THESIS ON NATURAL AND EXACT SCIENCES B172

Asymmetric Organocatalytic Synthesis of 3,3’-Disubstituted Oxindoles

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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 any other academic degree.

/Artur Noole/

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Asümmeetriline organokatalüütiline 3,3’-diasendatud oksindoolide süntees

ARTUR NOOLE

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KIRJASTUS

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I Noole, A.; Suckman, N.; Kabeshov, M.; Kanger, T.; Macaev, F.; Malkov, A. Highly Enantio- and Diastereoselective Generation of Two Quaternary Centers in Spirocyclopropanation of Oxindole Derivatives. *Chemistry - A European Journal*, **2012**, *18*, 14929 - 14933.

II Noole, A.; Järving, I.; Werner, F.; Lopp, M.; Malkov, A.; Kanger, T. Organocatalytic Asymmetric Synthesis of 3-Chlorooxindoles Bearing Adjacent Quaternary–Tertiary Centers. *Organic Letters*, **2012**, *14*, 4922 - 4925.

III Noole, A.; Ošeka, M.; Pehk, T.; Öeren, M.; Järving, I.; Elsegood, M.; Malkov, A.; Lopp, M.; Kanger, T. 3-Chlorooxindoles: Versatile Starting Materials for Asymmetric Organocatalytic Synthesis of Spirooxindoles. *Advanced Synthesis and Catalysis*, **2013**, *355*, 829 - 835.

IV Noole, A.; Malkov, A. V.; Kanger, T. Asymmetric Organocatalytic Synthesis of Spiro-cyclopropaneoxindoles. *Synthesis*, **2013**, *45*, 2520 - 2524.

V Noole, A.; Ilmarinen, K.; Järving, I.; Lopp, M.; Kanger, T. Asymmetric Synthesis of Congested Spiro-cyclopentaneoxindoles via an Organocatalytic Cascade Reaction. *Journal of Organic Chemistry*, **2013**, *78*, 8117 - 8122.

Author's Contribution

The contributions by the author to the papers included in the thesis are as follows:

I – V Participated in the planning of experiments and carried out the experiments, analysis of the final compounds and participated in the final manuscript preparation.

Abbreviations

Ac	acyl
(*R*)- BINAP	(*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazolines
Cat.	catalyst
CPME	cyclopentyl methyl ether
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DME	dimethoxyethane
DMP	2,2-dimethoxypropane
ee	enantiomeric excess
En	enamine
2-FBA	2-fluorobenzoic acid
HPLC	high-performance liquid chromatography
LPS	lipopolysaccharides
MBH	Morita-Baylis-Hillman
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
*n*Pr	*n*-propyl
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
pK_a	acid dissociation constant
PMP	*para*-methoxyphenyl
RT	room temperature
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine

THF	tetrahydrofurane
TMS	trimethylsilyl
VCD	vibrational circular dichroism

Introduction

The field of enantioselective (or asymmetric) synthesis was largely dominated by auxiliary-based synthesis or enzymatic and/or organometallic catalysis for most of the 20th century. It was not until the late 1990s that the fourth branch – organocatalysis was “born”. Although, not a new concept (sporadic examples had been reported before),[1] the real “kick-off” was largely inspired by a handful of papers published around the turn of the century.[2] Since then, more than 3000 papers have been published dealing with the concept of “enantioselective organocatalysis”, a remarkable number considering the fact that before the 1990s only erratic examples had been reported.

Currently, organocatalysis has become an accomplished field of organic synthesis, utilizing a number of intrinsic activation modes.[3] Taking advantage of this novel “toolkit” to construct complex molecular architectures from simple, readily available starting materials has become a mainstream field of research. Although achieving efficiencies close to nature’s (enzymatic catalysis) has remained an elusive task, this apparent shortcoming can be eliminated by the wider applicability of organocatalysis in a target-oriented synthesis. Over the last decade or so, organocatalysis has matured to become a powerful methodology, used in drug as well as drug-like molecule synthesis.

Oxindoles are an important class of bioactive molecules making up the core of many natural as well as synthetic compounds. In the following literature overview, the importance of the oxindole core structure, as well as its numerous biological activities, will be highlighted. Synthesis of chiral 3,3’-disubstituted oxindoles will be discussed in great detail, outlining the most relevant examples from the literature. Organocatalytic, organometallic and miscellaneous examples are included in this review, to provide a brief overview of the current state of the enantioselective synthesis of oxindoles.

1. Literature overview

In general, four main strategies have been used for the asymmetric synthesis of 3,3'-disubstituted oxindoles **E** (including *spiro*-oxindoles) (Figure 1). Methyleneindolinones **A** and isatines **B** are the most common precursors, although oxindoles **D** and 3-substituted oxindoles **C** have been used extensively as well. Both metal-catalyzed and organocatalytic methods have been reported, whereas the auxiliary-induced transfer of chirality is less common, and will therefore be excluded from further discussion.

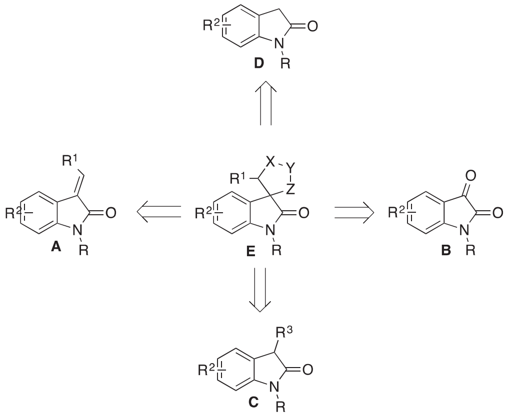


Figure 1. Strategies for 3,3'-disubstituted oxindoles **E** formation.

In metal-catalyzed methods, asymmetry is induced by chiral ligands that form complexes with various metal salts. All the precursors discussed above (Figure 1) can coordinate to these metal-ligand complexes and participate in annulation reactions. Alternatively, metal-ligand complexes have been used to activate the second starting material participating in the cyclization reaction. Although no general mechanism can be presented, various examples will be discussed in the following sections.

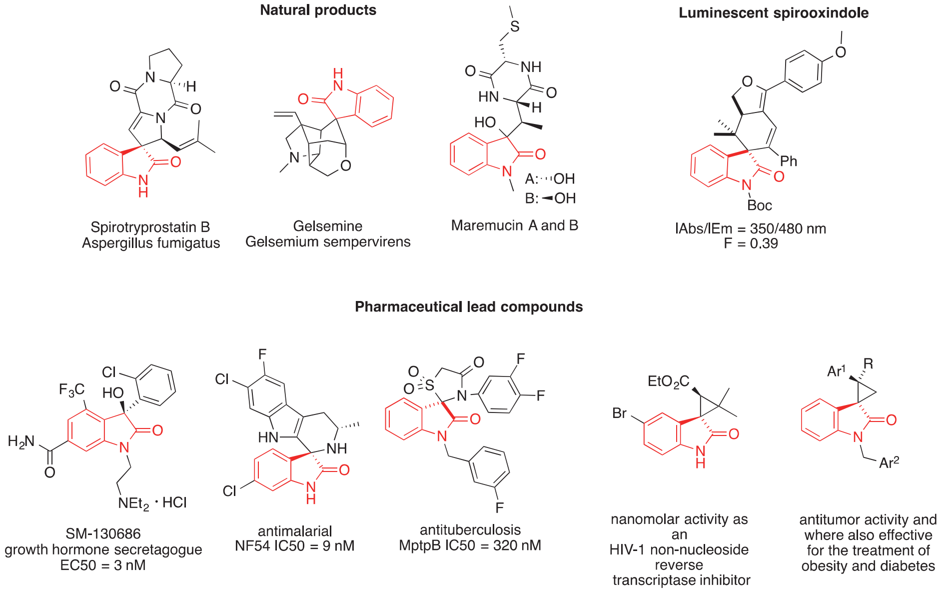
Organocatalysis has found increasing use in the asymmetric synthesis of 3,3'-disubstituted oxindoles **E**. The three most commonly used intrinsic activation modes in the field of enantioselective synthesis are aminocatalysis, hydrogen bond catalysis and more recently NHC catalysis.

Chiral amines have been used widely to activate aldehydes, ketones or corresponding unsaturated derivatives for stereospecific addition or annulation reactions with all types of oxindole **E** precursors (Figure 1). In hydrogen-bond catalysis, activation is usually achieved by means of forming hydrogen bonds with carbonyl groups of the substrate. However, often multiple starting materials are simultaneously coordinated by the catalyst, delivering high levels of stereocontrol.

NHC catalysis has been used for umpolung reactions of unsaturated aldehydes and ketenes with isatines **B**. Chiral carbenes (generated *in situ* from bench stable precursors) activate the unsaturated aldehydes or ketenes by means of covalent bond formation and are released during the cyclization step.

The 3,3'-disubstituted oxindole motif makes up the core of many natural products as well as synthetic compounds (Scheme 1).[4,5,6,7,8] The abundance of this structural feature in an excessive number of bioactive molecules has inspired an avalanche of research directed towards the development of new methods for the synthesis of oxindole containing chiral compounds. The biological activities attributed to oxindoles range from antimalarial,[9] anti-HIV[10,11] and anticancer[12,13] to anti-diabetes and obesity treatments.[14] All of this makes them ideal drug candidates against a variety of diseases.

The majority of these compounds can be classified as *spiro*-oxindoles. However, examples of 3-hydroxy-, 3-halo- and 3-aminooxindoles showing promising biological activities have also been reported. They can be used as building blocks in alkaloid synthesis[15] and, in many cases, as starting materials for medicinal chemistry.[16]

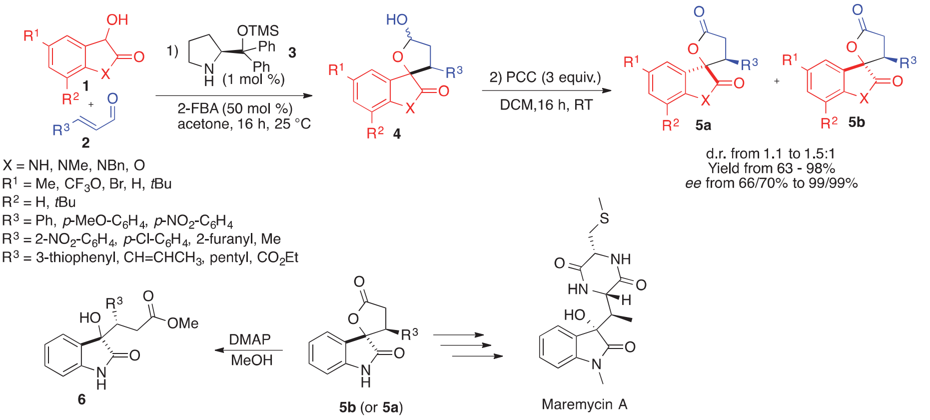


Scheme 1. Naturally occurring and biologically active oxindoles.

1.1. Asymmetric synthesis of 3-substituted 3-hydroxyoxindoles

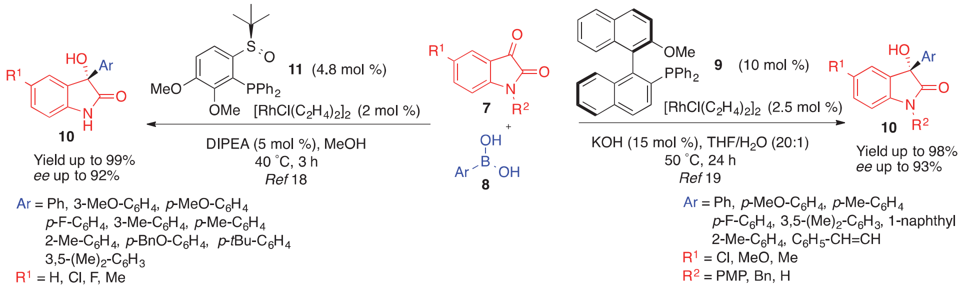
Hydroxy-bearing quaternary centers at C3 of the oxindole core can be found in many bioactive compounds and natural products (Scheme 1).

Melchiorre and Bergonzini[17] showed that 3-hydroxyoxindoles **1** can be used as starting materials in an aminocatalysed domino reaction with α,β-unsaturated aldehydes **2**. The corresponding lactoles **4** could be derived in high conversions and enantioselectivities and isolated after oxidation to the corresponding lactones **5a**/**5b** (Scheme 2).



Scheme 2. Synthesis of *spiro*-lactones **5a/5b**.

Although, diastereomeric ratios remained moderate, the isomers could easily be separated by column chromatography in the majority of cases. Furthermore, the authors have showed that lactones **5a**/**5b** can be converted to 3-hydroxyoxindole esters **6** and total synthesis of the natural product Maremycin A further demonstrated the synthetic utility of the process.

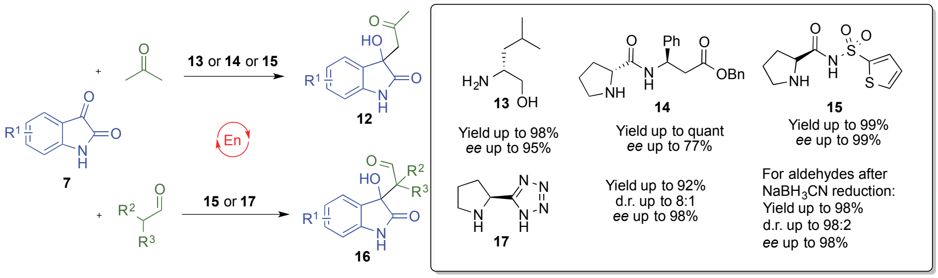


Scheme 3. Arylation and alkenylation of isatins **7**.

Hayashi *et al.* [18] developed a rhodium-catalyzed asymmetric addition of arylboronic acids **8** to isatines **7**, leading to biologically relevant

3-hydroxyoxindoles **10** in high yields (Scheme 3). Excellent levels of enantioselectivities (up to 93%) were achieved using a binaphthyl phosphine **9** derived rhodium complex as a catalyst. Most remarkably, even free *N*-H isatines **7** could be used as substrates without a decrease in reactivity, although enantioselectivity was compromised (*ee* 49% with free *N*-H *vs*. *ee* 79% for *N*-PMP). Using chiral sulfoxide phosphine **11** as a ligand, however, Gui *et al.*[19] were able to synthesize chiral 3-hydroxyoxindoles **10** with free *N*-H group in high enantioselectivities and yields (Scheme 3).

In a similar effort *de* Vries and Minnaard used a chiral phosphite-rhodium complex for the formation of 3-aryl-3-hydroxyoxindoles **10**, but enantioselectivities remained moderate (*ee* up to 55%).[20]

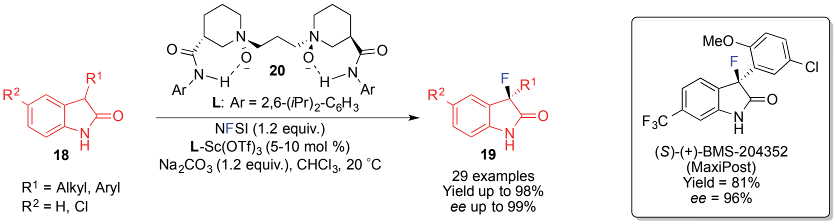


Scheme 4. Aldol reactions of isatines **7** with acetone and aldehydes.

Under enamine catalysis isatines **7** gave an aldol reaction with acetone (Scheme 4), providing ketones **12** in high yields and selectivities. [21,22,23]

Amines **15**[24] and **17**[25] catalyzed the addition of aldehydes to isatines **7** (Scheme 4). With aminocatalyst **15**, products **16** were isolated after reduction of aldehydes to respective alcohols. In both cases, high selectivities were observed, with yields reaching almost quantitative levels.

1.2. Asymmetric synthesis of 3-substituted 3-halooxindoles

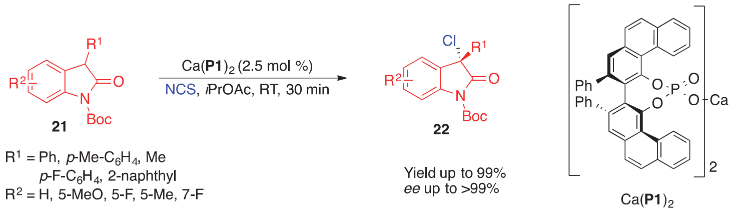


Scheme 5. Synthesis of 3-fluorooxindoles **19**.

Feng and Li[26] developed a highly efficient chiral scandium complex **20** catalyzed methodology for the fluorination of 3-alkyl- and 3-aryloxindoles **18** using *N*-fluorobenzenesulfonimide (NFSI) as a fluorine source (Scheme 5). Although several examples using stoichiometric quantities of *Cinchona* alkaloids as catalysts had been reported previously,[27,28] this represents the first catalytic fluorination of *N*-unprotected oxindoles **18**, offering as a proof of the concept one step access to MaxiPost (an optically active potassium channel opener).[29]

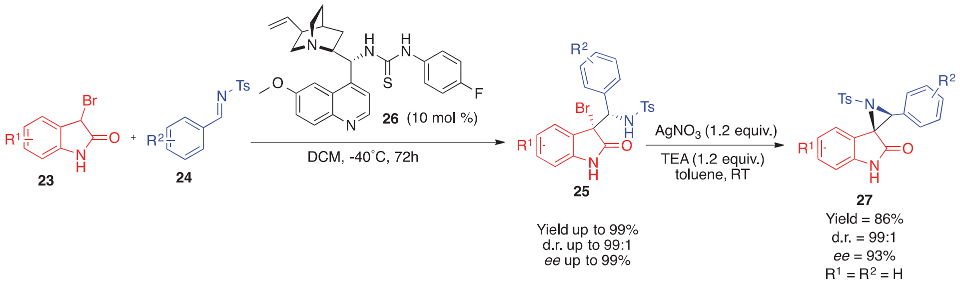
In a more recent work, Yang and Wu showed that an (*R*)-BINAP derived palladium catalyst is able to promote the same reaction with aryl oxindoles **21** with a *Boc* protective group (yield = 90-97%; *ee* = 88-99%).[30]

Antilla *et al.*[31] disclosed an enantioselective chlorination protocol of *Boc*-protected oxindoles **21** (Scheme 6).



Scheme 6. Asymmetric chlorination of oxindoles **21** in the presence of a Ca(**P1**)$_2$ catalyst.

Using a chiral calcium salt of phosphoric acid **P1** and NCS (*N*-chlorosuccinimide) as a chlorine source, 3-chloro-3-aryloxindoles **22** were uniformly isolated in high yields and selectivities. With 3-methyloxindole **21**, however, significantly lower enantioselectivity was attained (*ee* = 62%).

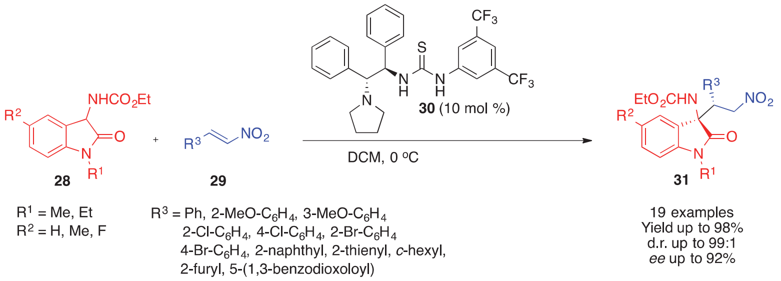


Scheme 7. Asymmetric Mannich reaction of 3-bromooxindoles **23** to *N*-tosyl-imines **24**.

Peng *et al.* showed that 3-bromooxindoles **23** could be used as nucleophiles in a Mannich reaction with *N*-tosyl imines **24** (Scheme 7).[32] The corresponding Mannich adducts **25** were synthesized in excellent enantio- and diastereoselectivities and high yields using a chiral thiourea catalyst **26**. It was further demonstrated, that in the presence of stoichiometric quantities of $AgNO_3$, 3-bromooxindole **25** was converted to *syn*-aziridine **27** *via* an S_N2- type substitution reaction.

1.3. Asymmetric synthesis of 3-substituted 3-aminooxindoles

Yuan and co-workers[33] developed a new method to synthesize optically active quaternary 3-aminooxindoles **31** from 3-monosubstituted precursors **28** and nitroalkenes **29** *via* a bifunctional thiourea **30** catalyzed Michael addition reaction (Scheme 8).



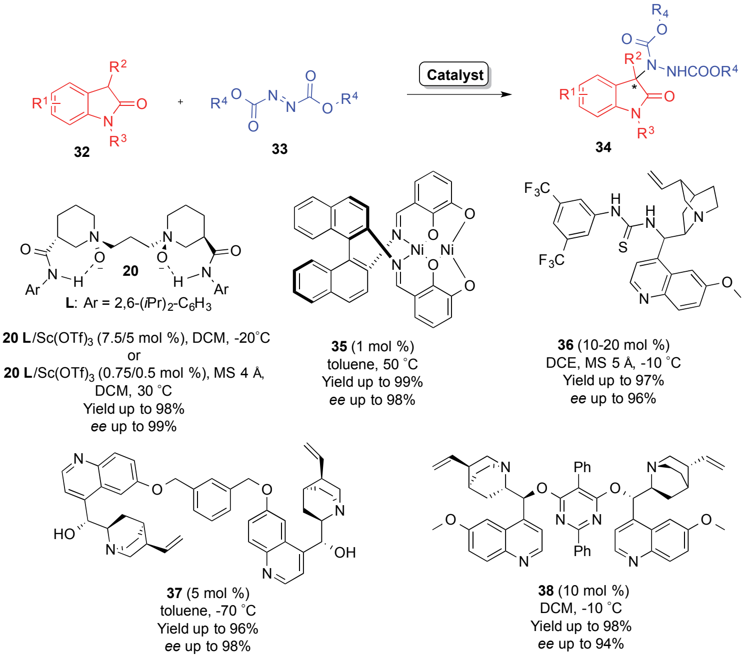
Scheme 8. Asymmetric organocatalytic synthesis of 3-aminooxindoles **31**.

Several groups have reported successful α-amination reactions of 3-aryl- and 3-alkyloxindoles **32** (Scheme 9). Feng *et al.*[34] developed a chiral scandium complex **20** catalyzed amination strategy of 3-substituted oxindoles **32**. Different aliphatic azodicarboxylates **33** were compatible with the reaction conditions, as well as substitutions at C3 and the indole ring of **32**. Catalyst loadings below 1 mol % could be used without a decrease in reactivity. Most significantly, no protective group was necessary on the N-H moiety.

Shibasaki[35] disclosed a similar approach to 3-aminooxindoles **34** using a chiral nickel complex **35** as a catalyst. As a major limitation, only *N*-Boc protected oxindoles **32** could be employed as substrates, although excellent selectivities were reported.

In an organocatalytic methodology developed by Zhou,[36] products **34** were obtained in high yields and selectivities in the presence of a thiourea catalyst **36**. Substituents at the indole ring were well tolerated as well as a free N-H group (Scheme 9).

Cinchona alkaloid derived C_2-symmetric catalysts **37** and **38**, developed by Zhou[37] and Barbas III,[38] respectively, successfully delivered α-aminated oxindoles **34**. Catalyst **37** was limited to 3-aryloxindoles **32**, whereas catalyst **38** could be used with aliphatic substrates as well. In both instances high levels of selectivity were reported with good to excellent isolated yields.



20 **L**/Sc(OTf)$_3$ (7.5/5 mol %), DCM, -20°C
or
20 **L**/Sc(OTf)$_3$ (0.75/0.5 mol %), MS 4 Å, DCM, 30 °C
Yield up to 98%
ee up to 99%

35 (1 mol %)
toluene, 50 °C
Yield up to 99%
ee up to 98%

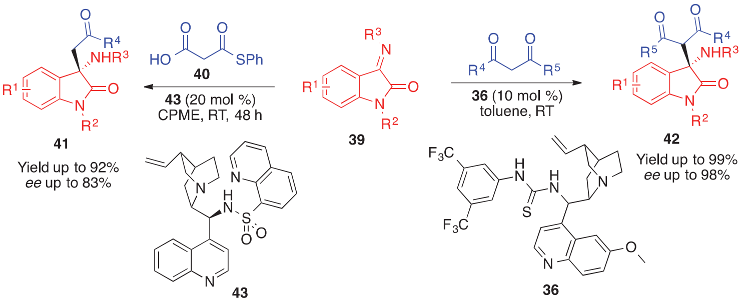
36 (10-20 mol %)
DCE, MS 5 Å, -10 °C
Yield up to 97%
ee up to 96%

37 (5 mol %)
toluene, -70 °C
Yield up to 96%
ee up to 98%

38 (10 mol %)
DCM, -10 °C
Yield up to 98%
ee up to 94%

Scheme 9. Enantioselective organocatalytic α-amination of oxindoles.

In an alternative pathway to 3-aminooxindoles, Shibata *et al.*[39] reported an enantioselective decarboxylative addition of malonic acid mono-thioester **40** to ketimines **39**. Catalyzed by quinidine-derived sulfonamide **43**, products were isolated in high yields and good selectivities.



43 (20 mol %)
CPME, RT, 48 h

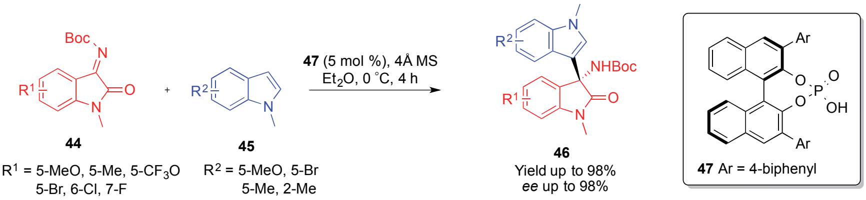
36 (10 mol %)
toluene, RT

Yield up to 92%
ee up to 83%

Yield up to 99%
ee up to 98%

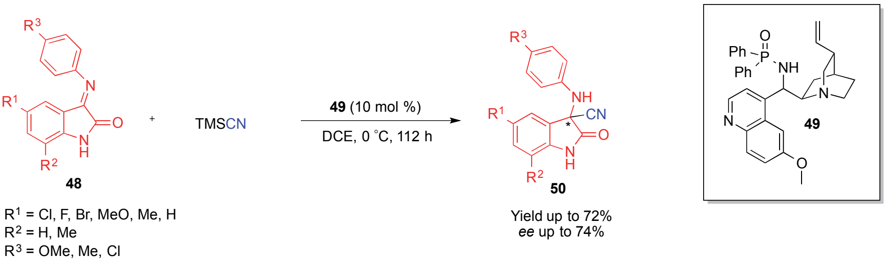
Scheme 10. Asymmetric addition of 1,3-dicarbonyl compounds to ketimines **39**.

Wang introduced a direct chiral thiourea **36** catalyzed addition of 1,3-dicarbonyl compounds to ketimines **39**.[40] Malonates, keto-esters and diketones were suitable nucleophiles. However, non-symmetrical 1,3-dicarbonyl compounds produced products in poor diastereoselectivities (high *ee* was retained).



Scheme 11. Asymmetric addition of indoles **45** to ketimines **44**.

Chiral phosphoric acid **47** promoted an *aza*-Friedel-Crafts addition of indoles **45** to *N*-Boc ketimines **44**.[41] In general, 3-aminooxindoles **46** were obtained in high yields and enantioselectivities (Scheme 11). Remarkably, when pyrrole, 4,7-dihydroindole or *N*-Me pyrrole was used as a nucleophile (instead of indole derivative **45**), reactions proceeded with almost quantitative yields and excellent enantioselectivities with just 2 mol % of the catalyst **47** loading (the reaction time was only 3 minutes).

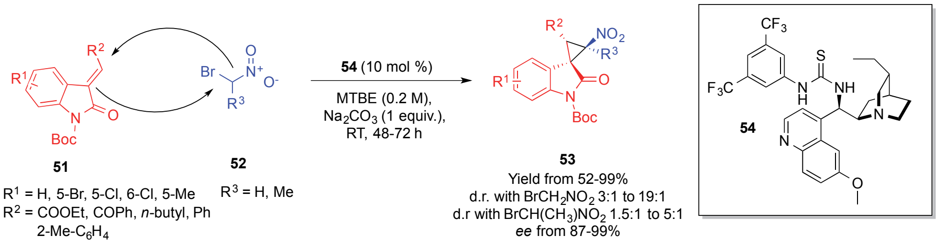


Scheme 12. Asymmetric Strecker reaction of ketimines **48**.

An asymmetric Strecker reaction of ketimines **48** with TMSCN provided, under bifunctional *Cinchona* alkaloid derived phosphinamide **49** catalysis, α-cyano-3-aminooxindoles **50** in moderate yields and good selectivities (Scheme 12).[42]

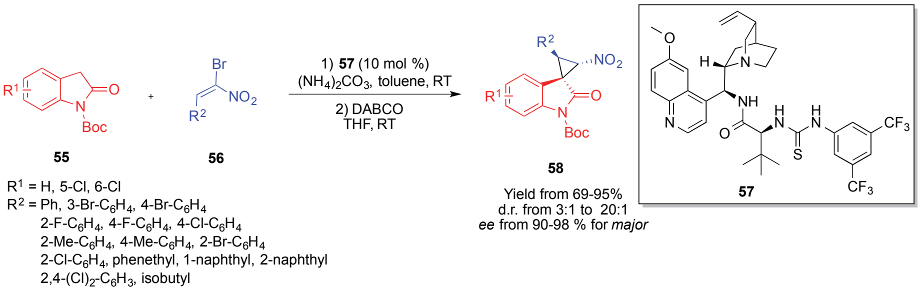
1.4. Asymmetric synthesis of *spiro*-cyclopropyloxindoles and 3-epoxyoxindoles

Bencivenni[43] reported a highly enantioselective cyclopropanation of *Boc*-protected alkylidene oxindoles **51** with bromonitromethane **52** and its homologues (Scheme 13). Thiourea **54** catalyzed a sequence of Michael-alkylation reactions delivering *spiro*-cyclopropyloxindoles **53** in good to excellent yields and selectivities. A significant drop in diastereoselectivity was, however, observed when α-bromonitroethane **52** was used as an alkylating agent. The reaction was highly versatile, allowing substitutions at various positions of the indole ring, and different R^2 groups were compatible (esters, ketones, alkyl and aryl substituents), with only a minor influence on enantioselectivity.



Scheme 13. Cyclopropanation of alkylidene oxindoles **51**.

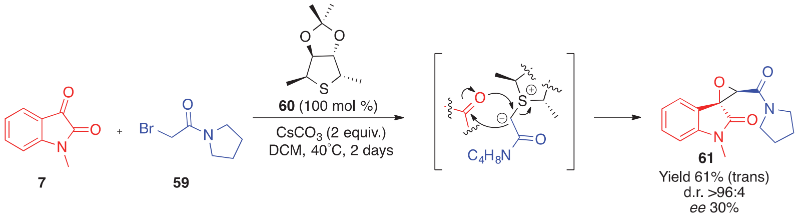
The reaction was proposed to proceed over a transition state, where both carbonyl groups of the alkylidene oxindole **51** were hydrogen-bonded to the catalyst **54**, and the positioning of nitroalkane **52** was controlled by a hydrogen bond with a protonated tertiary amine of the catalyst.



