Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5165

www.rsc.org/obc

PERSPECTIVE

Strategies for the enantioselective synthesis of spirooxindoles

Nicolas R. Ball-Jones, Joseph J. Badillo and Annaliese K. Franz*

Received 25th January 2012, Accepted 11th April 2012
DOI: 10.1039/c2ob25184a

Oxindoles and spirooxindoles are important synthetic targets that are often considered to be prevalidated with respect to their biological activity and applications for pharmaceutical lead discovery. This review features efficient strategies for the enantioselective synthesis of spirocyclic oxindoles, focusing on reports in 2010 and 2011. Although enantioselective synthesis remains an ongoing challenge, exciting recent advances in this area feature spirooxindoles with greater complexity, up to eight stereogenic centers, more practical synthetic methods, and new catalytic activation strategies. Developments in catalyst systems and reaction conditions have shown that many reactions can be optimized to control selectivity and provide access to isomeric products, which are important for biological testing. This review is organized based on two primary disconnection strategies, and then further subdivided into the type and ring size of the spirocycle that is generated. Strategies are also compared for the synthesis of non-spirocyclic 3,3′-disubstituted oxindoles.

Introduction

Natural and synthetic molecules containing an oxindole or spirooxindole core structure represent an interesting synthetic challenge due to their biological activity and physical properties (Fig. 1).[1–10] The number of publications related to the synthesis of spirocyclic oxindoles has continued to increase over the past ten years, with the most significant increase occurring in 2010–11 (Fig. 2).[11–15] While the synthesis of spirocyclic oxindoles has continued to gain attention, the development of enantioselective methods to access spirooxindoles remains an ongoing synthetic challenge. This review features recent strategies for the enantioselective synthetic of spirocyclic oxindoles, focusing on reports from 2010 and 2011, while also highlighting pioneering examples from earlier work. These strategies have focused on the development of more efficient synthetic methods and new catalytic activation methods to control selectivity and provide access to isomeric products, which are important for biological testing. While enantioselective synthesis is the primary focus of this review, notable examples of racemic syntheses are also included.

This review is organized based on two primary disconnection strategies that are typically utilized for the asymmetric synthesis of spirocyclic oxindoles (Fig. 3). Both strategies rely on a nucleophilic addition or annulation with a prochiral electrophilic oxindole, with the various reacting partners determining the type and ring size of the spirocycle that is generated. The first strategy involves addition and spirocyclization with alkylidene oxindole reagents (**2**), also referred to as methyleneindolinones, to afford cyclopentane, cyclohexane, cyclopropanes, as well as heterocycles such as pyrrolidine and epoxides. Cases have also been demonstrated where the alkylidene oxindole is formed *in situ* to provide multicomponent strategies. The second strategy involves addition and spirocyclization with indole-2,3-dione (isatin) reagents (**3**) to afford various spirocyclic heterocycles.

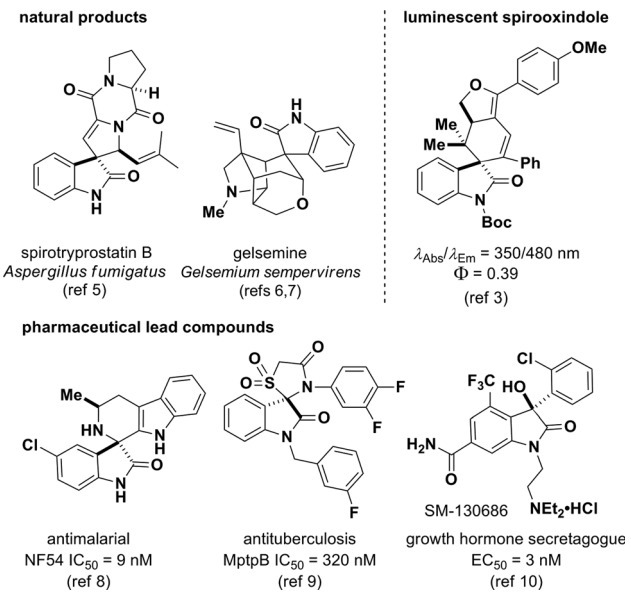


Fig. 1 Examples of natural products, pharmaceutical leads, and luminescent molecules containing an oxindole or spirooxindole core structure.

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States

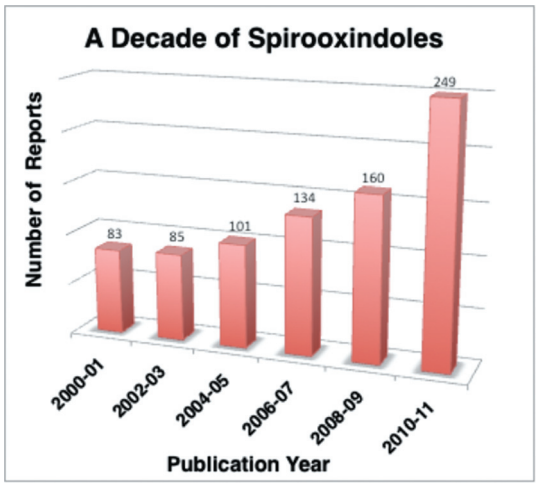


Fig. 2 Publication rate for spirooxindoles since 2000.

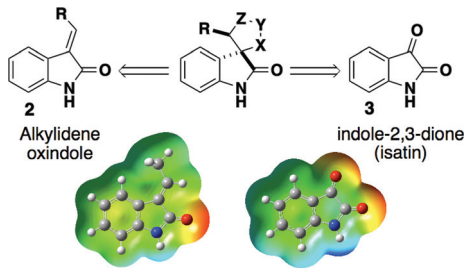


Fig. 3 Two primary disconnection strategies for the synthesis of spirooxindoles.

Alkylidene oxindole reactions

The use of alkylidene oxindoles (**2**) as prochiral electrophiles represents a broadly successful strategy for the catalytic asymmetric synthesis of spirooxindoles (Fig. 4). This strategy is particularly effective for the synthesis of challenging spirocycles containing a quaternary carbon. Furthermore, the reactions of alkylidene oxindoles allow efficient access to densely functionalized core structures that often contain three or more stereocenters.

