated products **161** with moderate to high yields (52–86%) and with high to excellent *er* values (96:4 to 99.5:0.5). The chiral *N*-alkylated products could be efficiently functionalized further, providing new classes of valuable heterocycles.



Scheme 32. Synthesis of chiral *N*,*N*′-acyl aminals.

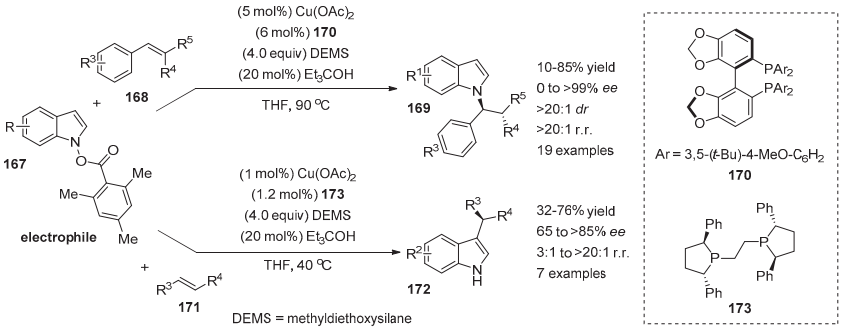
Propargylic compounds are important building blocks in synthetic chemistry because they can be transformed into a wide range of organic derivatives, including heterocycles [62,63]. Shao and coworkers investigated the enantioselective *N*-propargylation of indoles and carbazoles (Scheme 33) [64]. The method was based on the in situ generation of alkynyl *N*-Cbz or *N*-Boc imines **163a** from *N*,*O*-acetals **163** followed by the nucleophilic *N*-addition of indole derivatives **164**. The reaction was smoothly catalyzed by chiral lithium SPINOL phosphate **166**, which was responsible for the elimination of ethanol from *N*,*O*-acetal and participated in the transition state of the reaction, providing an excellent

level of stereocontrol (*ee* up to 99 %). The reaction proceeded with a very low catalyst loading without a significant loss of enantioselectivity or yield. Even 0.1 mol% of the catalyst still provided high enantioselectivity and yield (92% and 72%, respectively).



Scheme 33. Asymmetric *N*-propargylation of indoles.

A CuH-catalyzed regiodivergent method for the synthesis of chiral indoles was recently reported by Buchwald et al. (Scheme 34) [7]. This synthetic route has two distinctive features: the application of indole **167** as an electrophile and facile access to either *N*- or C3-alkylated indole products (**169** or **172**). The regioselectivity of the reaction was efficiently controlled by a chiral ligand **170** or **173** affording either *N*-alkylated products **169** with high selectivity (>20:1) or C3-alkylated products **172** with a moderate to high ratio (3:1 to >20:1). *N*-alkylation was achieved via *N*-oxidative addition of the alkylcopper(I) complex followed reductive elimination.



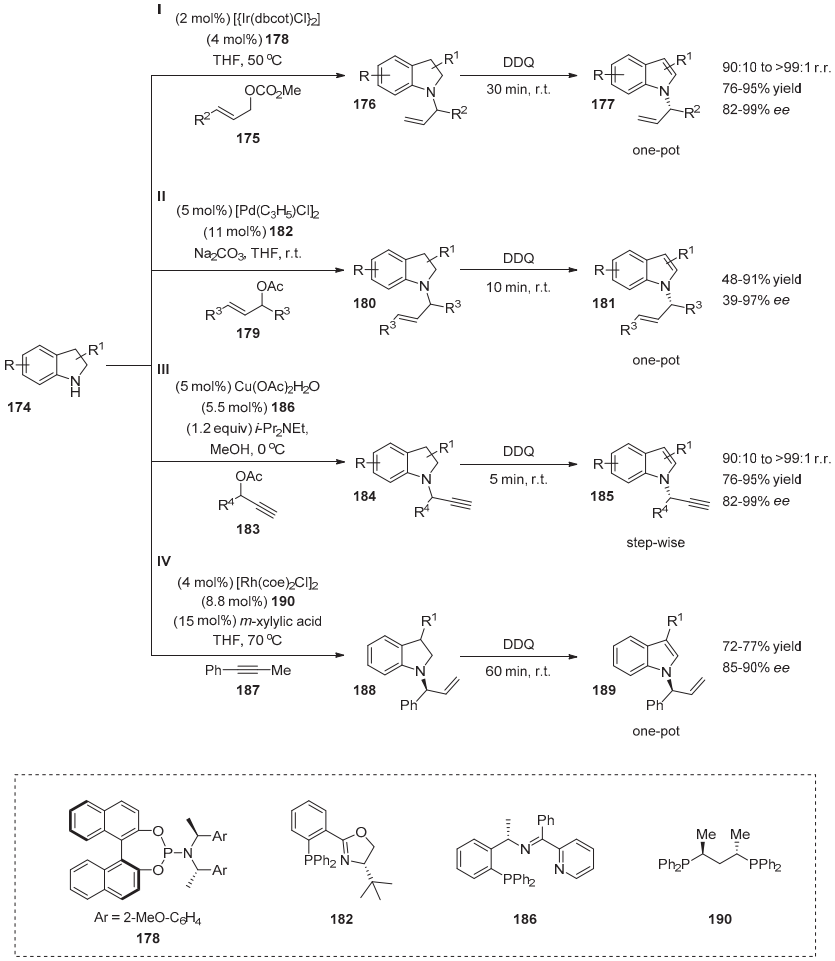
Scheme 34. Ligand-controlled regiodivergent Cu-catalyzed alkylation of indoles.

The *N*-alkylation of indoles was performed with various styrene derivatives **168** affording products with moderate to good yields (41–85%) with good to excellent *ee* values (81–99%). The exceptions were 4-methoxy- and 4-trifluoromethylstyrenes, which gave the desired products with low yields (10% and 17%, respectively). The scope of indole electrophiles revealed that a wide range of substituted indoles tolerated the reaction well. Notably, the 2-carbomethoxyindole was not reactive enough and provided a racemic product with a low yield. Moreover, C3-substituted indole reacted with a low yield and *ee* (16% yield, 17% *ee*).

6. Transition-Metal Catalyzed Indirect Methods

Chiral α-*N*-branched indoles were obtained from the corresponding indolines by transition-metal catalyzed *N*-alkylation/oxidation sequences (Scheme 35). The application of this route was first reported by You's group in 2012 (Scheme 35, **I**) [65]. The chiral *N*-allylindoles **177** were synthesized via a one-pot iridium-catalyzed allylic amination of indolines **174** followed by dehydrogenation of the resulting

N-substituted indolines **176** with DDQ (2,3-dichloro-5,6-dicyano-1,4- benzoquinone). The method was characterized by a broad substrate scope. The electron deficient and electron rich aryl allyl carbonates afforded the desired products with excellent yields (87–92%) with superb *ee*s (96–98%). The 2-thienyl- and alkyl-substituted allylcarbonates tolerated the reaction well and the corresponding products were obtained with good to high yields (up to 86%), with high branched-to-linear selectivity (up to 97:3) and excellent *ee*-values (up to 99%). Various indolines with electron-donating and electron-withdrawing groups at different positions were tested, demonstrating high levels of stereocontrol (92–99% *ee*; 96:4 to >99:1 r.r.).



Scheme 35. Indirect metal-catalyzed strategies for the construction of α-*N*-branched indoles.

The same group also described the asymmetric one-pot Pd-catalyzed version of the reaction (Scheme 35, **II**) [66]. The allylation proceeded smoothly in THF in the presence of 5 mol% of the palladium catalyst, 11 mol% of the Phox ligand **182** and 2 equivalents of Na_2CO_3 as a base. The obtained chiral indolines **180** were oxidized with DDQ in situ affording corresponding α-*N*-branched indoles **181**. The substrate scope was performed with a wide range of indolines. The electronic properties of the substituents of the indoline core did not affect the reaction outcome, providing the desired chiral indoles with moderate to good yields (72–82%) with excellent *ee*s (93–97%). However, the reaction of

2-phenylindoline with 1,3-diaryl allyl acetate gave a moderate yield but still high enantioselectivity (53% yield, 96% *ee*, respectively). A drastic decrease in *ee* was detected when (*E*)-1,3-dimethylallyl acetate was used as a coupling partner (48% yield, 39% *ee*).

The efficient copper-catalyzed propargylation of indolines with propargylic esters **183** followed by the DDQ oxidation of *N*-substituted indolines **184** was described by Hu et al. (Scheme 35, **III**) [67]. Copper salts were used as a metal source which made the method cheaper and easy to handle compared with the two methods discussed above. A disadvantage of this synthetic route is stepwise synthesis. The copper catalyst must be removed, and the methanol evaporated after the propargylation reaction; then the dehydrogenation of the chiral intermediate **184** proceeds in DCM at room temperature in 5 min. The propargylation was catalyzed with the bulky and structurally rigid chiral tridentate ketimine *P*,*N*,*N*-ligand **186** in the presence of Cu salt and base. The authors admitted that the type of copper salt did not noticeably affect the reaction outcome, but the role of the base was critical. When the reaction was performed without a basic additive, the product was formed with a low yield and enantioselectivity (45% yield, 25% *ee*). The addition of a base increased the yield and stereoselectivity of the reaction. Among the bases, the best results were obtained with Hünig's base (90% yield, 92% *ee*). Interestingly, the reaction was also catalyzed by an inorganic base, such as potassium carbonate. A one-pot version of the reaction was possible, but the reaction was low-yielding (35% yield, 92% *ee*). The scope of propargylic esters revealed that the substitution pattern and electronic properties of the phenyl ring had an impact on the yield and stereocontrol of the reaction. For instance, a 2-choloro substituted substrate gave a corresponding product in decreased yield and *ee* (79% yield, 85% *ee*) compared with a 4-choloro substituted substrate (91% yield, 91% *ee*). The reaction with an electron-rich 4-metoxy substituted indoline was slightly less enantioselective (85% yield, 83% *ee*). The heterocyclic 2-thienyl and 2-naphtyl tolerated the reaction well, affording the products with high yields (88–89%) with 87–91% *ee*. Methyl- and fluoro-substituted indolines were also applied as coupling partners, providing high yields and *ee* values (86–91% yield, 88–94% *ee*).

The preparation of chiral *N*-allylindoles was reported by Dong et al. [68]. The synthetic route was based on the hydroamination of alkynes **187** with indolines via rhodium catalysis, followed by the dehydroaromatization of *N*-substituted indolines **188** (Scheme 35, **IV**). Both the parent indoline and 3-methylated indoline tolerated the one-pot reaction well, affording the desired *N*-substituted indoles with good yields and high *ee* values (72–77% yield, 85–90% *ee*, respectively).

7. Conclusions

Significant progress has been made over the past two decades in the synthesis of chiral *N*-alkylated indoles. Direct methods provide an opportunity for the synthesis of chiral *N*-functionalized indoles in one step from substrates containing an indole core. In some cases, the desired *N*-regioselectivity could not be gained due to the side reactions that occur at C3- or C2-positions. To avoid this problem C3- or C2-substituted indoles are usually used as starting compounds for the enantioselective *N*-functionalization. The review illustrates the progress of *N*-selective functionalization, as only recently was high regioselectivity achieved. Sometimes, the introduction of specific substituents into an indole core is necessary for the activation of the *N*-position and for the stereocontrol of the reaction. Indirect methods are not as thoroughly studied as direct methods. These methods can afford selective *N*-alkylation and exclude the problem of regioselectivity. At the same time, multistep synthesis is required for the construction of *N*-functionalized chiral indoles that make indirect routes less efficient and attractive. The stereoselective functionalization of the *N*-atom of the indole was successfully achieved by different types of organocatalytic and transition metal catalysis-based methods. These approaches demonstrated efficient routes for the preparation of chiral *N*-functionalized indoles that could be further modified and could provide facile access to biologically active compounds. Moreover, some methods may be used not only for the construction of chiral *N*-indoles, but may also find applications in the enantioselective functionalization of other *N*-heterocyclic compounds, such as indoline, pyrrole and carbazole derivatives.

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Conflicts of Interest: The authors declare no conflict of interest.