Scheme 14. Diastereodivergent synthesis of *spiro*-cyclopropyloxindoles **58**.

In an alternative approach, Lu and Dou[44] started with oxindoles **55** and bromonitroalkenes **56** delivering a broad range of nitro-substituted *spiro*-cyclopropyloxindoles **58** in moderate to high diastereoselectivities and excellent enantioselectivities (Scheme 14). In contrast to Bencivenni's work, the *spiro*-center had an opposite configuration, further expanding the family of *spiro*-cyclopropyloxindoles. Due to the acidity of the α-nitro proton, Lu was able to show that a *cis*-isomer of **58** can be epimerized under basic conditions, effectively eliminating one of the isomers generated in the first step of the cascade, thereby increasing the yield and diastereomeric purity of the final products.

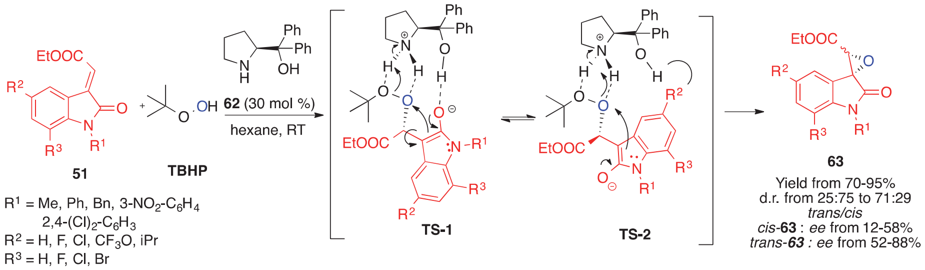
Spiro-oxiranes **61** are the oxygen analogues of *spiro*-cyclopropyloxindoles. The first asymmetric epoxidation of isatines **7** was published by Briére,[45] using stoichiometric quantities of thioether **60** as a catalyst (Scheme 15). Sulfide **60** forms a sulfonium ylide intermediate with bromoacetamide **59**, resulting in the formation of epoxide **61** *via* a nucleophilic addition-elimination sequence. Although sulfide **60** showed only moderate enantioselectivity (*ee* 30%), high diastereoselectivity towards *trans*-isomer was observed. It was demonstrated by the authors that amides **61** could be converted to ketones using a PhLi addition at -78 °C, with the retention of stereoselectivity.



Yield 61% (trans)
d.r. >96:4
ee 30%

Scheme 15. Asymmetric epoxidation of *N*-methyl isatine **7**.

Gasperi *et al.* developed a more general methodology for the synthesis of *spiro*-epoxyoxindoles **63** (Scheme 16).[46] Starting with simple alkylidene oxindoles **51**, under non-covalent chiral catalysis, the desired epoxides were isolated in high yields with moderate to good diastereo- and enantioselectivities. To account for the observed selectivity, a transition state **TS-1** was proposed. The proposed transition state leads to the formation of *trans*-oxirane **63**. However, when the σ-bond between Cα–Cβ rotates, a new transition state **TS-2**, accounts for the formation of *cis*-oxirane **63**. The proposed mechanism also explains the poor enantioselectivity of *cis*-oxirane **63**, as it is a consequence of both the less-favored *Si*-face attack and the continuous interconversion between **TS-1** and **TS-2** (when R^2 was halide, more *cis*-oxiran **63** formed, as **TS-2** became more stabilized by an additional H-bond between R^2 and OH of the catalyst **62**).



R^1 = Me, Ph, Bn, 3-NO$_2$-C$_6$H$_4$
2,4-(Cl)$_2$-C$_6$H$_3$
R^2 = H, F, Cl, CF$_3$O, iPr
R^3 = H, F, Cl, Br

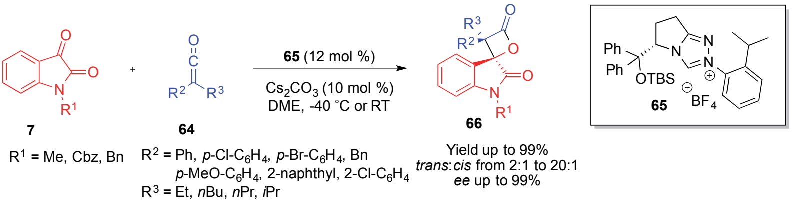
Yield from 70-95%
d.r. from 25:75 to 71:29
trans/cis
cis-**63** : *ee* from 12-58%
trans-**63** : *ee* from 52-88%

Scheme 16. Asymmetric epoxidation of alkylidene oxindoles **51**.

1.5. Asymmetric synthesis of *spiro*-β-lactoneoxindoles

Four-membered cyclic systems are among the most strained and therefore hardest to "construct" structures in organic synthesis. It stands to reason that introducing a spiral center to such a system is an extremely difficult and challenging task.

Ye and co-workers developed a general NHC **65** catalyzed method for the addition of ketenes **64** to isatines **7** (Scheme 17),[47] resulting in the formation of *spiro*-β-lactoneoxindoles **66** with two adjacent quaternary centers. Although, diastereoselectivities remained moderate for the majority of the products, enantioselectivities were excellent.

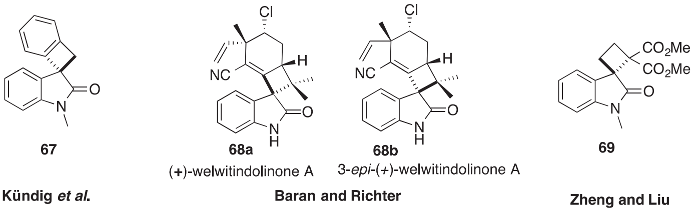


Scheme 17. Enantioselective [2+2] cycloaddition of ketenes **64** to isatines **7**.

Examples of *spiro*-cyclobutyloxindoles, with an all-carbon cyclobutane rings are scarce. Kündig *et al.*[48] disclosed a palladium-catalyzed asymmetric intermolecular α-arylation strategy, allowing for the synthesis of *spiro*-cyclobutyloxindoles **67** among other related compound with larger spiral rings (Scheme 18).

Total synthesis of (+)-welwitindolinone A **68a** (promising bioactivities and unprecedented molecular architecture) and its epimer **68b** was developed by Baran and Richter.[49]

Inspired by the structure of welwitindolinone, Zhang and Liu published a four-step sequence for the construction of *spiro*-oxindole **69**.[50]



Scheme 18. Examples of *spiro*-cyclobutyloxindoles.

1.6. Asymmetric synthesis of *spiro*-cyclopentyloxindoles

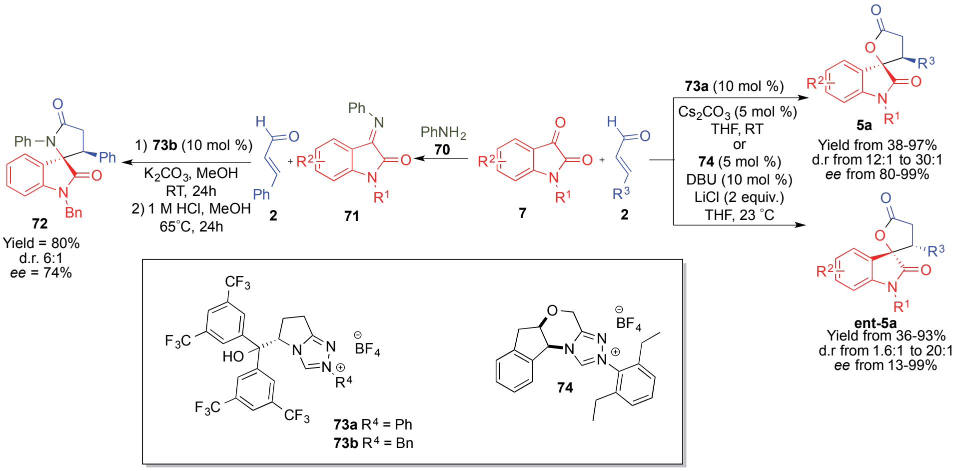
Not surprisingly, *spiro*-cyclopentyloxindoles make up one of the largest families of *spiro*-oxindoles. The core structure is well represented among natural products as well as synthetic compounds. In the following section, a brief look at the most important synthetic approaches for the construction of both all-carbon and heteroatom-containing (N, O and S) *spiro*-cyclopentyloxindoles will be discussed.

1.6.1. Synthesis of *spiro*-cyclopentyloxindoles starting from isatines and corresponding imines

Isatines **7** are commercial, readily available heterocyclic amides, making them ideal starting materials for the construction of *spiro*-oxindoles.

Taking advantage of chiral NHC-catalysis, Ye *et al.* reported a highly diastereo- and enantioselective [3+2] annulation of unsaturated aldehydes **2** and isatines **7** (Scheme 19).[51] Predating the work of Melchiorre, substantially higher diastereoselectivities were observed for the *spiro*-lactone **5a** (see Scheme 2). Both aromatic and aliphatic substituents were tolerated as R^3. However, only modest yield was obtained for the latter (38%, $R^3 = n$Pr).

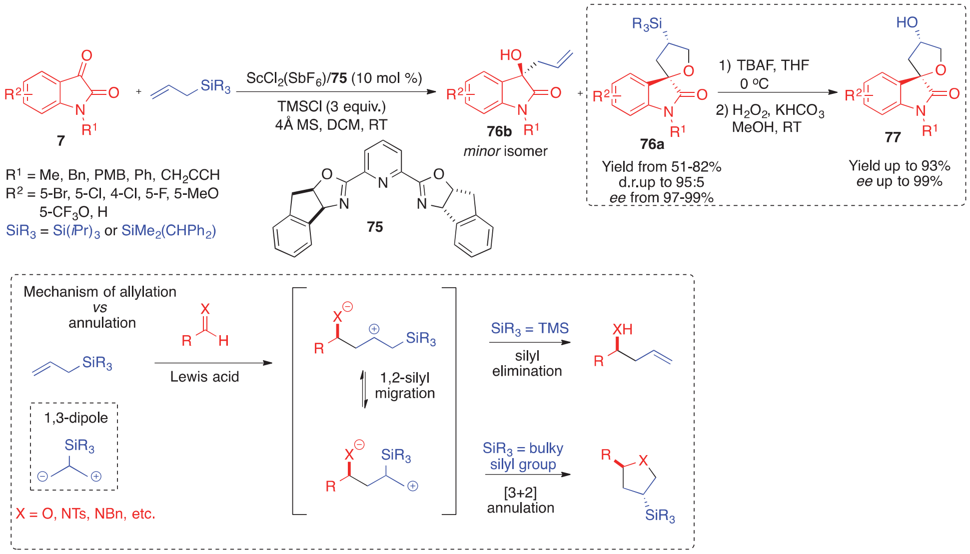
The swapping of the catalyst from **73a** to **74** by Scheidt *et al.*,[52] resulted in the formation of the enantiomer of *spiro*-lactone **5a**. Interestingly, LiCl, as a Lewis acid, played a crucial role in the catalytic cycle. With aromatic enals **2**, enantioselectivity was elevated in the presence of LiCl, whereas with aliphatic aldehydes **2** it had a detrimental effect on the enantioselectivity of the reaction (in the absence of LiCl, *spiro*-lactones ***ent*-5a** with aliphatic R^3 groups could be obtained in high selectivities and yields).



Scheme 19. Enantioselective synthesis of *spiro*-lactones **5** and *spiro*-lactams **72**.

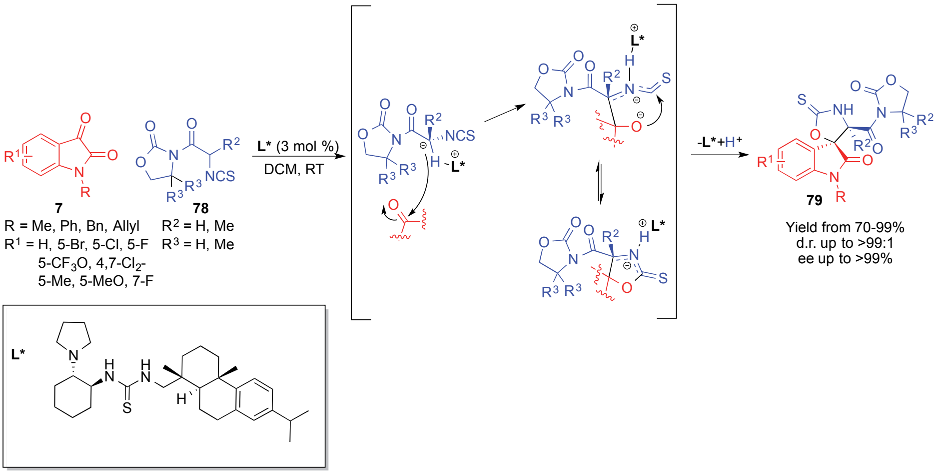
By switching from isatine **7** to the corresponding ketimine **71** and NHC catalyst **73b**, Jiao described[53] the synthesis of spirocyclic γ-lactam **72**. Although only one example of the asymmetric formation of lactam **72** was reported, the method nevertheless provides a direct route to nitrogen analogues of **5a**. The one-pot synthesis proceeds in two steps: 1) the addition of homoenolate to ketimine **71**, followed by the esterification of the intermediate to release the catalyst; 2) γ-lactam **72** is formed after the amidation step under acidic conditions.

Franz and co-workers[54] developed a highly efficient catalytic [3+2] annulation reaction of isatines **7** with allylsilanes (Scheme 20). Promoted by TMSCl, the chiral cationic complex of BOX **75** enables the reaction to proceed in a highly enantiocontrolled manner. The reaction can follow either the annulation pathway to yield *spiro*-lactones **76a**, or *via* silyl elimination (after the initial additions step) leading to the allylation product **76b** (see Scheme 20 for details). Optimal selectivity was achieved with benzhydryl allylsilane (the allylation pathway was remarkably persistent even with large silyl groups). Oxidation of the products **76a** resulted in a selective formation of corresponding alcohols **77**.



Scheme 20. Asymmetric [3+2] annulation of allylsilanes with isatines **7**.

Wang *et al.*[55] developed a drug-inspired synthesis of *spiro*-oxindoles **79**, analogues of Phytoalexin (potent antimicrobials, anti-tumor agents and oviposition-stimulants) (Scheme 21).



Scheme 21. Synthesis of chiral *spiro*-oxindoles **79**.

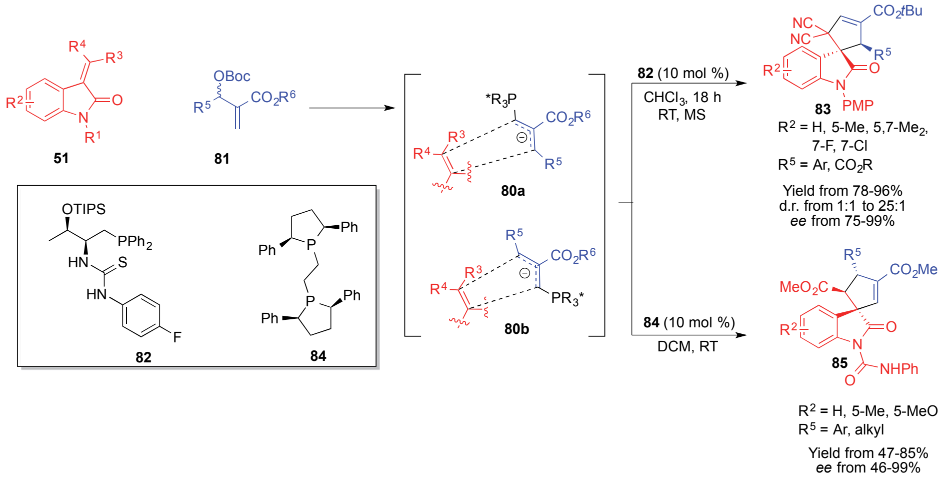
The reaction proceeds *via* an aldol-type addition of α-isothiocyanato imides **78** to isatines **7**, followed by intermolecular cyclization. The reaction is initiated by the thiourea catalyst **L*** with tertiary amine moiety, driving the reaction towards the formation of *spiro*-oxindoles **79**. Several new compounds were found to significantly reduce LPS-induced fever, using a model of acute neuroinflammation. Using α-isothiocyanato imides **78**, a similar reaction with alkylidene oxindoles **51** was also reported.

1.6.2. Synthesis of *spiro*-cyclopentyloxindoles starting from alkylidene oxindoles

Alkylidene oxindoles **51** make up the second class of important precursors for the synthesis of *spiro*-oxindoles. Similarly to isatines **7**, they can be used in cascade reactions initiated by the Michael addition and followed by a nucleophilic cyclization step. Many examples of successful annulation reactions starting with alkylidene oxindoles **51** for the synthesis of *spiro*-cyclopentyloxindoles have been developed.

Lu *et al.*[56] reported [3+2] annulation of *tetra*-substituted alkylidene oxindoles **51** with MBH carbonates **81** catalyzed by chiral phosphine **82** (Scheme 22). Excellent levels of enantioselectivity were achieved with high yields and in most cases, products with high diastereoselectivities were obtained.

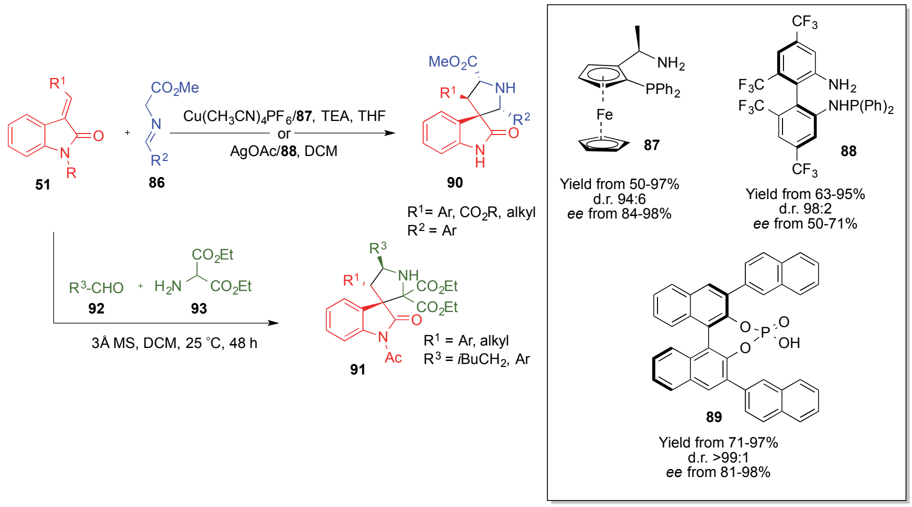
With chiral diphosphine **84**, Barbas III[57] was able to completely shift the regioselectivity of the cycloaddion reaction, resulting in the formation of *spiro*-oxindoles **85**. Reactions proceeded with a high level of stereocontrol for aromatic carbonates **81**, but only moderate enantioselectivity and yield was obtained for the aliphatic adduct (R^5 = Me, 47%, *ee* 46%).



Scheme 22. Phosphine-catalyzed asymmetric [3+2] annulation of alkylidene oxindoles **51**.

Spiro-pyrrolidinyloxindoles constitute the core structural element found in a huge family of natural alkaloids and synthetic compounds displaying promising biological activities. Not surprisingly, considerable efforts have been made to develop new synthetic methods for the construction of these structural skeletons in enantioenriched form.

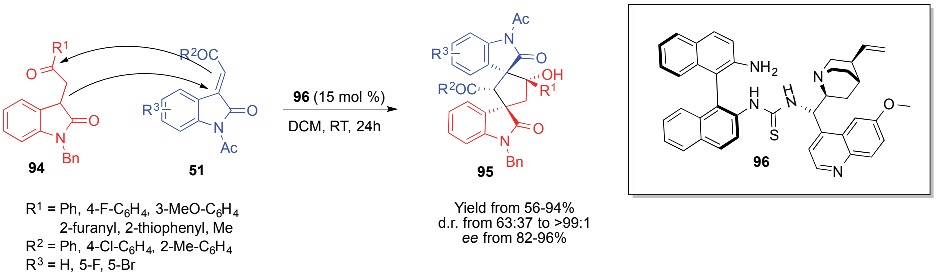
Gong *et al.*[58] disclosed the first catalytic enantioselective three-component synthesis of *spiro*-pyrrolidinyloxindoles **91**. Chiral phosphoric acids have been shown to activate imines and carbonyl compounds. The 1,3-dipolar cycloaddition is believed to proceed over a transition state, where both imine (formed *in situ* from aldehyde **92** and 2-aminomalonate **93**) and methyleneindolinone **51** are hydrogen-bonded to the catalyst **89**. Theoretical calculations supporting the proposed mechanism for the cycloaddion reaction were in accordance with the experimental results.



Scheme 23. Synthesis of *spiro*-pyrrolidinyloxindoles.

Using a copper-ferrocene **87** complex as a catalyst, Waldmann *et al.*[59] reported a highly stereoselective 1,3-dipolar cycloaddion of alkylidene oxindoles **51** with glycine ester imines **86** (Scheme 24). Interestingly, the authors observed a non-linear dependency of copper to ligand ratio, with the dimeric complexes leading to the highest diastereo- and enantioselectivities (copper-ligand 2:1).

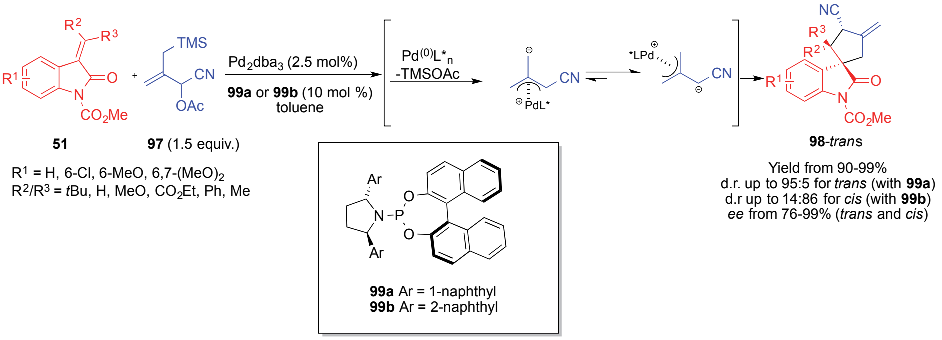
Wang showed that the same reaction could also be catalyzed by silver-chiral phosphine **88** complexes, [60] although enantioselectivities fell short of Waldmann's results (up to 71% *vs*. up to 98%).



Scheme 24. Synthesis of bispirooxindoles **95**.

Barbas III and co-workers published a highly diastereoselective methodology for the formation of bispirooxindoles **95** *via* a Michael-aldol cascade reaction using thiourea catalyst **96** (Scheme 24). [61] The high stereoselectivity of the reaction is assumed to derive from the dual-activation of both reacting partners. The 3-subsituted oxindole **94** is believed to be coordinated by multiple hydrogen bonds with the catalyst **96**, while the alkylidene oxindole **51** is bonded to the tertiary amine subunit of the catalyst. The importance of the latter interaction is further supported by the observation that when phenyl group was directly attached to the double bond of **51** poor results were obtained.

Trost *et al.* found an efficient chiral palladium complex catalyzed [3+2] cycloaddion reaction of methyleneindolinones **51** and allylsilanes **97** leading to all-carbon *spiro*-cyclopentyloxindoles **98** (Scheme 25).[62] Most remarkably, ligands **99a** and **99b** complemented each other, making a smooth selection of the desired diastereoisomer possible. With the latter, a *cis*-isomer is formed, whereas with a 1-naphtyl substituted catalyst **99a** strong *trans* selectivity was observed. It should be noted that protection of the methyleneindolinone **51** was crucial to obtaining products in high selectivities.



51 **97** (1.5 equiv.)

R^1 = H, 6-Cl, 6-MeO, 6,7-(MeO)$_2$
R^2/R^3 = *t*Bu, H, MeO, CO$_2$Et, Ph, Me

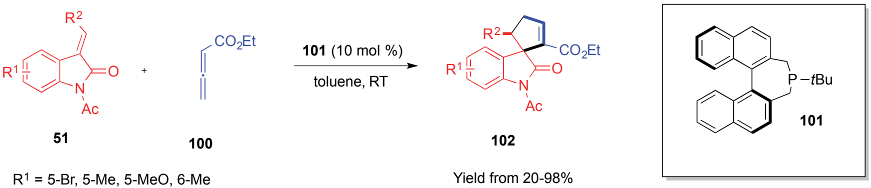
99a Ar = 1-naphthyl
99b Ar = 2-naphthyl

98-*trans*

Yield from 90-99%
d.r. up to 95:5 for *trans* (with **99a**)
d.r up to 14:86 for *cis* (with **99b**)
ee from 76-99% (*trans* and *cis*)

Scheme 25. Synthesis of *spiro*-cyclopentyloxindoles *via* a trimethylenemethane cyclization strategy.

In a related effort, Marinetti *et al.*[63] developed a similar annulation strategy using allenes **100** as C$_3$ coupling partners (Scheme 26). Different aromatic methyleneindolinones **51** were shown to react with 2,3-butadienoate **100**, yielding congested *spiro*-cyclopentyloxindoles **102** in good to high stereoselectivities. The reactions were catalyzed by chiral phosphine **101**, which was able to promote the reaction under mild conditions.



51 **100** **102** **101**

R^1 = 5-Br, 5-Me, 5-MeO, 6-Me
R^2 = Ph, 1-naphthyl, 2-naphthyl, 4-Ph-C$_6$H$_4$
4-CF$_3$-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-Cl-C$_6$H$_4$
3-Br-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 2-furyl, 2-quinolyl
-CCC$_5$H$_{11}$

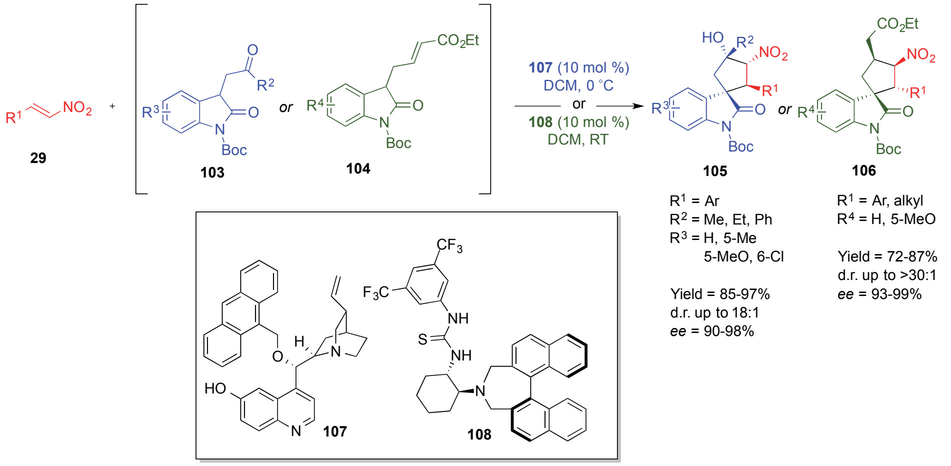
Yield from 20-98%
d.r. up to >95:5
ee from 86-99%

Scheme 26. Phosphine-promoted [3+2] annulation of alkylidene oxindoles **51**.

1.6.3. Miscellaneous examples of the synthesis of *spiro*-cyclopentyloxindoles

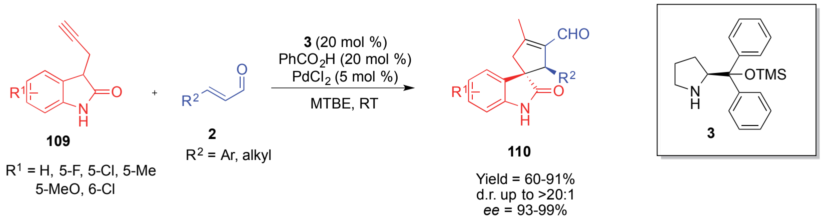
A wide range of methods taking advantage of 3-subsituted oxindoles as starting materials to construct the *spiro*-cyclopentyloxindole skeleton have been devised.

Quinidine-derived catalyst **107** was able to promote a Michael-Henry cascade between nitroolefins **29** and 3-substituted oxindoles **103**, leading to the formation of *spiro*-cyclopentyloxindoles **105** with four consecutive stereocenters (Scheme 27).[64] In a double Michael cascade reaction, reported by Shao and co-workers,[65] uniquely designed donor-acceptor oxindoles **104** were able to react with nitroalkenes, promoted by a thiourea catalyst with both central and axial chiral elements (Scheme 27). In both cases high levels of stereocontrol were achieved using a broad range of substituents in both reacting partners.



Scheme 27. Synthesis of *spiro*-cyclopentyloxindoles from nitroolefins **29**.

By combining an organocatalyst in a synergistic manner with metal salts, Wang *et al.* [66] disclosed a novel "organo-metal" domino reaction (Scheme 28). Enantioselectivity was achieved by a chiral amine **3** induced Michael addition of oxindoles **109** to unsaturated aldehydes **2**, followed by a palladium catalyzed cyclization step. The cooperative catalysis used in the reaction led to the formation of *spiro*-cyclopentyloxindoles **110** in good to excellent diastereo- and enantioselectivities with two adjacent stereocenters.



Scheme 28. Synthesis of oxindoles **110** via cooperative catalysis.

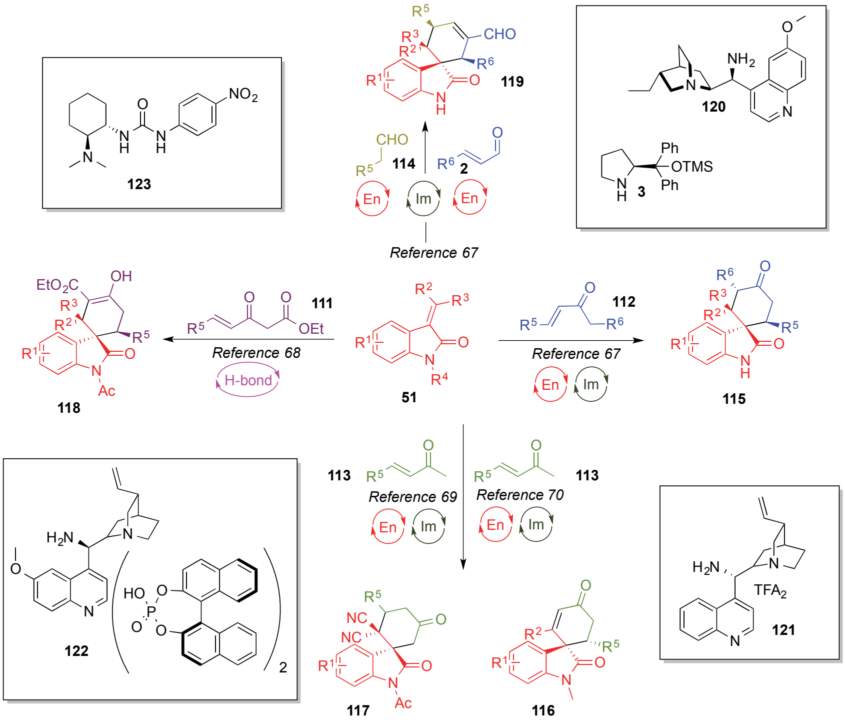
1.7. Asymmetric synthesis of *spiro*-cyclohexyloxindoles

The *spiro*-cyclohexyloxindole core structure is found in many natural bioactive compounds. This has caused a lot of interest in developing new methods for the synthesis of synthetic analogues based on a *spiro*-cyclohexyloxindole skeleton.