Spiropyrrolidine-oxindoles

Biological prevalidation is often used as a criteria to select relevant synthetic targets and is particularly significant for drug discovery efforts.[1] Spiro[pyrrolidine-3,3′-oxindole] derivatives such as **6** provide an attractive synthetic target[16] because this heterocycle core structure occurs in various alkaloid natural products, such as spirotryprostatin B (Fig. 1).[8,9,17] The first example of a catalytic asymmetric synthesis of spiro[pyrrolidine-3,3′-oxindole] was reported in 2009 by Gong and colleagues,[18] using a three-component dipolar cycloaddition reaction catalyzed by BINOL-derived phosphoric acid **5a** (Scheme 1). The 1,3-dipolar addition proceeds with high yields and excellent enantioselectivity (up to 98% ee) upon reaction between alkylidene oxindole **2** and azomethine ylides, which are generated *in situ* from aldehydes with amino ester **4**. While N–H isatin derivatives are typically used as dipolarophiles for auxiliary-induced reactions,[14] this reaction requires the *N*-acetate for high yields and regioselectivity. Oxindoles with chlorine and/or fluorine substituents

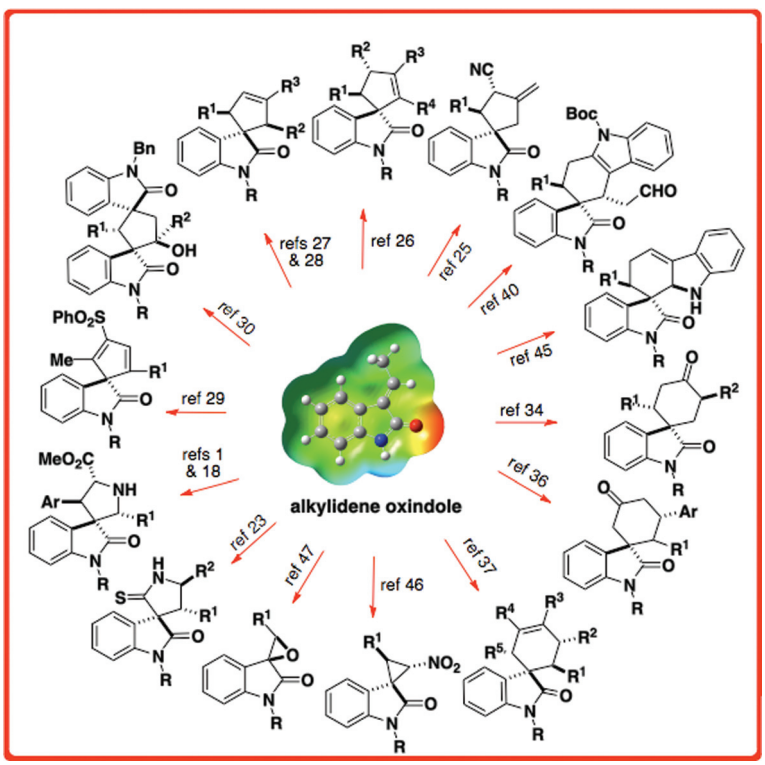
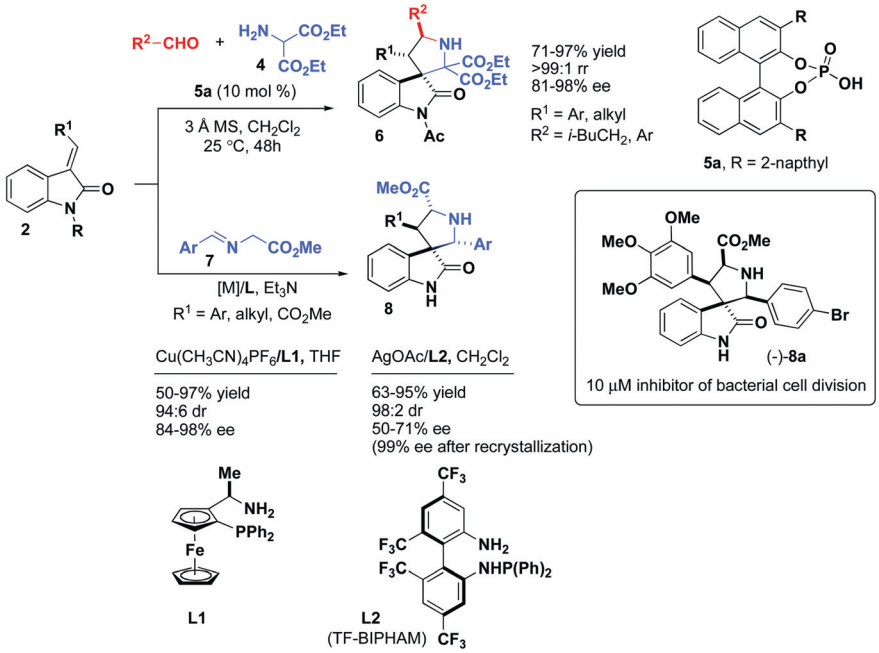


Fig. 4 Spirooxindoles synthesized from alkylidene oxindoles.



Scheme 1 Synthesis of pyrrolidine spirooxindoles using a dipolar cycloaddition strategy.

on the C(5) or C(6) position were selected due to their occurrence in important lead compounds for pharmacological activity. The regiochemistry of product **6** is rationalized based on stabilizing π–π stacking interactions between the oxindole ring and the conjugated ester, which is opposite to what would be expected if directed by an electronic effect.[14] To account for the high enantio- and regioselectivity of the reaction, theoretical studies for the mechanism were performed and transition state **TS-1** was proposed, in which both the azomethine ylide and the methyleneindolinone are hydrogen-bonded to chiral phosphoric acid catalyst **5a**.

Waldmann and co-workers subsequently reported the enantioselective synthesis of isomeric spiropyrrolidine oxindoles **8** using a copper-catalyzed dipolar cycloaddition reaction.[1] This reaction is also highly enantioselective with up to 98% ee. Using chiral ligand **L1**, a nonlinear relationship was observed for the ligand : Cu ratio (Scheme 1). A slight excess of ligand in a 1.1 : 1 ratio of ligand : Cu affords a 91 : 9 diastereomeric ratio with only 72% ee, while a 2 : 1 ratio affords a 94 : 6 diastereomeric ratio with 98% ee. Similar to Gong's stereochemical rationale, Waldmann proposes that the origin of the enantioselectivity is based on hydrogen-bonding interactions of the ligand complex with oxindole **2** while chelating of copper to imine **7**. Waldmann also speculates that stabilizing π–π stacking interactions contribute to the selectivity (Fig. 5, **TS-2**). In this case, a reversal of regioselectivity is observed in comparison to the Brønsted acid catalysts reported by Gong.[18] The goal of Waldmann's study was to investigate the biological activity of these compounds. Screening of all compounds was performed and compound (−)-**8a**, a minor diastereomer obtained in the reaction, was identified as a 10 μM inhibitor of cell division that arrested cell growth in the G2/M phase by interference with microtubule polymerization. No other molecules that were tested showed any notable activity in cell-based screening.