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Appendix 2

Publication II

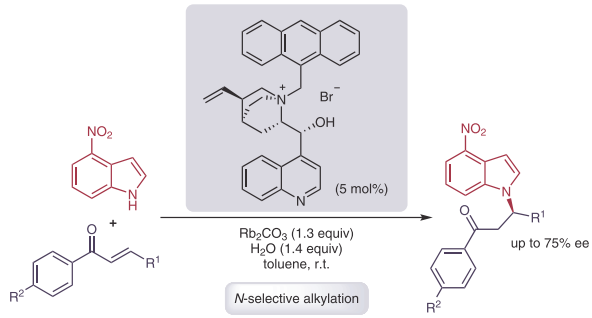
Trubitsõn, D.; Martõnova, J.; Erkman, K.; Metsala, A.; Saame, J.; Kõster, K.; Järving, I.; Leito, I.; Kanger, T. Enantioselective *N*-Alkylation of Nitroindoles under Phase-Transfer Catalysis. *Synthesis*, **2020**, *52*, 1047−1059.

Synthesis D. Trubitsõn et al. Paper

Enantioselective *N*-Alkylation of Nitroindoles under Phase-Transfer Catalysis

Dmitri Trubitsõn[a]
Jevgenija Martõnova[a]
Kristin Erkman[a]
Andrus Metsala[a]
Jaan Saame[b]
Kristjan Köster[b]
Ivar Järving[a]
Ivo Leito[b]
Tõnis Kanger*[a]

[a] Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia
tonis.kanger@taltech.ee
[b] Institute of Chemistry, University of Tartu, 50411 Tartu, Estonia



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Abstract An asymmetric phase-transfer-catalyzed *N*-alkylation of substituted indoles with various Michael acceptors was studied. Acidities of nitroindoles were determined in acetonitrile by UV-Vis spectrophotometric titration. There was essentially no correlation between acidity and reactivity in the aza-Michael reaction. The position of the nitro group on the indole ring was essential to control the stereoselectivity of the reaction. Michael adducts were obtained in high yields and moderate enantioselectivities in the reaction between 4-nitroindole and various Michael acceptors in the presence of cinchona alkaloid based phase-transfer catalysts. In addition to outlining the scope and limitations of the method, the geometries of the transition states of the reaction were calculated.

Key words asymmetric catalysis, heterocycles, Michael addition, organocatalysis, phase-transfer catalysis

Indole and its derivatives are very important scaffolds in medicinal chemistry,[1] being among the most prevalent ring system in small molecule drugs.[2] *N*-Substituted indole derivatives are used more seldom but there are still examples of biologically active pharmaceutical compounds containing this structural moiety (Figure 1).[3] The direct functionalization of the indole ring system has been an active area of research for decades.[4] The most widely exploited reaction is an electrophilic aromatic substitution at the C3 position.[5] Recently, methods have been developed for the direct electrophilic reactions at the C2 position via a transition-metal-catalyzed C–H activation.[6] At the same time, the enantioselective *N*-alkylation of indole remains underdeveloped. The aromaticity of the indole ring and, correspondingly, low nucleophilicity of the nitrogen atom make it challenging.

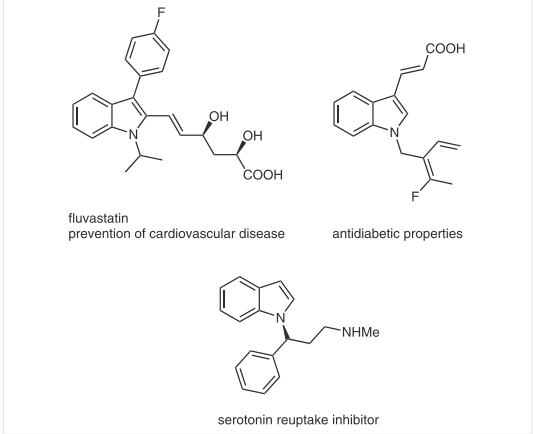
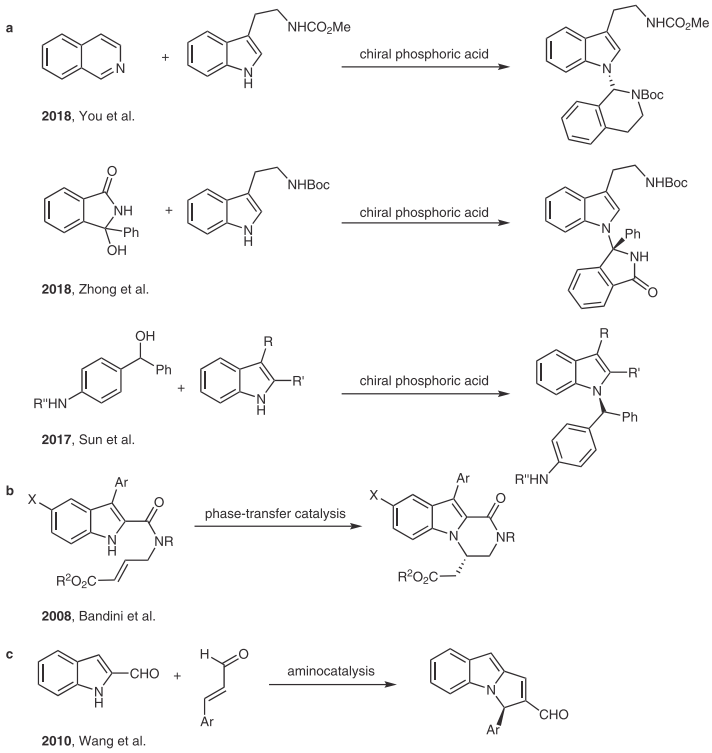


Figure 1 Examples of biologically active *N*-alkylated indoles

Mainly transition-metal-catalyzed reactions have been applied for the enantioselective *N*-addition to indole derivatives.[7] Only limited methodologies have been developed by employing asymmetric organocatalytic strategies for *N*-alkylation. Chiral phosphoric acids were applied as catalysts for the synthesis of *N*-substituted indoles (Scheme 1a).[8] In these examples strong electrophiles are generated under acidic conditions or the simultaneous activation of the electrophile and nucleophile takes place. Alternatively, under basic conditions an intramolecular *N*-alkylation led to the formation of tricyclic products via phase-transfer catalysis (Scheme 1b).[9] The introduction of an electron-withdrawing group reduces the p*Ka* value of the indole and increases the



Scheme 1 Organocatalytic enantioselective *N*-alkylation of indole derivatives

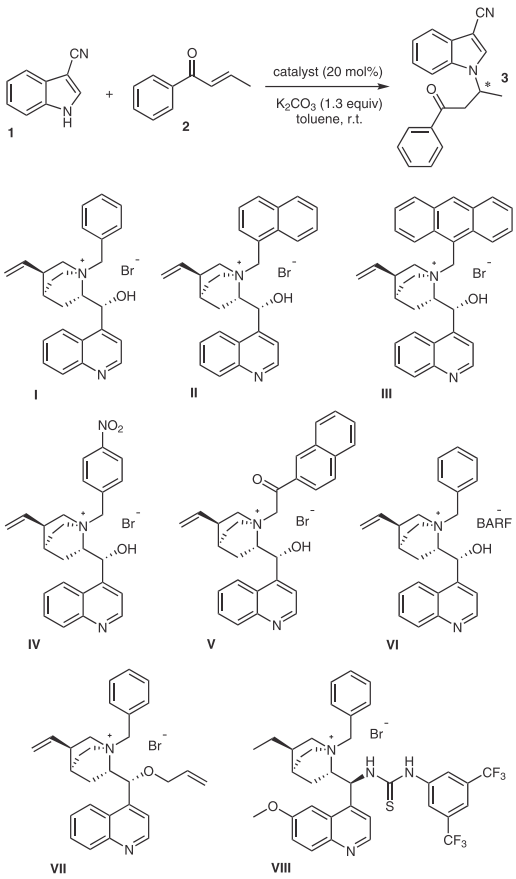
nucleophilicity of the N1 position, enabling an aminocatalytic intramolecular aza-Michael/aldol cascade reaction of 2-formyl-substituted indole, also affording tricyclic products in high enantio- and regioselectivities (Scheme 1c).[10]

In this article, we studied the dependence of the N–H acidity versus the position of the electron-withdrawing group on the indole ring; the synthetic potential of it was further harnessed to access enantiomerically pure indole derivatives via an aza-Michael reaction.[11]

Our initial studies focused on the reaction of 3-cyanoindole (**1**) with *trans*-crotonophenone **2**. An EWG on the third position of the indole ring increases the acidity of the N–H proton and protects the most reactive C3 position. Recently, Yang et al. published a non-asymmetric method consisting of a potassium hydroxide catalyzed intermolecular aza-Michael addition of indole derivatives to aromatic enones.[12] We studied an asymmetric phase-transfer-catalyzed (PTC) version of it. A library of different phase-transfer catalysts based on cinchona alkaloids was screened (Table 1).

The model reaction was performed at room temperature in toluene in the presence of an enantiomerically pure catalyst (20 mol%) and potassium carbonate as a base. First, the steric effect of the substituents of the ammonium salts **I–III** derived from cinchonidine on the reaction was studied. Almost full conversion of the starting compounds **1** and **2** was achieved in the case of benzyl-, naphthyl-, and anthracenyl-substituted catalysts (Table 1, entries 1–3). There was a clear dependence of the steric effect of the catalyst on the enantioselectivity of the reaction. Sterically more demanding catalysts afforded higher enantioselectivities but they remained modest (in the best case 42% ee; entry 3). Catalyst **IV** demonstrated the same conversion and quite similar stereoselectivity as the anthracenyl-substituted catalyst **III** (entry 4). Due to the low solubility of the ammonium salt **V** in toluene, the conversion and ee of product **3** were low (entry 5). The replacement of the bromide anion in catalyst **I** by the tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) anion dramatically affected the reaction rate and enantioselectivity (entry 6). The influence of the hydrogen-bond donor of the catalyst was essential.[13] Protecting the OH group as an allyl ether (catalyst **VII**) provided full conversion of the starting materials but the product was racemic (entry 7). The thiourea derived catalyst **VIII** afforded the opposite enantiomer **3** with low selectivity (entry 8). The obtained results were unsatisfying, and

Table 1 Catalyst Screening for the Reaction between 3-Cyanoindole and *trans*-Crotonophenone[a]



Entry	Catalyst	Time (h)	Conv. (%)[b]	ee (%)[c]
1	**I**	18	98	18
2	**II**	18	99	26
3	**III**	16	83	42
4	**IV**	16	80	36
5	**V**	16	26	4
6	**VI**	18	5	6
7	**VII**	16	99	*rac*
8	**VIII**	20	29	–28

[a] Reaction conditions: **1** (1.2 equiv), **2** (1 equiv), catalyst (20 mol%), base (1.3 equiv), r.t.
[b] Conversion determined by ^{1}H NMR of crude mixture.
[c] Determined by chiral HPLC analysis of the sample obtained by preparative TLC.

therefore a more systematic study of substituted indoles was performed. Nitroindoles were the compounds of choice because of their possible interaction with the phase-transfer catalyst.[14]

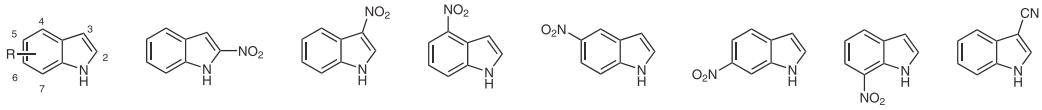
First, the acidities of the nitrosubstituted indoles were determined (Table 2). As expected, nitroindoles and 3-cyanoindole behave in acetonitrile as weak acids, with pK_a values in the range of 22–30, thus being by their acid strength approximately between benzoic acid[15] and phenol.[16] By acid strength, the nitroindoles fall into two distinct groups – the ones with nitro group on the five-membered ring (pK_a between 22 and 24) and the ones with the nitro group on the six-membered ring (pK_a between 27 and 30). The reason is evidently the good match between the electron-withdrawing abilities of the nitro group on the one hand and the vicinity of the nitro group to the acidity center in the five-membered ring, as well as the overall higher electron density in the five-membered ring. The strongest of the nitroindoles – 3-nitroindole – benefits from highly efficient resonance stabilization of the negative charge in the anion via conjugation of the nitro group with the acidity center.

In the following reactions, commercially available 4-nitroindole was used as a model compound. It was found that under similar conditions applied to 3-cyanoindole the reaction with 4-nitroindole in the presence of catalyst **III** was more selective (Table 3, entry 1). The reaction rate was increased when rubidium carbonate was used as a base, affording the *N*-alkylated product in 95% yield within 5 hours without any decrease in enantioselectivity (entry 2, 65% ee). An aqueous solution of rubidium carbonate decreased the rate of the reaction substantially and for the full conversion a reaction time of 24 hours was needed (entry 3). The enantiomeric purity of the product was increased to 74% by lowering the temperature of the reaction to –20 °C (entry 5). Cesium carbonate induced a less selective reaction (entry 6).