Methyleneindolinones **51** serve as an important precursor for many *spiro*-cyclohexyloxindoles (Scheme 29). In 2009 Melchiorre *et al.*[67] developed a *Cinchona* alkaloid derived primary amine **120** catalyzed cyclisation of alkylidene oxindoles **51** and enones **112**. This highly versatile tandem reaction allowed for the formation of *spiro*-oxindoles **115** with up to four stereocenters in good to excellent diastereo- and enantioselectivities (d.r. up to >19:1; *ee* up to 98%). A complementary triple-cascade was also reported, where an *o*-fluorobenzoic acid salt of amine **3** was used as a catalyst to construct *spiro*-oxindoles **119**. The cascade was initiated by a Michael addition of enamine (generated *in situ* from aldehyde **114** by the catalyst) to methyleneindolinone **51**, followed by a second Michael addition of the intermediate to unsaturated aldehyde **2** and concluded by aldol condensation of the formyl groups. Products were isolated in high selectivities (d.r. up to >19:1; *ee* up to >99%) and moderate to good yields (35-74%). Both methods complement each other, offering opportunities to synthesize a variety of *spiro*-cyclohexyloxindoles with different substitution patterns on the spiral ring.

Gond and Wei[68] reported an asymmetric formal [4+2] cycloaddion of Nazarov reagents **111** and methyleneindolinones **51** using a chiral urea derivative **123** as a Lewis base/Brønsted acid catalyst. According to the proposed mechanism the 1,3-dicarbonyl fragment of **111** was activated by the Lewis acid subunit of the catalyst (e.g. tertiary amine), while the urea formed hydrogen bonds with methyleneindolinone **51**. The dual activation ensured that the double Michael cascade proceeded with high selectivity, yielding the expected *spiro*-cyclohexyloxindoles **118** both in high diastereo- and enantioselectivities (d.r. up to 97:3; *ee* up to 94%).

Two cyclization protocols of unsaturated enones **113** with alkylidene oxindole derivatives **51** were reported by Wang *et al.*[69] and Zhang *et al.*,[70] respectively.



Scheme 29. Asymmetric synthesis of *spiro*-cyclohexyloxindoles.

Isatylidene malononitriles **51** were reacted with α,β-unsaturated ketones **113** using a chiral counteranion catalyst **122** to form a *spiro*-cyclohexyloxindole backbone **117** in optically pure form (d.r. from 94:6 to >99:1; *ee* from 95-99%). Alkylidene oxindoles **51** with leaving group (OTf) as R^3 yielded product **116** (d.r. >20:1; *ee* >99%) using *Cinchona* alkaloid derived catalyst **121**.

The methods described above (Scheme 29) constitute only a small part of all the procedures developed for the construction of compounds bearing the *spiro*-cyclohexyloxindole skeleton. Other approaches include starting with isatines, 3-substituted oxindoles etc.[71]

1.8. Summary of literature overview

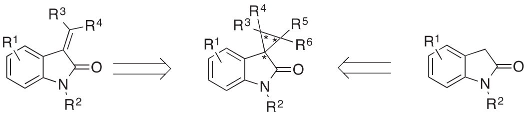
Oxindoles with a quaternary center at the 3rd position of the cycle are the key structural feature in an extensive number of natural and synthetic bioactive compounds. This has inspired a lot of research over the last decade in developing new, efficient methods for the construction of a “molecular library” of compounds, centered around the oxindole core structure.

The main challenge for the asymmetric synthesis of this class of compounds is the introduction of a chiral quaternary center at C3. Fully substituted carbon centers are considered one of the most difficult structural features to be incorporated into synthetic targets due to steric and electronic factors.[72] To overcome this barrier a “molecular handles” are often used (e.g. carbonyl groups), although the removal of the activating group at a later stage is not always a simple task. In the case of oxindoles, however, a carbonyl group at C2 provides a unique opportunity, as it can increase the negative charge on the adjacent carbon, thereby decreasing the activation barrier associated with quaternary center formation. To that end, commercially available isatines and various 3-substituted oxindoles have become fundamental building blocks for the synthesis of 3,3’-disubstituted oxindoles. Alternatively, postponing the introduction of quaternary stereocenters, until the cyclization step offers another possibility for *spiro*-center formation, making alkylidene oxindoles **51** uniquely suitable for such a task.

Metal-, cooperative- and organocatalysis have all been used as “tools” to construct various disubstituted oxindoles in high diastereo- and enantioselectivities (see citations above). Nevertheless, new and elegant synthetic approaches, to expand the “chemical space” around the oxindole framework continue to be of high importance.

1.9. Aims of the present work

Spiro-cyclopropyloxindoles are an exciting class of compounds with promising biological activities and complex molecular architecture. Although different racemic examples for the synthesis of *spiro*-cyclopropyloxindoles have been reported,[10,11,12,13,14] only a few asymmetric examples have been published to date.[43,44] The present work aims to expand the scope of methods available for enantio- and diastereoselective synthesis of this class of compounds.



51 **55**

Scheme 30. General methods available for asymmetric synthesis of *spiro*-cyclopropyloxindoles.

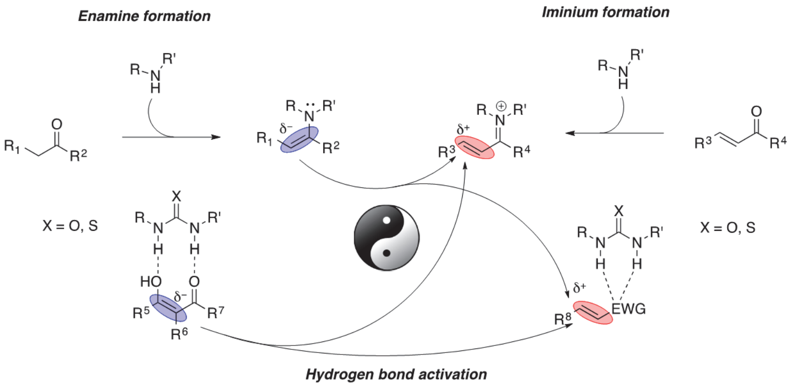
Two approaches reported for the asymmetric formation of *spiro*-cyclopropyloxindoles start with alkylidene oxindoles **51**[43] or oxindoles **55**[44] (Scheme 30). Based on this, the main aims of the thesis are:

- Expand the scope of nucleophiles available for asymmetric cyclopropanation of methyleneindolinones **51**;
- Develop new starting materials for the synthesis of *spiro*-cyclopropyloxindoles (in addition to alkylidene oxindoles **51** and oxindoles **55**);
- Elaborate the use of new nucleophiles as starting materials for 3,3'-disubstituted oxindole synthesis;
- Determine the relative and absolute stereochemistry of all products obtained.

2. Results and discussion

Developing new and efficient organocatalytic asymmetric cascade reactions has been and continues to be a driving force in our group.[73,74] As mentioned previously (see Introduction), organocatalysis has matured over the last couple of decades to became an important branch of organic synthesis. The two most prominent and oldest activation strategies, amino- and hydrogen-bond catalysis, have become standard "tools" used in an increasing number of enantioselective transformations.

In aminocatalysis, chiral primary and secondary amines react reversibly with carbonyl compounds to form enamine or iminium intermediates that can undergo nucleophilic or electrophilic addition reactions, respectively (Scheme 31).



Scheme 31. Generic amine or hydrogen-bond catalyzed activation of carbonyl and related compounds.

Saturated carbonyl compounds are therefore activated as nucleophiles (e.g. Michael donors), whereas corresponding unsaturated analogues can be used as Michael acceptors.

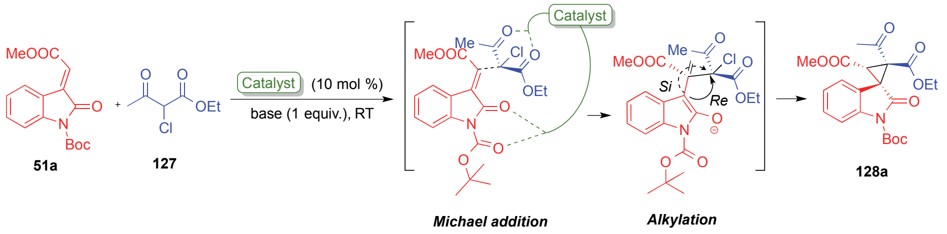
In hydrogen-bond catalysis, using weak, non-covalent interactions (e.g. hydrogen bonds), nucleophiles (e.g. 1,3-dicarbonyl compounds) and electrophiles (e.g. nitroolefins, enones etc.) can be activated *via* hydrogen-bond formation (Scheme 31). This lowers the activation barrier for the desired transformation to transpire. Further activation can be achieved if a basic or acidic subunit (depending on the reaction) has been incorporated into the structure of the catalyst itself (e.g. a bifunctional catalyst). In many cases, combining the two activation modes under cooperative catalysis can lead to new discoveries and expand the "chemical space".

2.1. Synthesis of *spiro*-cyclopropyloxindoles *via* the addition of α-chloro-1,3-dicarbonyl compounds to methyleneindolinones (Publication I)[75]

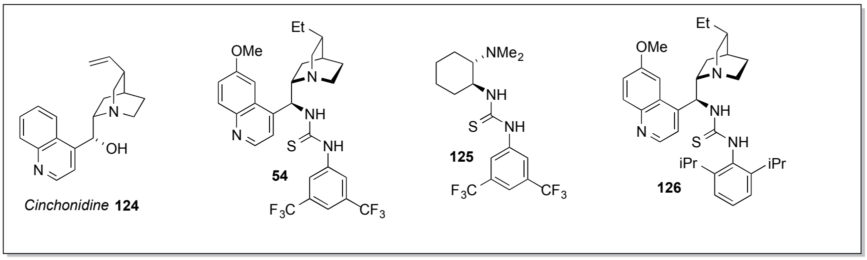
Methyleneindolinones **51** and oxindoles **55** can be efficiently activated for the formation of *spiro*-cyclopropyloxindoles by chiral thioureas, as was demonstrated by Bencivenni and Lu, respectively (see Schemes 13 and 14), although both methods were limited to nitro-substituted *spiro*-oxindoles.[43,44] This had the added advantage that the initial stereochemistry could be altered by the epimerization of the tertiary nitro-substituted stereocenter, driving the reaction towards thermodynamically more favored *trans*-geometry. At the same time, no reversal of stereochemistry was possible when nitro-substitution occurred at the quaternary center.

Inspired by the results outlined above, we set out to develop a general methodology to expand the scope of nucleophiles (with attached leaving groups) used in the *spiro*-annulation of alkylidene oxindoles **51**. At the outset, we focused on developing a formal [2+1] cycloaddion of methyleneindolinones **51** with various α-chloro-β-dicarbonyl compounds for the highly stereoselective formation of *spiro*-cyclopropyloxindoles (Scheme 32). A major challenge in this synthetic strategy is to control both the enantio- and diastereoselectivity of the reaction, as two adjacent quaternary centers are formed with no possibility of post-synthetic epimerization, as was the case with nitro-oxindoles discussed previously.

Both dicarbonyl compounds and alkylidene oxindoles **51** are known to be activated by hydrogen-bonding catalysts. To investigate the model reaction between ethyl α-chloroacetoacetate **127** and methyleneindolinone **51a** a set of four catalysts (Scheme 33) were selected for the preliminary screening.



Scheme 32. Model reaction between alkylidene oxindole **51a** and ethyl α-chloroacetoacetate **127**.



Scheme 33. Catalysts used in cyclopropanation of methyleneindolinones **51**.

Using potassium carbonate as a base for the synthesis of racemate, a mixture of all possible stereoisomers of **128a** was obtained after 24 h at RT (Table 1, entry 1).

For the asymmetric version, we first tested *cinchonidine* **124** (Scheme 33) as a chiral base (1 equiv., DCM, RT). The reaction produced a 3:1 mixture of the two main diastereoisomers and a minor quantity of a third diastereoisomer, which could be readily separated by flash chromatography (Table 1, entry 2). Importantly, the major product showed 96% *ee*. However, an attempted reduction of the catalyst loading to a more practical 10 mol % level had a detrimental effect on the reaction rate and selectivity. Therefore, we turned to bifunctional thiourea catalysts **54** and **125**, which proved successful in the asymmetric *spiro*-cyclopropanation of **51a** with bromonitromethane.[43]

Quinine-derived thiourea **54** (10 mol %, DCM, RT, 24 h) combined with $NaHCO_3$ (1 equiv.) afforded a 3:1 mixture of the same two diastereoisomers, as with **124**, in high enantioselectivity but low overall yield (Table 1, entry 3). To optimize the reaction efficiency, various solvents and bases were examined. In toluene (Table 1, entry 4) and MeCN (Table 1, entry 7), diastereoselectivity dropped significantly to give mixtures of all possible isomers. The highest enantioselectivity was attained in THF, though the yield and diastereoselectivity were poor (Table 1, entry 6). Chloroform emerged as a clear winner, showing the best overall performance (Table 1, entry 5). Other inorganic bases, such as Na_2CO_3 and CsF (Table 1, entries 8 and 9), proved slightly inferior to $NaHCO_3$. Catalyst **125** mirrored the results shown by **54**, delivering the same 3:1 mixture of diastereoisomers of the opposite enantiomeric series (Table 1, entry 10).

Table 1. Screening of reaction conditions for the synthesis of *spiro*-oxindoles **128a**.[a]

Entry	Catalyst	Base	Solvent	Yield (%)	d.r. (%)[b]	*ee* (%)[c]
1	**-**	K_2CO_3	DCM	86	1/1/1/1	n/a
2	**124**[d]	-	DCM	72	71/24/5	96/55/12
3	**54**	$NaHCO_3$	DCM	48	77/23	93/95
4	**54**	$NaHCO_3$	toluene	n.d.[e]	n.d.	n.d.
5	**54**	$NaHCO_3$	$CHCl_3$	97	78/22	94/96
6	**54**	$NaHCO_3$	THF	54	63/37	97/99
7	**54**	$NaHCO_3$	MeCN	87	9/31/52/8	n.d.
8	**54**	Na_2CO_3	$CHCl_3$	87	74/26	89/94
9	**54**	CsF	$CHCl_3$	76	77/23	93/95
10	**125**	$NaHCO_3$	$CHCl_3$	48	75/25	-93/-86
11	**126**	$NaHCO_3$	$CHCl_3$	82	93/7	91/94
12	**126**	$NaHCO_3$	$CHCl_3$	97[f]	91/9	91/82
13	**126**	$NaHCO_3$	$CHCl_3$	93[g]	90/10	87/83

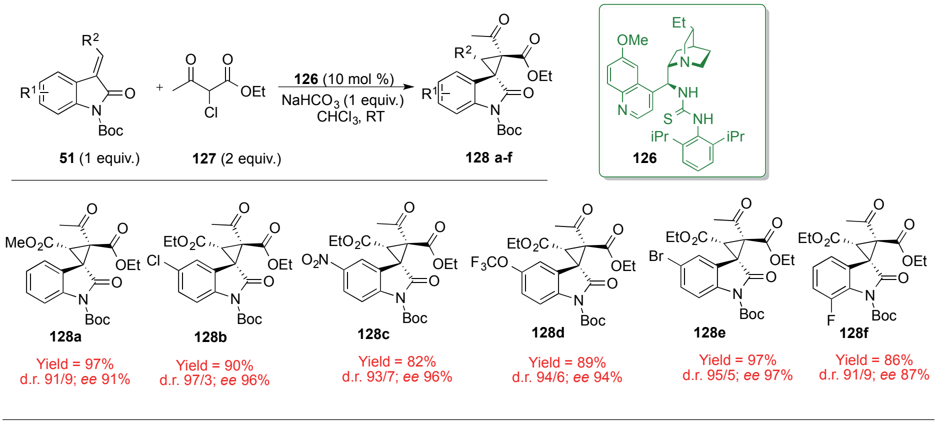
[a] Unless stated otherwise, the reactions were carried out on a 0.15 mmol scale as a 0.15 M solution at RT for 24 h with 1 equiv. of **51a**, 2 equiv. of **127**, 1 equiv. of base and 10 mol % catalyst loading; [b] determined by ^1H NMR from the crude mixture; [c] determined by chiral HPLC analyses after deprotection of *Boc*; [d] 1 equiv. of catalyst was used; [e] complex mixture of all possible diastereoisomers; [f] 0.3 M solution; [g] 4 equiv. of **127** used.

It appears that the commonly used commercial catalysts under a variety of experimental conditions exhibited a similar reactivity pattern favoring the formation of two diastereoisomers in a 3:1 ratio at best. Notably, the components of this mixture cannot be easily separated by chromatography, thus reducing the practical value of the method. Clearly, an improvement in the catalyst design was required to break the pattern.

A set of experiments revealed that the diastereoselectivity of the catalysts was influenced by substituents in the aromatic group of the thiourea fragment, in particular by those restricting rotation about the C-N bond. A real step-change improvement was achieved with a catalyst **126** with bulky *i*Pr groups occupying ortho positions: the diastereoselectivity soared to 13:1, while maintaining a good yield and a respectable enantioselectivity (Table 1, entry 11). Effectively, only one of eight possible stereoisomers was produced! The yield was further improved by doubling the concentration of the reactants (Table 1, entry 12), though using an excess of ethyl α-chloro acetoacetate **127** alone proved detrimental (Table 1, entry 13).

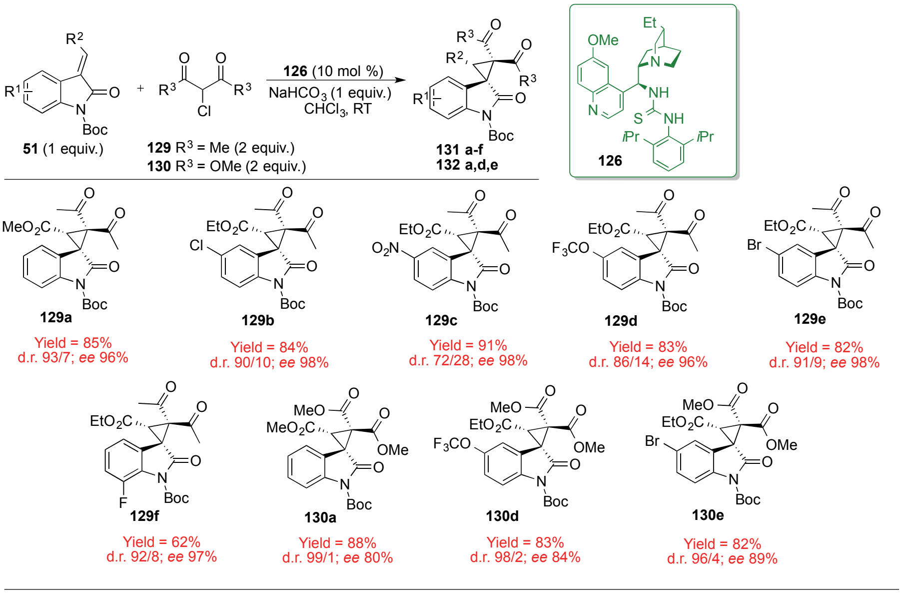
With the optimal conditions in hand ($CHCl_3$ 0.3 M, 2 equiv. **127**, 10 mol % **126**, RT) the substrate scope of the reaction was next examined (Table 2). Different substituents at the indole ring were tolerated, and no significant correlation between the electronic nature of the methyleneindolinones **51** and reaction rate or selectivity emerged. All products **128a-f** were isolated in high yields and enantio- and diastereoselectivities (Table 2).

Table 2. Screening of different alkylidene oxindoles **51** for cyclopropanation.



To further expand the substrate scope and elaborated on the origin of the selectivity of the reaction, we next screened symmetric 3-chloroacetoacetone **129** and dimethyl chloromalonate **130** in reaction with different alkylidene oxindoles **51** (Table 3). In general, all products were isolated in high yields, with 7-F methyleneindolinone **51f** being the only exception (Table 3, **129f)** (possibly due to unfavorable interactions between the fluorine and *t*-butyl group). With 5-nitro substituted methyleneindolinone **51c** only moderate diastereoselectivity was observed, whereas all other substrates furnished the product with significantly better selectivities. Although, with dimethyl chloromalonate **130** reaction times had to be increased to 48h (*vs*. 24h for other examples), substantially higher diastereoselectivities emerged (d.r. from 96:4 to 99:1) while enantioselectivities remained slightly lower.

Table 3. Scope of cyclopropanation reaction.



Based on the experimental results with asymmetrical (**127**) and symmetrical (**129** and **130**) nucleophiles, we propose, that the selectivity of the reaction originated from the first Michael addition step, and the alkylation (e.g. cyclization) was entirely controlled by the steric influence displayed by the adjacent tertiary center (Scheme 32).

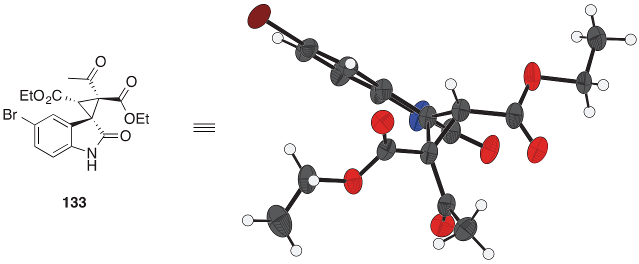
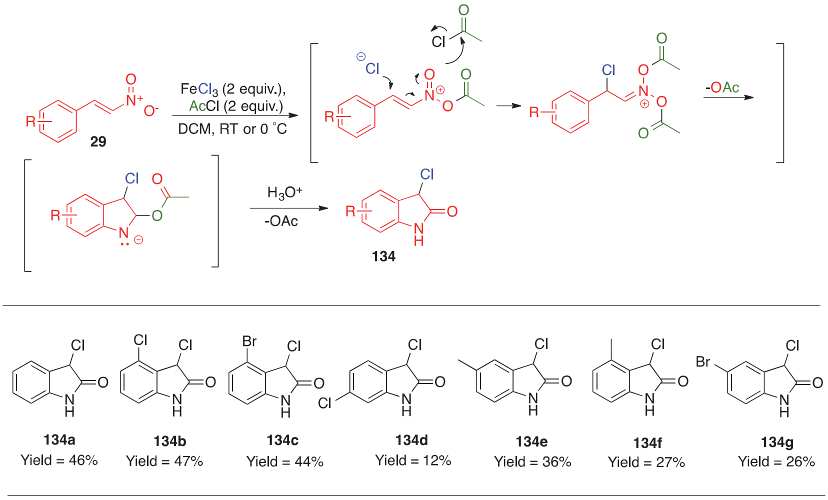


Figure 2. *X-ray* structure of unprotected *spiro*-cyclopropyloxindole **128e**.

The relative and absolute structure (Figure 2) of the product were determined by NMR and single crystal *x-ray* diffraction of one of the products (after deprotection), respectively. (It should be noted, that the initial determination of absolute stereochemistry was made using VCD spectroscopy, although the result proved erroneous when the *x-ray* structure was obtained.) The absolute structure of other products in the series was assigned based on analogy.

2.3. Synthesis of *spiro*-oxindoles from 3-chlorooxindoles (Publication III)[76]

A significant limitation with alkylidene oxindoles **51** and oxindoles **55** as starting materials for cyclopropanation is the need to attach the leaving group (necessary for the alkylation/cyclization step) to the Michael donor or acceptor, respectively. To further elaborate the substitution pattern of the spiral ring of *spiro*-cyclopropyloxindoles, a different approach was needed. Attaching the leaving group directly to the 3rd position of the oxindole ring might not only facilitate the above-mentioned transformations but also increase the nucleophilicity of C3 by lowering the pK_a value.



Scheme 34. Synthesis of 3-chlorooxindoles **134**.

Based on these considerations, we proposed that 3-chlorooxindoles **134** could serve as ideal precursors for *spiro*-cyclopropyloxindoles (Scheme 34). Starting from simple nitroolefins **29**, seven halo- and methyl-substituted 3-chlorooxindoles **134** were prepared according to Guillaumel *et al.*[77] Although, products were isolated in moderated to low yields (Scheme 34), the simplicity of the protocol and the high availability of low-cost starting materials made it practical. As a limitation, no nitro- or alkoxy-substituted derivatives can be synthesized based on this procedure, as the corresponding nitroalkenes **29** decompose under the reaction conditions.

With the 3-chlorooxindoles **134** in hand, we decided to investigate a model reaction between **134a** and *trans*-*p*-methoxycinnamaldehyde (Figure 3).

Asymmetric cyclopropanation of α,β-unsaturated aldehydes **2** under aminocatalysis has been known for quite a while. We proposed that a similar reaction with 3-chlorooxindoles **134** could lead to *spiro*-cyclopropyloxindoles **135** (Figure 3). The proposed catalytic cycle is initiated by the formation of the iminium intermediate, followed by a Michael addition of 3-chlorooxindole **134** and intermolecular cyclization/alkylation. The product would be released after hydrolysis, and the side product – hydrochloric acid would be consumed by sodium bicarbonate (to form NaCl, carbon dioxide and water).

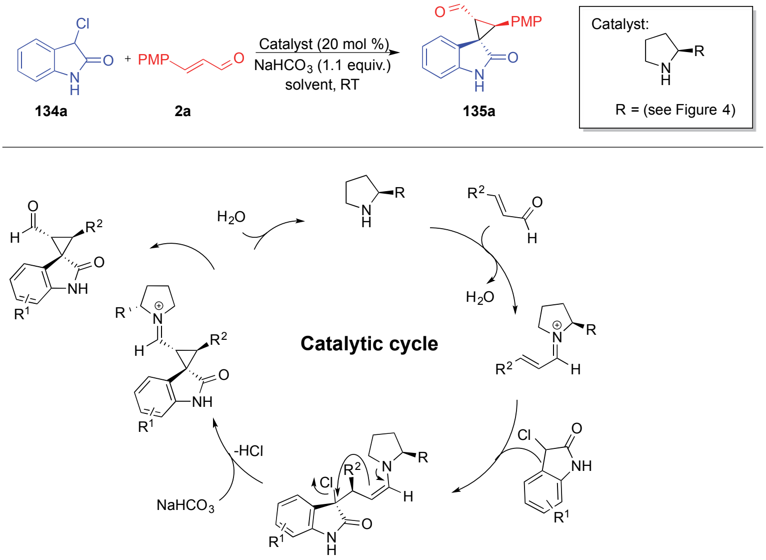


Figure 3. Proposed reaction for cyclopropanation of unsaturated aldehydes **2**.

To find the optimal conditions for the reaction, seven chiral secondary amines (Figure 4) were evaluated. Preliminary experiments revealed amine **137** with a bulky TBS group as the most selective and reactive catalyst for the reaction (Table 2, entry 11). Furthermore, it was noted that *spiro*-cyclopropyloxindole **135a** was slightly unstable and prone to epimerization, therefore, isolating the products as corresponding alcohols after *in situ* reduction with sodium borohydride was preferable and was used in subsequent experiments.

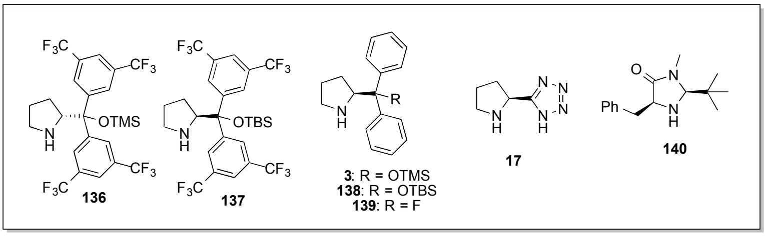


Figure 4. Amines used as the catalysts for cyclopropanation of *trans-p*-methoxycinnamaldehyde.

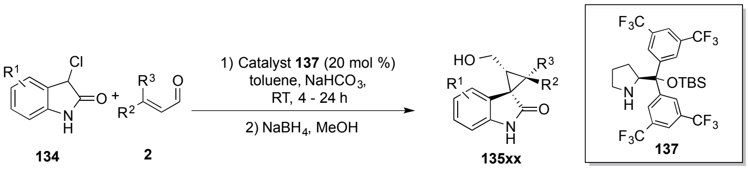
Table 2. Optimization of the reaction of 3-chlorooxindole **134a** and *trans-p*-methoxycinnamaldehyde.[a]

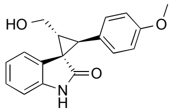
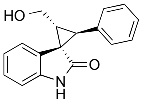
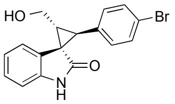
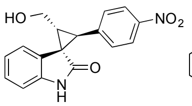
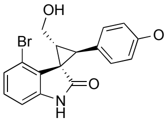
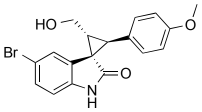
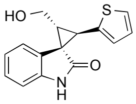
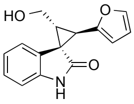
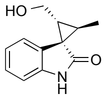
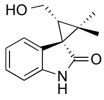
Entry	Cat.	Solvent	Time [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**136**	$CHCl_3$	3	95	3:1	-97
2	**137**	$CHCl_3$	3	89	4:1	98
3	**3**	$CHCl_3$	16	55	1.3:1	79
4	**138**	$CHCl_3$	16	61	1.2:1	95
5	**139**	$CHCl_3$	16	99	1.5:1	95
6	**17**	$CHCl_3$	3	95	2.7:1	8
7	**140**	$CHCl_3$	24	-	n.d.	n.d.
8	**136**	$CHCl_3$	15[e]	95	2.6:1	94
9	**137**	toluene	3	95	7.1:1	98
10	**137**	toluene	5.5[f]	95	5.3:1	97
11	**137**	toluene	9[g]	95	9:1	98

[a] Unless stated otherwise, the reactions were carried out on a 0.1 mmol scale as a 0.2 M solution (in respect to **134a**) at RT with 1 equiv. of **134a**, 1.2 equiv. of **2a**, 1.1 equiv. of $NaHCO_3$ and 20 mol % catalyst loading. PMP = *p*-methoxyphenyl; [b] Yield of isolated product; [c] Determined from crude product by ^1H NMR. Only two diastereoisomers were detected; [d] Determined by chiral HPLC analysis; [e] Reaction at 4 °C; [f] 10 mol % of catalyst used; [g] Reaction mixture 0.1 M.