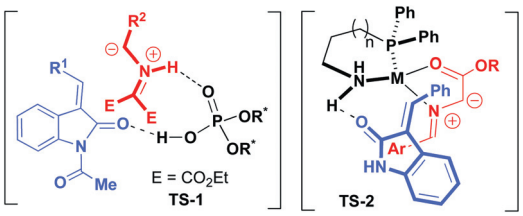


Fig. 5 Transition states proposed for pyrrolidine spirooxindole syntheses.

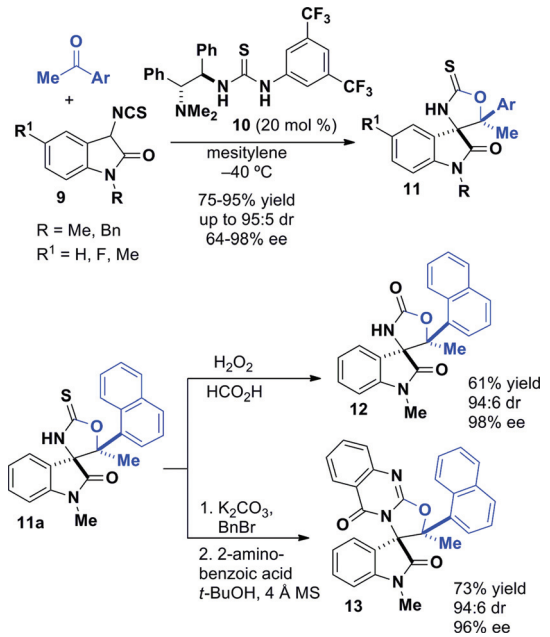
Wang and co-workers have recently reported a related Ag(I)-catalyzed synthesis of spiropyrrolidine oxindole **8** using TF-BiphamPhos (**L2**) as the optimized ligand (Scheme 1).[19,20] Using silver salts afforded consistently high diastereoselectivity (98 : 2 dr) and higher enantioselectivity compared to copper salts with this same ligand. While the enantioselectivities are generally modest (50–71% ee) relative to Waldmann's copper-catalyzed method, recrystallization afforded products with 99% ee.

Spirocyclic oxazolines

Yuan and co-workers have reported the synthesis of spirooxindoles **11** upon reaction of 3-isothiocyanato oxindoles **9** with ketones in a direct aldol reaction catalyzed by bifunctional thiourea catalyst **10** (Scheme 2).[21] Though isothiocyanates have previously been utilized to synthesize cyclic aldol products,[22] this represents the first example for the synthesis of spirooxindoles using isothiocyanatooxindoles in direct aldol transformations. Acetophenones with electron-donating and withdrawing substituents were tolerated, but limitations were observed with *ortho*-substituted aryl groups, which showed no conversion. Aliphatic ketones such as acetone and cyclohexanone were also

successful, albeit with lower enantioselectivity, with the exception of propiophenone, which was unreactive. The reaction can be performed on large scale (>1 g) without any reduction in yield or selectivity. The authors demonstrated that product **11** can be further transformed into heterocyclic spirooxindoles containing N–H oxazolidinines **12** or an oxazolidinimine such as **13**. During these various transformations, the stereochemistry and enantioenrichment of the product is retained.

Wang and co-workers have reported two different examples of reactions with α-isothiocyanato amides **14** to access spirocyclic heterocycles such as thioamides **16** and thiocarbamates **20** (Scheme 3). Reactions with either alkylidene oxindoles **2** or isatins **3** can be catalyzed using bifunctional thiourea catalyst **15** (derived from dehydroabietic acid, found in rosin) to afford



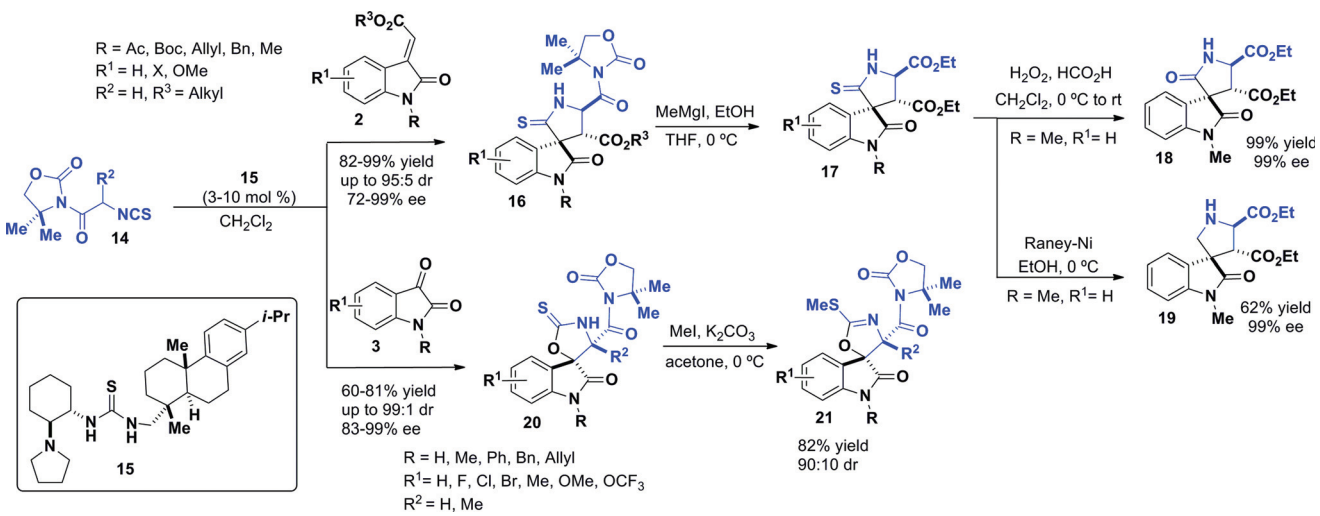
Scheme 2 Synthesis of oxazolidinethione oxindoles from isothiocyanatooxindoles using an aldol strategy.

richly-functionalized spirocycles with excellent diastereo- and enantioselectivity. In the first example, Wang utilizes a Michael/cyclization cascade sequence to afford spirooxindole thioamides **16**.[23] The authors also examined the scope of alkylidene oxindoles, including the use of oxygen and sulfur isosteres of the oxindole motif. The use of both electron-donating and withdrawing groups provide high yields, and diastereo- and enantioselectivity. The authors demonstrate that the Evans achiral auxiliary can be cleaved to produce diester **17**, followed by several further transformations to reduce the sulfur and afford either lactam **18** or pyrrolidine **19**.