During the optimization of the reaction conditions the effect of water on the reaction rate was revealed. Small amounts of water could significantly affect the rate of the reactions catalyzed by the quaternary ammonium salts.[17] The balance between the amount of water and amount of phase-transfer catalyst was screened (for the full optimization process, see the Supporting Information). It was found that both low concentrations and high concentrations of water decreased the reaction rate. With the optimum water concentration the amount of the catalyst **III** was decreased to 5 mol%. Increasing the amount of *trans*-crotonophenone from 1.2 equivalents to 2.1 equivalents afforded the *N*-alkylated 4-nitroindole **5a** in a reasonable time (5 h), high yield (95%), and moderate ee (69%).

Next, the influence of the position of the nitro group on the aza-Michael reaction was studied under the optimal conditions (Table 4). It was found that the most reactive

Table 2 Results of pK_a Measurements in Acetonitrile



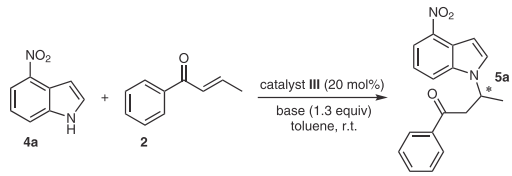
Acid (A)	Reference acid (Ra)	pK_a(Ra)	pK_a[a]	pK_a(A)	Assigned pK_a(A)
2-nitroindole	2-nitrophenol	22.85	–0.80	23.65	23.64
	9-MeO_2C-fluorene	23.53	–0.10	23.63	
3-nitroindole	2-nitrophenol	22.85	0.10	22.75	2.77
	9-MeO_2C-fluorene	23.53	0.74	22.79	
4-nitroindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	–0.88	27.84	7.8
	5-nitroindole	28.1	0.28	27.8	
5-nitroindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	–1.12	28.08	8.1
6-nitroindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	–0.85	27.81	7.7
	4-nitroindole	27.83	0.14	27.69	
7-nitroindole	5-nitroindole	28.1	–1.74	29.8	9.9
	6-nitroindole	27.74	–2.21	29.95	
	9-C_6F_5-fluorene	28.11	1.88	29.99	
3-cyanoindole	(4-MeC_6F_4)(C_6H_5)CHCN	26.96	0.93	26.03	6.0
	(C_6F_5)(C_6H_5)CHCN	26.14	0.18	25.96	

[a] pK_a(Ra) – pK_a(A)

derivatives were 4- and 5-nitroindoles (entries 1 and 3), but the former was more selective (69% and 38% ee, respectively). Also, 3- and 6-nitroindoles were less attractive substrates, affording products in low enantioselectivities (entries 2 and 4). In the case of 2- and 7-nitroindole, no reaction was detected during 24 hours, most probably because of steric reasons (entries 5 and 6). The obtained results show that the position of the nitro group is essential in determining the enantioselectivity and it participates in the transition state. Comparison of Tables 2 and 4 reveals that there is essentially no correlation between acidity and reactivity in the aza-Michael reaction. There is, however, a connection between reactivity and steric hindrance: the least reactive are 2- and 7-nitroindole, where the nitro groups are spatially closest to the acidity center.

The scope of the reaction was studied with the most selective 4-nitroindole **4a** (Scheme 2). Various α,β-unsaturated carbonyl compounds **2a–l**, unsaturated ester **2m**, and nitrostyrene **2n** were used as Michael acceptors. It was found that aromatic and heteroaromatic enones were the most reactive and selective starting compounds, affording products within 5 hours in moderate to high yields and moderate to good enantioselectivities. Neither electron-withdrawing (**4b**), nor electron-donating groups (**4c**) in the phenyl ring influenced the reaction substantially. The heteroaromatic furyl substituent did not affect the reaction enantioselectivity, and product **6d** was obtained in high yield. Steric hindrance in the β-position of the enone decreased the reaction rate, as demonstrated in experiments with the vinyl-substituted enones **2e** and **2f**.

Table 3 Optimization of the Reaction between 4-Nitroindole (**4a**) and *trans*-Crotonophenone (**2**)[a]

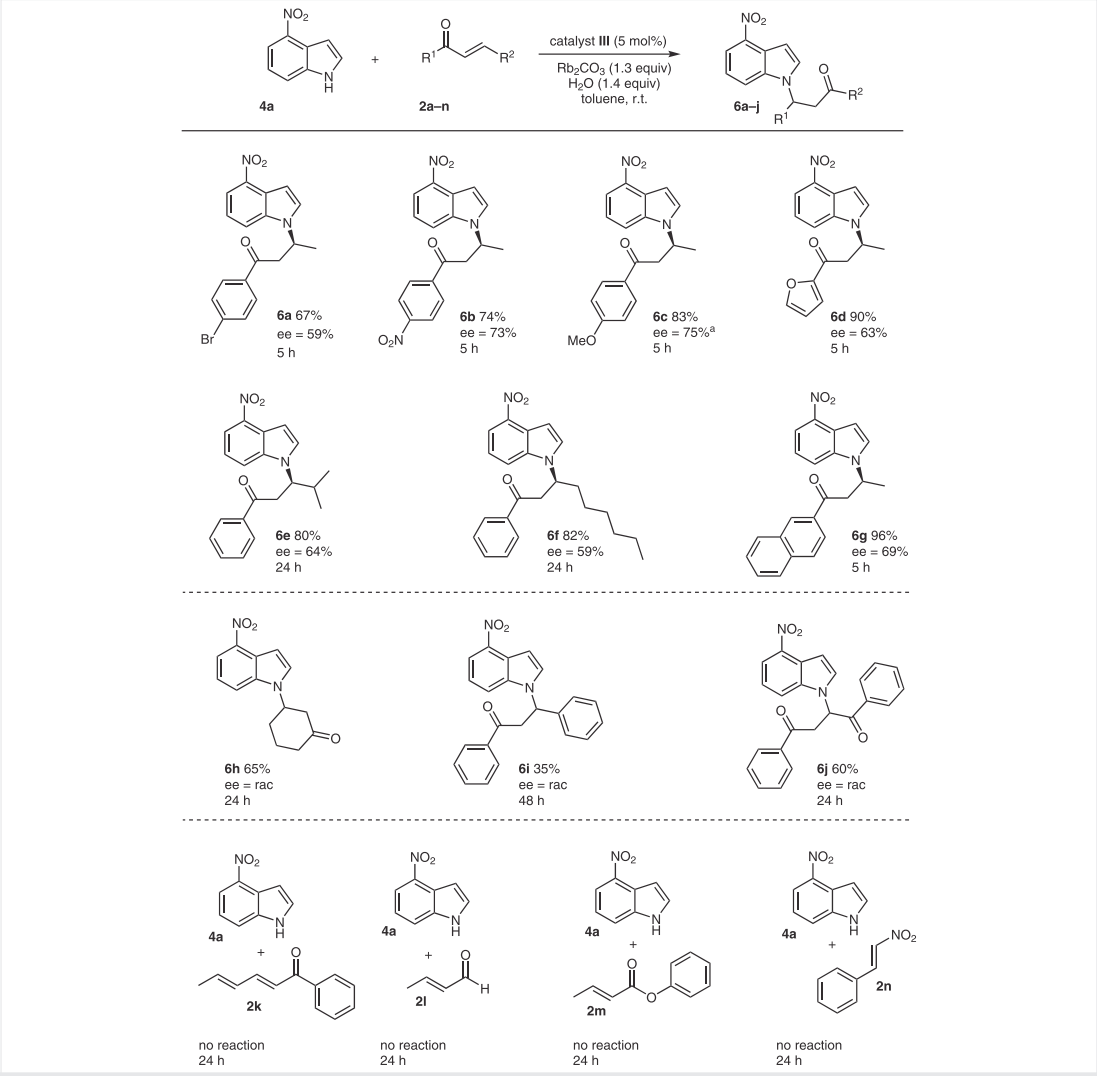


Entry	Base	Time	Yield (%)[b]	ee (%)[c]
1	K_2CO_3	21 h	95	65
2	Rb_2CO_3	5 h	92	65
3	5 M aq Rb_2CO_3	24 h	95	64
4[d]	Rb_2CO_3	24 h	97	70
5[e]	Rb_2CO_3	6 d	97	74
6	Cs_2CO_3	18 h	95	54

[a] Reaction conditions: **4a** (0.1 mmol, 1 equiv), **2** (2.1 equiv), catalyst **III** (20 mol%), Rb_2CO_3 (1.3 equiv), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Reaction at 5 °C.
[e] Reaction at –20 °C

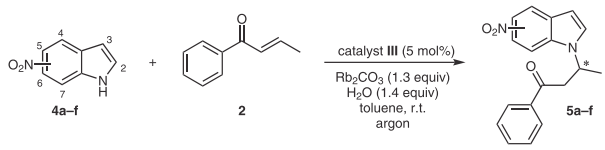
The absolute stereochemistry of compound **6c** was unambiguously assigned by single-crystal X-ray diffraction (Figure 2). The configurations of other compounds in the series were assigned by analogy.

To our disappointment, the reaction had limitations that could be divided into two categories: either the reaction proceeded, but racemic products were formed (**6h**, **6i**, **6j**), or there was no reaction (starting compounds **2k–n**). Sterically more hindered aliphatic cyclic ketone **2h** and *trans*-chalcone **2i** provided racemic products with lower reaction rates compared to the model compound **2a**. It was assumed that the long reaction time gave rise to a nonselective background reaction, leading to racemic products. In the case of the 1,4-diketone **6j**, racemization of the α-position of the carbonyl group through enolization under basic conditions is most probable. The reaction did not proceed



Scheme 2 The reaction scope and limitations. *Reagents and conditions*: **4a** (0.1 mmol, 1 equiv), **2a–n** (2.1 equiv), catalyst **III** (5 mol%), Rb_2CO_3 (1.3 equiv), H_2O (1.4 equiv), under argon atmosphere; all yields are isolated yields; ee values were determined by chiral HPLC analysis; [a] 90% ee was obtained after a single recrystallization.

Table 4 Effect of the Position of the Nitro Group on Nitroindole **4** on the Aza-Michael Reaction[a]



Entry	Product	NO_2 position	Time (h)	Yield (%)[b]	ee (%)[c]
1	**5a**	4	5	92	69
2	**5b**	3	5	65	42
3	**5c**	5	5	95	8
4	**5d**	6	5	82	5
5	**5e**	2	24	nr[d]	–
6	**5f**	7	24	nr[d]	–

[a] Reaction conditions: 0.1 mmol scale, 1 equiv of **4a–f**, 2.1 equiv of **2**, 5 mol% of catalyst **III**, 1.3 equiv of Rb_2CO_3 and 1.4 equiv of H_2O under argon atmosphere.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] nr = no reaction.

with (2*E*,4*E*)-1-phenylhexa-2,4-dien-1-one (**2k**), crotonaldehyde (**2l**), phenyl (*E*)-but-2-enoate (**2m**), and β-nitrostyrene (**2n**).

Generally, aromatic ketones were the best substrates for the *N*-alkylation of nitroindoles. The obtained results suggested the importance of π–π interactions in the transition state. To gain insight into the reaction mechanism, computational studies were conducted based on the density functional M062X/def2SVP method. In order to assess noncovalent interactions, a Natural Bond Orbital (NBO) analysis was performed using the M062X/def2TZVP method (for calculation details and NBO energies, see the Supporting Information). In the ternary complex INT1-S a strong hydrogen bond between the deprotonated N atom of indole **4a** and the hydroxyl group of catalyst **III**, together with the π–π interactions between the quinolone ring of the catalyst **III** and indole **4a**, form (Figure 3A). Distortion of the complex leads to the intermediate (INT2-S) with reorganized geometry: a hydrogen bond forms between the nitro group of indole and the hydroxyl of the catalyst (Figure 3B). The intermediate forms a product via a bond-forming step (TS1) (distance between Michael acceptor and donor site is 2.28

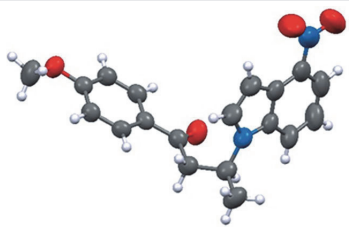


Figure 2 X-ray crystal structure of compound **6c** (CCDC 1923379)

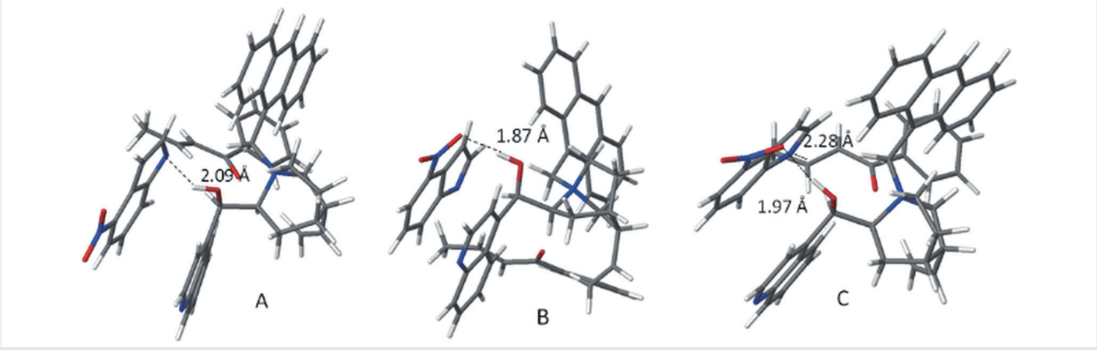


Figure 3 Optimized geometries of intermediates and transition state: A: INT1-S; B: INT2-S; C: TS1-S

Å) (Figure 3C). Throughout the reaction, π–π interactions remain important.