Under optimal conditions (toluene, RT, 1.2 or 2 equiv. aldehyde **2**, 20 mol % amine **137**), several unsaturated aldehydes **2** and 3-chlorooxindoles **134** were reacted to form *spiro*-cyclopropyloxindoles **135**. All cinnamic-type aldehydes **2a-d** yielded products with good diastereo- and high enantioselectivities. It is noteworthy that significant enrichment in diastereoselectivity could be effected during column chromatography, as in most cases the isomers were separable (Table 3). When an aliphatic aldehyde (crotonaldehyde) **2g** was subjected to the reaction conditions, the product was isolated with moderate diastereoselectivity but with good enantioselectivities for both isomers (Table 3, **135ag**). Most significantly, even prenal **2h** gave a smooth conversion to the desired product, although selectivity for the major isomer was moderate (Table 3, **135ah**). Substituents in the indol ring were well tolerated (Table 3, **135ba** and **135ca**), as well as heteroatoms in unsaturated aldehydes **2e** and **2f** yielding the products with high selectivities (Table 3, **135ae** and **135af**).

Table 3. Substrate scope experiments for the formation of *spiro*-cyclopropyloxindoles **135**.[a]



Structure	Compound	Yield	d.r.	ee
	**135aa**	71%[b,f]	19:1 (19:1)[c,d]	>99%[e]
	**135ab**	64%[b]	5:1 (10:1)[c,d]	>99%[e]
	**135ac**	44%[b]	5:1 (10:1)[c,d]	98%[e]
	**135ad**	53%[b]	4:1 (7:1)[c,d]	98%[e]
	**135ba**	66%[b,f]	10:1 (14:1)[c,d]	98%[e]
	**135ca**	76%[b,f]	19:1 (20:1)[c,d]	>99%[e]
	**135ae**	60%[b]	5:1 (10:1)[c,d]	96%[e]
	**135af**	69%[b]	19:1 (19:1)[c,d]	98%[e]
	**135ag**	62%[b,g]	2:1 (2:1)[c,d]	75/87%[e]
	**135ah**	69%[b,f]	4:1 (4:1)[c,d]	36/89%[e]

[a] Unless stated otherwise, the reactions were carried out on a 0.2 mmol scale as a 0.1 M solution at RT with 1 equiv. of **134**, 1.2 equiv. of **2**, 1.1 equiv. of $NaHCO_3$ and 20 mol % catalyst loading; [b] Yield of isolated product after reduction to an alcohol; [c] Determined from crude product after reduction to an alcohol by ^1H NMR; [d] Diasteriomeric ratio of isolated product in brackets; [e] Determined by chiral HPLC analysis from isolated product; [f] Reaction with 2 equiv. of **2**; [g] Reaction with 5 equiv. of **2**.

The relative and absolute configurations of the products **135xx** were determined by NMR and single crystal *x-ray* diffraction of one of the products (Figure 5), respectively. All other *spiro*-cyclopropyloxindoles **135xx** were assigned based on analogy.

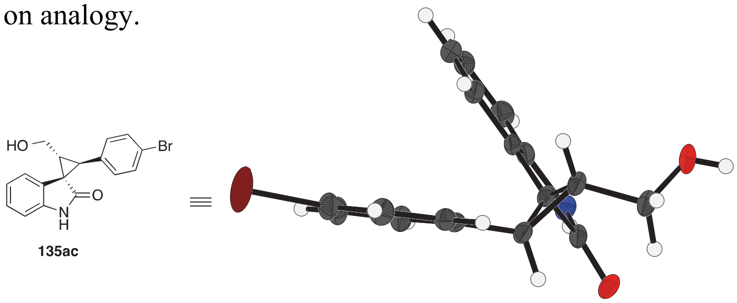
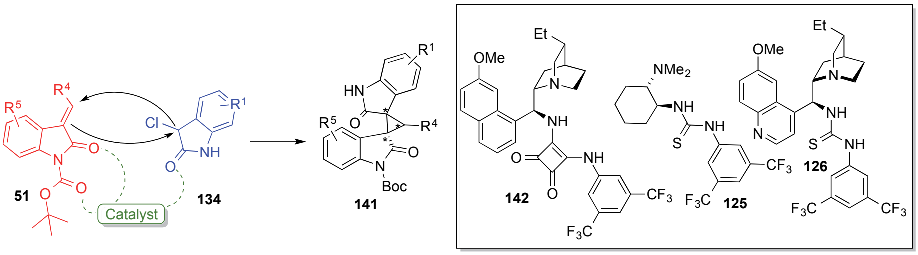

135ac

Figure 5. *X-ray* diffraction data of *spiro*-cyclopropyloxindole **135ac**.

Superseding our work, Melchiorre *et al*. recently demonstrated that a similar reaction between 3-chlorooxindoles **134** and 2,4-dienals would result in the formation of *spiro*-cyclopropyloxindoles *via* a 1,6-vinologous cascade reaction.[78]

2.4. Synthesis of bispirooxindoles 141 (Publication III)[76]

Inspired by the unique reactivity of 3-chlorooxindoles **134**, we hypothesized that similarly to α-chloro dicarbonyl compounds, they could undergo a formal [2+1] *spiro*-annulation with alkylidene oxindoles **51** to form bispirooxindoles **141** (Scheme 35). Based on previous work, chiral thioureas and squaramides were screened for the reaction. Preliminary experiments revealed that, although most of the catalysts were able to promote the reaction towards high enantioselectivity, diastereoselectivity was mainly controlled by the substituent at C4 of 3-chlorooxindoles **134** (Table 4, entry 4 *vs*. 1-3), which can be explained by sterical clashing between R^1 and R^4 during the Michael addition step (for a detailed proposed mechanism see Kanger *et al.*).[76]



Scheme 35. *Spiro*-annulation of methyleneindolinones **51** with 3-chlorooxindoles **134**.

Table 4. Preliminary screening experiments for bispirooxindoles **141** formation.

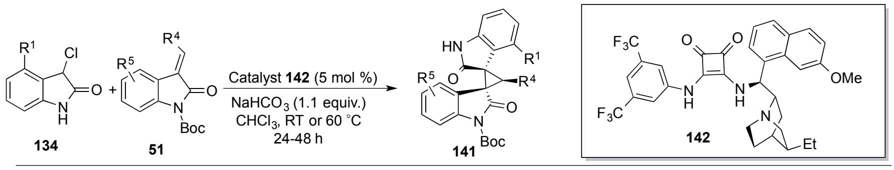
Entry	Cat.	Cat. loading (mol %)	R^1	Time (h)	Yield (%)[a]	d.r.[b]	*ee* (%)[c]
1	**142**	5	H	20	99	43:57	96/96
2	**125**	10	H	24	99	44:56	-83/-87
3	**126**	10	H	15	99	50:50	80/78
4	**142**	5	Cl	41	96	7:93	-/95

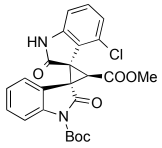
[a] Isolated yield after chromatography for the mixture of isomers; [b] Determined by ^{1}H NMR; [c] Determined by chiral HPLC analysis.

The highest enantioselectivity was obtained with squaramide **142**, which was chosen for substrate scope experiments (Table 5). In general, products were isolated in high yields, and enantio- and diastereoselectivities. Ester, cyano and ketone functional groups were tolerated as R^4 without significant influence on reactivity or selectivity. With 4-Me substituted 3-chlorooxindoles reactions were performed at elevated temperatures to ensure full conversion.

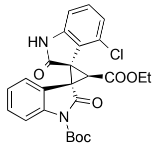
The relative stereochemistry of the products **141** was determined by NMR, whereas the absolute configuration was assigned by VCD spectroscopy measurements and calculations (Figure 6).

Table 5. Synthesis of bispirooxindoles **141**.[a]

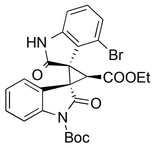




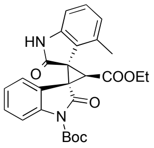
141da
Yield = 96%[b]
d.r. 14:1[c]; *ee* = 95%[d]



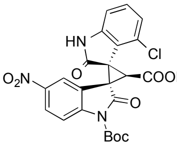
141db
Yield = 95%[b]
d.r. 30:1[c]; *ee* = 93%[d]



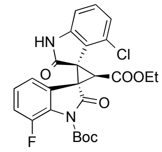
141bb
Yield = 91%[b]
d.r. 10:1[c]; *ee* = 92%[d]



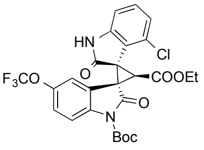
141eb
Yield = 71%[b,e]
d.r. 12:1[c]; *ee* = 89%[d]



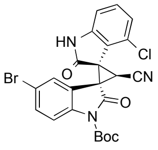
141dc
Yield = 95%[b]
d.r. 12:1[c]; *ee* = 84%[d]



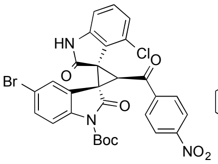
141dd
Yield = 99%[b]
d.r. 12:1[c]; *ee* = 90%[d]



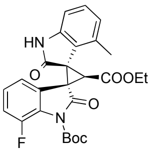
141de
Yield = 81%[b]
d.r. 12:1[c]; *ee* = 90%[d]



141df
Yield = 87%[b]
d.r. 20:1[c]; *ee* = 99%[d]



141dg
Yield = 71%[b]
d.r. 20:1[c]; *ee* = 83%[d]



141ed
Yield = 75%[b,e]
d.r. 20:1[c]; *ee* = 86%[d]

[a] Unless stated otherwise, the reactions were carried out on a 0.1 mmol scale as a 0.2 M solution at RT with 1 equiv. of **134**, 1.2 equiv. of **51**, 1 equiv. of $NaHCO_3$ and 5 mol % catalyst loading; [b] Yield of isolated product; [c] Determined from crude product by ^{1}H NMR; [d] Determined by chiral HPLC analysis; [e] Reaction conditions: 1 equiv. of **134**, 1.2 equiv. of **51**, 2 equiv. of $NaHCO_3$ and 10 mol % of catalyst **142** at 60 °C.

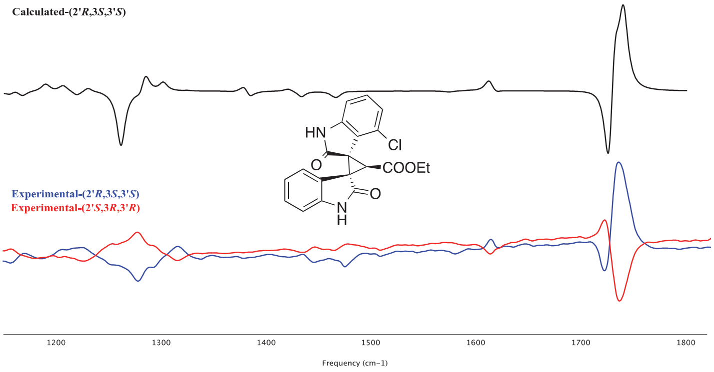
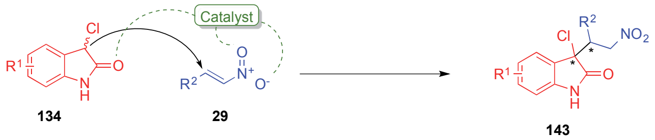


Figure 6. Calculated and experimental VCD spectra of bispirooxindole **141 db-no-boc**.

2.5. Asymmetric addition of 3-chlorooxindoles 134 to nitroolefins 29 (Publication II)[79]

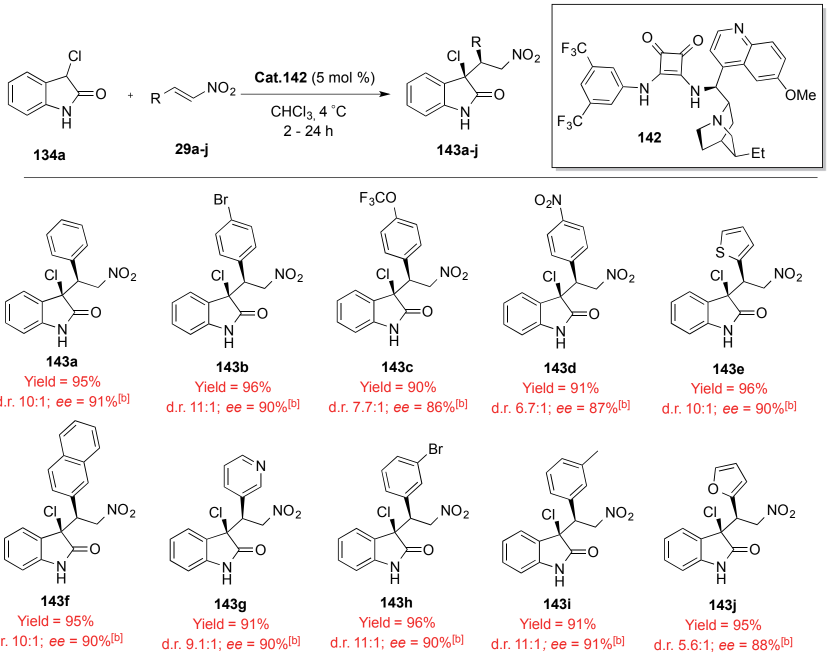
Asymmetric synthesis of 3-halo-disubstituted oxindoles has mainly been accomplished using metal catalysis. In that respect, organocatalysis presents a unique opportunity, as trace metals will be absent from the final products.



Scheme 36. Addition of 3-chlorooxindoles **134** to nitroolefins **29**.

Motivated by these considerations, we saw an opportunity to take advantage of the enhanced reactivity of 3-chlorooxindoles **134** (compared to 2-oxindoles) in a hydrogen-bond catalyzed Michael addition to nitroolefins **29** (Scheme 36). The resulting products **143** would bear chlorine at the quaternary center, which could be used to modify the final products if necessary. We envisioned that both 3-chlorooxindoles **134** and nitroolefins **29** could form hydrogen bonds with the catalyst, thereby permitting a smooth reaction (Scheme 36).

Table 6. Substrate screening for the addition of 3-chlorooxindole **134a** to nitroalkenes **29**.[a]



143a
Yield = 95%
d.r. 10:1; *ee* = 91%[b]

143b
Yield = 96%
d.r. 11:1; *ee* = 90%[b]

143c
Yield = 90%
d.r. 7.7:1; *ee* = 86%[b]

143d
Yield = 91%
d.r. 6.7:1; *ee* = 87%[b]

143e
Yield = 96%
d.r. 10:1; *ee* = 90%[b]

143f
Yield = 95%
d.r. 10:1; *ee* = 90%[b]

143g
Yield = 91%
d.r. 9.1:1; *ee* = 90%[b]

143h
Yield = 96%
d.r. 11:1; *ee* = 90%[b]

143i
Yield = 91%
d.r. 11:1; *ee* = 91%[b]

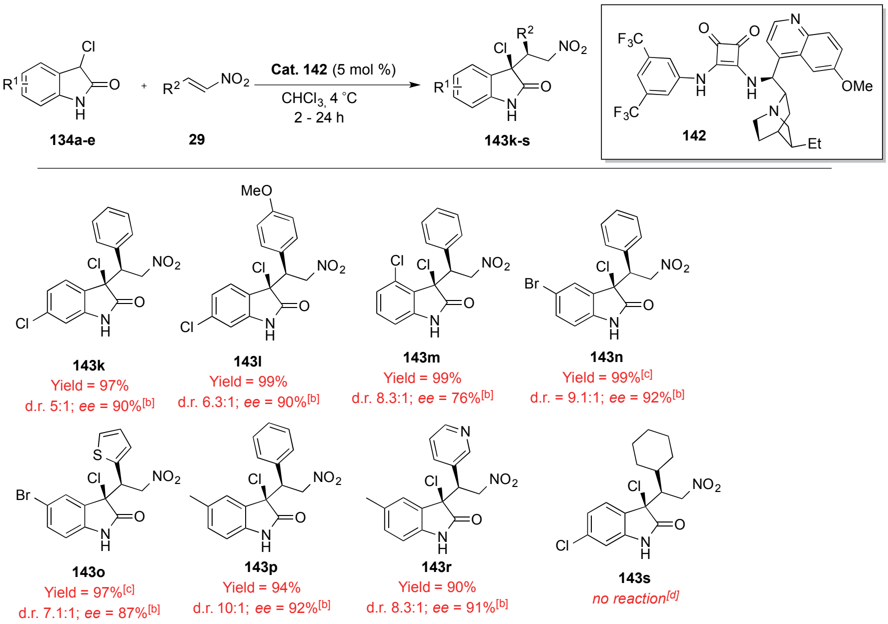
143j
Yield = 95%
d.r. 5.6:1; *ee* = 88%[b]

---

[a] Reaction conditions: 0.1 mmol (1 equiv.) **134a**, 0.12 mmol (1.2 equiv.) of **29** and 0.05 mmol (5 mol %) of squaramide **142** were stirred at ambient temperature in chloroform (0.5 mL), the reaction was monitored by TLC; [b] d.r. was determined by ^{1}H NMR and *ee* by chiral HPLC analysis.

Gratifyingly, preliminary screening revealed squaramide **142** to as most selective catalyst for the reaction. With the optimal conditions in hand (5 mol % **142**, $CHCl_3$, 4 °C), 3-chlorooxindole **143a** was subjected to the reaction with different aromatic nitroalkenes **29** (Table 6). All products were uniformly isolated in high yields and good to excellent diastereoselectivities, with *ee*-s hovering slightly below or above 90%.

Table 7. Substrate screening for the addition of 3-chlorooxindoles **134** to nitroalkenes **29**.[a]



143k
Yield = 97%
d.r. 5:1; *ee* = 90%[b]

143l
Yield = 99%
d.r. 6.3:1; *ee* = 90%[b]

143m
Yield = 99%
d.r. 8.3:1; *ee* = 76%[b]

143n
Yield = 99%[c]
d.r. = 9.1:1; *ee* = 92%[b]

143o
Yield = 97%[c]
d.r. 7.1:1; *ee* = 87%[b]

143p
Yield = 94%
d.r. 10:1; *ee* = 92%[b]

143r
Yield = 90%
d.r. 8.3:1; *ee* = 91%[b]

143s
no reaction[d]

[a] Reaction conditions: 0.1 mmol (1 equiv.) **134 a-e**, 0.12 mmol (1.2 equiv.) of **29** and 0.05 mmol (5 mol %) of squaramide **142** were stirred at ambient temperature in chloroform (0.5 mL), and the reaction was monitored by TLC; [b] d.r. was determined by ^{1}H NMR and *ee* by chiral HPLC analysis; [c] reaction conducted at ambient temperature; [d] temperature was increased from 4 °C to up to 60 °C, but no reaction occurred.

A similar trend occurred with substituted ($R^1 \neq$ H) 3-chlorooxindoles **134**, although 3,4-dichlorooxindole **134b** yielded the product **143m** with slightly lower enantioselectivity (*ee* = 76%) which may have been influenced by the sterically bulky substituent at C4 (Table 7). With aliphatic cyclohexyl nitroolefin no reaction occurred (Table 7, **143s**), setting a limit on the methodology.

To further expand the substrate scope of the reaction, 3-chlorobenzofuran **145** was prepared according to literature procedures (Scheme 37, Part A),[80,81] and reacted with *trans-β*-nitrostyrene **29b** under similar conditions (2 equiv. of **29b** was used instead of 1.2 equiv.) as 3-chlorooxindoles **134** (Scheme 37, Part B).

The reaction proceeded smoothly to yield the expected product **146** in 85% yield and good enantio- and diastereoselectivities in just 5 hours.

The relative and absolute stereochemistry of products was assigned by single crystal *X-ray* diffraction of oxindole **143m** (Figure 7), other examples in the series were assigned based on analogy.

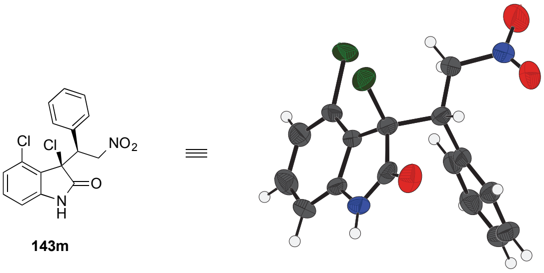
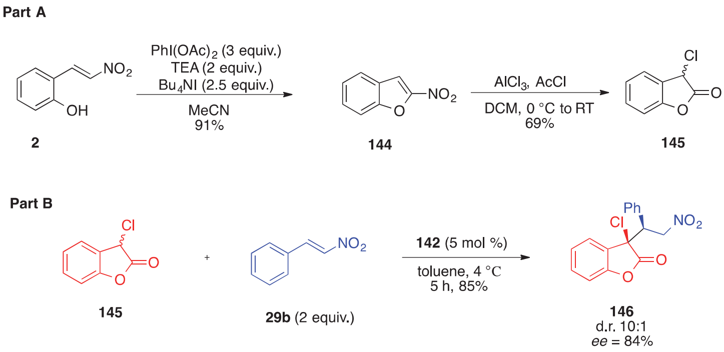


Figure 7. X-ray of oxindole **143m**.

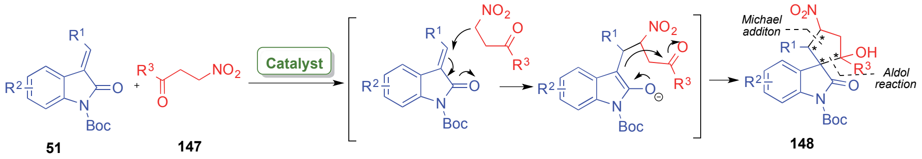


Scheme 37. Synthesis of 3-chlorobenzofuran **145** and reaction with nitrostyrene **29b**.

2.6. Asymmetric synthesis of *spiro*-cyclopentyloxindoles 148 (Publication V)[82]

The *spiro*-cyclopentyloxindole core structure is without a doubt one of the most widespread structural fragments found in many natural products and bioactive compounds. Discovering new, efficient ways to incorporate the *spiro*-cyclopentyloxindole skeleton into synthetic targets has a high value.

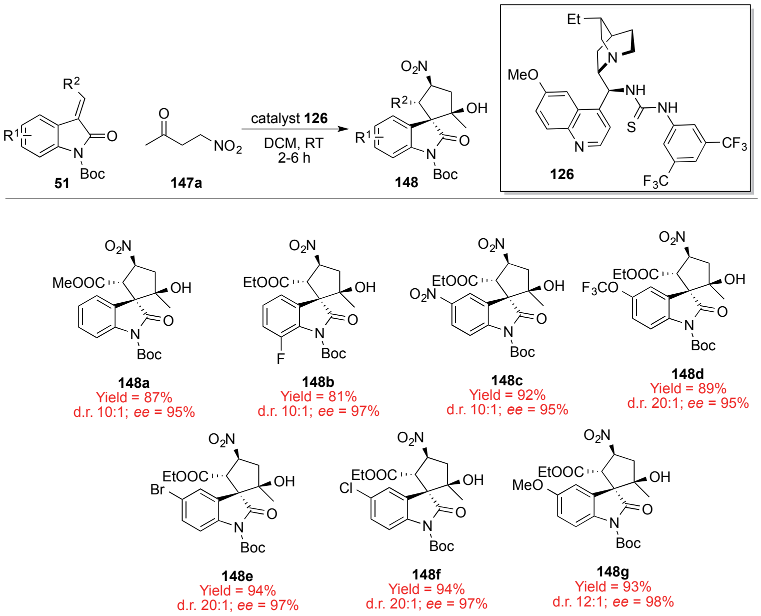
Motivated by the work of Barbas III[64] and Shao,[65] we proposed an alternative approach for the synthesis of *spiro*-cyclopentyloxindole derivatives **148** from methyleneindolinones **51** and nitroketones **147** (Scheme 38).



Scheme 38. Synthesis of *spiro*-cyclopentyloxindoles **148**.

Based on the considerations outlined above, nitroketone **147**, activated by a hydrogen-bonding catalyst, would give a Michael addition with alkylidene oxindole **51**, and the spiral ring would form as a result of the intermolecular aldol reaction. In total, four consecutive stereocenters would form, two of them quaternary, providing structural analogues to oxindoles **105** and **106** (Scheme 27).

Table 8. Synthesis of *spiro*-cyclopentyloxindoles **148**.[a]



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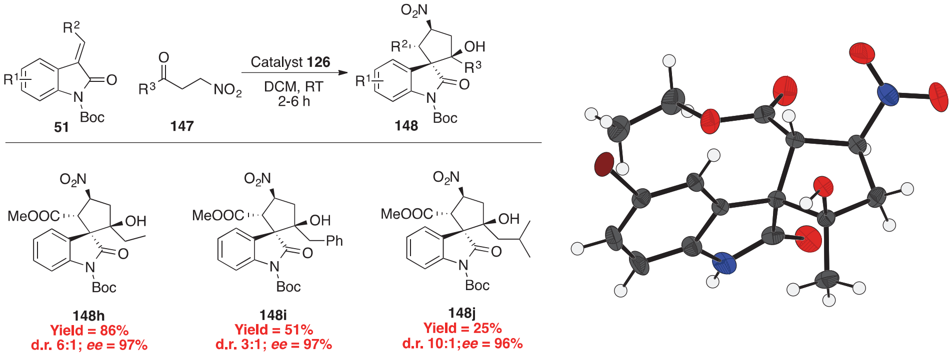
[a] Reaction conditions: 1 equiv. of alkylidene oxindole **51** (0.15 mmol), 2 equiv. of nitroketone **147a** (0.3 mmol) and 10 mol % of catalyst **126** (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).

Preliminary screening revealed that thiourea **126** was the most active and selective catalyst for the reaction. Under optimal conditions (DCM, RT, 2 equiv. **147**) alkylidene oxindole **51a** and nitroketone **147a** gave the product in 87% yield, 10:1 d.r. and 95% *ee* (Table 8, **148a**). The electronic nature of alkylidene oxindole **51** had little to no effect on the reactivity and selectivity of the reaction. All other products were obtained in high yields (81-94%), and good to excellent diastereoselectivities (from 10:1 to 20:1) and high enantioselectivities (Table 8). The absolute stereochemistry of the products was unambiguously assigned by single crystal *x-ray* diffraction of *spiro*-cyclopentyloxindole **148e** after the *Boc* group had been cleaved (Table 9). Other compounds in the series were assigned based on analogy.

To further extend the substrate scope of our methodology, different nitroketones **147** were synthesized and subjected to the reaction conditions (Table 9). A clear correlation between the size of substituent R^3 and reaction rate, as well as selectivity emerged. With the ethyl group as R^3, only a slight drop in diastereoselectivity was observed (d.r. 6:1) as the product was obtained in high yield and 97% *ee* for the major isomer. The benzyl substituent proved more challenging as only moderate selectivity (d.r. 2:1) and yield (51%) were achieved (Table 9). The sterically bulkiest isobutyl group produced the product with high d.r. 10:1 but with low yield (25 %). Finally, phenyl substituted nitroketone **147** was prepared, but under the reaction conditions no product was obtained. It is noteworthy, however, that in all cases high enantioselectivity was retained.

As a further extension of the protocol, *spiro*-annulation of benzofuran **149** with nitroketone **147a** was attempted (Table 10).

Table 9. Substrate screening of different nitroketones **147**[a] and X-ray structure of **148e** without a *Boc* group.



148h
Yield = 86%
d.r. 6:1; *ee* = 97%

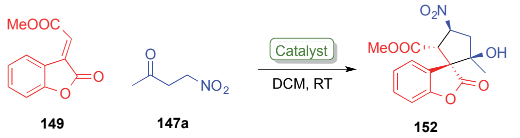
148i
Yield = 51%
d.r. 3:1; *ee* = 97%

148j
Yield = 25%
d.r. 10:1;*ee* = 96%

---

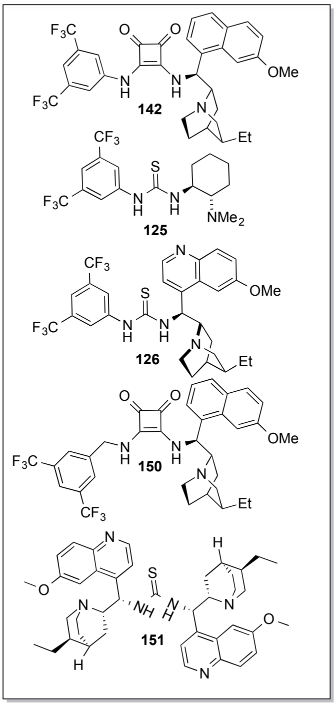
[a] Reaction conditions: 1 equiv. of alkylidene oxindole **51** (0.15 mmol), 2 equiv. of nitroketone **147a** (0.3 mmol) and 10 mol % of catalyst **126** (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).

Table 10. Synthesis of *spiro*-cyclopentylbenzofurans **152**.



Entry	Cat.	Time [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**126**	4	56	19:1	58
2	**125**	3	73	10:1	64
3	**142**	8	27	19:1	82
4	**150**	24	73	19:1	46
5	**151**	19	83	15:1	61

[a] Reaction conditions: 1 equiv. of benzofuran **149** (0.15 mmol), 2 equiv. of nitroketone **147a** (0.3 mmol) and 10 mol % of catalyst (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).



Thiourea **126** was able to promote the reaction, although the product was isolated with moderate enantioselectivity (Table 10, entry 1). Alternative hydrogen bonding catalysts were screened for the reaction, with the squaramide **142** providing the *spiro*-benzofuran **152** in the highest enantioselectivity but in moderate yield (Table 10, entry 3). Extending the reaction time did not increase the yield, although decomposition of the nitroketone increased over a prolonged reaction time. With other catalysts, only minor improvements (Table 10, entries 2 and 5) in selectivity were attained (compared to catalyst **126**), whereas with catalyst **150** enantioselectivity decreased even further (Table 10, entry 4). The difference in selectivity, compared to alkylidene oxindoles **51** can be explained by the absence of an additional coordinative group (*Boc*) in benzofuran **149**, which can significantly reduce the rigidity of the transition state complex during the annulation step.

Conclusions

- In the present study, the asymmetric *spiro*-annulation of alkylidene oxindoles **51**, using various α-chloro-1,3-dicarbonyl compounds under hydrogen-bond catalysis was realized.

- Under hydrogen-bond catalysis, *spiro*-cyclopropyloxindoles **128**, **131** and **132** with two adjacent quaternary centers were synthesized in high yields, and enantio- and diastereoselectivities.

- 3-Chlorooxindoles **134** were introduced as a new class of starting materials for the formal [2+1] asymmetric cycloaddion to α,β-unsaturated aldehydes **2** under aminocatalysis, and to alkylidene oxindoles **51** promoted by the chiral squaramide catalyst **142**.

- The unprecedented reactivity of 3-chlorooxindoles **134** was further elaborated by a novel reaction with nitroalkenes **29**, delivering 3,3'-disubstituted oxindoles with chlorine at the quaternary center. High reactivity and selectivity were achieved. The method was extended to include 3-chlorobenzofuran **145** as a Michael donor.