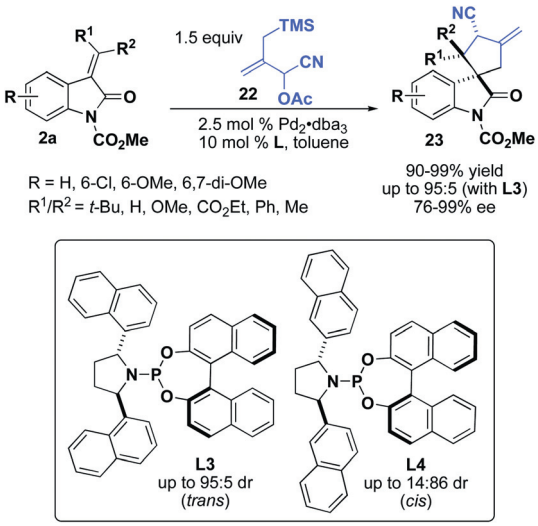
In a second report, Wang *et al.* utilize the α-isothiocyanato amides **14** in a parallel enantioselective 1,3-dipolar cycloaddition strategy with isatin **3** to form spiro[thiocarbamate-3,3′-oxindole]s **20** (Scheme 3).[24] A tertiary amine (TEA or DIEA) is an effective catalyst for the formation of racemic products, and the bifunctional thiourea **15** (3 mol%) containing an appended tertiary amine is capable of inducing asymmetry. Isatins substituted at the 4- and 7-positions are well tolerated, giving excellent yields (99%), and high enantio- and diastereoselectivities (99% ee, 95 : 5 dr). Both methyl and unsubstituted α-isothiocyanato amides were employed successfully. The authors demonstrate that spirooxindole **20** can be converted to spirooxazoline **21** in one step using methyl iodine and potassium carbonate. In general, the reactions of N–H isatins proceed with lower yields (65–73%) for the two-step process. Preliminary biological screening identified several spirooxazolines that were effective in suppressing lipopolysaccharide (LPS) induced fever in a mouse model.

Spirocyclopentenes and pentanes

Alkylidene oxindoles also provide access to a variety of spirocyclopentenes and pentanes containing quaternary carbon spirocenters within a functionalized carbocycle. Trost and co-workers first reported the synthesis of spirocyclic cyclopentenes **23** in 2007, using a transition metal-catalyzed [3 + 2]-cycloaddition reaction of trimethylenemethane derived from allylic silanes **22** (Scheme 4).[25] In this transformation, allylic silane **22** is



Scheme 3 Synthesis of spirooxindoles using isothiocyanate amides in a cycloaddition strategy.

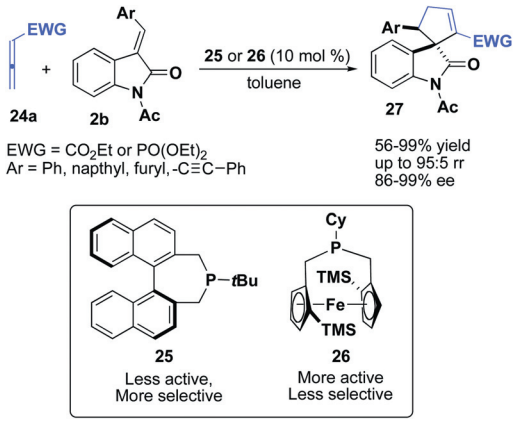


Scheme 4 Synthesis of spirooxindole *via* a trimethylene methane cyclization strategy.

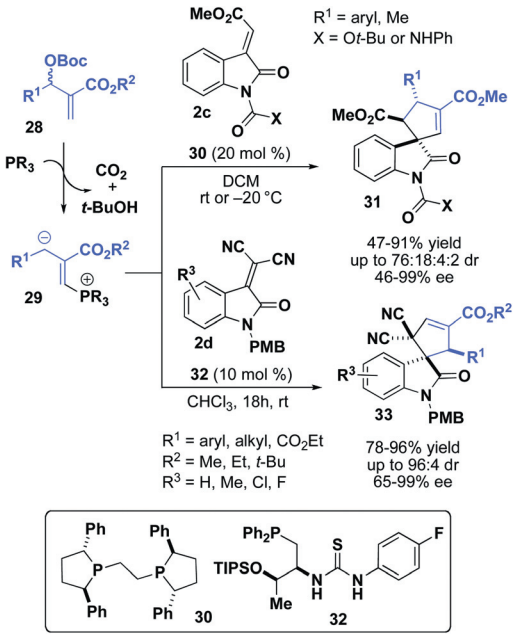
converted to a trimethylenemethane anion, which cyclizes with alkylidene oxindole **2a**. Initial investigations using hexamethylphosphoramide as a ligand for the Pd(0) catalyst afforded a 2 : 1 mixture of *trans*/*cis*-diastereomers of spirooxindole **23**. Using phosphoramide ligands **L3** and **L4**, which differ only by the position of the naphthyl substitution on the pyrrolidine ring, afforded selective access to each diastereomer (up to 99 : 1 *trans*/*cis*). In some cases an inherent preference for one diastereomer still overrides the selectivity dictated by the ligand. The authors identified that an electron-withdrawing group on the nitrogen of the alkylidene greatly improved reactivity, a trend that is consistent for most reactions of alkylidene oxindoles. Additionally, the substitution of the alkylidene oxindole could be varied with unsymmetrical substitution on the alkene, allowing for an additional contiguous stereocenter to be generated, albeit in significantly lower selectivity (72 : 28 to 95 : 5 dr, 20–99% ee).

More recently, several researchers have reported strategies utilizing Morita–Baylis–Hillman (MBH) reactions to access various spirocyclopentene oxindoles. Marinetti and co-workers first reported access to spirocyclopentenes such as **27** using chiral phosphine catalysts in a MBH reaction with allenes **24a** and alkylidene oxindoles (Scheme 5).[26] Several phosphine catalysts were investigated to identify the appropriate balance of activity and selectivity in this reaction. Although (*S*)-*t*-Bu-binepine **25** afforded the highest enantioselectivity and regioselectivity, this catalyst led to lower yields with more challenging substrates, such as electron-rich alkylidene substrates. The authors demonstrated that the more active catalyst **26** affords a better balance of activity and selectivity though reactions were slightly less selective (*e.g.* 90% *vs.* 97% ee).