We have revealed here a systematic study of the *N*-alkylation of nitroindoles. It was found that a *Cinchona* alkaloid-derived PTC reaction with various Michael acceptors led exclusively to aza-Michael adducts in high yields and moderate to good enantioselectivities. The acidity of the N–H proton was not the decisive factor in determining the reactivity and selectivity of the reaction. Instead, the position of the nitro group on the indole ring plays a crucial role in the reaction.

All commercially available reagents were used without further purification. All air- or moisture-sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. The reactions were monitored by TLC with silica-gel-coated aluminum plates (Merck 60 F254) and visualized with $KMnO_4$, anisaldehyde, vaniline, or ninhydrine stain. Yields refer to chromatographically purified products. ^{1}H NMR spectra were recorded on a Bruker Avance III instrument at 400 MHz and are reported in ppm (δ) referenced to the residual solvent signal ($CDCl_3$: δ = 7.26; CD_3OD, δ = 3.31). ^{13}C NMR spectra were recorded at 101 MHz and are reported in parts per million (δ) referenced to the residual solvent signal ($CDCl_3$: δ = 77.16; CD_3OD: δ = 49.00). HRMS spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. Optical rotations were obtained with an Anton Paar GWB Polarimeter MCP500 at 20 °C in $CHCl_3$ and are calibrated with pure solvent as a blank. Chiral HPLC was performed by using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OJ-H (250 × 4.6 mm), or Chiralcel OD-H (250 × 4.6 mm) columns. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40–63 μm. The measured melting points are uncorrected. All crystalline products are obtained from chloroform. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorus pentoxide. PE has a boiling point of 40–60 °C. The reactions were performed under air without additional moisture elimination unless stated otherwise.

Acidity Measurements

UV-Vis spectrophotometric titration was used to determine the acidity (pK_a values) of the nitroindoles and 3-cyanoindole in acetonitrile. Measurements were carried out in a glovebox, applying a method described earlier.[15] The argon atmosphere (5.0) as the environment for all experiments was kept dry and oxygen-free (both contents below 1 ppm) and only freshly prepared solutions in MeCN (H_2O < 5 ppm) were used. UV-Vis spectra were collected on Agilent Cary 60 and PerkinElmer Lambda 12 spectrophotometers using an external cell compartment inside the glovebox. CF_3SO_2OH and $EtN{=}P_2(dma)_5$ (or *tert*-butyliminotri(pyrrolidino)phosphorane) solutions in MeCN were used as acidic and basic titrants, respectively. In titration experiments the concentration of the indoles and reference acids were in the range of 10^{-5} to 10^{-4} M.

Phase-transfer catalysts **I–III**,[18] **VII**,[18] **IV**,[19,20] **V**,[21] **VI**,[22] and **VIII**[23] were prepared by corresponding literature procedures and the

Analytical data matched those in the literature.

Indole derivatives **1**, **4a**, **4c**, **4d**, and **4f** were purchased from Fluorochem Ltd and used as received. 2-Nitroindole (**4e**)[24] and 3-nitroindole (**4b**)[25] were prepared according to literature procedures and the analytical data matched those in the literature.

Synthesis of Unsaturated α,β-Enones 2 and 2a–n

(*E*)-1-Phenylbut-2-en-1-one (2)[26]

To a 1 M solution of phenylmagnesium bromide in THF (25 mL, 25 mmol) in THF (75 mL) crotonaldehyde (2.07 mL, 25 mmol) was added dropwise at 0 °C under argon. The mixture was stirred for 45 min at the same temperature and then quenched with sat. aq NH_4Cl (25 mL). The organic solvent was removed under reduced pressure and aq NH_4Cl (20 mL) was added. The reaction mixture was extracted with EtOAc (5 × 50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated to dryness under reduced pressure to provide a yellow oil. The Grignard product was dissolved in DCM (40 mL) and MnO_2 (21.7 g, 250 mmol, 10 equiv) was added under vigorous stirring. The reaction mixture was stirred overnight. The mixture was filtered through a pad of Celite, washed with DCM, and purified by column chromatography (silica gel, 2–10% EtOAc–PE).

Yield: 1.988 g (54%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.89 (m, 2 H), 7.58–7.51 (m, 1 H), 7.49–7.43 (m, 2 H), 7.07 (dq, *J* = 15.3, 6.8 Hz, 1 H), 6.91 (dq, *J* = 15.3, 1.6 Hz, 1 H), 2.00 (dd, *J* = 6.8, 1.6 Hz, 3 H).

Analytic data were in agreement with the literature data.

2-En-1-ones 2a,c–f,k by Wittig Reaction; General Procedure

The aldehyde (1.2 equiv) was added to the mixture of phosphonium ylide (1 equiv) in DCM (0.2 M). The reaction was monitored by TLC. Upon completion of the reaction, the DCM was evaporated to give a solid residue that was triturated with hexane. The solid triphenylphosphine oxide was filtered off and the hexane layer was dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The crude mixture was purified by column chromatography (silica gel).

(*E*)-1-(4-Bromophenyl)but-2-en-1-one (2a)

Following the general procedure, starting from 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.75 g, 3.8 mmol) and acetaldehyde (256 μL, 4.56 mmol), the mixture was stirred for 7 d. The title compound was obtained after purification by column chromatography (silica gel, 1–6% EtOAc–PE).

Yield: 611 mg (71%); white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.75 (m, 2 H), 7.64–7.56 (m, 2 H), 7.08 (dq, *J* = 15.3, 6.9 Hz, 1 H), 6.86 (dq, *J* = 15.3, 1.6 Hz, 1 H), 2.00 (dd, *J* = 6.9, 1.6 Hz, 3 H).

Analytic data were in agreement with the literature data.[27]

(*E*)-1-(4-Methoxyphenyl)but-2-en-1-one (2c)

Following the general procedure starting from 1-(4-metoxyphenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.97 g, 4.8 mmol) and acetaldehyde (326 μL, 5.8 mmol), the mixture was stirred for 7 d. The title compound was obtained after purification by column chromatography (silica gel, 1–10% EtOAc–PE).

Yield: 700 mg (83%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.90 (m, 2 H), 7.06 (dq, *J* = 15.2, 6.7 Hz, 1 H), 6.97–6.89 (m, 3 H), 3.87 (s, 3 H), 1.99 (dd, *J* = 6.8, 1.5 Hz, 3 H).

Analytic data were in agreement with the literature data.[28]

(*E*)-1-(Furan-2-yl)but-2-en-1-one (2d)

Following the general procedure starting from 1-(4-furan-2-yl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.4 g, 3.78 mmol) and acetaldehyde (255 µL, 4.54 mmol), the mixture was stirred for 6 d. The title compound was obtained after purification by column chromatography (silica gel, 2–8% EtOAc–PE).

Yield: 210 mg (41%); white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.57 (m, 1 H), 7.24–7.22 (m, 1 H), 7.22–7.11 (m, 1 H), 6.82 (dq, *J* = 15.4, 1.7 Hz, 1 H), 6.55 (dd, *J* = 3.5, 1.7 Hz, 1 H), 1.99 (dd, *J* = 6.9, 1.7 Hz, 3 H).

Analytic data were in agreement with the literature data.[28]

(*E*)-4-Methyl-1-phenylpent-2-en-1-one (2e)

Following the general procedure starting from 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.75 g, 4.6 mmol) and isobutyraldehyde (440 µL, 4.8 mmol, 1.05 equiv), the mixture was stirred for 6 d. The title compound was obtained after purification by column chromatography (silica gel, 2% EtOAc–PE).

Yield: 220 mg (28%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.89 (m, 2 H), 7.59–7.52 (m, 1 H), 7.50–7.42 (m, 2 H), 7.03 (dd, *J* = 15.5, 6.7 Hz, 1 H), 6.82 (dd, *J* = 15.5, 1.4 Hz, 1 H), 2.66–2.51 (m, 1 H), 1.14 (d, *J* = 6.8 Hz, 6 H).

Analytic data were in agreement with the literature data.[29]

(*E*)-1-Phenylnon-2-en-1-one (2f)

Following the general procedure starting from 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.1 g, 2.9 mmol) and heptanal (494 µL, 3.5 mmol), the mixture was stirred for 5 d. The title compound was obtained after purification by column chromatography (silica gel, 1–6% EtOAc–PE).

Yield: 250 mg (40%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.90 (m, 2 H), 7.59–7.52 (m, 1 H), 7.51–7.42 (m, 2 H), 7.07 (dt, *J* = 15.4, 6.9 Hz, 1 H), 6.87 (dt, *J* = 15.4, 1.4 Hz, 1 H), 2.37–2.27 (m, 2 H), 1.58–1.46 (m, 2 H), 1.42–1.21 (m, 6 H), 0.93–0.84 (m, 3 H).

Analytic data were in agreement with the literature data.[29]

(2*E*,4*E*)-1-Phenylhexa-2,4-dien-1-one (2k)

Following the general procedure starting from 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (1.1 g, 2.9 mmol) and (*E*)-but-2-enal (290 µL, 3.5 mmol), the mixture was stirred for 5 d. The title compound was obtained after purification by column chromatography (silica gel, 2–4% EtOAc–PE).

Yield: 250 mg (40%); yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.90 (m, 2 H), 7.57–7.51 (m, 1 H), 7.50–7.36 (m, 3 H), 6.87 (dd, *J* = 15.1, 0.8 Hz, 1 H), 6.40–6.19 (m, 2 H), 1.90 (dd, *J* = 6.1, 1.0 Hz, 3 H).

Analytic data were in agreement with the literature data.[30]

(*E*)-1-(4-Nitrophenyl)but-2-en-1-one (2b)

3-Hydroxy-1-(4-nitrophenyl)butan-1-one

To a dry flask under argon was added diisopropylamine (1.4 mL, 10 mmol) in THF (15 mL). The mixture was cooled to –20 °C and 2.5 M *n*-BuLi in hexane (4 mL, 10 mmol, 1.05 equiv) was added. The mixture was stirred for 30 min, cooled to –78 °C, and *p*-nitroacetophenone (1 equiv) was added. The reaction mixture was stirred for 20 min at –78 °C and acetaldehyde (590 µL, 10.5 mmol, 1.1 equiv) was added. After 1 h the mixture was quenched with sat. aq $NaHCO_3$ and warmed to r.t. The crude mixture was poured into Et_2O and washed with H_2O, 1% aq HCl (2 × 50 mL), sat. aq $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 5–30% EtOAc–PE) providing 3-hydroxy-1-(4-nitrophenyl)butan-1-one; yield: 470 mg (24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.29 (m, 2 H), 8.14–8.09 (m, 2 H), 4.54–4.37 (m, 1 H), 3.18–3.12 (m, 2 H), 2.98 (s, 1 H, OH), 1.33 (d, *J* = 6.4 Hz, 3 H).

Analytic data were in agreement with the literature data.[31]

2b

3-Hydroxy-1-(4-nitrophenyl)butan-1-one (470 mg, 2.25 mmol) was dissolved in a mixture of DCM (7 mL) and pyridine (1.8 mL) and treated with mesyl chloride (174 µL, 2.25 mmol) under an argon atmosphere for 4 h. H_2O (10 mL) was added and reaction mixture was extracted with DCM (3 × 20 mL). The organic phase was washed with sat. aq $CuSO_4$ (4 × 30 mL) and brine (2 × 30mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The title compound was obtained after purification by column chromatography (silica gel, 2–10% EtOAc–PE).