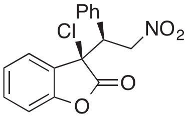
- A new method was developed for the *spiro*-annulation of methyleneindolinones **51** with simple nitroketones **147**, resulting in the formation of *spiro*-cyclopentyloxindoles **148** with four consecutive stereocenters in moderate to high yields and good to excellent selectivities. With benzofuran analogues **149**, the reaction proceeded in moderate enantioselectivity but with good yield and diastereoselectivity.

3. Experimental

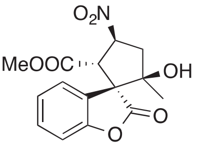
General

Full assignment of ^{1}H and ^{13}C chemical shifts was based on the 1D and 2D FT NMR spectra of a 400 MHz instrument. Chemical shifts were reported in ppm with internal reference of tetramethylsilane and *J* values are given in Hertz. All HPLC analyses were done using a Chiralcel OD-H column. Precoated silica gel 60 F254 plates were used for TLC. Dichloromethane was freshly distilled from P_2O_5, and toluene from sodium. Commercial reagents were used as received.

(*R*)-3-chloro-3-((*S*)-2-nitro-1-phenylethyl)benzofuran-2(3*H*)-one 146.



3-Chlorobenzofuran-2(3H)-one **145** (17 mg, 0.1 mmol), (*E*)-(2-nitrovinyl)benzene **29b** (18 mg, 0.12 mmol) and squaramide **142** (3.2 mg, 5.00 μmol) were dissolved in toluene (0.5 mL) and stirred at RT until TLC showed full conversion. The mixture was directly purified by silica gel column chromatography using a mixture of heptane and ethyl aceteate as an eluent (10:1) to yield 27 mg of product (85%). The diasteromeric ratio was determined by ^{1}H NMR from the crude reaction mixture before purification (10:1) and *ee* by chiral HPLC of the final isolated product (84%; Chiralcel OD-H, Hexane-*i*PrOH 9:1, 1 mL/min, 25 °C, 230 nm, t_r (major) = 11.19 and t_r (minor) = 16.63). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 (td, *J* = 7.9, 1.4 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.19 (m, 3H), 7.05 – 6.90 (m, 4H), 5.61 (dd, *J* = 13.4, 3.7 Hz, 1H), 5.15 (dd, *J* = 13.4, 11.2 Hz, 1H), 4.36 (dd, *J* = 11.2, 3.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.38, 152.38, 132.24, 131.72, 129.65, 129.48, 128.99, 125.71, 125.36, 125.26, 111.83, 75.14, 64.41, 51.23.



Methyl-(2'*R*,3*S*,4'*S*,5'*S*)-2'-hydroxy-2'-methyl-4'-nitro-2-oxo-2*H*-spiro[benzofuran-3,1'-cyclopentane]-5'-carboxylate 152. (*E*)-Methyl-2-(2-oxobenzofuran-3(2H)-ylidene)acetate **149** (31 mg, 0.15 mmol), 4-nitrobutan-2-one **147a** (35 mg, 0.3 mmol) and thiourea **151** (10.4 mg, 0.015 mmol) were dissolved in dichloromethane (0.5 mL) and left stirring at RT until TLC showed full conversion. The mixture was directly purified by silica gel column chromatography using a mixture of heptane and ethyl aceteate as an eluent (10:1) to yield 40 mg of product (83%). The diasteromeric ratio was determined by ^{1}H NMR from the crude reaction mixture before purification (15:1) and *ee* by chiral HPLC of the final isolated product (61%; Chiralcel OD-H, Hexane-*i*PrOH 9:1, 1 mL/min, 25 °C, 230 nm, t_r (major) = 15.38 and t_r (minor) = 18.10).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.43 (td, *J* = 7.9, 1.4 Hz, 1H), 7.28 – 7.16 (m, 2H), 5.51 (ddd, *J* = 10.2, 6.1, 1.8 Hz, 1H), 4.75 (d, *J* = 6.1 Hz, 1H), 3.61 (s, 3H), 3.17 (ddd, *J* = 15.5, 10.3, 1.3 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.29 (s, 1H), 1.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

176.66, 169.79, 154.24, 130.30, 125.31, 125.04, 124.72, 110.99, 84.90, 82.36, 64.54, 55.04, 53.21, 43.23, 21.69.

Table 11. Supporting information pertaining to compounds discussed in the thesis.

Entry	Compound number in thesis	Compound number in publication				
		I	**II**	**III**	**IV**	**V**
1	**128a**	**11a**				
2	**128b**	**11b**				
3	**128c**	**11c**				
4	**128d**	**11d**				
5	**128e**	**11e**				
6	**128f**	**11f**				
7	**129a**	**14a**				
8	**129b**	**14b**				
9	**129c**	**14c**				
10	**129d**	**14d**				
11	**129e**	**14e**				
12	**129f**	**14f**				
13	**130a**	**15a**				
14	**130d**	**15d**				
15	**130e**	**15e**				
16	**134a**		**1a**			
17	**134b**		**1b**			
18	**134g**		**1c**			
19	**134e**		**1d**			
20	**134d**		**1e**			
21	**135a**			**9a**		
22	**135aa**			**9aa**		
23	**135ab**			**9ab**		
24	**135ac**			**9ac**		
25	**135ad**			**9ad**		
26	**135ba**			**9ba**		
27	**135ca**			**9ca**		
28	**135ae**			**9ae**		
29	**135af**			**9af**		
30	**135ag**			**9ag**		
31	**135ah**			**9ah**		
32	**134c**			**7b**		
33	**134f**			**7e**		
34	**141da**			**10da**		
35	**141db**			**10db**		

36	**141bb**		**10bb**	
37	**141eb**		**10eb**	
38	**141dc**		**10dc**	
39	**141dd**		**10dd**	
40	**141de**		**10de**	
41	**141df**		**10df**	
42	**141dg**		**10dg**	
43	**141ed**		**10ed**	
44	**143a**	**3a**		
45	**143b**	**3b**		
46	**143c**	**3c**		
47	**143d**	**3d**		
48	**143e**	**3e**		
49	**143f**	**3f**		
50	**143g**	**3g**		
51	**143h**	**3h**		
52	**143i**	**3i**		
53	**143j**	**3j**		
54	**143k**	**3k**		
55	**143l**	**3l**		
56	**143m**	**3m**		
57	**143n**	**3n**		
58	**143o**	**3o**		
59	**143p**	**3p**		
60	**143r**	**3r**		
61	**143s**	**3s**		
62	**146**			
63	**148a**			**3aa**
64	**148b**			**3ba**
65	**148c**			**3ca**
66	**148d**			**3da**
67	**148e**			**3ea**
68	**148f**			**3fa**
69	**148g**			**3ga**
70	**148h**			**3ab**
71	**148i**			**3ac**
72	**148j**			**3ad**
73	**152**			

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Publication I

Noole, A.; Suckman, N.; Kabeshov, M.; Kanger, T.; Macaev, F.; Malkov, A. Highly Enantio- and Diastereoselective Generation of Two Quaternary Centers in Spirocyclopropanation of Oxindole Derivatives. *Chemistry - A European Journal*, **2012**, *18*, 14929 - 14933.

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Highly Enantio- and Diastereoselective Generation of Two Quaternary Centers in Spirocyclopropanation of Oxindole Derivatives.

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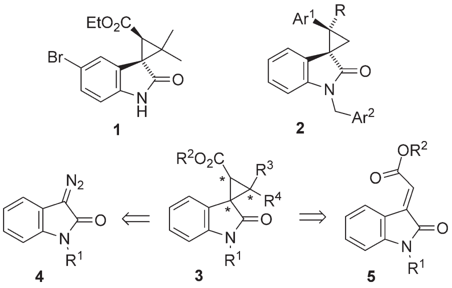
Biologically active spirocyclopropane derivatives of indoles emerged recently as potent drug candidates. Thus, spirooxindole **1** exhibited nanomolar activity as an HIV-1 non-nucleoside reverse transcriptase inhibitor on both wild-type and drug-resistant mutant viruses,[1,2] whereas compounds of type **2** showed promising antitumor activity[3,4] and were also effective for treatment of obesity and diabetes (Scheme 1).[5] The stereochemistry of these compounds plays a crucial role in their biological activity.



Scheme 1. Biologically active spirocyclopropane derivatives of indoles.

In the past, the main strategies for the construction of spirocylopropyl oxindole motif **3** relied either on transition-metal-catalyzed cylopropanation using diazo oxindoles **4** with a suitable alkene partner[1,6–9] or addition of a carbenoid species to unsaturated oxindoles **5**.[1–3,10] Both strategies produced various degrees of diastereoselectivity, but so far were confined to racemic series. More recently, a few examples of successful asymmetric cyclopropanation of the parent oxindoles were reported.[4,11]

Organocatalytic approaches to spiro-annulation of oxindoles **5** offer a high degree of stereo- and enantiocontrol and have become extremely popular for the construction of five- and six-membered spiro-rings.[12–18] However, examples of a direct spirocyclopropanation of indole derivatives remain scarce.[19] The major challenge in the synthesis of **3** is to ensure a stringent control in the formation of the three contiguous stereocenters, which, in theory, can give rise up to eight stereoisomers (four diastereomeric pairs of enantiomers). In a recent report,[20] spirooxindoles **3**, featuring one quaternary center, were obtained in excellent diastereo- and enantioselectivities by a cascade cyclopropanation of **5** with bromonitromethane catalyzed by chiral thioureas. However, for the next member of the homologue series, 1-bromonitroethane, in which two adjacent quaternary centers are created, the diastereocontrol dropped dramatically. Furthermore, it has been recently revealed[11] that in the case of spirooxindoles **3**, in which $R^3 = NO_2$ and $R^4 = H$, the diastereomeric composition can be significantly enriched in favor of the more thermodynamically stable isomer by a base-catalyzed equilibration. Naturally, this option is not available for **3** with R^3, $R^4 \neq H$, which leaves the issue of diastereoselectivity in the asymmetric organocatalytic cyclopropanation wide open.

Herein, we focused on developing a formal [2+1] cycloaddition method for the highly enantio- and diastereoselective construction of spirocyclopropane oxindoles **3** featuring two quaternary centers using chiral catalysts **6**–**9** (Figure 1).

In recent years, α-halo-β-dicarbonyl compounds acquired a successful track record in asymmetric organocatalytic and metal-catalyzed cyclopropanations of α,β-unsaturated compounds including aldehydes,[21,22] the related conjugated ketones and esters,[23,24] and nitroalkenes.[25] The key feature of α-halocarbonyl compounds is the dual nucleophilic/electrophilic reactivity of the α-carbon, which is a prerequisite for the cascade cyclopropanation.

In a background racemic run, oxindole **5a** was treated with ethyl α-chloroacetoacetate **10** in the presence of K_2CO_3 in CH_2Cl_2 at room temperture to afford an equimolar mixture of all four possible diastereoisomers after 24 h (Table 1, entry 1). It is worth noting that the same reaction with un-

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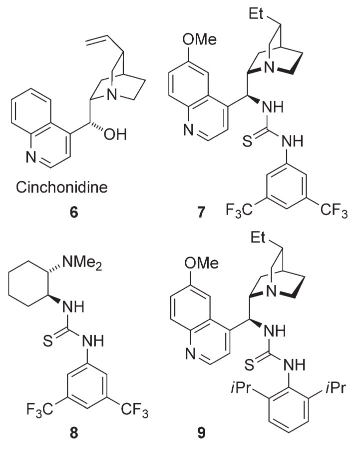
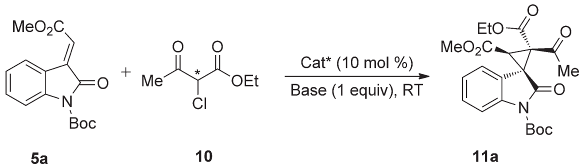


Figure 1. Chiral catalysts.

Table 1. Optimization of the reaction conditions.[a]



Entry	Cat.	Base	Solvent	Yield [%][b]	d.r. [%][b]	*ee* [%][c]
1	–	K_2CO_3	CH_2Cl_2	86	25:25:25:25	n.a.
2	**6**[d]	–	CH_2Cl_2	72	71:24:5	96:55:12
3	**7**	$NaHCO_3$	CH_2Cl_2	48	77:23	93:95
4	**7**	$NaHCO_3$	toluene	n.d.[e]	n.d.	n.d.
5	**7**	$NaHCO_3$	$CHCl_3$	97	78:22	94:96
6	**7**	$NaHCO_3$	THF	54	63:37	97:99
7	**7**	$NaHCO_3$	MeCN	87	9:31:52:8	n.d.
8	**7**	Na_2CO_3	$CHCl_3$	87	74:26	89:94
9	**7**	CsF	$CHCl_3$	76	77:23	93:95
10	**8**	$NaHCO_3$	$CHCl_3$	48	75:25	−93:−86
11	**9**	$NaHCO_3$	$CHCl_3$	82	93:7	91:94
12	**9**	$NaHCO_3$	$CHCl_3$	97[f]	91:9	91:82
13	**9**	$NaHCO_3$	$CHCl_3$	93[g]	90:10	87:83

[a] Unless stated otherwise, the reactions were carried out on a 0.15 mmol scale as a 0.15 M solution at RT for 24 h with 1 equiv of **5a**, 2 equiv of **10**, 1 equiv of base and 10 mol % catalyst loading. [b] Yield of isolated product. [c] Determined by chiral HPLC analyses after deprotection of *t*Boc. [d] 1 Equiv of catalyst was used. [e] Complex mixture of all possible diastereoisomers. [f] 0.3 M Solution. [g] 4 Equiv of **10** used.

protected oxindole **5** was complete in just 1 h and gave a similar outcome, but we opted for *tert*-butoxycarbonyl (Boc) protection, which may benefit stereodifferentiation in the presence of a chiral controller.

For the enantioselective version, we first tested cinchonidine **6**[26] (Figure 1) as a chiral base (1 equiv, CH_2Cl_2, RT). The reaction produced a 3:1 mixture of two main diastereoisomers and a minor quantity of a third diastereoisomer, which could be readily separated by flash chromatography (entry 2). Importantly, the major product showed 96 % *ee*. However, attempted reduction of the catalyst loading to a more practical 10 mol % level had a detrimental effect on the reaction rate and selectivity. Therefore, we next turned to bifunctional thiourea catalysts **7**[27–29] and **8**,[30] which proved successful in the asymmetric spirocyclopropanation of **5** with bromonitromethane.[20]

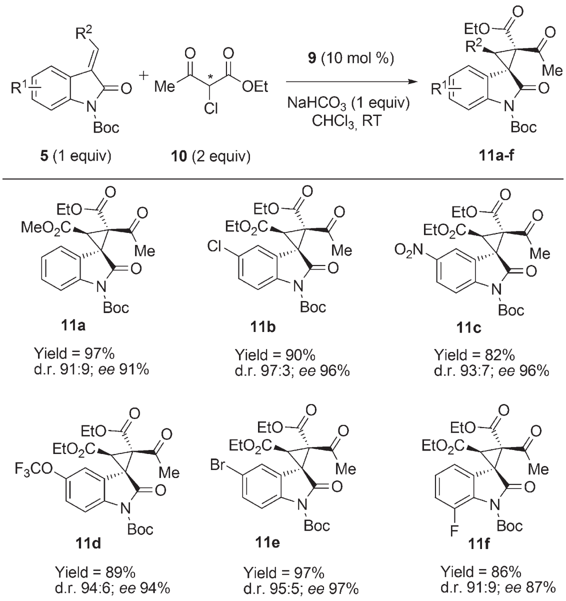
Quinine-derived thiourea **7** (10 mol %, CH_2Cl_2, RT, 24 h) combined with $NaHCO_3$ (1 equiv) afforded a 3:1 mixture of the same two diastereoisomers, as with **6**, in high enantioselectivity, but a low overall yield (entry 3). To optimize the reaction efficiency, various solvents and bases were examined. In toluene (entry 4) and MeCN (entry 7), diastereoselectivity dropped significantly to give mixtures of all possible isomers. The highest enantioselectivity was attained in THF, though the yield and diastereoselectivity were poor (entry 6). Chloroform emerged as a clear winner, showing the best overall performance (entry 5). Other inorganic bases, such as Na_2CO_3 and CsF (entries 8 and 9), proved slightly inferior to $NaHCO_3$. Catalyst **8** mirrored the results shown by **7** delivering the same 3:1 mixture of diastereoisomers of the opposite enantiomeric series (entry 10).

It appears that the commonly used commercial catalysts **6**–**8** under a variety of experimental conditions exhibited a similar reactivity pattern favoring formation of two diastereoisomers in a 3:1 ratio at best. Notably, the components of this mixture cannot be easily separated by chromatography, thus reducing the practical value of the method. Clearly, improvement in the catalyst design was required to overcome this problem.

A set of experiments revealed that diastereoselectivity was influenced by the substituents on the aromatic group of the thiourea catalyst, in particular by those restricting rotation about the C−N bond. A major improvement was achieved with catalyst **9** with bulky *i*Pr groups occupying the *ortho* positions; the diastereoselectivity soared to 13:1 while maintaining a good yield and a respectable enantioselectivity (entry 11). Effectively, only one of eight possible stereoisomers was produced! The yield was further improved by doubling the concentration of the reactants (entry 12), though using an excess of ethyl α-chloroacetoacetate **10** alone proved detrimental (entry 13).

The reaction scope was investigated following the optimized protocol: chloroform as a solvent (0.3 M solution), **5** (1 equiv), **10** (2 equiv), $NaHCO_3$ (1 equiv), and **9** (10 mol %) at room temperature. Under these conditions, the reactions were complete within 24 h (Scheme 2). The substitution pattern in the aromatic ring of the starting oxindoles **5a**–**f** did not affect the efficacy of the process: the spirocyclopropanes **11a**–**f** were uniformly obtained in high yields and high enantio- or diastereoselectivities.

The reaction is likely to proceed by Michael addition of the enolate of **10** to the unsaturated amide fragment in **5** to generate two new stereogenic centers followed by cyclization to create the final spiro-stereocenter. To shed more light on the stereoselectivity in each step, symmetrical

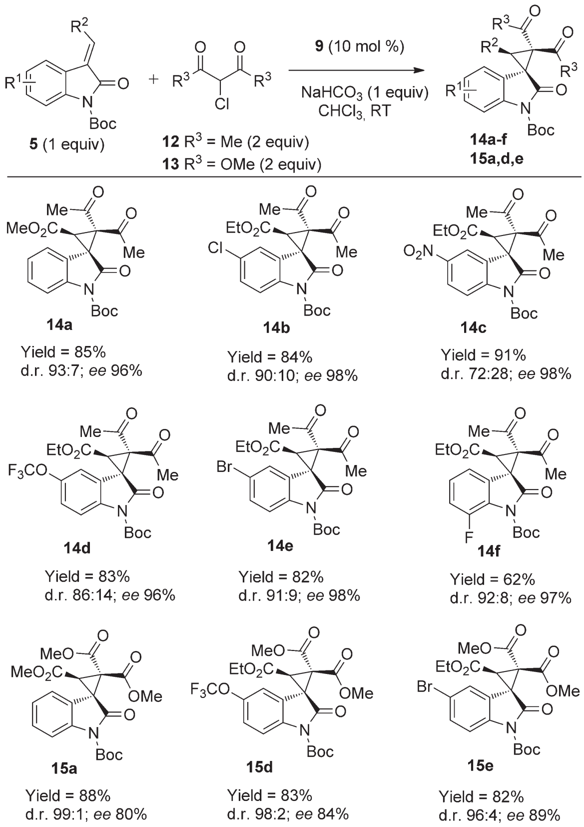


Scheme 2. Cyclopropanation of oxindoles **5** with 2-chloroacetoacetate (**10**).

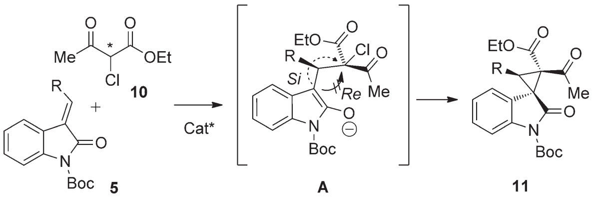
3-chloroacetylacetone (**12**) and dimethyl chloromalonate (**13**) were examined (Scheme 3).

3-Chloroacetylacetone (**12**) exhibited reactivity virtually identical to **10** furnishing **14a–f** in high yield and with high level of stereocontrol. The lower diastereomeric ratios observed in the case of **14c** and **d** resulted from the reversed diastereoselectivity in the racemic series, in which the minor isomers were formed predominantly. Chloromalonate **13** proved the least reactive of the three halodicarbonyl reagents. Under identical conditions, the reaction required 48 h to reach completion. The reduced reactivity appears to have a beneficial effect on the diastereoselectivity: the respective spirooxindoles **15a**, **d**, and **e** were formed as virtually single diastereoisomers, though in slightly lower enantioselectivity.

Dissecting the cyclopropanation cascade into two separate steps provides a useful insight into the role of the new catalyst **9** in attaining efficient stereodifferentiation. NOE NMR experiments revealed that the two diastereoisomers of **14a** differ by configuration of their single tertiary center in the cyclopropane ring, which is created in the first Michael addition step (for establishment of the relative configuration of diastereoisomers, see Supporting Information). Taking into account that catalyst **7** afforded **14a** in only a 3:1 diastereomeric ratio (**5a** + **12**, yield 58%, 43 h), the new catalyst **9** appears to have significantly enhanced enantioselectivity of the Michael addition. Similarity in the enantio- and diastereoselective outcome exhibited by chiral **10** and achiral **12** also indicates that Michael addition of **10** to **5** proceeds with remarkable diastereocontrol, since the configuration of stereogenic centers thus formed are not "adjusted" in the later stages of the reaction. The spirocenter is created in the second cyclization step, which in the case of **11** occurs through intermediate **A** (Scheme 4). In this step, both catalysts **7** and **9** proved equally competent ensuring *Si* facial selectivity for the major diastereoisomer (the opposite enantiomer was formed in the case of **8**). It can be speculated that in the C–C bond-forming event, the catalyst brings the two reactants together: the thiourea motif binds to the oxin-



Scheme 3. Cyclopropanation of oxindoles **5** with 3-chloroacetylacetone (**12**; 24 h) and dimethylchloromalonate (**13**; 48 h).



Scheme 4. Facial selectivity in the spirocyclopropanation step (only nucleophilic attack from the *Si* face takes place).

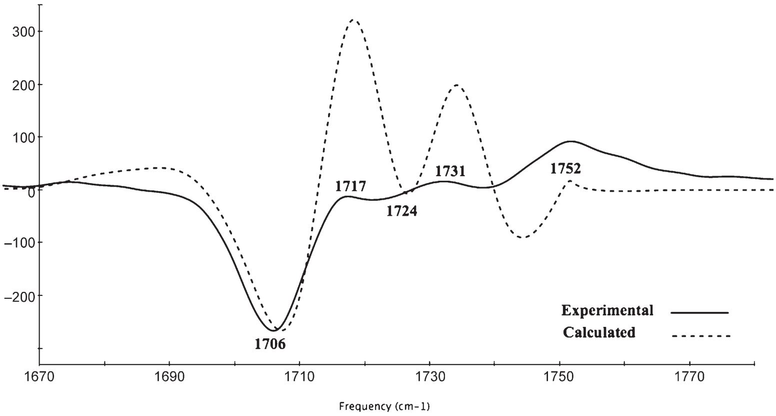


Figure 2. VCD analysis of **14a′**.

dole-Boc fragment by hydrogen-bonding, whereas the quinuclidine part binds the β-dicarbonyl nucleophile. However, a detailed computational analysis is required to build a more accurate mechanistic picture.

The absolute configuration of the spirooxindoles was determined by vibrational circular dichroism (VCD) of unprotected oxindole **14a′**. The carbonyl region of the compound produced the strongest VCD signal and was therefore chosen for the direct comparison with calculated spectra (for details see the Supporting Information). The calculated and experimental spectra provided an excellent match (Figure 2); other compounds in a series were assigned analogously.

In conclusion, we have developed an efficient enantio- and diastereoselective spirocyclopropanation of alkylidene oxindoles generating two quaternary centers. The structure of the quinine-derived thiourea catalyst **9** was optimized to provide high stereoselectivity in both cascade steps. With the new catalysts, cyclopropanation of alkylidene oxindoles with ethyl 2-chloroacetoacetate remarkably produced only one out of eight possible stereoisomers. Mechanistic and computational analysis to determine the mechanism of stereodifferentiation is in progress.

Experimental Section

General procedure for spirocyclopropanation (Schemes 2 and 3): Alkylidene oxindoles **5a–f** (0.15 mmol), sodium hydrogen carbonate (13 mg, 0.15 mmol), thiourea **9** (8.2 mg, 10 mol %, 0.015 mmol) and substrates **10**, **12** or **13** (0.3 mmol) were dissolved in chloroform (0.5 mL) and stirred at RT until TLC showed full conversion. The reaction mixture was directly purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate as eluent. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy and enantiomeric excess by chiral HPLC analysis.

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Keywords: asymmetric catalysis · cascade reactions · cyclization · organocatalysis · spiro compounds

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Organocatalytic Asymmetric Synthesis of 3-Chlorooxindoles Bearing Adjacent Quaternary–Tertiary Centers

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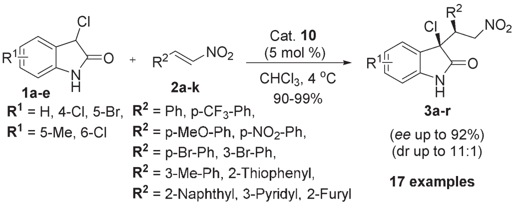
ABSTRACT



A new methodology was developed for the synthesis of enantiomerically enriched 3,3-disubstituted 3-chlorooxindoles 3 via a Michael addition of 3-chloroxindoles to nitroolefins 2, catalyzed by chiral squaramide 10. Products with adjacent quaternary–tertiary centers were isolated in excellent yields (up to 99%), high diastereoselectivities (up to 11:1), and enantiomeric purities (up to 92%). This is the first example where 3-chloroxoindoles 1 have been used as nucleophiles in a highly stereoselective organocatalytic reaction.

Oxindoles bearing a chiral quaternary center at C3 make up the core of many natural products and pharmaceuticals.[1] These compounds are used as building blocks in alkaloid synthesis[2] and, in many cases, as starting materials in medicinal chemistry.[3]

The syntheses of biologically important chiral 3-fluorooxindoles, 3-hydroxyoxindoles,[4] and 3-aminooxindoles have been described;[5] however, the 3,3-disubstituted 3-chlorooxindoles have been synthesized only via asymmetric chlorination of Boc-protected 3-substituted oxindoles.[6] From a synthetic point of view, use of unprotected NH oxindole would be advantageous.[7] However, for oxindoles this is not straightforward due to the high pK_a value of the C–H bond at C3 (pK_a 18.2 in DMSO)[8] and only a small number of successful transformations have been reported.[9] This limitation is usually tackled by introducing an electron-withdrawing protective group (e.g., Boc or acetyl) to the nitrogen atom, thus reducing the pK_a value of the substrate.[10] Alternatively, the same effect can be achieved by placing an electronegative

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atom at the 3-position of the oxindole ring. This is a case of 3-chlorooxindoles where the electronegativity of chlorine will increase the acidity of the C3 proton. This approach not only makes the use of unprotected 3-substituted oxindoles as nucleophiles possible but also presents an opportunity to introduce a chlorine atom at a quaternary center.

To the best of our knowledge, no examples of using 3-chlorooxindoles as nucleophiles in asymmetric 1,4-Michael addition reactions have been reported. This chemistry will provide unconventional access to 3-chlorooxindoles with a chiral quaternary center. A number of successful examples of conjugated addition reactions to nitroolefins using both protected and unprotected 3-aryl- and 3-alkyl-oxindoles have been described previously by Barbas III,[11] Shibasaki,[10a] Maruoka,[12] Zhou,[9b] Enders,[10b] and others. More recently, Melchiorre and co-workers reported a similar transformation of 3-hydroxyoxindoles.[13]

The addition of oxindoles to nitroolefins serves as a potent source of precursors in the synthesis of alkaloids and their derivatives. Also, a number of pharmaceutical agents contain chiral centers with chloro-substitution.[14]

Chiral thioureas[15,16] and, more recently, squaramides[17] are widely used as catalysts to activate nitroolefins for Michael addition reactions. In the conjugated addition reaction described in the present work, the reactivity of both substrates, 3-chlorooxindole **1** and nitroolefin **2**, can be tuned by the appropriate catalyst.

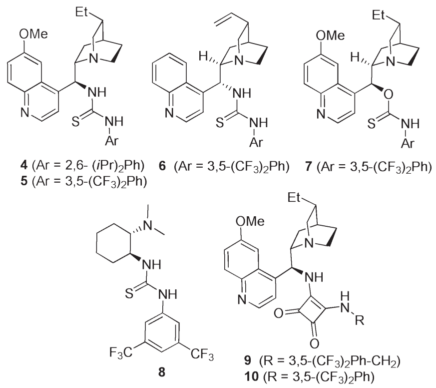
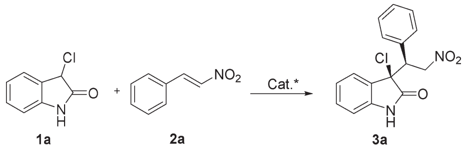


Figure 1. Catalysts used.

Scheme 1. Model Reaction between 3-Chloroxoindole **1a** and β-Nitrostyrene **2a**[a]



[a] Reaction conditions: 0.1 mmol (1 equiv) of **1a**, 0.12 mmol (1.2 equiv) of **2a**, and 0.05 or 0.1 mmol (5 or 10 mol %) of catalyst.

It was conjured that bifunctional thioureas or squaramides represent an ideal choice for this role, where the H-bond donor part of the catalyst would serve as an activator to nitroolefin **2**, whereas the tertiary amine subunit, as a chiral base, would facilitate deprotonation/enolization of the 3-chlorooxindole **1**, thus holding both reactants together and promoting the C−C bond formation.

Our initial studies were focused on the reaction of 3-chlorooxindole **1a** with β-nitrostyrene **2a** (Scheme 1), catalyzed by a thiourea or squaramide catalyst (Figure 1).

Preliminary screening of the catalysts was conducted in chloroform at ambient temperature using 10 mol % of the appropriate catalyst (**4**−**10**, Figure 1) (for details see Supporting Information (SI)). This revealed that, although thioureas **5** and **8** (introduced by Soós[18] and Takemoto[19] respectively) provide high levels of diastereo- and enantiocontrol, squaramides **9** and **10** proved superior in every respect. Catalysts **9** and **10** yielded products with similar enantioselectivities (93% and 90% *ee* respectively); however, the latter provided a slightly better diastereocontrol (3:1 to 6:1, respectively) and was therefore chosen for optimization studies. Screening of the temperature, catalyst loading, and solvent identified the optimal conditions for the reaction as follows: chloroform as a solvent (0.5 M), 1 equiv of **1**, 1.2 equiv of **2**, and 5 mol % of catalyst **10** at 4 °C. Under these conditions, **3a** was obtained in 95% yield, 91% *ee*, and 10:1 dr (Table 1).