Using a similar Morita–Baylis–Hillman strategy, Barbas and Lu have independently reported the synthesis of related spirocycles **31** and **33** with moderate to high yields and up to 99% ee (Scheme 6).[27,28] These reactions, proceeding by the same general mechanism, are initiated by nucleophilic addition of a bifunctional phosphine catalyst to carbonate **28**, which liberates CO_2 with a *tert*-butoxide counterion to afford the active



Scheme 5 Synthesis of spirooxindoles using an allene MBH strategy.



Scheme 6 Synthesis of spirocyclopentene oxindoles using phosphine-catalyzed MBH reactions.

nucleophilic species **29**. While the same active nucleophilic species **29** is formed in each reaction, different cyclopentenes are obtained based on the choice of alkylidene to produce spirocyclopenteneoxindole **31** or **33** after liberation of the phosphine catalyst. Both Barbas and Lu use a bifunctional phosphine catalyst. Barbas and co-workers obtain moderate to high yields with excellent enantioselectivity using C_2-symmetric biphosphine **30** while Lu utilizes a bifunctional L-threonine-derived phosphine catalyst **32** (Scheme 6).

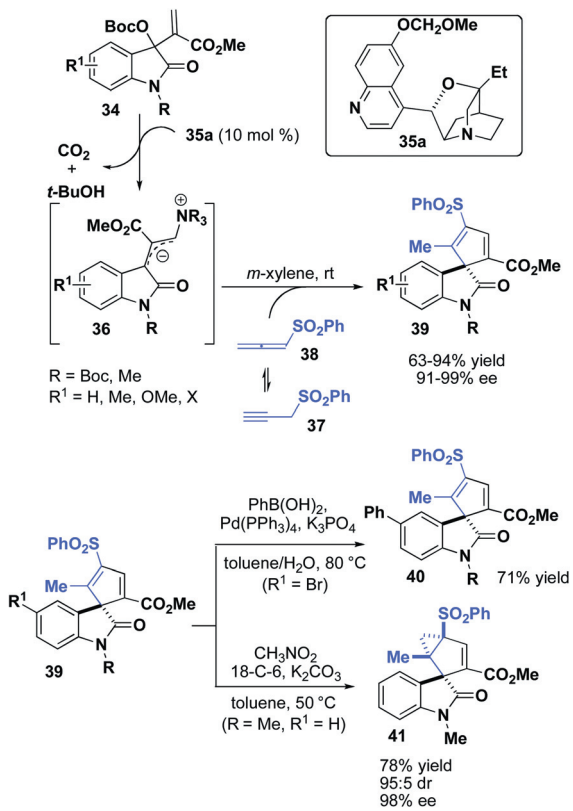
This reaction highlights the important influence of the nitrogen protecting group on the alkylidene **2** to affect yield and selectivity. Barbas reported that the carbamoyl (CONHPh) protecting group (**2c**) affords the optimal yield and enantioselectivity (99% ee, 84% yield), especially at room temperature.[27] Based on initial screening, the *N*-Boc variant of **2c** afforded suboptimal enantioselectivity (82% ee) while the *N*-PMB substrate proceeded with a much higher enantioselectivity (97% ee), albeit

with lower yield (48% yield). However, excellent enantioselectivity up to 97% ee could still be obtained with *N*-Boc substrates by lowering the reaction temperature to −20 °C. The authors speculate that the π–π stacking of the catalyst and substrate may contribute to the stereoselectivity of the reaction.

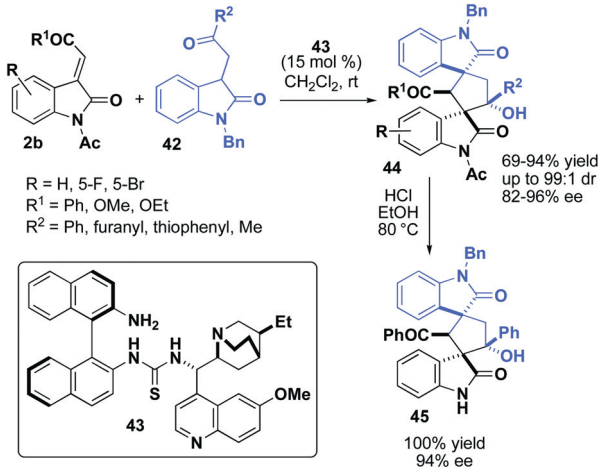
Lu demonstrated that the regioselectivity was improved by employing *N*-PMB oxindole **2d**, which provided 93 : 7 regioselectivity.[28] The authors additionally performed a one-pot reaction procedure with malononitrile, isatin, and MBH carbonate **28**. Lu demonstrated that *tert*-butoxide generated *in situ* is necessary for the reaction; the cyclization did not proceed when MBH acetate was used instead of the carbonate. Both the thiourea component and the electron withdrawing groups within catalyst **32** were demonstrated to be integral in controlling the enantioselectivity and yield, respectively.

A MBH strategy has also been reported by Chen and co-workers using oxindole **34**, which provide access to spirocyclopentadiene oxindoles **39** upon reaction with propargyl sulfones **37** (Scheme 7).[29] Using a modified cinchona alkaloid catalyst (**35a**), the spirocyclic products are generated in moderate to high yield and excellent enantioselectivity (up to 99% ee). Oxindole **34** liberates *tert*-butoxide to generate the active nucleophile in the form of deprotonated MBH carbonate **36**, which reacts with the activated allenyl sulfone **38**. The authors demonstrate several transformations of the resulting spirocyclopentadienes, including cross-coupling (where R^1 = Br) and cyclopropanation.

Various strategies have also been reported for the synthesis of functionalized spirocyclopentanes, which have the advantage



Scheme 7 Transformation of an alkylidene oxindole through a reversal of traditional MBH nucleophiles.