Yield: 175 mg (41%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.26 (m, 2 H), 8.07–7.99 (m, 2 H), 7.12 (dq, *J* = 15.4, 6.9 Hz, 1 H), 6.87 (dq, *J* = 15.3, 1.7 Hz, 1 H), 2.03 (dd, *J* = 6.9, 1.7 Hz, 3 H).

Analytic data were in agreement with the literature data.[32]

(*E*)-1-(Naphthalen-2-yl)but-2-en-1-one (2g)

3-Hydroxy-1-(2-naphthalenyl)-1-butanone

Diisopropylamine (1.37 mL, 9.8 mmol) was dissolved in THF (18 mL) under argon. The mixture was cooled to –20 °C and 2.5 M *n*-BuLi in hexane (3.92 mL, 9.8 mmol) was added; then the mixture was stirred for 30 min and cooled to –78 °C before 1-(naphthalen-2-yl)ethan-1-one (1.59 g, 9.3 mmol) was added. The mixture was stirred for 20 min at –78 °C and acetaldehyde (570 µL, 10.26 mmol) was added. The mixture was stirred for an additional 1 h and was quenched with sat. aq $NaHCO_3$ and warmed to r.t. The crude mixture was poured into Et_2O, washed with H_2O, 1% aq HCl (2 × 50 mL), sat. aq $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude mixture was purified by column chromatography (silica gel, 5–30% EtOAc–PE); this provided 3-hydroxy-1-(2-naphthalenyl)-1-butanone; yield: 1.788 g (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 1.7 Hz, 1 H), 8.11–7.80 (m, 4 H), 7.67–7.52 (m, 2 H), 4.53–4.41 (m, 1 H), 3.41 (d, *J* = 3.0 Hz, 1 H, OH), 3.31 (dd, *J* = 17.6, 2.8 Hz, 1 H), 3.18 (dd, *J* = 17.6, 8.9 Hz, 1 H), 1.35 (d, *J* = 6.4 Hz, 3 H).

Analytic data were in agreement with the literature data.[31]

2g

3-Hydroxy-1-(2-naphthalenyl)-1-butanone (900 mg, 4.2 mmol) was dissolved in pyridine (3.2 mL) and treated with mesyl chloride (325 µL, 4.2 mmol) under argon for 24 h. After H_2O was added to the flask, the mixture was extracted with Et_2O (3 × 50 mL). The organic phase was washed with sat. aq $CuSO_4$ (4 × 30 mL) and brine (2 × 40 mL), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The crude 4-(naphthalen-2-yl)-4-oxobutan-2-yl methanesulfonate and TEA (608 µL, 4.2 mmol) were mixed in Et_2O (20 mL) overnight. The crude mixture was concentrated and purified by column chromatography (silica gel, 1–8% EtOAc–PE), providing product **2g**.

Yield: 480 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47–8.42 (m, 1 H), 8.03 (dd, *J* = 8.6, 1.8 Hz, 1 H), 8.00–7.94 (m, 1 H), 7.94–7.85 (m, 2 H), 7.63–7.51 (m, 2 H), 7.21–7.02 (m, 2 H), 2.05 (dd, *J* = 6.4, 1.1 Hz, 3 H).

Analytic data were in agreement with the literature data.[33]

Phenyl (*E*)-But-2-enoate (2m)

Compound **2m** was prepared according to a literature procedure.[34]

Yield: 573 mg (35%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 2 H), 7.27–7.07 (m, 4 H), 6.05 (dq, *J* = 15.6, 1.7 Hz, 1 H), 1.96 (dd, *J* = 6.9, 1.7 Hz, 3 H).

***N*-Alkylation of Nitroindoles; General Procedure**

Indole **1** or **4** (0.1 mmol), phase-transfer catalyst **III** (0.005 mmol), and Rb_2CO_3 (0.13 mmol) were loaded in a 1 mL vial. The mixture of compounds was held for 1 h under vacuum. The vial was filled with an argon atmosphere. Toluene (1 mL), ketone **2** (0.21 mmol), and H_2O (0.14 mmol) were added and the reaction mixture was stirred at r.t. for 5 h under argon unless stated otherwise. The progress of the reaction was monitored by TLC and NMR spectroscopy. After completion of the reaction, the reaction mixture was directly purified by column chromatography to afford pure products **3**, **5**, or **6**.

(*S*)-3-(4-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5a)

The reaction time was 24 h. Title compound **5a** was obtained according to the general procedure from 4-nitroindole (**4a**; 162.2 mg, 1 mmol) and **2** (307 mg, 2.1 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 281 mg (91%); orange amorphous solid; 65% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R = 21.3 (major), t_R = 29.9 (minor)]; $[\alpha]_D^{20}$ –21.4 (*c* 0.033, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 3:1).

IR (KBr): 2979, 1685, 1597, 1511, 1498, 1448, 1361, 1332, 1312, 1268, 755, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.91–7.86 (m, 2 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.60–7.54 (m, 1 H), 7.51 (d, *J* = 3.3 Hz, 1 H), 7.47–7.41 (m, 2 H), 7.31–7.26 (m, 2 H), 5.42–5.31 (m, 1 H), 3.58 (dd, *J* = 17.3, 5.8 Hz, 1 H), 3.47 (dd, *J* = 17.3, 7.3 Hz, 1 H), 1.70 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.8, 140.6, 137.9, 136.4, 133.9, 128.9 (2 C), 128.6, 128.1 (2 C), 123.1, 120.6, 117.8, 116.6, 101.1, 48.2, 42.7, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1227.

(*S*)-3-(3-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5b)

Title compound **5b** was obtained according to the general procedure from 3-nitroindole (**4b**; 16.2 mg, 0.1 mmol) and **2** (30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 20 mg (65%); rose amorphous solid; 42% ee [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R = 41.0 (major), t_R = 45.1 (minor)]; $[\alpha]_D^{20}$ –4.7 (*c* 0.034, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 3:1).

IR (KBr): 3128, 1685, 1597, 1525, 1481, 1449, 1379, 1303, 1225, 750, 689 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.26 (m, 2 H), 7.94–7.89 (m, 2 H), 7.63–7.54 (m, 2 H), 7.49–7.44 (m, 2 H), 7.44–7.36 (m, 2 H), 5.42–5.29 (m, 1 H), 3.62 (dd, *J* = 17.6, 5.4 Hz, 1 H), 3.53 (dd, *J* = 17.6, 7.5 Hz, 1 H), 1.73 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.0, 136.1, 135.0, 134.1, 129.5, 129.0 (2 C), 128.1 (2 C), 127.8, 124.7, 124.5, 121.14, 121.12, 111.0, 48.9, 45.2, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1228.

(*S*)-3-(5-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5c)

Title compound **5c** was obtained according to the general procedure from 5-nitroindole (**4c**; 16.2 mg, 0.1 mmol) and **2** (30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 29.3 mg (95%); orange amorphous solid; 38% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R = 31.8 (minor), t_R = 35.9 (major)]; $[\alpha]_D^{20}$ –76.4 (*c* 0.032, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 2980, 1685, 1610, 1580, 1470, 1450, 1319, 1219, 1070, 743, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 2.3 Hz, 1 H), 8.12 (dd, *J* = 9.1, 2.3 Hz, 1 H), 7.93–7.84 (m, 2 H), 7.60–7.54 (m, 1 H), 7.51 (d, *J* = 9.2 Hz, 1 H), 7.48–7.38 (m, 3 H), 6.71 (d, *J* = 3.4 Hz, 1 H), 5.39–5.26 (m, 1 H), 3.58 (dd, *J* = 17.3, 6.0 Hz, 1 H), 3.46 (dd, *J* = 17.3, 7.1 Hz, 1 H), 1.69 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 141.7, 138.5, 136.4, 133.8, 128.9 (2 C), 128.1 (2 C), 127.7, 127.4, 118.4, 117.4, 109.8, 105.0, 48.3, 45.5, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1232.

(*S*)-3-(6-Nitro-1*H*-indol-1-yl)-1-phenylbutan-1-one (5d)

Title compound **5d** was obtained according to the general procedure from 6-nitroindole (**4d**; 16.2 mg, 0.1 mmol) and **2** (30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–15% EtOAc–PE).

Yield: 25.3 mg (82%); yellow solid; mp 168–170 °C; 35% ee [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R =16.6 (major), t_R = 22.6 (minor)]; $[\alpha]_D^{20}$ –76.4 (*c* 0.035, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 2978, 1684, 1580, 1511, 1495, 1462, 1330, 1219, 1070, 777, 730, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50–8.43 (m, 1 H), 8.00 (dd, *J* = 8.7, 2.0 Hz, 1 H), 7.93–7.86 (m, 2 H), 7.63 (d, *J* = 8.7 Hz, 1 H), 7.60–7.49 (m, 2 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 6.62 (d, *J* = 3.2 Hz, 1 H), 5.41–5.29 (m, 1 H), 3.62 (dd, *J* = 17.2, 6.1 Hz, 1 H), 3.50 (dd, *J* = 17.2, 7.1 Hz, 1 H), 1.71 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.5, 143.1, 136.4, 134.2, 133.8, 133.5, 130.5, 128.9 (2 C), 128.1 (2 C), 121.0, 115.2, 107.0, 103.1, 48.6, 45.4, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1226.

(*S*)-1-(4-Bromophenyl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6a)

Title compound **6a** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(4-bromophenyl)but-2-en-1-one (**2a**; 47.3 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2a** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 2–15% EtOAc–PE).

Yield: 25.9 mg (67%); orange amorphous solid; 59% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ =254 nm): t_R =27.2 (major), t_R = 35.2 (minor)]; $[\alpha]_D^{20}$ –25.4 (*c* 0.050, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 10:1).

IR (KBr): 2979, 1686, 1585, 1568, 1511, 1498, 1361, 1331, 1304, 1269, 1105, 790, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.09 (m, 1 H), 7.82 (d, *J* = 8.3 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.60–7.54 (m, 2 H), 7.49 (d, *J* = 3.3 Hz, 1 H), 7.32–7.26 (m, 2 H), 5.40–5.29 (m, 1 H), 3.54 (dd, *J* = 17.3, 5.9 Hz, 1 H), 3.42 (dd, *J* = 17.4, 7.2 Hz, 1 H), 1.69 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.7, 140.5, 137.8, 135.0, 132.1 (2 C), 129.5 (2 C), 129.0, 128.4, 122.5, 120.6, 117.7, 116.5, 102.9, 47.9, 45.5, 21.3

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_2O_3Br$: 387.0339; found: 387.0342.

(*S*)-3-(4-Nitro-1*H*-indol-1-yl)-1-(4-nitrophenyl)butan-1-one (6b)

Title compound **6b** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(4-nitrophenyl)but-2-en-1-one (**2b**; 40.1 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2b** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 3–20% EtOAc–PE).

Yield: 26.1 mg (74%); yellow solid; mp 64–68 °C; 73% ee [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 70:30, flow rate 0.9 mL/min, *T* = 35 °C, λ = 254 nm): t_R =23.2 (minor), t_R = 49.8 (major)]; $[\alpha]_D^{20}$ –40.2 (*c* 0.041, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 3109, 2929, 1693, 1603, 1524, 1347, 1318, 1269, 790, 786 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30–8.24 (m, 2 H), 8.16–8.09 (m, 1 H), 8.05–8.00 (m, 2 H), 7.85–7.80 (m, 1 H), 7.50 (d, *J* = 3.3 Hz, 1 H), 7.33–7.27 (m, 2 H), 5.45–5.29 (m, 1 H), 3.64 (dd, *J* = 17.6, 6.0 Hz, 1 H), 3.51 (dd, *J* = 17.7, 6.9 Hz, 1 H), 1.73 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.3, 150.7, 140.63, 140.61, 137.8, 129.2 (2 C), 128.4, 124.1 (2 C), 122.6, 120.8, 117.9, 116.5, 103.2, 47.9, 46.2, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3O_5$: 354.1084; found: 354.109.

(*S*)-1-(4-Methoxyphenyl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6c)

Title compound **6c** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(4-methoxyphenyl)but-2-en-1-one (**2c**; 37 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 3–20% EtOAc–PE).

Yield: 28 mg (83%); yellow crystals; mp 100–104 °C; 75% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 80:20, flow rate 1.0 mL/min, *T* = 35 °C, λ= 254 nm): t_R =15.8 (major), t_R = 23.6 (minor)]; $[\alpha]_D^{20}$ –34.3 (*c* 0.065, $CHCl_3$); R_f = 0.3 (PE–EtOAc, 3:1).