With optimal reaction conditions in hand, the substrate scope was explored by reacting 3-chlorooxindole **1a** with different nitroolefins (Table 1). All the reactions were complete within 24 h (Table 1). The substitution pattern in the aromatic ring of the starting nitroolefin **2a**−**j** did not affect the efficacy of the process: the 3-chlorooxindoles **3a**−**j** were uniformly obtained in high yields (90−96%) and high enantio- or diastereoselectivities (*ee* up to 91% and dr up to 11:1).

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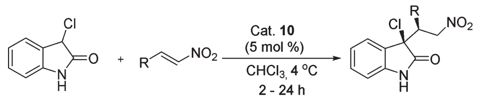
Table 1. Substrate Scope for the Reaction of 3-Chlorooxindole **1a** with Different Nitroolefins[a]

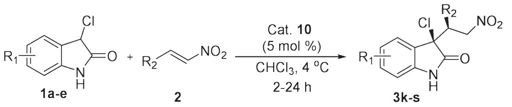


1a **2a-j** **3a-j**

2	3	R	time (h)	yield (%)	dr[b]	*ee* (%)[b]
2a	**3a**	Ph	15	95	10:1	91
2b	**3b**	4-Br-Ph	24	96	11:1	90
2c	**3c**	4-CF_3O-Ph	5	90	7.7:1	86
2d	**3d**	4-NO_2-Ph	23	91	6.7:1	87
2e	**3e**	2-thiophenyl	3	96	10:1	90
2f	**3f**	2-naphthyl	18	95	10:1	90
2g	**3g**	3-pyridyl	7	91	9.1:1	90
2h	**3h**	3-Br-Ph	5	96	11:1	90
2i	**3i**	3-Me-Ph	24	91	11:1	91
2j	**3j**	2-furyl	2	95	5.6:1	88

[a] Reaction conditions: 0.1 mmol (1equiv) of **1a**, 0.12 mmol (1.2 equiv) of **2**, and 0.05 mmol (5 mol %) of squaramide **10** were stirred at ambient temperature in chloroform (0.5 mL); the reaction was monitored by TLC. [b] dr was determined by ^1H NMR, and *ee* by chiral HPLC analysis.

Table 2. Expanding the Substrate Scope[a]

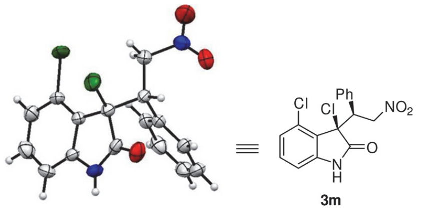


1a-e **2** **3k-s**

1a (R^1=H); **1b** (R^1=4-Cl)
1c (R^1=5-Br); **1d** (R^1=5-Me)
1e (R^1=6-Cl)

2	3	R^1	R^2	yield (%)	dr[b]	*ee* (%)[b]
2a	**3k**	6-Cl	Ph	97	5:1	90
2k	**3l**	6-Cl	4-MeO-Ph	99	6.3:1	90
2a	**3m**	4-Cl	Ph	99	8.3:1	76
2a	**3n**	5-Br	Ph	99[c]	9.1:1	92
2e	**3o**	5-Br	2-thiophenyl	97[c]	7.1:1	87
2a	**3p**	5-Me	Ph	94	10:1	92
2g	**3r**	5-Me	3-pyridyl	90	8.3:1	91
2l	**3s**	6-Cl	*c*-hexyl	–[d]	–	–

[a] Reaction conditions: 0.1 mmol (1equiv) of **1a–e**, 0.12 mmol (1.2 equiv) of **2**, and 0.05 mmol (5 mol %) of squaramide **10** were stirred at ambient temperature in chloroform (0.5 mL); the reaction was monitored by TLC. [b] dr was determined by ^1H NMR, and *ee* by chiral HPLC analysis. [c] Reaction conducted at ambient temperature. [d] Temperature was increased from 4 °C to up to 60 °C, but no reaction occurred.



3m

Figure 2. Molecular moiety in the crystal structure of oxindole **3m**. For clarity, only one formula unit is shown (*Z*′ = 3). Displacement ellipsoids are drawn at the 50% probability level.

To further expand the substrate scope, a series of substituted 3-chlorooxindoles **1a–e** were synthesized (for details, see SI). Electronegative substituents at the C5 and C6 of the oxindole core were well tolerated (Table 2, **3k**, **3l**, **3n**, and **3o**), yielding products with nearly quantitative yields, high enantioselectivities (up to 92%), and dr's ranging from 5:1 to 9.1:1 (isomers were inseparable by column chromatography). 5-Methyl substituted 3-chlorooxindole **1d** provided the products (Table 2, **3p** and **3r**) with *ee*'s of 91% and 92%, respectively, and excellent diastereocontrol. 3,4-Dichlorooxindole **1b** proved to be a more challenging substrate, as the product was isolated with high dr but slightly lower *ee* (Table 2, **3m**). This can be explained by the close proximity of chlorine at the 4-position, which may have influenced the formation of the transition state complex.

As a limitation to the method, aliphatic nitroolefin **2l** failed to react with 3-chlorooxindole **1a** under the reaction conditions, even at elevated temperatures (Table 2, **3s**).

The relative and absolute stereochemistry of 3-chlorooxindole **3m** was unambiguously assigned by single crystal X-ray diffraction (Figure 2).

Other compounds in the series were assigned based on the analogy. According to the observed *syn* geometry of the product, the following transition state for the 1,4-addition to nitroolefins was proposed (Figure 3).

It can be assumed that nitroalkene **2** was activated by the H-bonding to squaramide **10** whereas deprotonation/enolization of 3-chorooxindole **1** was facilitated by the tertiary amine moiety of the catalyst. The *re-face* attack of enolate to the *re-face* of nitroolefin led to the formation of the product with adjacent quaternary–tertiary centers.

These results are in agreement with the literature observations, where 3-alkyloxindoles or 3-aryloxindoles have been used as nucleophiles in a conjugated addition to nitroalkenes under H-bond catalysis.[9a,b,10b,11]

The introduction of a chlorine atom at the quaternary center of oxindole presents a distinctive advantage, as chlorine can serve as a leaving group in nucleophilic substitution reactions. Indeed, it has been shown that in similar 3-chlorooxindoles the chlorine can be substituted by a number of *C*-nucleophiles, as well as being dehalogenated stereospecifically.[20]

Although under the catalysis of squaramide **10** no cyclopropanation or formation of a five-membered ring by the attack of nitronate oxygen was observed, we envisioned that the utility of 3-chlorooxindoles could be expanded by using them as starting materials in a novel cascade reaction, resulting in the formation of spiro-bisoxindoles **12** (Scheme 2).

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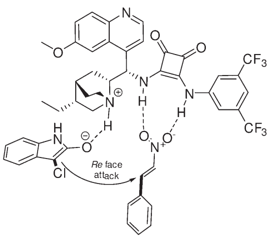
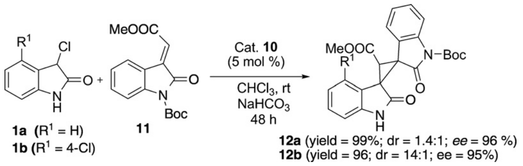


Figure 3. Proposed transition state for the conjugated addition of 3-chlorooxindoles to nitroolefins.

Scheme 2. Synthesis of Spiro-bisoxindoles **10**



To investigate the proposed cascade outlined in Scheme 2, a model reaction between oxindole **11** and 3-chlorooxindole **1a** was chosen. Much to our delight, a high level of enantiocontrol (*ee* 96% for both isomers) was observed with a moderate level of diastereoselectivity (Scheme 2, **12a**).

As a likely scenario of the process, oxindole **11** is activated by the H-bonding to catalyst **10**, whereas 3-chlorooxindole **1** is coordinated by the tertiary amine, resulting in a stereospecific Michael addition followed by the intramolecular cyclization, where chlorine acts as the leaving group. As a result of this cascade of reactions, three contiguous stereogenic centers are formed, two of them being quaternary. From a practical viewpoint, sodium hydrogen carbonate was used as a scavenging agent to neutralize the hydrogen chloride released during the reaction, as excess HCl could render the catalyst inactive.

Of eight possible stereoisomers, only two were formed. The observed similar levels of enantiomeric purity of both diastereoisomers lead us to speculate that, as a likely scenario, diastereoselectivity could be determined by the first Michael addition step, although without knowing the relative stereochemisty of both isomers we cannot really unambiguously determine where the diastereoselectivity is derived. Further support of this hypothesis, however, was received when a sterically bulky substituent within 3-chlorooxindole **1b** caused a remarkable increase in diastereoselectivity (Scheme 2, **12b**). These results present an important avenue for further studies. The substrate scope, as well as the stereochemistry of the reaction, will be further investigated by our group and reported in due course.

In conclusion, we have developed a novel methodology for the synthesis of 3,3-disubstituted 3-chlorooxindoles **3a–r** *via* a conjugated addition of 3-chlorooxindoles to nitroolefins under organocatalytic conditions. High levels of diastereoselectivity (dr up to 11:1) and enantioselectivity (*ee* up to 92%) were observed, with the yields ranging from 90 to 99%. Both electron-donating and -withdrawing groups were well tolerated at the aromatic ring of nitroalkenes as well as the heteroaromatic substituents. To the best of our knowledge, this represents the first catalytic asymmetric reaction where 3-chlorooxindoles **1** have been used as nucleophiles to yield products with adjacent quaternary–tertiary stereocenters. It was further demonstrated that, under similar reaction conditions, oxindoles **11** could be also used as Michael acceptors resulting in the formation of spiro-bisoxindoles **12** with high levels of diastereo- and enantiocontrol. Elaboration of this method will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, ^{1}H, ^{13}C NMR spectra, chiral HPLC chromatograms, and X-ray data of **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

Publication III

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3-Chlorooxindoles: Versatile Starting Materials for Asymmetric Organocatalytic Synthesis of Spirooxindoles

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Abstract: 3-Chlorooxoindoles have emerged as versatile precursors in the synthesis of spirocyclopropyl oxindoles. High enantio- and diastereoselectivity was attained under conditions of both iminium/enamine and H-bonding catalysis.

Keywords: asymmetric synthesis; organocatalysis; oxindoles; spiro compounds

Spirocyclic oxindole scaffolds in recent years have continued to draw attention as important and challenging structural motifs featuring in many natural and synthetic compounds.[1–3] The core structure can be found in many bioactive molecules exhibiting a diverse range of biological activities. For instance, spirooxindole **1** showed nanomolar activity as an HIV-1 non-nucleoside reverse transcriptase inhibitor,[4,5] whereas compounds of type **2** exhibited promising antitumor activity[6,7] and were also effective for the treatment of obesity and diabetes (Figure 1).[8] It is worth noting that the compounds in question were tested as racemates, making them highly desirable targets for asymmetric synthesis and subsequent biological evaluation in the enantiopure form. Recently, spiroindolone **3** showed good antimalarial activity at low nanomolar concentrations making this class of compounds potential drug candidates against malaria.[9]

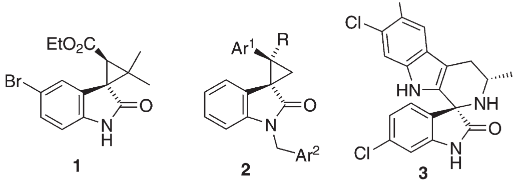


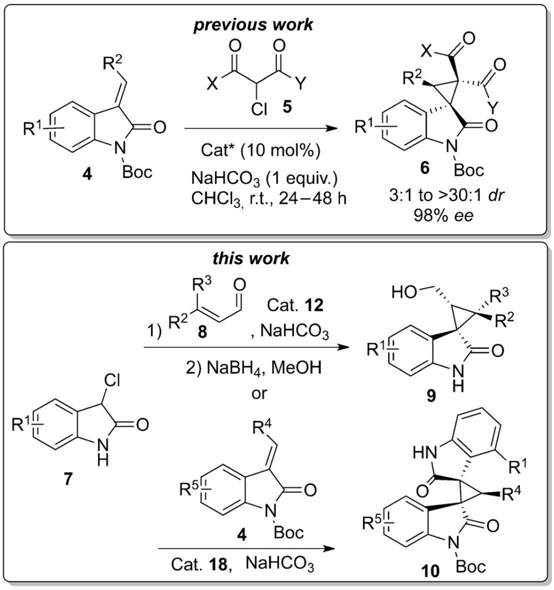
Figure 1. Bioactive spirooxindoles.

Generation of a chiral quaternary center at the 3-position of the oxindole ring remains a major challenge in the synthesis of spirooxindoles. Furthermore, it is often followed by sequential formation of arrays of other quaternary/tertiary centers, adding to the complexity of diastereo- and enantioselective synthesis. In general, the construction of even a single quaternary center is considered a challenge in asymmetric synthesis.[10]

Organocatalytic asymmetric cascades represent a promising strategy for the formation of spirooxindoles with efficient diastereo- and enantiocontrol, as the chirality generated in the first step of the sequence further influences the formation of the adjacent centers.

Currently, there are two main organocatalytic strategies for setting up a spiro stereocenter at the 3-position of the oxindole ring. The first one relies on Michael addition to exocyclic α,β-unsaturated oxindoles followed by spirocyclization.[11–15] Alternatively, the nucleophilicity of C-3 of oxindoles as enhanced by an electron-withdrawing group at this position, is exploited. The latter approach was recently employed by Melchiorre et al.[16] in a cascade addition of 3-hydroxyoxindoles to unsaturated aldehydes leading to spirolactones, and by us[17] using 3-chlorooxindoles. It is worth noting that 3-hydroxyoxindoles experienced a rather poor diastereocontrol resulting in nearly equimolar quantities of two diastereoisomers.[18]

The dual nucleophilic/electrophilic character of C-3 in 3-chlorooxindoles **7** provides an excellent opportunity for constructing an all-carbon quaternary center at this position by organocatalytic cascade reactions.



Scheme 1. Previous and present work.[19,20]

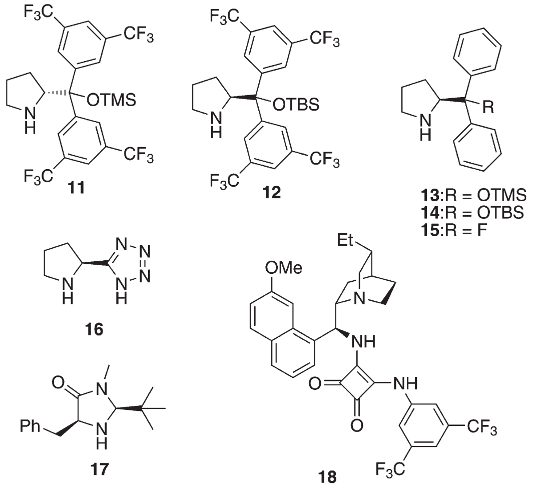


Figure 2. Chiral catalysts.

Thus, increased acidity of the C–H bond due to the presence of chlorine renders the 3-position more nucleophilic, while the chloride serves as a good leaving group for the subsequent cyclization step.

We recently also reported a novel domino reaction between methyleneindolinones **4** and 2-chloro-1,3-dicarbonyl compounds **5** leading to the highly stereoselective formation of spirooxindoles **6** under H-bond catalysis (Scheme 1).[20] In an effort to diversify the substitution pattern of the cyclopropane ring, 3-chlorooxindoles **7** were shown to lead to the formation of bis-spirooxindoles **10**.[17]

Herein, we present a new reaction of 3-chlorooxindoles **7** with α,β-unsaturated aldehydes **8** leading to the formation of spirooxindoles **9**, and also disclose an expanded substrate scope for the synthesis of bis-spirooxindoles **10**.

Motivated by the pronounced biological activity of the spirooxidole-containing compounds, in association with diversity oriented synthesis,[21] we set out to develop a general methodology to access the core spirocyclopropane motif[22,23] starting from 3-chlorooxindoles **7**. Two different strategies were envisioned: (i) aminocatalysis, for the reaction with α,β-unsaturated aldehydes **8** and (ii) H-bond catalysis, for the reaction with methyleneindolinones **4** (Scheme 1). The common feature of both strategies is the generation of two stereogenic centers in the initial Michael addition, followed by diastereoselective cyclization. During the course of the cascade, three stereogenic centers are formed and, therefore, a high level of stereocontrol has to be effected to ensure that the resulting products are formed with high enantio- and diastereoselectivities.

We have demonstrated earlier that 3-chlorooxindoles **7** can undergo a Michael addition to nitroolefines under H-bond catalysis.[17] Therefore, we envisioned that under conditions of aminocatalysis a similar reaction with α,β-unsaturated aldehydes **8** would give rise to spirooxindoles **9**.

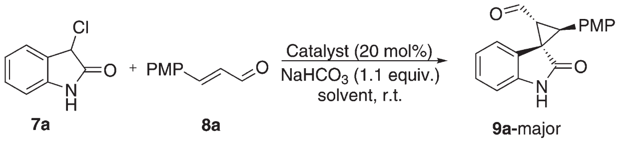
Preliminary optimization experiments were carried out employing model substrates – 3-chlorooxindole **7a** and *para*-methoxycinnamaldehyde **8a** (Table 1).

Catalyst screening revealed the catalyst **12** (Figure 2) to be the most selective and active for the reaction, resulting in a smooth conversion within three hours (Table 1, entry 2). The diastereoselectivity was further improved by changing the solvent from chloroform to toluene (Table 1, entry 9) and by reducing the concentration of oxindole **7a** (Table 1, entry 11). Both changes, lowering the temperature (Table 1, entry 8) and catalyst loading (Table 1, entry 10) had a detrimental effect on the reaction rate and diastereoselectivity.

The reaction product, aldehyde **9a**, turned out to be relatively unstable and prone to epimerization, thus complicating purification. Therefore, throughout the investigation, the products were *in situ* reduced to the corresponding alcohols with sodium borohydride.

With optimal conditions in hand (Table 1, entry 11), the reaction scope was examined next (Table 2). Gratifyingly, the diastereomeric ratios using 3-chlorooxindoles **7** were much higher than those observed for 3-hydroxyoxindoles. In the case of **7a**, using a two-fold excess of **8a** not only increased the reaction rate but also significantly improved the diastereoselectivity

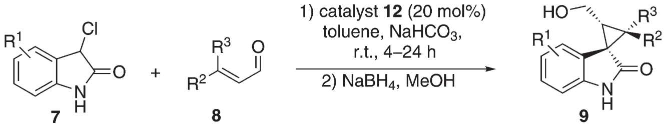
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**11**	$CHCl_3$	3	95	3:1	−97
2	**12**	$CHCl_3$	3	89	4:1	98
3	**13**	$CHCl_3$	16	55	1.3:1	79
4	**14**	$CHCl_3$	16	61	1.2:1	95
5	**15**	$CHCl_3$	16	99	1.5:1	95
6	**16**	$CHCl_3$	3	95	2.7:1	8
7	**17**	$CHCl_3$	24	–	n.d.	n.d.
8	**11**	$CHCl_3$	15[e]	95	2.6:1	94
9	**12**	toluene	3	95	7.1:1	98
10	**12**	toluene	5.5[f]	95	5.3:1	97
11	**12**	toluene	9[g]	95	9:1	98

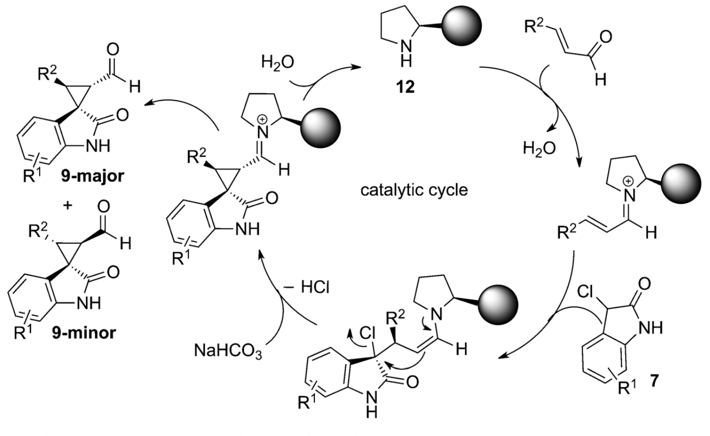
[a] Unless stated otherwise, the reactions were carried out on a 0.1-mmol scale as a 0.2 M solution (in respect to **7a**) at room temperature with 1 equiv. of **7a**, 1.2 equiv. of **8a**, 1.1 equiv. of $NaHCO_3$ and 20 mol% catalyst loading. PMP = *p*-methoxyphenyl.
[b] Yield of isolated product.
[c] Determined from crude product by ^{1}H NMR. Only two diastereoisomers were detected.
[d] Determined by chiral HPLC analysis.
[e] Reaction at 4 °C.
[f] 10 mol% of catalyst used.
[g] Reaction mixture 0.1 M.

Table 2. Cyclopropanation of α,β-unsaturated aldehydes **8a–h** with 3-chlorooxindoles **7a–c**.[a]

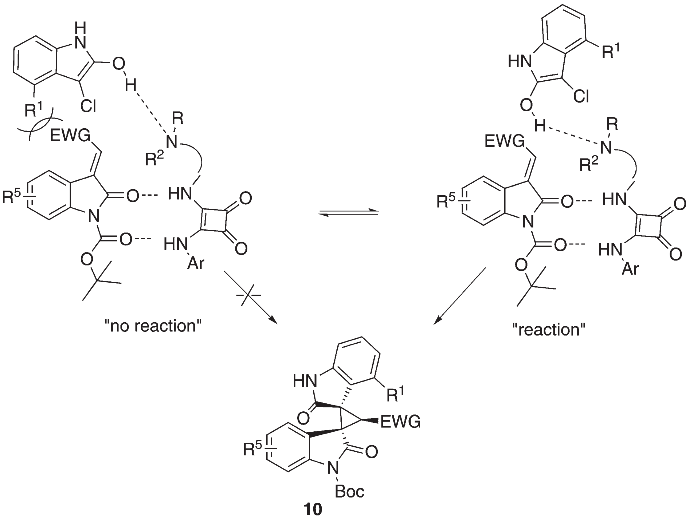


9	**7**	**8**	R^1; R^2; R^3	Yield [%][b]	dr[c,d]	*ee* [%][e]
9aa	**7a**	**8a**	H/4-MeO-C_6H_4/H	71[f]	19:1 (19:1)	>99
9ab	**7a**	**8b**	H/Ph/H	64	5:1 (10:1)	>99
9ac	**7a**	**8c**	H/4-Br-C_6H_4/H	44	5:1 (10:1)	98
9ad	**7a**	**8d**	H/4-NO_2-C_6H_4/H	53	4:1 (7:1)	98
9ba	**7b**	**8a**	4-Br/4-MeO-C_6H_4/H	66[f]	10:1 (14:1)	98
9ca	**7c**	**8a**	5-Br/4-MeO-C_6H_4/H	76[f]	19:1 (20:1)	>99
9ae	**7a**	**8e**	H/thiophen-2-yl/H	60	5:1 (10:1)	96
9af	**7a**	**8f**	H/furan-2-yl/H	69	19:1 (19:1)	98
9ag	**7a**	**8g**	H/Me/H	62[g]	2:1 (2:1)	75/87
9ah	**7a**	**8h**	H/Me/Me	69[f]	4:1 (4:1)	36/89

[a] Unless stated otherwise, the reactions were carried out on a 0.2-mmol scale as a 0.1 M solution at room temperature with 1 equiv. of **7**, 1.2 equiv. of **8**, 1.1 equiv. of $NaHCO_3$ and 20 mol% catalyst loading.
[b] Yield of isolated product after reduction to an alcohol.
[c] Determined from crude product after reduction to an alcohol by ^{1}H NMR.
[d] Diastereomeric ratio of isolated product in the brackets.
[e] Determined by chiral HPLC analysis from isolated product.
[f] Reaction with 2 equiv. of **8**.
[g] Reaction with 5 equiv. of **8**.



Scheme 2. Proposed catalytic cycle for the synthesis of spirooxindoles **9**.



Scheme 3. Proposed transition state for the synthesis of bis-spirooxindoles **10**.

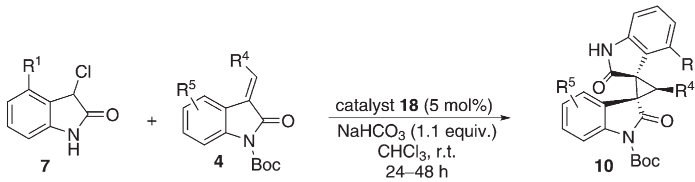
(Table 1, entry 11 and Table 2, entry 1). Unfortunately, this trend did not prove to be general with other α,β-unsaturated aldehydes **8**. Therefore, to maximize the atom economy and the reaction selectivity, 1.2 equivalents of aldehyde **8** were used in most cases (Table 2, see footnotes).

All cinnamic-type aldehydes **8a–d** yielded products with good diastereo- and high enantioselectivities. It is noteworthy that significant enrichments in diastereoselectivity could be effected during column chromatography, as the isomers were separable in most cases (Table 2).

When an aliphatic aldehyde, crotonaldehyde (**8g**), was subjected to the reaction conditions, the product was isolated with moderate diastereoselectivity but with good enantioselectivities for both isomers (Table 2, **9ag**). Most significantly, even prenal **8h** gave a smooth conversion to the desired product, although selectivity for the major isomer was moderate (Table 2, **9ah**). Substituents in the indole ring were well tolerated (Table 2, **9ba** and **9ca**), as well as heteroatoms in unsaturated aldehydes **8e** and **8f** yielding the products with high selectivities (Table 2, **9ae** and **9af**).

The reaction is believed to proceed over the cascade of initial Michael addition followed by cyclization (Scheme 2). That assumption was supported by the fact that in the case of spirooxindole **9ba** the un-

Table 3. Synthesis of bis-spirooxindoles.[a]



10	7	4	R1; R4; R5	Yield [%][b]	*dr*[c]	*ee* [%][d]
10aa	**7a**	**4a**	H/COOMe/H	99	1.4:1	96
10da	**7d**	**4a**	Cl/COOMe/H	96	14:1	95
10 db	**7d**	**4b**	Cl/COOEt/H	95	30:1	93
10bb	**7b**	**4b**	Br/COOEt/H	91	10:1	92
10eb	**7e**	**4b**	Me/COOEt/H	71e)	12:1	89
10dc	**7d**	**4c**	Cl/COOEt/5-NO_2	95	12:1	84
10dd	**7d**	**4d**	Cl/COOEt/7-F	99	12:1	90
10de	**7d**	**4e**	Cl/COOEt/5-CF_3O	81	12:1	90
10df	**7d**	**4f**	Cl/CN/5-Br	87	20:1	99
10dg	**7d**	**4g**	Cl/4-NO_2-C_6H_4CO/5-Br	71	20:1	83
10ed	**7e**	**4d**	Me/COOEt/7-F	75[e]	20:1	86

[a] Unless stated otherwise, the reactions were carried out on a 0.1-mmol scale as a 0.2 M solution at room temperature with 1 equiv. of **7**, 1.2 equiv. of **4**, 1 equiv. of $NaHCO_3$ and 5 mol% catalyst loading.

[b] Yield of isolated product.

[c] Determined from crude product by ^1H NMR.

[d] Determined by chiral HPLC analysis.

[e] *Reaction conditions:* 1 equiv. of **7**, 1.2 equiv. of **4**, 2 equiv. of $NaHCO_3$ and 10 mol% of catalyst **18** at 60 °C.

cyclizised intermediate of the Michael addition was also isolated as a minor product (for details see the Supporting Information).

Next, we turned our attention to the cascade spirocyclization to furnish bis-spirooxindoles **10**. We envisioned that a similar domino reaction, involving Michael addition followed by an intramolecular nucleophilic substitution of chloride could be catalyzed by a bifunctional catalyst, incorporating both H-bond donor and acceptor groups. The use of a bifunctional catalyst did indeed allow for simultaneous activation of Michael donor **7** and acceptor **4** (Scheme 3). Based on our previous results[20] and preliminary screening, a number of *Cinchona* alkaloid-derived thioureas and squaramides were tested in the reaction. Squaramide **18** was found to be the most selective catalyst for this cascade (for details see the Supporting Information).

Under optimal reaction conditions, unsubstituted 3-chlorooxindole **7a** and methyleneindolinone **4a** provided the product in nearly quantitative yield and with high enantioselectivity, although the diastereoselectivity remained low (Table 3, **10aa**). However, a significant improvement in diastereoselectivity was observed when a substituent was introduced in the 4-position of the oxindole ring (Table 3, **10da**). Chlorine, bromine and methyl groups were well tolerated as R1, although higher temperature and increased catalyst loading proved necessary in the latter instance for complete conversion. The electronic properties of the oxindole ring in **4** had little or no effect on the selectivity of the reaction.

The substrate scope was broadened by replacing the ester functionality with nitrile or ketone. Both re-

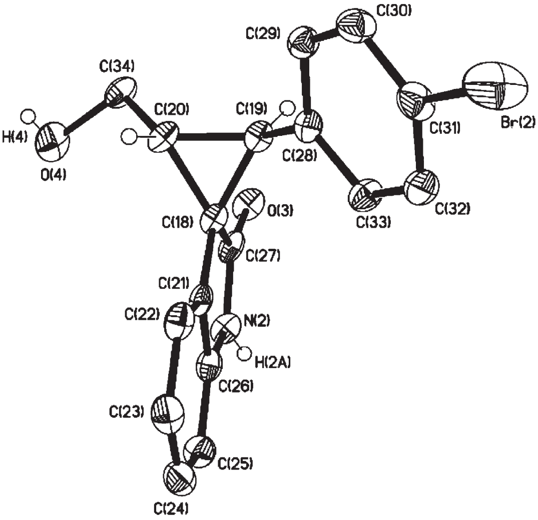


Figure 3. X-ray structure of spirooxindole **9ac** (one of two similar molecules in the asymmetric unit).[24,25]

acted smoothly, almost with no changes in reactivity and selectivity (Table 3, **10df** and **10dg**).

The relative stereochemistry of spirooxindoles **7** (both major and minor isomer) and bis-spirooxindoles **10** was established by NMR NOE experiments, the absolute stereochemistry by X-ray diffraction (Figure 3) and VCD experiments, respectively (for details see the Supporting Information).

In summary, we have demonstrated that 3-chlorooxindoles **7** can serve as useful precursors in the synthesis of spirocyclopropyl oxindoles under conditions of two different activation modes and, hence, employing two different classes of catalysts. We have developed a general methodology to access both spirooxindoles **9** and bis-spirooxindoles **10** in good to excellent yields and high diastereo- and enantioselectivities. Both reaction pathways feature a wide substrate scope including various substitution patterns at the indole ring.