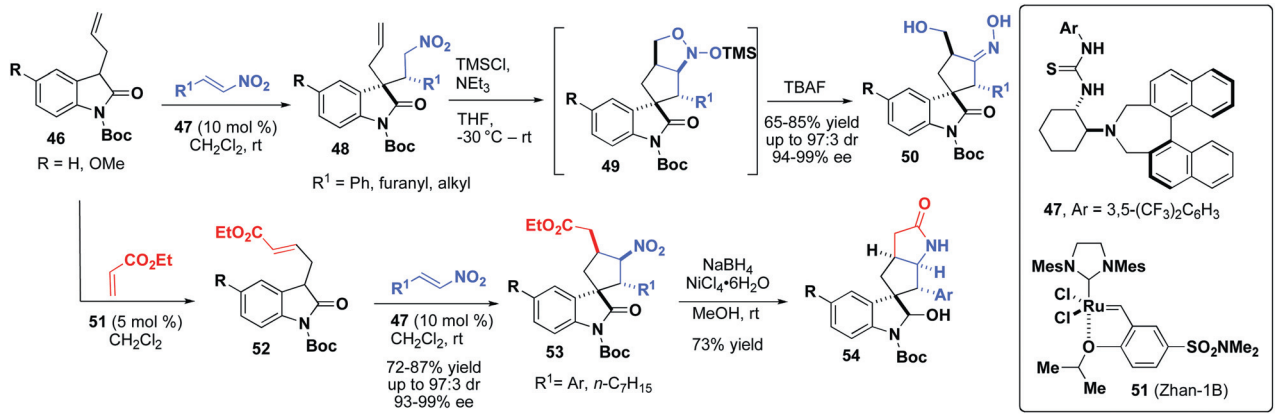


Scheme 8 Synthesis of bispirooxindoles using a Michael–Aldol cascade strategy.

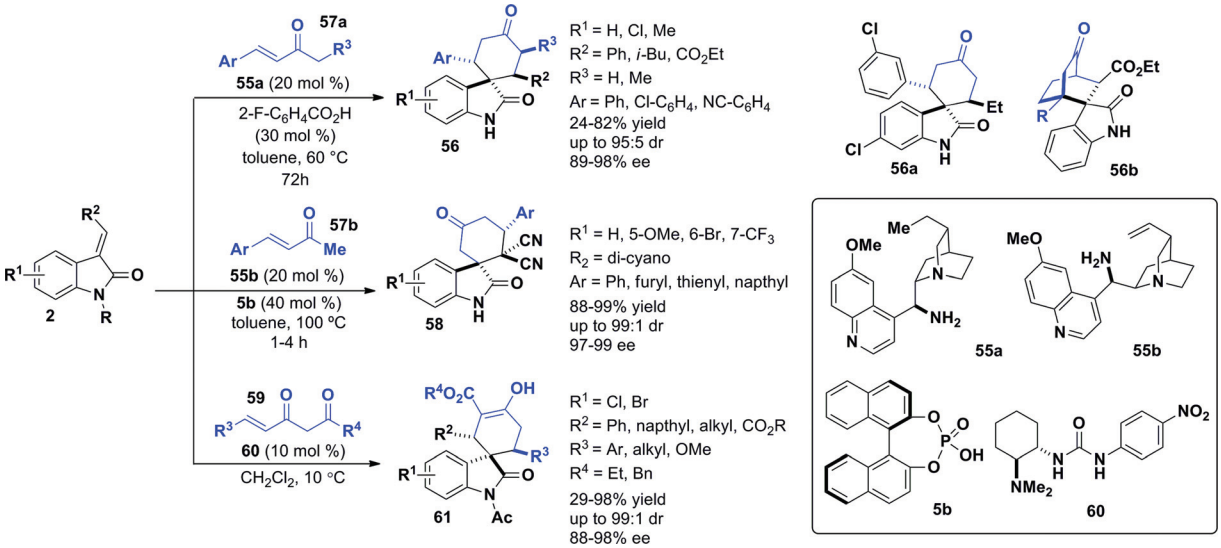
(and challenge) of containing multiple stereogenic centers. Barbas and co-workers have reported the synthesis of pentacyclic bispirooxindoles **44** from oxindole **42** and alkylidene oxindoles using a Michael–Aldol cascade reaction (Scheme 8).[30] Initially, quinine and several other cinchona catalysts were investigated and shown to provide good yield and high diastereoselectivity; however, enantioselectivity was only moderate with these catalysts. Further investigations led to the design of an optimized trifunctional catalyst **43**, providing enantioselectivity up to 96% ee. The alkylidene ester was identified as a key feature for activity because no reaction was observed with the phenyl alkylidene. The other enantiomer of bispirooxindole **44** was shown to be accessible using another diastereomer of catalyst. Conversion to the N–H product **45** was demonstrated with retention of enantiomeric excess.

Shao and co-workers utilize allyl oxindole **46** in a thiourea-catalyzed asymmetric Michael reaction with nitrostyrene to afford oxindole **48** (Scheme 9).[31] There is only one previous report for the Michael addition of 3-allyl-substituted oxindoles to nitroolefins using an bifunctional thiourea/cinchona alkaloid catalyst, which was reported to proceed with lower diastereo- and enantioselectivity.[32] Here, the authors demonstrate that bifunctional thiourea **47** affords good yield, and high diastereo- and enantioselectivities for both aryl and alkyl nitroolefins. Michael product **48** can be further transformed using an intramolecular silyl nitronate-olefin cycloaddition (ISOC) to generate spirooxindole **50**. The corresponding propargyl oxindole was also effective as a substrate for the Michael reaction, but the subsequent ISOC fragmentation resulted in a 'complex and inseparable' mixture.

In a separate publication, Shao demonstrates the conversion of allyl oxindole **46** to afford oxindole ester **52**, which is then utilized in a double Michael addition with nitro olefins to generate densely-functionalized spirocyclopentaneoxindoles **53** containing four stereocenters (Scheme 9).[33] The same bifunctional thiourea catalyst **47** was identified in this case as the optimal catalyst for high selectivity. The reaction tolerates both aryl and aliphatic nitro olefins. The further synthetic potential of spirocycle **53** was demonstrated by reduction of the nitro group with



Scheme 9 Synthesis of spirocyclopentanes from 3-allyl oxindoles using a Michael addition strategy.



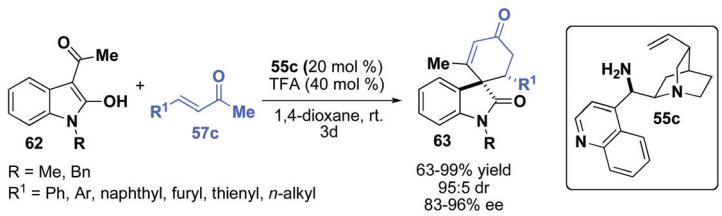
Scheme 10 Synthesis of spirocyclohexane oxindoles using cascade Michael reactions.

$NaBH_4$ and $NiCl_2$ to afford a primary amine that cyclizes to afford tetracyclic γ-lactam **54**.