IR (KBr): 2976, 1675, 1600, 1575, 1511, 1456, 1361, 1308, 1266, 1171, 759, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.9 Hz, 1 H), 7.88–7.79 (m, 3 H), 7.49 (d, *J* = 3.3 Hz, 1 H), 7.29–7.23 (m, 2 H), 6.91–6.85 (m, 2 H), 5.39–5.28 (m, 1 H), 3.83 (s, 3 H), 3.49 (dd, *J* = 17.0, 5.8 Hz, 1 H), 3.39 (dd, *J* = 17.0, 7.3 Hz, 1 H), 1.67 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.2, 164.1, 140.5, 137.9, 130.4 (2 C), 129.5, 128.7, 122.6, 120.6, 117.7, 116.7, 114.0 (2 C), 102.8, 55.7, 48.3, 45.3, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_4$: 339.1339; found: 339.1341.

CCDC 1923379 contains the supplementary crystallographic data for **6c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(*S*)-1-(Furan-2-yl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6d)

Title compound **6d** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(furan-2-yl)but-2-en-1-one (**2d**; 28.6 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2d** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 26.8 mg (90%); orange crystals; mp 85–90 °C; 63% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, *T* = 25 °C, λ = 254 nm): t_R =19.4 (major), t_R = 26.5 (minor)]; $[\alpha]_D^{20}$ –37.8 (*c* 0.030, $CHCl_3$); R_f = 0.3 (PE–EtOAc, 3:1).

IR (KBr): 3132, 2980, 1672, 1567, 1511, 1499, 1467, 1361, 1332, 1308, 760, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.54–7.43 (m, 2 H), 7.25–7.20 (m, 2 H), 7.09 (d, *J* = 3.6 Hz, 1 H), 6.46 (dd, *J* = 3.6, 1.7 Hz, 1 H), 5.33–5.20 (m, 1 H), 3.41 (dd, *J* = 16.5, 6.4 Hz, 1 H), 3.26 (dd, *J* = 16.5, 7.1 Hz, 1 H), 1.64 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.8, 152.5, 147.0, 140.6, 137.9, 128.5, 122.6, 120.7, 117.82, 117.78, 116.6, 112.8, 103.0, 48.1, 45.5, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_4$: 299.1026; found: 299.1032.

(*R*)-4-Methyl-3-(4-nitro-1*H*-indol-1-yl)-1-phenylpentan-1-one (6e)

The reaction time was 24 h. Title compound **6e** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-4-methyl-1-phenylpent-2-en-1-one (**2e**; 36.6 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 26.9 mg (80%); orange amorphous solid; 64% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R =17.3 (major), t_R = 20.8 (minor)]; $[\alpha]_D^{20}$ –31.9 (*c* 0.037, $CHCl_3$); R_f = 0.7 (PE–EtOAc, 3:1).

IR (KBr): 2966, 1686, 1597, 1565, 1512, 1499, 1448, 1361, 1327, 1302, 1273, 758, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.07 (m, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 7.86–7.79 (m, 2 H), 7.58–7.50 (m, 1 H), 7.45–7.36 (m, 3 H), 7.32–7.23 (m, 2 H), 5.00–4.90 (m, 1 H), 3.67 (dd, J = 17.3, 8.4 Hz, 1 H), 3.55 (dd, J = 17.3, 4.3 Hz, 1 H), 2.38–2.23 (m, 1 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.74 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.9, 140.5, 139.1, 136.5, 133.7, 129.2, 128.9 (2 C), 128.1 (2 C), 122.2, 120.6, 117.7, 117.2, 103.0, 58.4, 42.0, 34.2, 20.4, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_3$: 337.1547; found: 337.1543.

(*S*)-3-(4-Nitro-1*H*-indol-1-yl)-1-phenylnonan-1-one (6f)

The reaction time was 24 h. Title compound **6f** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-phenylnon-2-en-1-one (**2f**; 45.4 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 2–15% EtOAc–PE).

Yield: 31.0 mg (82%); orange amorphous solid; 59% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 95:5, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R =19.4 (major), t_R = 22.4 (minor)]; $[\alpha]_D^{20}$ –12.2 (*c* 0.064, $CHCl_3$); R_f = 0.6 (PE–EtOAc, 4:1).

IR (KBr): 3106, 2928, 2856, 1685, 1597, 1580, 1361, 1323, 1274, 755, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.89–7.82 (m, 3 H), 7.59–7.51 (m, 1 H), 7.48–7.38 (m, 3 H), 7.32–7.24 (m, 2 H), 5.26–5.15 (m, 1 H), 3.58 (dd, J = 17.3, 6.7 Hz, 1 H), 3.46 (dd, J = 17.3, 6.1 Hz, 1 H), 2.08–1.92 (m, 2 H), 1.35–0.97 (m, 8 H), 0.81 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1, 140.8, 138.9, 136.6, 134.0, 129.1 (2 C), 129.0, 128.3 (2 C), 122.6, 120.9, 117.9, 117.0, 103.3, 52.8, 45.0, 36.1, 31.8, 29.1, 26.4, 22.8, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_3$: 379.2016; found: 379.2021.

(*S*)-1-(Naphthalen-2-yl)-3-(4-nitro-1*H*-indol-1-yl)butan-1-one (6g)

Title compound **6g** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1-(naphthalen-2-yl)but-2-en-1-one (**2g**; 41.2 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2g** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 3–20% EtOAc–PE).

Yield: 34.2 mg (96%); orange amorphous solid; 69% ee [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R =27.8 (major), t_R = 42.4 (minor)]; $[\alpha]_D^{20}$ –87.9 (*c* 0.032, $CHCl_3$); R_f = 0.5 (PE–EtOAc, 3:1).

IR (KBr): 2979, 1680, 1626, 1565, 1510, 1498, 1469, 1361, 1331, 1302, 1269, 756, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 1.7 Hz, 1 H), 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.97–7.81 (m, 5 H), 7.64–7.52 (m, 3 H), 7.39–7.19 (m, 2 H), 5.47–5.36 (m, 1 H), 3.70 (dd, J = 17.2, 5.8 Hz, 1 H), 3.61 (dd, J = 17.1, 7.2 Hz, 1 H), 1.74 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.7, 140.5, 137.9, 135.9, 133.7, 132.5, 130.0, 129.7, 129.0, 128.8, 128.7, 127.9, 127.2, 123.5, 122.7, 120.6, 117.8, 116.7, 102.9, 48.3, 45.8, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_2O_3$: 359.1390; found: 359.1389.

3-(4-Nitro-1*H*-indol-1-yl)cyclohexan-1-one (6h)

The reaction time was 24 h. Title compound **6h** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and cyclohex-2-en-1-one (**2h**; 20.2 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–30% EtOAc–PE).

Yield: 16.8 mg (65%); yellow amorphous solid; racemic [HPLC (Daicel Chiralpak AD-H, hexane–^{i}PrOH, 90:10, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_{R1} = 23.2, t_{R2} = 26.8]; R_f = 0.1 (PE–EtOAc, 3:1).

IR (KBr): 2952, 1713, 1512, 1498, 1449, 1362, 1333, 1307, 1284, 792, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.0 Hz, 1 H), 7.68 (d, J = 8.2 Hz, 1 H), 7.47 (d, J = 3.3 Hz, 1 H), 7.36–7.27 (m, 2 H), 4.80–4.70 (m, 1 H), 2.99–2.87 (m, 1 H), 2.87–2.74 (m, 1 H), 2.62–2.32 (m, 3 H), 2.30–2.12 (m, 2 H), 1.91–1.76 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.2, 140.8, 137.6, 128.2, 122.8, 120.9, 118.0, 116.0, 103.2, 54.7, 48.4, 40.9, 31.7, 22.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077; found: 259.1081.

3-(4-Nitro-1*H*-indol-1-yl)-1,3-diphenylpropan-1-one (6i)

The reaction time was 48 h. Title compound **6i** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (2*E*)-1,3-diphenylprop-2-en-1-one (**2i**; 43.7 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2i** was added before evacuation of the system. The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 13.0 mg (35%); yellow solid; mp = 79–83 °C; racemic [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 70:30, flow rate 1.0 mL/min, T = 35 °C, λ = 254 nm): t_{R1} = 15.7, t_{R2} = 33.4]; R_f = 0.3 (PE–EtOAc, 3:1).

IR (KBr): 3063, 1685, 1596, 1580 1521, 1497, 1448, 1361, 1329, 1296, 753, 737, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 8.0, 0.8 Hz, 1 H), 7.98–7.90 (m, 2 H), 7.76 (d, J = 8.2 Hz, 1 H), 7.63–7.56 (m, 1 H), 7.51–7.44 (m, 3 H), 7.36–7.18 (m, 7 H), 6.50–6.43 (m, 1 H), 4.07 (dd, J = 17.4, 7.8 Hz, 1 H), 3.95 (dd, J = 17.4, 6.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.8, 140.6, 139.7, 138.4, 136.3, 134.0, 129.6 (2 C), 129.3 (2 C), 129.0, 128.5, 128.2 (2 C), 126.4 (2 C), 123.0, 121.0, 117.9, 117.1, 103.0, 55.7, 43.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_3$: 371.1390; found: 371.1387.

2-(4-Nitro-1*H*-indol-1-yl)-1,4-diphenylbutane-1,4-dione (6j)

The reaction time was 24 h. Title compound **6j** was obtained according to the general procedure from 4-nitroindole (**4a**; 16.2 mg, 0.1 mmol) and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**2j**; 49.6 mg, 0.21 mmol). Following a modification of the general procedure, ketone **2i** was added before evacuation of the system. The product was isolated by two sequential column chromatography procedures (silica gel; first: 3–20% EtOAc–PE; second: 50% DCM–PE).

Yield: 22.6 mg (60%); yellow amorphous solid; racemic [HPLC (Daicel Chiralpak OD-H, hexane–^{i}PrOH, 70:30, flow rate 1.0 mL/min, T = 35 °C, λ = 254 nm): t_{R1} = 11.1, t_{R2} = 20.8]; R_f = 0.7 (PE–EtOAc, 3:1).

IR (KBr): 3063, 1680, 1596, 1580, 1516, 1502, 1359, 1332, 1293, 1230, 760, 737, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.0, 0.8 Hz, 1 H), 8.00–7.88 (m, 5 H), 7.63–7.57 (m, 1 H), 7.57–7.50 (m, 1 H), 7.50–7.44 (m, 2 H), 7.43 (d, J = 3.3 Hz, 1 H), 7.42–7.34 (m, 3 H), 7.28 (dd, J = 3.4, 0.8 Hz, 1 H), 6.74 (dd, J = 8.1, 5.0 Hz, 1 H), 4.33 (dd, J = 17.8, 8.1 Hz, 1 H), 3.53 (dd, J = 17.8, 5.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.6, 194.2, 140.9, 137.6, 135.9, 134.7, 134.4, 134.1, 130.7, 129.1 (2 C), 129.0 (2 C), 128.6 (2 C), 128.3 (2 C), 123.3, 121.6, 118.2, 116.2, 104.3, 55.9, 40.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{43}H_{19}N_2O_4$: 399.1339; found: 399.1347.

(*S*)-1-(4-Oxo-4-phenylbutan-2-yl)-1*H*-indole-3-carbonitrile (3)

Title compound **3** was obtained according to the general procedure from 3-cyanoindole (**1**; 14.2 mg, 0.1 mmol) and (*E*)-1-phenylbut-2-en-1-one (**2**; 30.9 mg, 0.21 mmol). The product was isolated by direct column chromatography (silica gel; 5–25% EtOAc–PE).

Yield: 27.4 mg (95%); white solid; mp 59–61 °C; 42% ee [HPLC (Daicel Chiralpak OJ-H, hexane–^{i}PrOH, 80:20, flow rate 1.0 mL/min, T = 25 °C, λ = 254 nm): t_R = 41.7 (major), t_R = 46.2 (minor)]; $[\alpha]_D^{20}$ –19.6 (*c* 0.033, $CHCl_3$); R_f = 0.4 (PE–EtOAc, 3:1).

IR (KBr): 3121, 2217, 1685, 1597, 1580, 1530, 1461, 1449, 1361, 1288, 1214, 1184, 744, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 2 H), 7.79–7.71 (m, 2 H), 7.63–7.51 (m, 2 H), 7.49–7.40 (m, 2 H), 7.39–7.26 (m, 2 H), 5.39–5.26 (m, 1 H), 3.58 (dd, J = 17.4, 5.4 Hz, 1 H), 3.47 (dd, J = 17.4, 7.6 Hz, 1 H), 1.71 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.4, 136.3, 135.0, 134.0, 132.0, 129.0 (2 C), 128.11 (2 C), 128.06, 124.0, 122.4, 120.2, 116.0, 111.0, 86.6, 48.8, 45.2, 21.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1325.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690751.