Experimental Section

General Procedure for Spirocyclopropanation (Table 2)

α,β-Unsaturated aldehyde **8** (0.40 mmol), oxindole **7** (0.20 mmol), amine **12** (26 mg, 20 mol%, 0.04 mmol), and $NaHCO_3$ (1.1 equiv., 18 mg, 0.22 mmol) were dissolved in toluene (2 mL) and stirred at room temperature. The reaction was monitored by TLC. Upon completion, the mixture was diluted with MeOH (2 mL) and cooled in an ice bath. $NaBH_4$ (2 equiv., 15 mg, 0.40 mmol) was added and the reaction mixture stirred for 30 min. The mixture was poured into 10 mL of saturated aqueous NH_4Cl solution, extracted with DCM (3×10 mL). The organics were combined, concentrated and directly purified by silica gel column chromatography using a mixture of heptane and EtOAc as eluent. Diastereomeric ratios were determined from the crude reaction mixture by ^1H NMR and enantiomeric purity by chiral HPLC analysis.

General Procedure for the Formation of Bis-spirooxindoles (Table 3)

3-Chlorooxindole **7** (1 equiv., 0.1 mmol), methyleneindolinone **4** (1.2 equiv., 0.12 mmol), $NaHCO_3$ (1 equiv., 8.4 mg, 0.1 mmol) and squaramide **18** (5 mol%, 3.2 mg) were dissolved in chloroform (0.5 mL) and stirred at room temperature. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was directly purified by silica gel column chromatography using a mixture of heptane and EtOAc as eluent. The diastereomeric ratio was determined by ^1H NMR and the enantiomeric purity by chiral HPLC analysis.

Supporting Information

Experimental details, NMR spectral characterization data for all compounds are given in the Supporting Information.

Acknowledgements

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[19] In our previous paper, the configuration of spirooxindoles **6** was assumed by analogy from the calculated VCD data for dimethyl malonate derivative, herein, we present X-ray evidence for ethyl acetoacetate analogue (for details see the Supporting Information), unambiguously confirming the absolute configuration. CCDC 916342 contains the supplementary crystallographic data for compounds **6**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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[24] *Crystal data* for **9ac**: $C_{17}H_{14}BrNO_2$, $M = 344.20$, colourless tablet, $0.96 \times 0.66 \times 0.12$ mm^3, orthorhombic, $P2_12_12_1$, $a = 8.2115(7)$, $b = 13.4656(12)$, $c = 26.810(2)$ Å, $V = 2964.5(4)$ Å^3, $Z = 8$, μ(Mo-Kα) $= 2.78$ mm^{-1}, $\rho_{calcd} = 1.542$ g cm^{-3}, 8968 reflections measured with graphite monochromated Mo-Kα radiation at $T = 150$ K ($\lambda = 0.71073$ Å), 7553 unique, $R_{int} = 0.051$, solved by direct methods,[25] $R_1[F^2 > 2\sigma(F^2)] = 0.039$, wR_2 (all data) $= 0.096$. Largest difference map features within ± 0.86 e Å^{-3}. Two similar molecules in the asymmetric unit. Flack $x = 0.000(8)$; absolute structure reliably determined. CCDC 916343 contains the supplementary crystallographic data for compound **9ac**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Publication IV

Noole, A.; Malkov, A. V.; Kanger, T. Asymmetric Organocatalytic Synthesis of Spiro-cyclopropaneoxindoles. *Synthesis*, **2013**, *45*, 2520 - 2524.

Asymmetric Organocatalytic Synthesis of Spiro-cyclopropaneoxindoles

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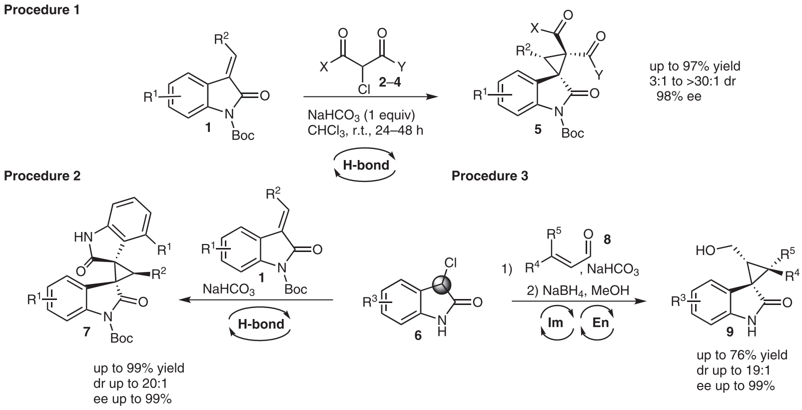
Abstract: Straightforward cascade reactions for the synthesis of spiro-cyclopropaneoxindoles are described. The target compounds are obtained in high yields and in good enantio- and diastereoselectivities via hydrogen bonding or iminium catalysis.

Key words: spiro compounds, organocatalysis, oxindoles, 3-chlorooxindoles, asymmetric synthesis



Scheme 1 General approaches toward spiro-cyclopropaneoxindoles; Im = iminium catalysis, En = enamine catalysis

Enantiomerically pure spiro-cyclopropaneoxindoles are challenging synthetic targets due to their strained three-membered rings with three contiguous stereogenic centers, at least one of which is quaternary.[1] The main synthetic routes to these compounds are based on reactions of alkylidene oxindoles, or additions to 3-substituted oxindole derivatives followed by cyclization of the formed 3,3-disubstituted oxindole. Both approaches can be carried out organocatalytically with high levels of asymmetric induction. Taking into account their wide spectrum of biological activities,[2–4] the enantioselective synthesis of spiro-cyclopropaneoxindoles is of high practical value.

To the best of our knowledge, only a few asymmetric organocatalytic procedures for the formation of spiro-cyclopropaneoxindoles have been reported, which employed the chiral thiourea catalyzed addition of α-bromonitroalkenes to alkylidene oxindoles. High enantio- and diastereoselectivity was reported in the case of bromonitromethane, whereas the introduction of a second quaternary center by employing 2-bromonitroethane resulted in poor diastereoselectivity.[5] The method proposed by Lu[6] afforded spiro-cyclopropaneoxindoles in high diastereo- and enantioselectivities, however, the scope of the reaction was limited to nitro compounds. Although the nitro functionality is versatile and susceptible to a number of transformations, the direct introduction of different functional groups would be preferable, and thus a more general approach to access the spiro-cyclopropane core structure asymmetrically is needed.

Alternatively, cyclopropanation of α,β-unsaturated aldehydes with α-chloro-1,3-dicarbonyl compounds under aminocatalysis has been described in the literature.[7] We envisioned that 3-chlorooxindoles **6**[8] would react in a similar manner, resulting in the formation of spiro-cyclopropaneoxindoles.

Herein, we report three general procedures for the synthesis of spiro-cyclopropaneoxindoles in high enantio- and diastereoselectivities, with up to two adjacent quaternary centers.[9]

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Scope and Limitations

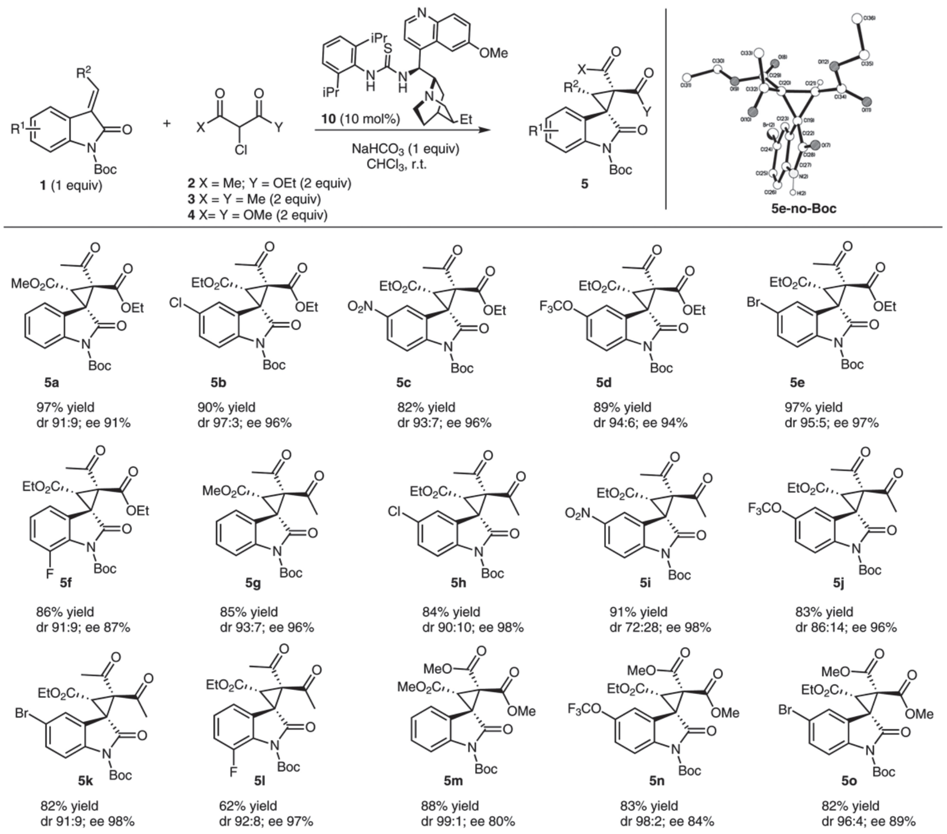
Procedure 1

The starting materials, alkylidene oxindoles **1** and α-chlorodicarbonyl compounds **2**–**4**, were either commercially available or could easily be prepared using simple, inexpensive reagents (for details, see the Supporting Information).

Chiral thioureas are well known to activate alkylidene oxindoles as well as 1,3-dicarbonyl compounds.[10] The cascade reaction involving Michael addition of the enolate of the 1,3-dicarbonyl compound, followed by the formation of the spirocenter via substitution of chloride occurred in the presence of a chiral bifunctional thiourea catalyst, leading to spiro-cyclopropaneoxindoles with two adjacent quaternary centers.

During reaction optimization experiments (see the Supporting Information), thiourea-based catalyst **10** emerged as the most suitable, providing the spiro-cyclopropaneoxindole **5a** in excellent enantio- and diastereoselectivity and in almost quantitative yield (Scheme 2).

Next, the substrate scope was investigated under the optimized conditions. When ethyl 2-chloro-3-oxobutanoate (**2**) was used as the nucleophile, all the reactions were complete within 24 hours. Substituents on the aromatic ring had only a minor influence on the reaction outcome, as all the products were isolated in high yields and stereoselectivities (Scheme 2, products **5a**–**f**). Similarly, when 3-chloropentane-2,4-dione (**3**) or dimethyl 2-chloromalonate (**4**) (which required 48 h for complete conversion) were used as the nucleophiles, the corresponding spiro-cyclopropaneoxindoles **5g**–**o** were isolated in good to excellent enantio- and diastereoselectivities, and chemical yields. All the reactions were conducted at ambient temperature with no special precautions taken to avoid air or moisture. As a limitation, an ester functionality on the alkylidene oxindole was essential to provide the products in good stereoselectivities. When the R^2 group was cyano or carbonyl, a mixture of all the possible diastereoisomers was formed. The absolute stereochemistry of product **5e** (following removal of the Boc group) was determined unambiguously by single crystal X-ray diffraction (Scheme 2), and the remaining products by analogy (see the Supporting Information).



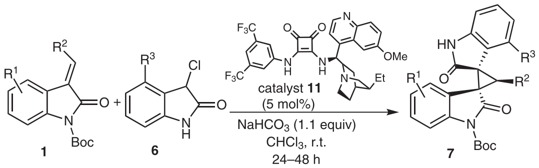
Scheme 2 Organocatalytic cyclopropanation of alkylidene oxindoles

Procedure 2

To further expand the substitution pattern on the cyclopropane ring, 3-chlorooxindoles **6** were shown to react with alkylidene oxindoles **1** leading to the formation of bis-spirooxindoles **7** (Table 1).

Under squaramide **11** catalysis, the products were obtained in good to excellent yields as well as enantio- and diastereoselectivities. It was shown that the diastereoselectivity of the reaction was under substrate control, as only 3-chlorooxindoles **6** with a bulky substituent at C-4 produced products with excellent stereocontrol. In the case of an unsubstituted 3-chlorooxindole, only moderate diastereoselectivity was observed (Table 1, product **7a**).

Table 1 Synthesis of Bis-Spirooxindoles **7**[a]



Product	R^1	R^2	R^3	Yield (%)[b]	dr[c]	ee (%)[d]
7a	H	COOMe	H	99	1.4:1	96
7b	H	COOMe	Cl	96	14:1	95
7c	H	COOEt	Cl	95	30:1	93
7d	H	COOEt	Br	91	10:1	92
7e	H	COOEt	Me	71[e]	12:1	89
7f	5-O$_2$N	COOEt	Cl	95	12:1	84
7g	7-F	COOEt	Cl	99	12:1	90
7h	5-F$_3$CO	COOEt	Cl	81	12:1	90
7i	5-Br	CN	Cl	87	20:1	99
7j	5-Br	4-O$_2$NC$_6$H$_4$CO	Cl	71	20:1	83
7k	7-F	COOEt	Me	75[e]	20:1	86

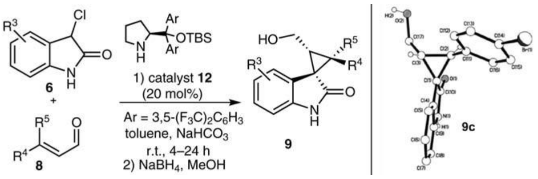
[a] Unless stated otherwise, the reactions were carried out on a 0.1 mmol scale (0.2 M soln) at r.t., with **6** (1 equiv), **1** (1.2 equiv), NaHCO$_3$ (1.1 equiv) and a 5 mol% catalyst loading.
[b] Yield of isolated product.
[c] Determined from the ^{1}H NMR spectrum of the crude product.
[d] Determined by chiral HPLC analysis.
[e] Reaction conditions: **6** (1 equiv), **1** (1.2 equiv), NaHCO$_3$ (2 equiv), catalyst **11** (10 mol%), 60 °C.

The substrate scope was broadened by replacing the ester functionality of alkylidene oxindole **1** with a nitrile or ketone (Table 1, products **7i** and **7j**). The relative stereochemistry of the products was established by NOE experiments, and the absolute stereochemistry by vibrational circular dichroism (VCD) spectroscopy (see the Supporting Information).

Procedure 3

This approach is based on the iminium-catalyzed reaction of 3-chlorooxindoles with α,β-unsaturated aldehydes. The screening identified amine **12** as the catalyst of choice providing high activity, good selectivity and a smooth conversion within 4–24 hours (Table 2, product **9a**).

Table 2 Cyclopropanation of α,β-Unsaturated Aldehydes **8** with 3-Chlorooxindoles **6**[a]



Product	R^3	R^4	R^5	Yield (%)[b]	dr[c,d]	ee (%)[e]
9a	H	4-MeOC$_6$H$_4$	H	71[f]	19:1 (19:1)	>99
9b	H	Ph	H	64	5:1 (10:1)	>99
9c	H	4-BrC$_6$H$_4$	H	44	5:1 (10:1)	98
9d	H	4-O$_2$NC$_6$H$_4$	H	53	4:1 (7:1)	98
9e	4-Br	4-MeOC$_6$H$_4$	H	66[f]	10:1 (14:1)	98
9f	5-Br	4-MeOC$_6$H$_4$	H	76[f]	19:1 (20:1)	>99
9g	H	thien-2-yl	H	60	5:1 (10:1)	96
9h	H	furan-2-yl	H	69	19:1 (19:1)	98
9i	H	Me	H	62[g]	2:1 (2:1)	75/87
9j	H	Me	Me	69[f]	4:1 (4:1)	36/89

[a] Unless stated otherwise, the reactions were carried out on a 0.2 mmol scale (0.1 M soln) at r.t., with **6** (1 equiv), **8** (1.2 equiv), NaHCO$_3$ (1.1 equiv) and a 20 mol% catalyst loading.
[b] Yield of isolated product after reduction into the corresponding alcohol.
[c] Determined from the ^{1}H NMR spectrum of the crude product after reduction into the corresponding alcohol.
[d] Diastereomeric ratio of the isolated product in brackets.
[e] Determined by chiral HPLC analysis of the isolated product; ee values for both diastereoisomers were determined by chiral HPLC analysis as the minor isomer was formed in significant quantities.
[f] Reaction with **8** (2 equiv).
[g] Reaction with **8** (5 equiv).

All cinnamic-type aldehydes **8** yielded products with good diastereoselectivities and high enantioselectivities. It is noteworthy that significant enrichment of the diastereoselectivity could be effected during column chromatography, as the isomers were separable in most cases (Table 2). When an aliphatic crotonaldehyde was subjected to the reaction conditions, the product was isolated with moderate diastereoselectivity, but with good enantioselectivities for both isomers (Table 2, product **9i**). Most significantly, even prenal gave a smooth conversion into the desired product, although the selectivity for the major isomer was moderate (Table 2, product **9j**). The presence of substituents on the indole ring were well tolerated (Table 2, products **9e** and **9f**), as were heterocycle-derived unsaturated aldehydes, which yielded the expected products with high selectivities (Table 2, products **9g** and **9h**).

The absolute stereochemistry of spirooxindole **9c** (Table 2) was determined by single crystal X-ray diffraction,[11] and those of the other products **9** were assigned based on analogy (see the Supporting Information).

In conclusion, three new procedures have been developed which provide a general access to the spiro-cyclopropane scaffold. The starting materials used in the syntheses were either commercially available or could be prepared using one-pot procedures. Different substituents were introduced to all the positions of the cyclopropane ring, as well as various positions of the indole ring. High yields, and good to excellent enantioselectivities and diastereoselectivities were observed. The reactions were operationally simple and could be carried out on a bench-top without the need to avoid air or moisture. The procedures described above enable the asymmetric synthesis of a large library of spiro-cyclopropaneoxindoles, providing convenient access to both enantiomeric series.

Commercial reagents were generally used as received. CH_2Cl_2 and EtOAc were distilled from P_2O_5. Petroleum ether (PE) refers to the fraction boiling in the 40–60 °C range. Precoated Merck (60 mesh) silica gel 60 F_{254} plates were used for TLC. Column chromatography was accomplished using Merck silica gel. IR spectra were recorded on a Bruker Tensor 27FT spectrophotometer. Full assignment of the ^1H and ^{13}C NMR chemical shifts was based on 1D and 2D FT NMR spectra recorded on a Bruker Avance III 400 MHz spectrometer. Solvent signals ($CHCl_3/CDCl_3$: $\delta = 7.26/77.16$) were used as chemical shift references. The diastereomeric ratios were determined by ^1H NMR spectroscopy. HRMS was performed on an Agilent Technologies 6540 UHD Accurate Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Chiral HPLC was performed on an Agilent Technologies 1200 Series instrument using Chiralcel OD-H, Chiralpak AD-H and Chiralpak AS-H columns.

(1*S*,2*R*,3*S*)-1′-(*tert*-Butyl) 2-Ethyl 3-Methyl 2-Acetyl-2′-oxospiro[cyclopropan-1,3′-indoline]-1′,2,3-tricarboxylate (5a); Typical Procedure 1

(*E*)-*tert*-Butyl 3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**1a**) (0.15 mmol), $NaHCO_3$ (13 mg, 0.15 mmol), thiourea catalyst **10** (8.2 mg, 0.015 mmol, 10 mol%) and ethyl 2-chloro-3-oxobutanoate (**2**) (0.3 mmol) were mixed together in a 5 mL round-bottomed flask and $CHCl_3$ (0.5 mL) was added. The mixture was stirred at r.t. until TLC indicated full conversion. The resulting mixture was purified directly by silica gel column chromatography (PE–EtOAc; 5:1). The enantiomeric excess (91%) was determined by chiral HPLC analysis [Chiralpak IB-3, hexane–*i*-PrOH, 95:5, 1 mL/min, 254 nm; major ($t_R = 23.3$ min) and minor ($t_R = 21.9$ min)] after cleavage of the Boc group.

Yield: 63 mg (97%); colorless oil; dr 91:9.

IR (KBr): 1774, 1726, 1482, 1466, 1369, 1350, 1297, 1251, 1152 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (d, $J = 8.2$ Hz, 1 H), 7.31 (ddd, $J = 8.5, 7.1, 1.9$ Hz, 1 H), 7.09–6.99 (m, 2 H), 4.23–4.04 (m, 2 H), 3.76 (s, 3 H), 3.66 (s, 1 H), 2.47 (s, 3 H), 1.62 (s, 9 H), 1.11 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 193.56$, 168.20, 165.42, 164.30, 149.04, 140.83, 129.30, 124.02, 122.58, 121.11, 115.16, 84.73, 63.34, 56.71, 52.92, 39.30, 38.02, 30.16, 28.21, 14.02.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{25}NO_8Na$: 454.1472; found 454.1466.

(2′*S*,3*R*,3′*R*)-1-(*tert*-Butyl) 3′-Methyl 4″-Chloro-2,2″-dioxodispiro[indoline-3,1′-cyclopropane-2′,3″-indoline]-1,3′-dicarboxylate (7b); Typical Procedure 2

3,4-Dichloroindolin-2-one (**6b**) (0.1 mmol, 1 equiv), (*E*)-*tert*-butyl 3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**1a**) (0.12 mmol, 1.2 equiv), $NaHCO_3$ (8.4 mg, 0.1 mmol, 1 equiv) and squaramide **11** (3.2 mg, 5 mol%) were mixed together in a 2 mL conical flask. $CHCl_3$ (0.5 mL) was added and the resulting heterogeneous mixture was stirred at r.t. until TLC indicated full conversion. The mixture was purified directly by silica gel column chromatography (heptane–EtOAc, 4:1 to 1:1) to afford bis-spirooxindole **7b**. The enantiomeric excess (95%) was determined by chiral HPLC analysis of the major isomer [Chiralcel OD-H, hexane–*i*-PrOH, 95:5, 1 mL/min, 230 nm; major ($t_R = 16.6$ min) and minor ($t_R = 18.0$ min)].

Yield: 45 mg (96%); white solid; dr 14:1.

IR (KBr): 3303, 1789, 1740, 1615, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$–7.73 (m, 1 H), 7.65–7.48 (m, 2 H), 7.33 (tt, $J = 8.0, 1.3$ Hz, 1 H), 7.17–7.08 (m, 2 H), 6.99 (ddd, $J = 8.3, 2.2, 1.0$ Hz, 1 H), 6.68 (dd, $J = 7.7, 1.0$ Hz, 1 H), 5.02 (s, 1 H), 3.85 (s, 3 H), 1.56 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 169.99$, 168.53, 164.27, 148.58, 143.42, 140.55, 133.95, 129.82, 129.36, 127.74, 124.96, 123.32, 118.97, 118.93, 114.05, 108.27, 84.88, 52.82, 49.73, 47.40, 34.34, 28.16.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{24}H_{21}ClN_2O_6Na$: 491.0980; found 491.0980.

(1*S*,2*R*,3*S*)-2-(Hydroxymethyl)-3-(4-methoxyphenyl)spiro[cyclopropan-1,3′-indolin]-2′-one (9a); Typical Procedure 3

p-Methoxycinnamaldehyde **8** (R^4 = H, R^5 = 4-$MeOC_6H_4$) (0.40 mmol, 65 mg, 2 equiv), 3-chloroindolin-2-one **6** (R^3 = H) (0.20 mmol, 33 mg, 1 equiv), amine catalyst **12** (26 mg, 0.04 mmol, 20 mol%) and $NaHCO_3$ (18 mg, 0.22 mmol, 1.1 equiv) were mixed together in a 5 mL round-bottomed flask. Toluene (2 mL) was added and the resulting heterogeneous mixture was stirred at r.t. until TLC indicated full conversion. The mixture was diluted with MeOH (2 mL) and cooled in an ice bath. $NaBH_4$ (15 mg, 0.40 mmol, 2 equiv) was added and the resulting mixture stirred for 30 min. The mixture was poured into sat. aq NH_4Cl soln (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, concentrated and the residue purified by silica gel column chromatography (heptane–EtOAc, 5:1) to afford spiro-cyclopropane **9a**. The enantiomeric excess (>99%) was determined by chiral HPLC analysis [Chiralcel OJ-H, hexane–*i*-PrOH, 85:15, 1 mL/min, 230 nm; major ($t_R = 11.0$ min) and minor ($t_R = 18.5$ min)].

Yield: 44 mg (71%); white solid; dr 91:1.

IR (KBr): 3250, 1696, 1620, 1516, 1469, 1248, 911, 653 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.49$ (s, 1 H), 7.08–7.00 (m, 3 H), 6.86 (dt, $J = 7.7, 1.0$ Hz, 1 H), 6.80–6.74 (m, 2 H), 6.66 (td, $J = 7.7, 1.0$ Hz, 1 H), 5.99–5.94 (m, 1 H), 4.30 (d, $J = 5.3$ Hz, 2 H), 4.12 (s, 1 H), 3.77 (s, 3 H), 3.59 (d, $J = 8.2$ Hz, 1 H), 2.64 (dt, $J = 8.2, 5.3$ Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 179.01$, 158.82, 140.36, 130.94, 127.99, 126.48, 126.44, 121.61, 120.77, 113.72, 109.75, 58.83, 55.19, 39.94, 39.15, 37.72.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_3$: 296.1281; found 296.1279.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(11) CCDC 916343 contains the supplementary crystallographic data for compound **9c**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Publication V

Noole, A.; Ilmarinen, K.; Järving, I.; Lopp, M.; Kanger, T. Asymmetric Synthesis of Congested Spiro-cyclopentaneoxindoles via an Organocatalytic Cascade Reaction. *Journal of Organic Chemistry*, **2013**, *78*, 8117 - 8122.

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Asymmetric Synthesis of Congested Spiro-cyclopentaneoxindoles via an Organocatalytic Cascade Reaction

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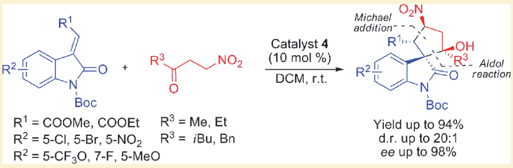
Supporting Information



ABSTRACT: Starting from simple alkylidene oxindoles and nitroketones, a highly stereoselective methodology was developed for the synthesis of spiro-cyclopentaneoxindoles with four consecutive stereogenic centers. Using an organocatalytic cascade of Michael and aldol reactions in the presence of a chiral thiourea catalyst products were obtained in moderate to high yields and excellent enantioselectivities. Nitro, ester, and hydroxyl groups were introduced to the spiro ring, which could be used to facilitate further functionalization of the products.

A spirooxindole scaffold makes up the core of many natural and synthetic bioactive compound[1−4] exhibiting a broad range of activities, including antitumor[5] and antimalarial activity[6] (Figure 1). For those reasons, the asymmetric synthesis of spirooxindoles has received considerable attention (for recent reviews, see refs 7 and 8). However, the formation of spiro rings with multiple consecutive stereocenters still remains an inspiring and difficult task.[9−11]

The main challenges en route to chiral spirooxindoles are the formation of a quaternary spiro center and the need to exhibit a stringent control over the stereochemical outcome of the reaction, as in most cases multiple stereocenters are formed.

Many strategies have been devised for spirooxindole core formation, with the ones employing alkylidene oxindoles as precursors being most prominent.[12−15] Alkylidene indolinones are activated via the carbonyl group for the initial Michael addition, effectively delaying the formation of the quaternary center that takes place during the cyclization step to form the spiro ring. This tactic allows us to overcome the high energy barrier associated with quaternary center formation, as well as delivering the chiral induction for the later stages of the cascade by the initial chirality generated by a Michael addition step.

Among the other spirooxindoles, the synthesis of functionalized all-carbon spiro-cyclopentane derivatives is still a challenge.[16−20] More important than the size of the cycle is its substitution pattern enabling constructing various derivatives of spiro-cyclopentaneoxindoles with promising medicinal properties. In a recent paper,[21] we described a new methodology for the asymmetric synthesis of spiro-cyclopropyloxindoles[22] starting from alkylidene indolinones. Inspired by this work, as well as recent literature examples and success in our own laboratory in organocatalytic Michael[23−27] and aldol reactions,[28] we set out to develop a new methodology for the formation of highly substituted spiro-cyclopentaneoxindoles (the structural core of many natural products) employing alkylidene oxindoles and nitroketones as precursors. β-Nitroketones **2** with an ethylene bridge between functional groups, which both can be activated by hydrogen bonding, can act as versatile substrates for organocatalysis.[29] Although the nucleophilic and electrophilic sites are present in the same molecule, a sufficiently short linker ensures a suppressed intramolecular reaction making them ideal building blocks for cascade reactions. With these considerations, we envisioned a new Michael−aldol cascade using alkylidene oxindoles and nitroketones leading to the formation of highly functionalized spiro-cyclopentaneoxindoles (Scheme 1). Nitro, ester, and hydroxyl groups in the target compound are reactive sites for further transformations making obtained spiro-cyclopentaneoxindoles highly valuable building blocks.

This two-step cascade reaction involves an initial Michael addition of nitronate to alkylidene oxindole **1**, followed by intramolecular cyclization via an aldol reaction. In the course of the cascade, four consecutive stereogenic centers are formed, two of which are quaternary. From the outset, it was envisioned, that the reaction could be catalyzed by bifunctional thiourea or a squaramide catalyst (Figure 2),[30−32] as both alkylidene indolinones **1** and nitroketones **2** can by activated by hydrogen bonding. It was deemed necessary for the alkylidene oxindole to bear a protecting group, as this could provide an additional hydrogen bond acceptor group, as well as increasing the solubility of the substrate. It is known that the protective group at nitrogen of the oxindole influences the stereoselectivity of the aldol reaction.[33,34] From the synthetic point of view it was reasonable to use easily removable Boc-group. For the generation of a nitronate, however, the presence of a tertiary amine subunit within the catalyst was considered to be crucial (deprotonation during nitronate formation).

To investigate the proposed cascade, a model reaction between alkylidene oxindole **1a** and nitroketone **2a** was chosen (Table 1). Initial optimization experiments were conducted in

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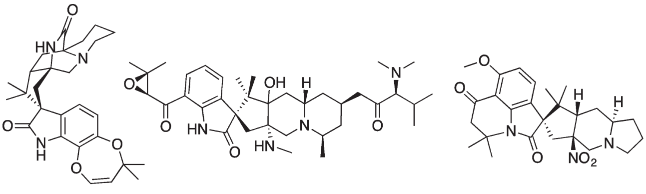


marcfortine B ***Cintrinadin A*** ***Cyclopiamine B***

Figure 1. Spirooxindole-containing natural products.