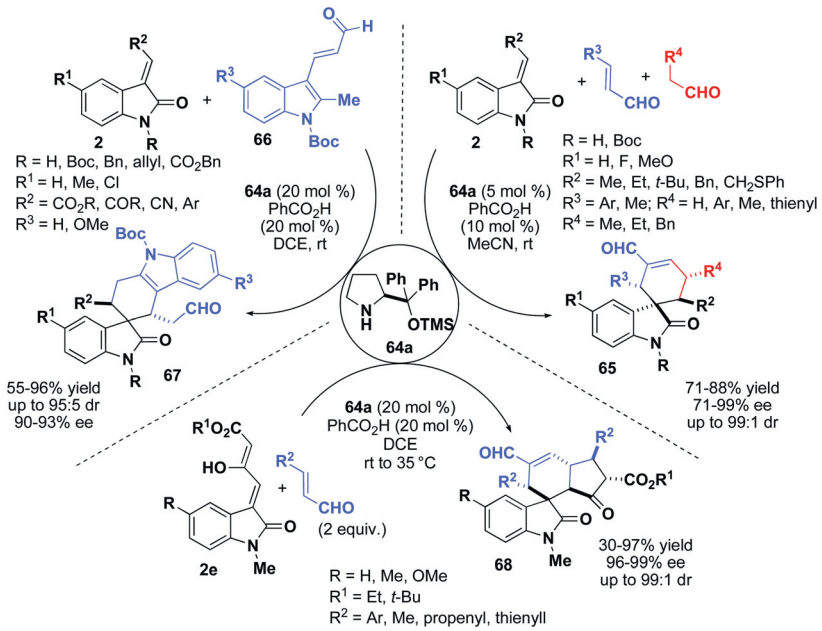
Spirocyclohexanes

Several authors have reported organocatalytic strategies relying on cascade Michael reactions with alkylidene oxindoles for the synthesis of spirocyclohexanes. With the expanded ring size, these strategies can lead to more stereocenters and increased functionality relative to cyclopentane spirocycles. Melchiorre and co-workers have developed an asymmetric organocascade reaction that exploits the ability of chiral cinchona alkaloid **55a** to combine both enamine and iminium catalyst activation of carbonyls in one step to produce complex spirooxindole cyclohexane derivatives **56** in excellent diastereo- and enantioselectivity (Scheme 10).[34] The authors also use a three-component enantioselective Michael/enamine/iminium reaction that proceeds with good yield and excellent selectivity. Advantages to this chemistry include tolerance of free N–H oxindoles and access to several notable structures. For example, compound **56a** was prepared in one-step and serves as a potent inhibitor of the MDM2-p53 interaction, a target for the discovery of anti-cancer agents.[35] This route also provides access to bicyclo[2.2.2]-octane **56b**, which contains two quaternary carbon stereocenters, albeit in low yield (24%).

Lan has reported a highly enantio- and diastereoselective synthesis of spirocyclic cyclohexanone oxindoles **58** in a double Michael reaction (Scheme 10).[36] Here, in order to obtain high diastereoselectivity as well as high enantioselectivity, the authors use a synergistic counterion strategy with two chiral components. This optimal catalyst system utilizes 20 mol% of cinchona alkaloid **55b** with 40 mol% of chiral 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate **5b** as a co-catalyst. When chiral cinchona alkaloid **55b** was investigated with achiral acid additives, the reaction afforded products with high enantioselectivities and yields, but lower diastereoselectivities (84 : 16) were observed. Other chiral acid additives were also evaluated, but the low selectivity indicates a 'mismatched' system. Based on the requirement for two chiral components, this method requires high overall catalyst loading relative to other Michael reactions that have been reported.



Scheme 11 Synthesis of spirocyclohexene oxindole using a Michael/ketone aldol/dehydration strategy.



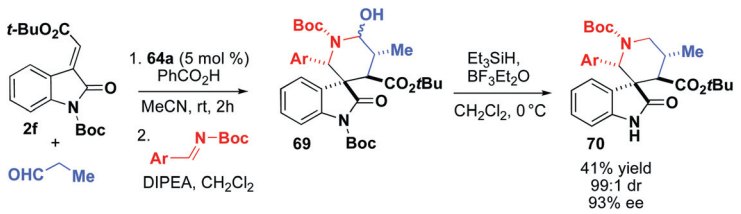
Scheme 12 Several enantioselective strategies for spirocyclic oxindole cyclohexanes utilizing pyrrolidine catalyst **64a**.

Wei and Gong have reported a double Michael reaction for the synthesis of spirooxindole cyclohexenes **61** from dicarbonyl **59** and alkylidine oxindole **2**, using chiral bifunctional organocatalyst **60** (Scheme 10).[37] This transformation generates three new chiral centers in high yields, diastereo- and enantioselectivity. The reaction is primarily limited to alkyl and aryl groups at the R^3 position. When R^3 is a methoxy group, the yield drops to 29%, although the enantio- and diastereoselectivity remain high (93% ee and 99 : 1 dr).

Wang and co-workers have reported a related enantioselective Michael/ketone aldol/dehydration strategy for the synthesis of spiro[cyclohex-2-enone]-oxindoles **63** starting with 2-hydroxyindole **62**.[38] The reaction is also catalyzed using a cinchona alkaloid catalyst **55c** to achieve the desired high yields and selectivities (Scheme 11). While there was not a strong solvent preference for the reaction, a survey of acid additives determined that the addition of 40 mol% TFA is essential for both yield and enantioselectivity. No product was observed using triflic acid and only poor conversion was obtained with *p*-toluene sulfonic acid (PTSA). It was also noted that the stoichiometries of indole and ketone reagents play an important role. It was observed that a 1 : 1 ratio of **62** : **57** afforded a slightly diminished 85% yield, where a 2 : 1 or 1 : 2 ratio afforded 95% yield. In general, high yields and selectivities were maintained for both alkyl and aryl groups on the enone, and electronic effects of the aryl groups had minimal effect. Only the *N*-benzyl and *N*-methyl substrates were examined, both of which proceeded with high yield and selectivity.

The Hiyashi–Jørgensen pyrrolidine organocatalyst **64a** has been shown to be effective in several synthetic strategies to create spirocyclic oxindole cyclohexanes with high enantioselectivity (Scheme 12).[39–41] Chen and co-workers have developed a [2 + 2 + 2] annulation strategy to create spirocyclic oxindole cyclohexanes **65** with six contiguous stereocenters using pyrrolidine **64a** with benzoic acid as a co-catalyst (Scheme 12).[39] This strategy is applicable with various electrophilic components (*e.g.* α,β-unsaturated aldehydes, nitrostyrene, *N*-Boc-imines). When *N*-Boc-imines are used, this strategy affords spirocyclic oxindole piperidines **70** containing four stereocenters with high enantioselectivity (93% ee) (Scheme 13). These reactions generally proceed with high yields and enantioselectivity, but require *N*-Boc-protected olefinic oxindoles **2**.