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Appendix 3

Publication III

Trubitsõn, D.; Martõnova, J.; Kudrjašova, M.; Erkman, K.; Järving, I.; Kanger, T. Enantioselective Organocatalytic Michael Addition to Unsaturated Indolyl Ketones. *Org. Lett.*, **2021**, *23*, 1820−1824.

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Enantioselective Organocatalytic Michael Addition to Unsaturated Indolyl Ketones

Dmitri Trubitsõn, Jevgenija Martõnova, Marina Kudrjašova, Kristin Erkman, Ivar Järving, and Tõnis Kanger*

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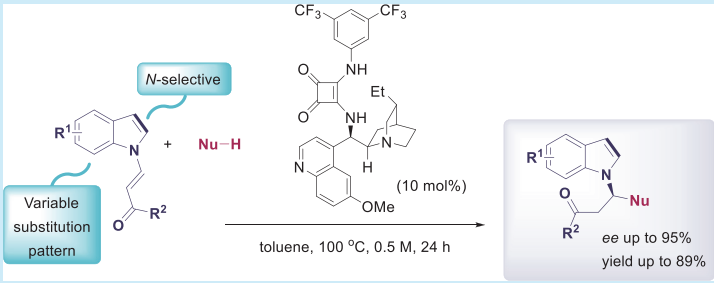

ABSTRACT: An efficient enantioselective organocatalytic method for the synthesis of *N*-alkylated indoles with α-branched alkyl substituents from the corresponding unsaturated indolyl ketones via a Michael addition has been developed. The resulting products were obtained in high enantioselectivities and in good yields. Various nucleophiles (nitroalkanes, malononitrile, malonic esters) can be used. The substitution pattern of the indole ring had no significant impact on the reaction outcome. Both electron-withdrawing and electron-donating substituents in any position of the heteroaromatic ring were well-tolerated.

Molecules bearing indole scaffolds can be found in a wide range of natural products, pharmaceutical compounds, and agrochemicals.[1] Some biologically active indoles contain a stereogenic center at the α-position of the *N*-atom (Figure 1). Therefore, such compounds have recently gained wide interest in synthetic chemistry[2−4] and in medicinal chemistry.[5]

The stereoselective derivatization of indole at the nitrogen atom with electrophilic reagents is still challenging because the most reactive nucleophilic center of the indole core is at C3.[6] To avoid C3-alkylation and to achieve high *N*-selectivity, the third position of the ring can be protected by substitution or, alternatively, the *N*−*H* acidity and nucleophilicity of the nitrogen atom can be increased by substituents in different positions of the indole core. The application of these two additional conditions provides high regioselectivity of the nucleophilic attack but also changes electronic and steric properties of indole core and limits the scope of the synthetic methodologies.[7]

During the past two decades, the interest in new enantioselective methodologies for the synthesis of chiral *N*-substituted indoles with a branched alkyl substituent has increased considerably.[8] Both direct methods of the derivatization of the indole core and indirect methods starting from other nitrogen-containing heterocycles (isatin, indoline, dihydroindole, etc.) via metal-catalyzed or organocatalytic reactions have been used. Since Trost et al. demonstrated the first enantioselective synthesis of chiral indolocarbazole derivatives (Scheme 1, **I**),[9] several other strategies have been exploited. These methods generally consider indole to be a nucleophilic coupling fragment reacting with different electrophilic partners. However, difficulty in controlling regioselectivity is often a problem.

Recently, Buchwald et al. reported the first polarity reversal strategy where an indole derivative was used as an electrophile in the enantioselective ligand-controlled metal-catalyzed reaction to achieve *N*-alkylated products (Scheme 1, **II**).[10] The method is based on the CuH-catalyzed *N*-alkylation of *N*-(2,4,6-trimethylbenzoyloxy)indole with alkenes.

Based on the approach where an indole derivative was applied as a non-nucleophile,[11] we decided to employ the electrophilic activation mode of the α-carbon of the nitrogen atom by converting an indole to a Michael acceptor (Scheme

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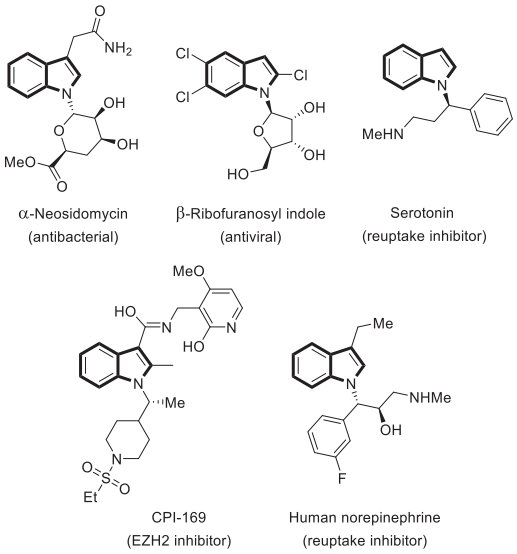
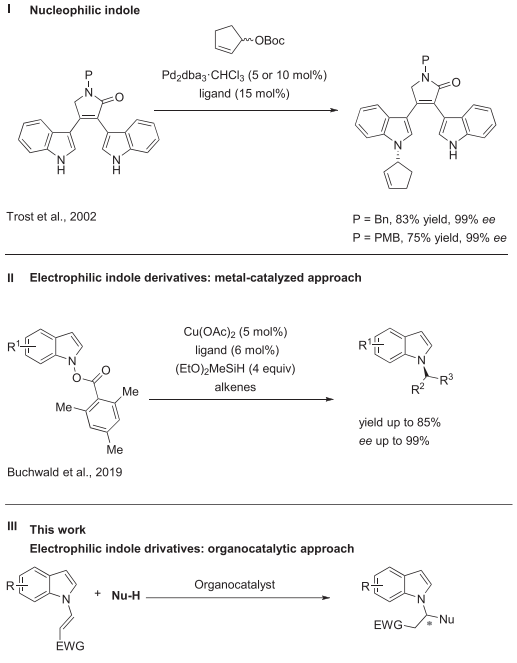


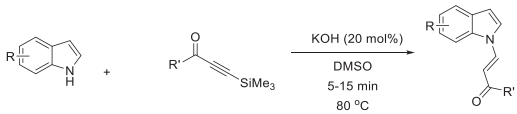
Figure 1. Selected biologically active enantiomeric *N*-substituted indoles.

Scheme 1. Different Approaches to the Enantioselective Synthesis of *N*-Substituted Indoles with Branched Substituents



1, **III**). An appropriate starting material can be prepared by the hydroamination of the corresponding silyl alkynes with an indole (Scheme 2).[12] It is a specific reaction where the only

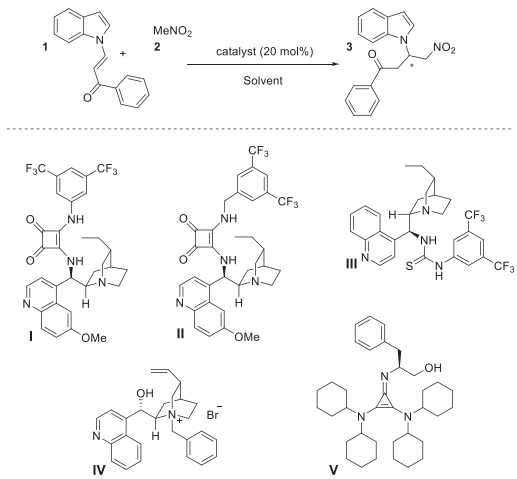
Scheme 2. Hydroamination of Indoles



reaction center in the indole ring is the *N*-atom. The simple synthetic route provides easy access to enaminones possessing indole core and Michael acceptor moiety. An asymmetric 1,4-conjugate addition to the acceptor provides a direct entry to the enantioselective synthesis *N*-substituted indoles with a branched alkyl substituents. This two-step sequence totally excludes the formation of C3-side product due to the application of indole *N*-adducts as electrophiles.

Here, we describe the first enantioselective organocatalytic formal *N*-alkylation of indoles using an indole derivative as a Michael acceptor. To test our hypothesis, compound **1** was synthesized and used as a model compound in a reaction with nitromethane **2** in the presence of organocatalysts (Table 1). For the stereoselective conjugate addition of nitroalkanes to electron-deficient alkenes, various catalysts have been used.[13] The screening of the catalyst was started with hydrogen

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	time (h)	temp (°C)	solvent	conv[b] (%)	ee[c] (%)
1	**I**	48	rt	DCM	nr	nd
2	**I**	48	80	DCE	71	92
3	**II**	48	80	DCE	traces	nd
4	**III**	48	80	DCE	12	−88
5[d]	**IV**	1	rt	DCE	99	*rac*
6	**V**	24	rt	DCE	31	*rac*
7	**I**	48	80	1.4-dioxane	69	94
8	**I**	48	80	toluene	82	94
9	**I**	48	100	toluene	85	94
10[e]	**I**	48	100	toluene	93	92

[a]Reaction conditions: 0.1 mmol scale, 1 equiv of **1**, 10 equiv of **2**, 20 mol % of catalyst, solvent (0.5 mL). [b]Conversion was determined by ^{1}H NMR from the crude mixture. [c]Determined by chiral HPLC analysis. [d]1 equiv of Rb_2CO_3 was added. [e]Toluene (0.2 mL).

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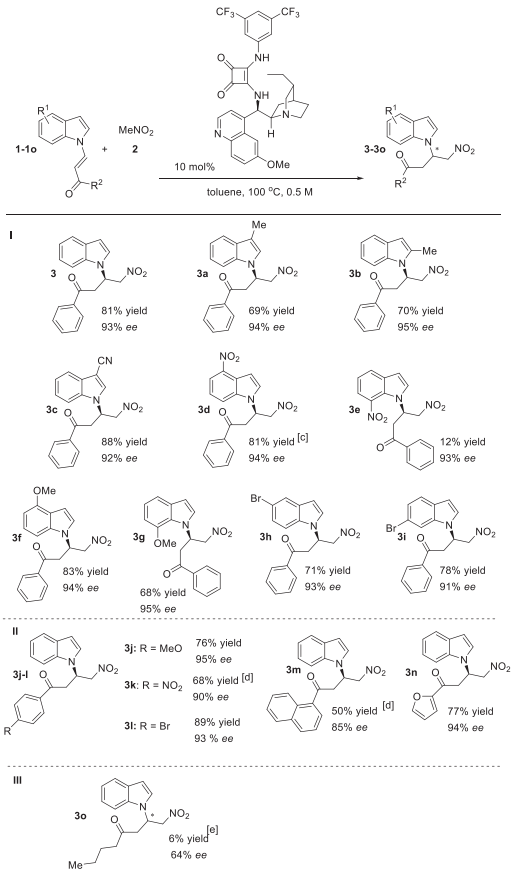
bonding catalysts. Bifunctional cinchona alkaloid-based squaramides **I**, **II**, and thiourea **III** are widely used with nitro-group containing Michael donors.[14,15] The reaction did not take place in the presence of catalyst **I** at room temperature in DCM, although increasing the temperature to 80 °C led to moderate conversion (71%) and afforded product in high ee (92%) in DCE in 2 days (Table 1, entries 1 and 2). Only traces of the product were detected in the presence of the catalyst **II** under the same conditions (Table 1, entry 3). The reaction in the presence of quinine-based thiourea **III** afforded product in high enantioselectivity but the conversion was unreasonably low (Table 1, entry 4). According to our previous experience with indole chemistry with phase-transfer catalysis,[7a] PTC **IV** was used (Table 1, entry 5). Full conversion was achieved at room temperature but the formed product was racemic. Next, cyclopropenimines as enantioselective Brønsted base catalysts were applied.[16] With the catalyst **V**, low conversion of the starting material and obtained racemic product were characteristic (Table 1, entry 6). Next, a brief screening of the solvents with the most selective catalyst **I** revealed that toluene was the best solvent in terms of both yield and enantioselectivity (Table 1, entry 8). A slightly higher reactivity was achieved when the temperature was raised to 100 °C (Table 1, entry 9). Moreover, almost full conversion was reached by increasing the concentration from 0.2 to 0.5 M without a significant impact on the stereoselectivity (Table 1, entry 10).

Additionally, the influence of the catalyst amount on the reaction rate was examined (see, Figure S1). There was no significant difference when 10 or 20 mol % of the catalyst was used. However, the experiment with 5 mol % of the catalyst was inefficient demonstrating a considerable decline in reaction rate and the conversion was only 78% in 26 h. Notably, the catalyst amount did not affect the enantioselectivity of the reaction, and the ee value remained constant and high during the entire experiment.