Scheme 1. Retrosynthetic Analysis for Spirocyclopentaneoxindole Formation

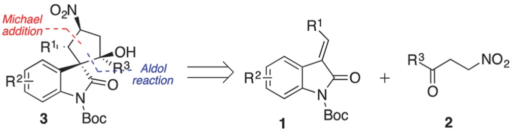
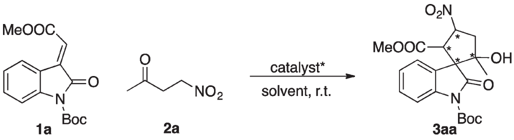


Table 1. Screening Results[a]



entry	2 (equiv)	catalyst (mol %)	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	2	**4** (10 mol %)	toluene	3	86	10:1	96
2	1.2	**4** (5 mol %)	toluene	20	57	10:1	96
3	1.2	**5** (5 mol %)	toluene	46	29	3:1	82
4	1.2	**6** (5 mol %)	toluene	24	49	7:1	−94
5	2	**6** (10 mol %)	toluene	3	75	7:1	−99
6	2	**7** (10 mol %)	toluene	2	71	5:1	−99
7	2	**4** (10 mol %)	DCM	2	87	10:1	95

[a] Reaction conditions: alkylidene oxindole, nitroketone, and catalyst were mixed and stirred at rt until TLC showed full conversion. [b] Isolated yield. [c] Determined by ^{1}H NMR; [d] Determined by chiral HPLC.

toluene at ambient temperature. To our delight, when 10 mol % of thiourea **4** catalyst was used, in the presence of 2 equiv of nitroketone **2a**, product was isolated in 86% yield with a 10:1 diastereomeric ratio and 96% ee (Table 1, entry 1). Lowering the catalyst loading and excess of nitroketone had a detrimental effect on the reaction rate and yield (Table 1, entry 2). Squaramide **5** as well as thioureas **6** and **7** provided inferior results in respect to catalyst **4** (Table 1, entries 3–6). When solvent was switched from toluene to DCM, however, the reaction rate was slightly increased with only a minor influence on the stereoselective outcome of the reaction (Table 1, entry 7).

With the optimal conditions in hand (1 equiv of **1**, 2 equiv of **2**, 10 mol % of thiourea **4** in DCM), next we set out to determine the full substrate scope for the reaction (Scheme 2). Different alkylidene oxindoles **1** were subjected to the reaction conditions, both with electron-withdrawing and -donating groups at the aromatic ring.

The electronic nature of an alkylidene oxindole **1** had little to no effect on the reactivity and selectivity of the reaction. All products were obtained in high yield (79–94%) and good to excellent diastereoselectivities (from 10:1 to 20:1) and high enantioselectivities (Scheme 2). Although it should be noted that the ester moiety was essential for the successful reaction outcome, as with phenyl, cyano, or 4-nitrobenzoyl groups either no reaction occurred or a complex mixture of products was detected by TLC.

The absolute stereochemistry of the product was unambiguously assigned by a single-crystal X-ray diffraction of spirocyclopentanoxindole **3ea** after the Boc-group had been cleaved (Figure 3). Other compounds in the series were assigned on the basis of analogy. Taking into account the structural information gained from the X-ray structure, we propose that after the initial Michael addition of the nitronate to alkylidene oxindole has occurred ester and nitro groups are in *trans* orientation. The carbonyl group of the ketone and nitro group are hydrogen-bonded to the catalyst, efficiently fixing their orientation for the cyclization to proceed stereospecifically. This ensures a preferred *cis*-configuration of the nitro and hydroxyl groups in the final product.

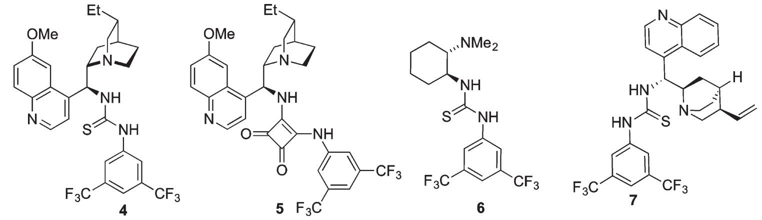
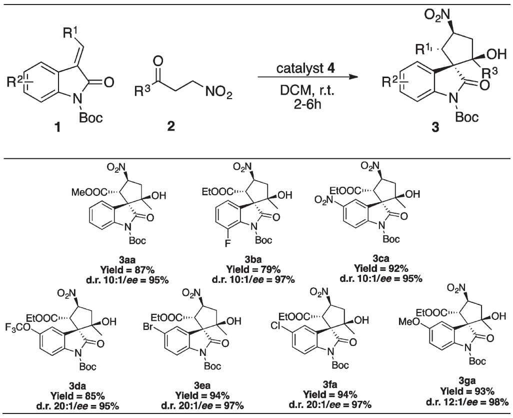


Figure 2. Catalysts used.

Scheme 2. Substrate Scope Experiments[a]



[a]Reaction conditions: 1 equiv of alkylidene oxindole **1** (0.15 mmol), 2 equiv of nitroketone **2** (0.3 mmol), and 10 mol % of catalyst **4** (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).

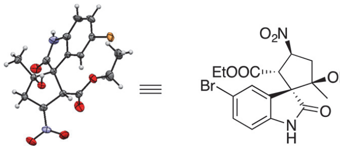
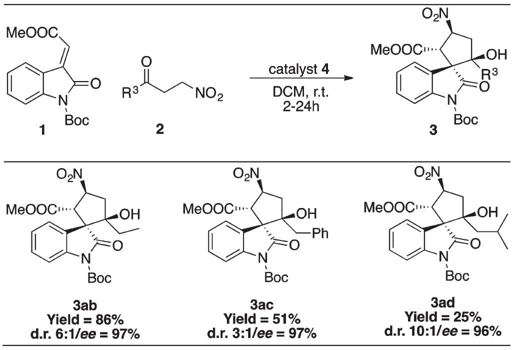


Figure 3. X-ray structure of spirooxindole **3ea′** (one of two similar molecules in the asymmetric unit).

To further expand the substrate scope of our methodology, different nitroketones **2** were synthesized and subjected to the reaction conditions (Scheme 3). A clear correlation between the size of the substituent R^3 and reaction rate, as well as selectivity, emerged. With the ethyl group as R^3, only a slight drop in diastereoselectivity was observed (dr 6:1) as the product was obtained in high yield and 97% ee for the major isomer. The benzyl substituent proved more challenging as only moderate selectivity (dr 2:1) and yield (51%) were achieved (Scheme 3). The sterically bulkiest isobutyl group produced product with high dr 10:1 but with low yield (25%). Finally, phenyl-substituted nitroketone was prepared, but under optimal cascade reaction conditions no product was obtained. It is noteworthy, however, that in all cases high enantioselectivity was retained.

Scheme 3. Substrate Scope Experiments[a]



[a]Reaction conditions: 1equiv of alkylidene oxindole **1** (0.15 mmol), 2 equiv of nitroketone **2a** (0.3 mmol) and 10 mol % of catalyst **4** (0.015 mmol) were mixed at ambient temperature in DCM (0.5 mL).

In conclusion, we have developed a new organocatalytic, highly enantioselective methodology for the synthesis of spirocyclopentaneoxindoles via a Michael−aldol cascade reaction. During the cascade reaction, four consecutive stereogenic centers were formed, two of which were quaternary. In most cases, high diastereoselectivities were observed (up to 20:1) which were only diminished when sterically more demanding nitroketones were employed as reaction substrates. The final product can be easily unprotected to obtain free spirooxindoles, and versatile functional groups (nitro, hydroxyl, and ester) were introduced to the spiro ring, which could easily be transformed to other functionalities. This represents a novel strategy for the synthesis of highly functionalized spirooxindoles with an all-carbon spiro ring.

■ EXPERIMENTAL SECTION

General Methods. Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a 400 MHz instrument. Solvent peaks ($CHCl_3/CDCl_3$ δ = 7.26/77.16) were used as chemical shift references. Chiral HPLC was performed using Chiralcel OD-H, Chiralpak AD-H, and Chiralpak AS-H columns. Mass spectra were recorded by using Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Precoated silica gel 60 F_{254} plates were used for TLC, whereas for column chromatography Merck silica gel was used. Commercial reagents were generally used as received. DCM and EtOAc were distilled from P_2O_5.

Synthesis of Catalysts. Thiourea **6** was commercially available from Strem and used as received. Thioureas **4** and **7** and squaramide **5** were prepared according to literature procedures.[35−37]

Synthesis of Starting Materials. Methylene indolinones **1a**−**g** were prepared according to literature procedures from commercially available isatines using a Boc protection−Wittig sequence.[38] Nitroketones **2** were prepared as described by Miyakoshi et al.[39]

5-Methyl-1-nitrohexan-3-one 2d. Synthesis was based on the literature procedure.[39] 5-Methylhex-1-en-3-one (0.6 g, 5.4 mmol) and sodium nitrite (0.74 g, 10.7 mmol) were dissolved in THF (2.7 mL). Acetic acid (0.6 mL, 10.7 mmol) was added dropwise and the mixture stirred at ambient temperature for overnight. The reaction mixture was extracted with water/DCM, and the organics were back-extracted with satd $NaHCO_3$ and dried over $MgSO_4$. The mixture was filtered, concentrated, and purifed by silica gel column chromatography (eluent petroleum ether/acetone 20:1) to yield 337 mg (40%) of product as yellow oil: IR ν 2961, 1717, 1557 cm^{-1}; ^1H NMR (400 MHz, chloroform-*d*) δ 4.67−4.62 (m, 2H), 3.04 (t, J = 6.0 Hz, 2H), 2.40 (d, J = 7.0 Hz, 2H), 2.26−2.12 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7, 69.0, 51.9, 38.9, 24.7, 22.6; HRMS (ESI) calcd for $[M + Na]^+$ $(C_7H_{13}NO_3Na)^+$ requires m/z 182.0788, found 182.0788.

General Procedure for the Synthesis of Spiro-cyclopentaneoxindoles. Methylene oxindole **1** (0.15 mmol, 1 equiv), nitroketone **2** (0.3 mmol, 2 equiv), and thiourea **4** (10 mol %, 0.015 mmol) were dissolved in DCM (0.5 mL) and stirred at ambient temperature until TLC showed complete disappearance of the limiting starting material. The mixture was directly purified by silica gel column chromatography using a mixture of heptane/EtOAc as eluent. The diastereomeric ratio was determined by ^1H NMR and enantioselectivity by chiral HPLC analysis.

1′-*tert*-Butyl 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxy-

late 3aa. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane:EtOAc as an eluent in 87% yield (55 mg) with dr 10/1 and ee 99% that was determined after the cleavage of the Boc-group [Chiralcel AD-H, Hex/*i*-PrOH 80:20, 1 mL/min, 230 nm; *major* (t_R = 9.44 min) and *minor* (t_R = 8.04 min)]: IR ν 3497, 2981, 2258, 1783, 1739, 1556 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.87 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.47 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.42−7.36 (m, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 5.55 (ddd, *J* = 10.4, 6.3, 1.9 Hz, 1H), 4.70 (d, *J* = 6.3 Hz, 1H), 3.56 (s, 3H), 3.18 (dd, *J* = 15.3, 10.4 Hz, 1H), 2.61 (dd, *J* = 15.1, 1.9 Hz, 1H), 2.20 (s, 1H), 1.63 (s, 9H), 1.03 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.9, 169.9, 148.8, 140.8, 129.6, 125.2, 124.7, 124.5, 115.2, 85.2, 85.0, 82.4, 65.8, 54.8, 52.9, 43.2, 28.2, 21.6; HRMS (ESI) calcd for [M + Na]$^+$ ($C_{20}H_{24}N_2O_8Na$)$^+$ requires *m*/*z* 443.1425, found 443.1423.

1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-7′-Fluoro-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ba. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-7-fluoro-2-oxoindoline-1-carboxylate **1b** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 79% yield (54 mg) with dr 10/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* (t_R = 10.01 min) and *minor* (t_R = 11.02 min)]: IR ν 3503, 2983, 2259, 1783, 1743, 1556 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.25−7.12 (m, 2H), 5.56 (ddd, *J* = 10.3, 6.0, 1.7 Hz, 1H), 4.66 (d, *J* = 5.9 Hz, 1H), 4.12−3.93 (m, 2H), 3.22−3.10 (m, 1H), 2.69−2.60 (m, 1H), 2.25−2.20 (m, 1H), 1.59 (s, 9H), 1.09−1.01 (m, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.1, 169.1, 148.5 (d, *J* = 251.0 Hz), 147.1, 128.9 (d, *J* = 2.2 Hz), 127.5 (d, *J* = 9.5 Hz), 125.5 (d, *J* = 7.0 Hz), 120.6 (d, *J* = 3.5 Hz), 117.7 (d, *J* = 20.3 Hz), 85.2 (d, *J* = 32.7 Hz), 82.6, 66.2 (d, *J* = 1.7 Hz), 62.1, 54.8, 42.9, 27.7, 21.4, 13.6; HRMS (ESI) calcd for [M + H]$^+$ ($C_{21}H_{26}FN_2O_8$)$^+$ requires *m*/*z* 453.1668, found 453.1660.

1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4,5′-dinitro-2′-oxospiro-[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ca. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-5-nitro-2-oxoindoline-1-carboxylate **1c** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 92% yield (66 mg) with dr 10/1 and ee 95% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* (t_R = 12.73 min) and *minor* (t_R = 8.13 min)]: IR ν 3502, 2983, 1791, 1765, 1740, 1557, 1526 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.34 (d, *J* = 2.5 Hz, 1H), 8.26 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 5.51 (ddd, *J* = 10.5, 6.4, 1.8 Hz, 1H), 4.72−4.58 (m, 1H), 4.04 (qd, *J* = 7.1, 3.4 Hz, 1H), 3.89 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.16 (dd, *J* = 15.5, 10.3 Hz, 1H), 2.57 (dd, *J* = 15.5, 1.8 Hz, 1H), 2.39 (s, 1H), 1.57 (s, 9H), 1.04−0.91 (m, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.9, 168.9, 148.3, 146.0, 144.7, 127.1, 125.7, 121.2, 115.0, 86.3, 85.1, 82.8, 65.4, 62.4, 55.7, 43.8, 28.2, 21.6, 13.8; HRMS (ESI) calcd for [M + K]$^+$ ($C_{21}H_{25}N_3O_{10}K$)$^+$ requires *m*/*z* 518.1172, found 518.1169.

1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4-nitro-2′-oxo-5′-(trifluoromethoxy)spiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3da. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxo-5-(trifluoromethoxy)indoline-1-carboxylate **1d** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 85% yield (66 mg) with dr 20/1 and ee 95% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* (t_R = 5.41 min) and *minor* (t_R = 4.77 min)]: IR ν 3496, 2983, 1787, 1739, 1557 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.90 (d, *J* = 8.9 Hz, 1H), 7.41−7.38 (m, 1H), 7.29−7.21 (m, 1H), 5.56 (ddd, *J* = 10.3, 6.2, 1.8 Hz, 1H), 4.60 (d, *J* = 6.2 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.94 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.20 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.61 (dd, *J* = 15.3, 1.8 Hz, 1H), 2.26 (s, 1H), 1.62 (s, 9H), 1.06 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.2, 169.1, 148.6, 145.9 (d, *J* = 2.2 Hz), 139.2, 127.4, 122.1, 120.58 (d, *J* = 257.4 Hz), 118.7, 115.9, 85.4, 85.1, 82.7, 65.8, 62.1, 55.3, 43.5, 28.2, 21.6, 13.7; HRMS (ESI) calcd for [M + Na]$^+$ ($C_{22}H_{25}F_3N_2O_9Na$)$^+$ requires *m*/*z* 541.1402, found 541.1408.

1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-5′-Bromo-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ea. Synthesized according to the general procedure from *tert*-butyl (*E*)-5-bromo-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1e** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 94% yield (72 mg) with dr 20/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* (t_R = 8.39 min) and *minor* (t_R = 5.85 min)]: IR ν 3496, 2981, 1785, 1738, 1556 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.7, 2.1 Hz, 1H), 5.48 (ddd, *J* = 10.3, 6.2, 1.8 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.12 (ddd, *J* = 15.4, 10.3, 1.3 Hz, 1H), 2.55 (dd, *J* = 15.3, 1.7 Hz, 1H), 2.16 (d, *J* = 1.1 Hz, 1H), 1.55 (s, 9H), 1.01−0.93 (m, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.9, 169.0, 148.5, 139.7, 132.3, 128.0, 127.6, 117.6, 116.5, 85.2, 85.1, 82.6, 65.6, 62.0, 55.1, 43.2, 28.1, 21.5, 13.6; HRMS (ESI) calcd for [M + Na]$^+$ ($C_{21}H_{25}BrN_2O_8Na$)$^+$ requires *m*/*z* 535.0686, found 535.0687.

1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-5′-Chloro-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3fa. Synthesized according to the general procedure from 1′-*tert*-butyl 5-ethyl (1*S*,2*R*,4*S*,5*S*)-5′-bromo-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate **1f** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane:EtOAc as an eluent in 94% yield (66 mg) with dr 20/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* (t_R = 7.67 min) and *minor* (t_R = 5.69 min)]: IR ν 3499, 2982, 1786, 1738, 1556 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.49 (ddd, *J* = 10.3, 6.1, 1.8 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 4.05 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.12 (ddd, *J* = 15.3, 10.3, 1.2 Hz, 1H), 2.55 (dd, *J* = 15.4, 1.6 Hz, 1H), 2.15 (d, *J* = 1.2 Hz, 1H), 1.55 (s, 9H), 1.04−0.89 (m, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.1, 169.1, 148.7, 139.3, 130.2, 129.5, 127.4, 125.3, 116.2, 85.3, 85.2, 82.7, 65.7, 62.1, 55.3, 43.4, 28.2, 28.2, 21.6, 13.7; HRMS (ESI) calcd for [M + Na]$^+$ ($C_{21}H_{25}ClN_2O_8Na$)$^+$ requires *m*/*z* 491.1191, found 491.1193.

1′-*tert*-Butyl 5-Ethyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-5′-methoxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ga. Synthesized according to the general procedure from (*E*)-ethyl 2-(5-methoxy-2-oxoindolin-3-ylidene)acetate **1g** and 4-nitrobutan-2-one **2a**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 93% yield (65 mg) with dr 12/1 and ee 98% [Chiralcel OD-H, Hex/*i*-PrOH 95:5, 1 mL/min, 230 nm; *major* (t_R = 15.57 min) and *minor* (t_R = 20.66 min)]: IR ν 2984, 2254, 1789, 1739, 1556 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.78 (d, *J* = 8.9 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 8.9, 2.7 Hz, 1H), 5.55 (ddd, *J* = 10.4, 6.1, 1.8 Hz, 1H), 4.61 (d, *J* = 6.1 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.90 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.82 (s, 3H), 3.16 (ddd, *J* = 15.3, 10.4, 1.6 Hz, 1H), 2.61 (dd, *J* = 15.2, 1.8 Hz, 1H), 2.23 (d, *J* = 1.6 Hz, 1H), 1.61 (s, 9H), 1.05−0.97 (m, 6H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.8, 169.4, 156.9, 148.9, 134.0, 126.9, 116.0, 114.0, 111.1, 85.3, 84.7, 82.6, 66.1, 61.9, 55.8, 54.9, 43.1, 28.2, 21.6, 13.7; HRMS (ESI) calcd for [M + Na]$^+$ ($C_{22}H_{28}N_2O_9Na$)$^+$ requires *m*/*z* 487.1687, found 487.1692.

1′-*tert*-Butyl 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Ethyl-2-hydroxy-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ab. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 1-nitropentan-3-one **2b**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 86% yield (56 mg) with dr 6/1 and ee 97% [Chiralcel AD-H, Hex/*i*-PrOH 90:10, 1 mL/min, 230 nm; *major* (t_R = 11.87 min) and *minor* (t_R = 7.41 min)]: IR ν 3502, 2980, 1784, 1739, 1556 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.86 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.48 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.42−7.35 (m, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 5.58 (ddd, *J* = 10.5, 6.6, 2.0 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H), 3.57 (s, 3H), 3.13–3.04 (m, 1H), 2.58 (dd, J = 15.3, 1.9 Hz, 1H), 2.06 (d, J = 1.6 Hz, 1H), 1.63 (s, 9H), 1.54–1.42 (m, 1H), 1.12–0.99 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 169.9, 148.8, 140.9, 129.6, 125.6, 124.7, 124.4, 115.3, 85.2, 85.1, 85.0, 66.0, 55.1, 52.9, 41.0, 28.2, 28.2, 27.66, 7.7; HRMS (ESI) calcd for [M + Na]$^+$ $(C_{21}H_{26}N_2O_8Na)^+$ requires *m/z* 457.1581, found 457.1587.

1′-*tert*-Butyl 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Benzyl-2-hydroxy-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ac. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 4-nitro-1-phenylbutan-2-one **2c**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 51% yield (38 mg) with dr 3/1 and ee 97% for major isomer [Chiralcel OD-H, Hex/*i*-PrOH 95:5, 1 mL/min, 230 nm; *major* (t_R = 15.72 min) and *minor* (t_R = 17.51 min)]: IR ν 3494, 2982, 2258, 1785, 1742, 1555 cm^{-1}; for the *major* isomer: ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.80–7.75 (m, 1H), 7.51 (dd, J = 7.5, 1.3 Hz, 1H), 7.33 (td, J = 7.9, 1.4 Hz, 1H), 7.20–7.13 (m, 5H), 7.09–7.03 (m, 1H), 6.97–6.92 (m, 2H), 5.49 (ddd, J = 10.4, 6.4, 1.7 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 3.51 (s, 3H), 3.34–3.24 (m, 1H), 2.69–2.63 (m, 1H), 2.24–2.17 (m, 1H), 2.01 (s, 1H), 1.59 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 169.8, 148.8, 140.8, 134.4, 130.1, 129.5, 128.9, 128.2, 127.6, 125.8, 125.3, 115.0, 85.1, 84.9, 83.9, 65.3, 55.5, 52.9, 42.4, 40.5, 28.3; HRMS (ESI) calcd for [M + Na]$^+$ $(C_{26}H_{28}N_2O_8Na)^+$ requires *m/z* 519.1738, found 519.1740.

1′-*tert*-Butyl) 5-Methyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-isobutyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-1′,5-dicarboxylate 3ad. Synthesized according to the general procedure from *tert*-butyl (*E*)-3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate **1a** and 5-methyl-1-nitrohexan-3-one **2d**. Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent in 25% yield (17 mg) with dr 10/1 and ee 96% for major isomer [Chiralcel OD-H, Hex/*i*-PrOH 95:5, 1 mL/min, 230 nm; *major* (t_R = 12.35 min) and *minor* (t_R = 6.80 min)]: IR ν 3512, 2958, 2873, 2258, 1786, 1739, 1556 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.90–7.83 (m, 1H), 7.47 (dd, J = 7.5, 1.3 Hz, 1H), 7.41 (td, J = 7.9, 1.4 Hz, 1H), 7.23 (td, J = 7.6, 1.0 Hz, 1H), 5.58 (ddd, J = 10.5, 6.6, 1.9 Hz, 1H), 4.66 (d, J = 6.6 Hz, 1H), 3.56 (s, 3H), 3.17 (ddd, J = 15.3, 10.5, 1.6 Hz, 1H), 2.67 (dd, J = 15.2, 2.0 Hz, 1H), 2.05 (d, J = 1.8 Hz, 1H), 1.64 (s, 9H), 1.34–1.24 (m, 2H), 0.92–0.89 (m, 1H), 0.83 (dd, J = 15.1, 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 169.9, 148.8, 140.9, 129.6, 125.6, 124.8, 124.3, 115.4, 85.4, 85.3, 85.0, 66.7, 54.6, 52.9, 43.0, 41.8, 28.2, 24.4, 24.3, 24.1; HRMS (ESI) calcd for [M + K]$^+$ $(C_{23}H_{30}N_2O_8K)^+$ requires *m/z* 501.1634, found 501.1630.

Methyl (1*S*,2*R*,4*S*,5*S*)-2-Hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-5-carboxylate 3aa′. Title compound was prepared for the determination of enantiomeric purity of spiro-oxindole **3aa** by treatment with TFA at ambient temperature. Ee 99% [Chiralcel AD-H, Hex/*i*-PrOH 80:20, 1 mL/min, 230 nm; *major* (t_R = 9.44 min) and *minor* (t_R = 8.04 min)]: IR ν 3421, 2989, 1730, 1699, 1546 cm^{-1}; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.48 (ddd, J = 7.6, 1.3, 0.6 Hz, 1H), 7.28 (td, J = 7.7, 1.3 Hz, 1H), 7.07 (td, J = 7.6, 1.1 Hz, 1H), 6.92 (dt, J = 7.8, 0.8 Hz, 1H), 5.54 (ddd, J = 10.5, 6.3, 1.9 Hz, 1H), 4.73 (d, J = 6.2 Hz, 1H), 3.52 (s, 3H), 3.13 (dd, J = 14.9, 10.5 Hz, 1H), 2.61–2.51 (m, 1H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 180.8, 172.1, 144.0, 129.7, 129.1, 127.2, 123.1, 110.4, 86.3, 82.3, 67.3, 55.1, 52.8, 44.7, 21.2. Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.12; H, 5.06; N, 8.72.

Ethyl (1*S*,2*R*,4*S*,5*S*)-5′-Bromo-2-hydroxy-2-methyl-4-nitro-2′-oxospiro[cyclopentane-1,3′-indoline]-5-carboxylate 3ea′. Title compound was prepared by treatment of oxindole **3ea** (0.13 mmol, 66 mg) with TFA (50 equiv, 6.4 mmol, 0.5 mL) in DCM (5 mL) at ambient temperature (reaction monitored by TLC). Product was isolated after silica gel column chromatography using a mixture of heptane/EtOAc as an eluent to afford 52 mg (yield = 98%) of product as white solid (mp = 168–170 °C). Product was used to grow a single crystal for X-ray diffraction. Optical rotation for the enantipure compound (single crystal): $[\alpha]$ = −142.3 (c = 0.07, MeOH); IR ν 3419, 2990, 1733, 1698, 1544 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.11 (s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 8.3, 2.1 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 5.56 (ddd, J = 10.2, 6.3, 1.8 Hz, 1H), 4.62 (d, J = 6.3 Hz, 1H), 4.14–3.95 (m, 2H), 3.19 (dd, J = 15.3, 10.4 Hz, 1H), 2.59 (dd, J = 15.4, 1.9 Hz, 1H), 2.35 (s, 1H), 1.12–1.03 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 169.5, 140.8, 132.2, 129.3, 128.8, 115.6, 111.3, 85.1, 82.2, 65.8, 62.1, 54.6, 43.4, 21.6, 13.8; HRMS (ESI) calcd for [M + H]$^+$ $(C_{16}H_{18}BrN_2O_6)^+$ requires *m/z* 413.0343, found 413.0341.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, HPLC chromatograms, and crystallographic data of compound **3ea**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Abstract

The 3,3’-disubstituted oxindole core structure has been found in the skeleton of many natural and synthetic compounds with unique biological properties. Although significant advances have been made in the asymmetric synthesis of oxindoles with five- or six-membered *spiral*-rings, cyclopropyl analogues are still lacking general methods to facilitate the formation of the core structure in highly enantioenriched form and varying substitutions at the *spiral*-ring.

Cyclopropanation of methyleneindolinones **51** with α-chloro-1,3-dicarbonyl compounds (**127**, **129** or **130**) was developed. Taking advantage of chiral thiourea catalysis **126**, *spiro*-cyclopropyloxindoles (**128**, **131** and **132**) with two adjacent quaternary centers were synthesized in excellent diastereo- and enantioselectivities (d.r. up to 99:1; *ee* = 80-98%).

To further elaborate the substitution pattern of the *spiral*-ring, 3-chlorooxindoles **134** were introduced as new precursors to *spiro*-cyclopropyloxindoles **135** and bispirooxindoles **141**, in a reaction with unsaturated aldehydes **2** (chiral amine catalyst **137**) and alkylidene oxindoles **51** (squaramide catalyst **142**), respectively. In both cases, high yields and stereoselectivities were observed.

It was further demonstrated that 3-chlorooxindoles **134** can also serve as nucleophiles in a Michael reaction with nitroalkenes **29**, providing 3,3’-disubstituted oxindoles **143** with chlorine at the quaternary center in high diastereo- and enantioselectivities (d.r. up to 11:1; *ee* = 76-92%). The high reactivity of 3-chlorooxindoles allowed protective group free synthesis to proceed smoothly in the presence of chiral squaramide catalyst **142**.

Finally, a new method for the synthesis of *spiro*-cyclopentyloxindoles **148** with four consecutive stereocenters was reported. In a cascade reaction, promoted by chiral thiourea catalyst **126**, alkylidene oxindoles **51** reacted with simple nitroketones **147** to undergo a formal [3+2] annulation reaction, resulting in the formation of the *spiro*-cyclopentyloxindoles **148**. In all cases high enantioselectivities were obtained (*ee* = 95-98%), although diastereoselectivities varied from moderate to excellent (d.r. = 3:1 – 20:1), depending on the steric hindrance exhibited by the nitroketone substituents.

Kokkuvõte

3,3’-diasendatud oksindoolid on oluliseks struktuurifragmendiks paljudes looduslikes ja sünteetilistes ühendites, millel on avastatud huvitavaid bioloogilisi omadusi ning mis omavad kõrget potentsiaali ravimiarenduses. Kuigi on välja töötatud palju meetodeid viie- ja kuuelüliliste tsüklitega *spiro*-oksindoolide asümmeetriliseks moodustamiseks, on avaldatud vaid üksikuid näiteid analoogsete *spiro*-tsüklopropüüloksindoolide sünteesist.

Töötati välja uus meetod alkülideenoksindoolide **51** tsüklopropaneerimiseks 3-kloro-1,3-dikarbonüülühenditega (**127**, **129** või **130**). Kasutades kiraalset tiokarbamiidi **126** sünteesiti kõrgete diastereo- ja enantioselektiivsustega (d.r. kuni 99:1; *ee* = 80-98%) *spiro*-tsüklopropüüloksindoolid (**128**, **131**, **132**), mis sisaldavad kahte järjestikust kvaternaarset tsentrit.

Kasutades 3-klorooksindoole **134** *α,β*-küllastamata aldehüüdide **2** ja alkülideenoksindoolide **51** tsüklopropaneerimiseks, vastavalt amino- või vesiniksideme katalüüsi tingimustes, sünteesiti uued *spiro*-tsüklopropüüloksindoolid **135** ja bispirooksindoolid **141** kõrgete saagiste, diastereo- ja enantioselektiivsustega.

3-klorooksindoolide **134** kõrge reaktiivsuse tõttu näidati, et nende reaktsioonil nitroalkeenidega **29** kiraalse skvaaramiidi **142** manulusel moodustuvad vastavad 3,3’-diasendatud oksindoolid **143** kõrgete saagiste, enantio- ja diasteroselektiivustega (d.r. kuni 11:1; *ee* = 76-92%).

Alkülideenoksindoolide **51** reaktsioonil nitroketoonidega **147** saadi *spiro*-tsüklopentüüloksindoolid **148**. Reaktsioonides kasutati katalüsaatorina kiraalset tiokarbamiidi **126** ning produktid isoleeriti kõrgete enantio-, kuid tagasihoidlike või heade diasteroselektiivsustega (*ee* = 95-98%; d.r. = 3:1 kuni 20:1).

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Great things are done by a series of small things brought together.
Vincent Van Gogh

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