Under optimized reaction conditions (toluene, 100 °C, 10 mol % of catalyst **I**, and reaction time 24 h), the substrate scope of the reaction was investigated. Initially, variations on the indolyl scaffold were evaluated (Scheme 3, **I**). The reaction was run with monosubstituted indole derivatives that differentiated from each other in the position and nature of the substituent. The incorporation of the methyl group into the C2- or C3-position did not have a significant impact on the reaction yield or on the enantioselectivity. Substrates with electron-withdrawing substituents at the C3- or C4-positions tolerated the reaction well, providing the products **3c** and **3d** in good yields (88 and 81%) and high *ee*-s (92% and 94%). A drastic decline in the reaction yield was detected (most probably a retro-Michael reaction occurred) when the 7-nitro-substituted Michael acceptor **1e** was used (yield 12%). However, the *ee* value of the product **3e** remained high (93%). The tolerance toward electron-donating groups (and also the substituent at the seventh position) on the indolyl ring was well represented by 4- and 7-metoxy-substituted *N*-functionalized indoles. The electron-donating groups did not affect the reactivity, and the desired products **3f** and **3g** were isolated in good yields (83% and 68%) and excellent enantioselectivities (94% and 95%). Halogen-substituted C5- and C6-unsaturated *N*-indolyl ketones reacted smoothly, affording *N*-alkylated indoles **3h** and **3i** in good yields (71% and 78%) and high ee's (93% and 91%). Thus, the substitution pattern of the indole ring is not essential and the method is applicable to the monosubstituted indole derivatives possessing

Scheme 3. Scope and Limitations of the Reaction with Nitromethane[a]



[a]Reaction conditions: 0.2 mmol scale, 1 equiv of **1**−**1o**, 10 equiv of nitromethane, 10 mol % of catalyst **I**, in 0.4 mL of toluene (0.5 M), 24 h. [b]ee was determined by chiral HPLC analysis. [c]0.2 M. [d]0.1 mmol scale. [e]Reaction time 7 days.

substituents in any position. The absolute stereochemistry of product **3g** was unambiguously assigned by single-crystal X-ray diffraction (see the SI), and other compounds in the series were assigned based on the analogy.

Next, we turned our attention to the scope of Michael acceptors with parent indolyl scaffolds (Scheme 3, **II**). Both electron-withdrawing and electron-donating substituents at the *para*-position of a phenyl ring did not have a significant impact on the reaction yield (68% and 76%), but slightly better enantioselectivity (95%) was achieved in the case of methoxy-substituted substrate **1j**. The *p*-bromo-substituted product **3l** was isolated in high yield (89%), and the achieved ee was comparable with the model compound **3**. The bulky 1-naphthyl substituent of **1m** led to a moderate yield (50%) and slightly decreased the *ee* value (85%). Heteroaromatic furyl derivative **3n** was obtained in high yield and ee (77% and 94%, respectively). Notably, the reaction rate and stereoselectivity dropped drastically when the substrate **1o** with the aliphatic

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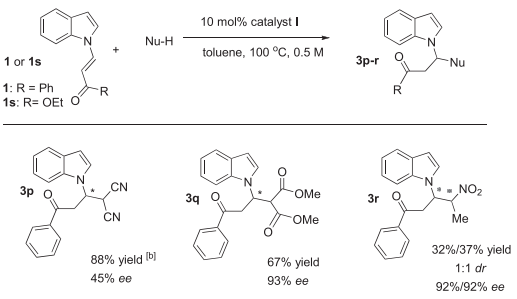
butyl chain was used instead of a phenyl ring (Scheme 3, **III**). The reaction was unacceptably slow, indicating the importance of $\pi-\pi$ interactions. The product **3o** was isolated after 7 days in only 6% yield.

Next, the scope of Michael donors and acceptors was studied briefly (Scheme 4). The reaction with malononitrile

Scheme 4. Scope of Michael Donors and Acceptors[a]

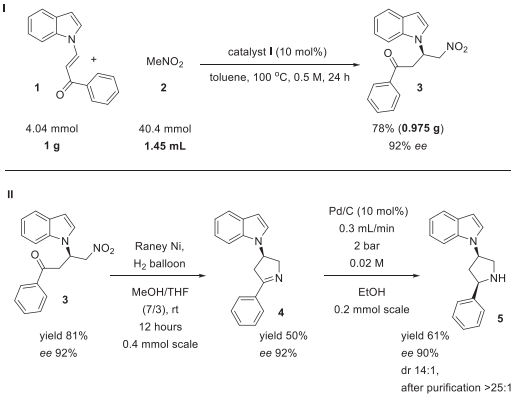


[a]Reaction conditions: 0.2 mmol scale, 1 equiv of **1** or **1o**, 10 equiv of nucleophile, 10 mol % of catalyst **I**, in 0.4 mL of toluene (0.5 M), 24 h. [b]Reaction time 1 h.

was complete with 1h but the enantiomeric purity of the product **3p** was considerably lower. There was no reaction with acetonitrile. Malonic ester reacted smoothly affording product **3q** in 67% yield and 93% ee. A 1:1 mixture diastereomers **3r** was obtained with nitroethane in high ee's (92%/92%). To our delight, the diastereomers of **3r** were chromatographically separable. The reaction with 2,4-pentanedione led to the mixture of products. The substitution of the phenyl ring with an alkoxycarbonyl group in the indole-based Michael acceptor (compound **1s**) led to the substantial decrease of the reactivity and no reaction was detected with nitromethane.

To evaluate the synthetic potential of the current methodology, a gram-scale experiment was performed with substrate **1** (Scheme 5, **I**). The scale-up of the reaction did not affect either the reaction yield or enantioselectivity (78% yield, 92% ee). Furthermore, the synthetic transformation of compound **3** was

Scheme 5. Demonstration of Synthetic Utility



explored. It was converted to a 5-HT_6 receptor modulator analogue precursor **5**.[17] The treatment of compound **3** with Raney nickel induced the reduction of the nitro group to an amino group followed by intramolecular cyclization, affording the corresponding chiral imine **4** without the loss of enantioselectivity (Scheme 5, **II**). The imine **4** was later easily hydrogenated in a flow reactor with Pd/C cartridge providing chiral pyrrolidine derivative **5** in high dr ratio (14:1) and good yield (62%). The *cis*-configuration of the substituents in the pyrrolidine ring was determined by selective NOESY (details in the SI). The diastereomeric ratio of the product **5** was improved after the purification of the reaction (>25:1).

In summary, we have developed the first enantioselective organocatalytic method for the synthesis of *N*-alkylated indoles starting from unsaturated indolyl ketones. The main feature of our method is exploiting an indole derivative as an electrophile totally avoiding the regioselectivity problems common with other *N*-alkylation methods. A wide range of electrophilic indole *N*-adducts bearing various substituents provide exclusively *N*-alkylated indoles with a branched substitutents in good yields (up to 89%) and high to excellent ee values (up to 95%). The enantioselectivity of the reaction does not depend on the substitution pattern of the indole ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00222.

Synthesis of starting compounds, copies of ^{1}H and ^{13}C spectra, and HPLC chromatograms (PDF)

Accession Codes

CCDC 2054770 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Tõnis Kanger − *Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia;* orcid.org/0000-0001-5339-9682; Email: tonis.kanger@taltech.ee

Authors

Dmitri Trubitsõn − *Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia*

Jevgenija Martõnova − *Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia*

Marina Kudrjašova − *Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia*

Kristin Erkman − *Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia*

Ivar Järving − *Department of Chemistry and Biotechnology, Tallinn University of Technology, 12618 Tallinn, Estonia*

Complete contact information is available at:

https://pubs.acs.org/10.1021/acs.orglett.1c00222

Notes

The authors declare no competing financial interest.

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Author's Other Publications and Conference Presentations

Other publications

1. Trubitsõn, D.; Žari, S.; Kaabel, S.; Kudrjashova, M.; Kriis, K.; Järving, I.; Pehk, T.; Kanger, T. Asymmetric Organocatalytic Cascade Synthesis of Tetrahydrofuranyl Spirooxindoles. *Synthesis*, **2018**, *50*, 314–322.

Conference presentations

1. Trubitsõn, D.; Kanger, T. Enantioselective *N*-alkylation of nitroindoles under phase-transfer catalysis. 27th International Society of Heterocyclic Chemistry Congress (27th ISHC), **2019**, Kyoto, Japan. (Poster)
2. Trubitsõn, D.; Kudrjašova, M.; Kanger, T. Enantioselective *N*-alkylation of indole derivatives. XXII International Conference on Organic Synthesis (22-ICOS), **2018**, Florence, Italy. (Poster)
3. Trubitsõn, D.; Kudrjašova, M.; Kanger, T. Enantioselective *N*-alkylation of indole derivatives. Balticum Organicum Syntheticum 2018 (BOS 2018), **2018**, Tallinn, Estonia. (Poster)
4. Trubitsõn, D.; Žari, S.; Kudrjašova, M.; Erkman, K.; Ošeka, M.; Kanger, T. Enantioselective organocatalytic synthesis of oxa-spirooxindole derivatives. Balticum Organicum Syntheticum 2016 (BOS 2016), **2016**, Riga, Latvia. (Poster)

Curriculum Vitae

Personal data

Name:	Dmitri Trubitsõn
Date of birth:	25.10.1991
Place of birth:	Tallinn, Estonia
Citizenship:	Estonian

Contact data

E-mail:	dtrubitson@gmail.com

Education

2017 – ...	Tallinn University of Technology, Chemistry and Biotechnology, Ph.D.
2015 – 2017	Tallinn University of Technology, Applied Chemistry and Biotechnology, M.Sc. (cum laude)
2011 – 2014	Tallinn University of Technology, Applied Chemistry and Biotechnology, B.Sc. (cum laude)
2008 – 2011	Tallinn Mustamäe Real Gymnasium (gold medal)

Language competence

Estonian (fluent), Russian (native) and English (fluent)

Professional employment

2017 – ...	Tallinn University of Technology, Department of Chemistry and Biotechnology, early stage researcher

Professional associations

2018 – …	The Estonian Chemical Society, member

Honours and awards

2019	Dora Plus T1.1 short-term mobility scholarship (The Archimedes Foundation, Estonia)
2018	Dora Plus T1.1 short-term mobility scholarship (The Archimedes Foundation, Estonia)
2018	Ene Silla Scholarship (Estonian Students Fund in the USA)
2016	Elsa D. & Edgar Mathiesen Scholarship (Estonian Students Fund in the USA)

Teaching experience

Autumn 2019	Organic chemistry I, exercise tutorials (undergraduate course)
Spring 2018	Stereochemistry and exercise tutorials (graduate course).

Elulookirjeldus

Isikuandmed

Nimi:	Dmitri Trubitsõn
Sünniaeg:	25.10.1991
Sünnikoht:	Tallinn, Eesti
Kodakondsus:	eesti

Kontaktandmed

E-post:	dtrubitson@gmail.com

Hariduskäik

2017 – ...	Tallinna Tehnikaülikool, Keemia ja biotehnoloogia, Ph.D.
2015 – 2017	Tallinna Tehnikaülikool, Rakenduskeemia ja biotehnoloogia, M.Sc. (*cum laude*)
2011 – 2014	Tallinna Tehnikaülikool, Rakenduskeemia ja biotehnoloogia, B.Sc. (*cum laude*)
2008 – 2011	Tallinna Mustamäe Reaalgümnaasium (kuldmedal)

Keelteoskus

eesti (kõrgtase), vene (emakeel), inglise (kõrgtase)

Teenistuskäik

2017 – ...	Tallinna Tehnikaülikool, Keemia ja biotehnoloogia instituut, nooremteadur

Kuuluvus erialaühingutesse

2018 – …	Eesti Keemiaselts, liige

Teaduspreemiad ja tunnustused

2019	Dora Pluss T1.1 lühiajalise õpirände stipendium (SA Archimedes, Eesti)
2018	Dora Pluss T1.1 lühiajalise õpirände stipendium (SA Archimedes, Eesti)
2018	Ene Silla nimeline stipendium (Eesti Üliõpilaste Toetusfond USAs)
2016	Elsa D.& Edgar Mathiesen nimeline stipendium (Eesti Üliõpilaste Toetusfond USAs)

Õpetamiskogemus

Sügis 2019	Orgaaniline keemia I, harjutustunnid (bakalaureuseõpe)
Kevad 2018	Stereokeemia, harjutustunnid (magistriõpe).

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