Melchiorre and co-workers harness an asymmetric Diels–Alder reaction upon *in situ* generation of indole-2,3-quinodimethane (from indole **66** in the presence of catalyst **64a**) to access spirocyclic tetrahydrocarbazoles **67** (Scheme 12).[40] Generation of the diene upon proton elimination was inspired by a silyl elimination strategy employed by Magnus and co-workers.[42,43] The authors evaluated a variety of pyrrolidine catalysts and demonstrated that catalyst **64a** was optimal compared



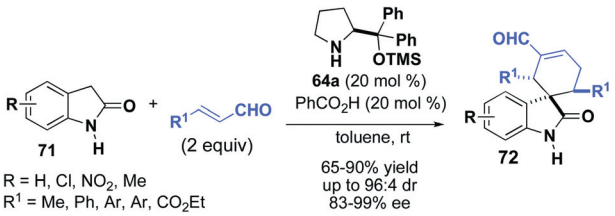
Scheme 13 Synthesis of spirocyclic oxindole piperidines using a [2 + 2 + 2] annulation strategy.

to other aminocatalysts based on preliminary yield and enantioselectivity of 90% ee (*e.g.* proline and the *tert*-butyl variant of the MacMillan catalyst afforded <5% yield). The reaction was also highly dependent on the acid co-catalyst employed. Investigation of various acid co-catalysts revealed that 20 mol% of benzoic acid was optimal, affording product in 95% yield with 95 : 5 diastereoselectivity and 97% ee. The authors also demonstrate that this methodology can be extended to pyrrole and furan substrates; however, the extension to N–H *o*-quinodimethane substrates was not tolerated.

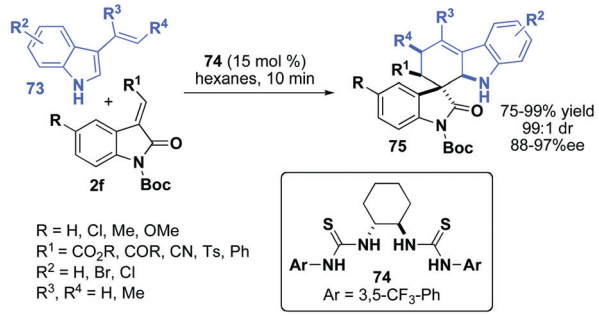
Chen and co-workers have reported the synthesis of enantioenriched spirooxindole hydroindanes **68** upon reaction of (*E*)-4-(1-methyl-2-oxindolin-3-ylidene)-3-oxobutanoates **2e** with two equivalents of an α,β-unsaturated aldehyde (Scheme 12).[41] This reaction also utilizes catalyst **64a**, proceeding *via* a quadruple iminium–enamine–iminium–enamine cascade. Notably, this reaction produces spirocycles with six to eight contiguous stereocenters with high diastereoselectivity and excellent enantioselectivity. While yields are often high, the authors describe that low yields (30%) were observed for some substrates due to unidentified side products.

Using oxindole **71** in place of an alkylidene oxindole, Rios and co-workers have reported the synthesis of spirocyclic oxindole cyclohexenes **72** using an enantioselective Michael–Michael–Aldol cascade reaction (Scheme 14).[44] This reaction also utilizes the Hiyashi–Jørgensen catalyst **64a** with benzoic acid as a co-catalyst for promoting the irreversible dehydration step. Michael accepters with substituted aryl α,β-unsaturated aldehydes are well-tolerated and provide excellent diastereo- and enantioselectivity (96 : 4 dr and 99% ee). In contrast, alkyl substituted α,β-unsaturated aldehydes proceed with poor diastereoselectivity (88 : 12 dr), but excellent enantioselectivity (99% ee). It was noted that the unprotected N–H oxindole is important for selectivity because the *N*-methyl oxindole afforded reduced diastereo- and enantioselectivities (93 : 7 dr and 83% ee).

Barbas and co-workers have reported a highly efficient (*e.g.* 10 min) synthesis of pentacyclic spirooxindoles **75** using a Diels–Alder reaction with vinyl indoles **73** catalyzed by C_2-symmetric bis-thiourea catalyst **74** (Scheme 15).[45] The authors describe several interesting features about the selectivity and the practical utility of this reaction. First, it was noted that high enantioselectivity is specific to the use of the *N*-Boc oxindole **2f**; no stereoinduction was observed with N–H or *N*-Bn oxindole derivatives. A control experiment demonstrates that the reaction with the N–H oxindole proceeds efficiently in the absence of catalyst, providing a quantitative yield of the product in only 2 hours. Investigating the concentration effects demonstrated that a lower concentration of alkylidene **2f** led to slightly higher enantioselectivity (92% ee for 0.1 M compared to 96% ee for



Scheme 14 Michael–Michael–Aldol cascade strategy for spirocyclic oxindole cyclohexanes.

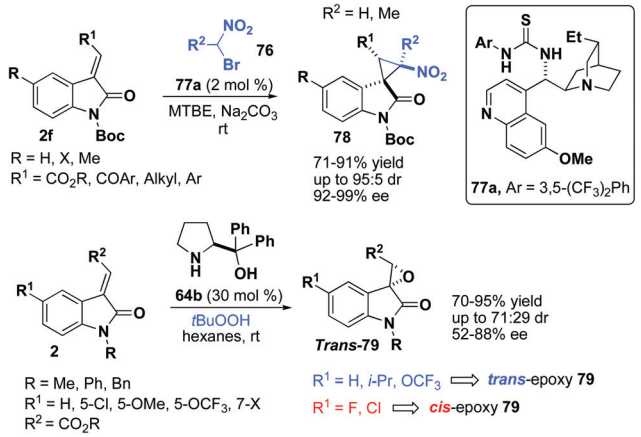


Scheme 15 Synthesis of pentacyclic spirooxindoles using a Diels–Alder strategy.

0.025 M). For practical utility, it was noted that the product was insoluble and immediately precipitated, allowing isolation by filtration while the catalyst remained in solution and could be easily recovered and reused. Catalyst recycling experiments demonstrated the continued efficacy of the catalyst. It was demonstrated that the Boc-protected carbazolespirooxindoles **75** could be successfully deprotected with TFA in 81% yield with retention of enantiomeric excess. The product was also transformed *via* a [1,3]-H shift performed under acidic conditions with HCl without affecting the ester or the enantiomeric excess.

Spirocyclic three-membered rings

Two recent reports have demonstrated the enantioselective synthesis of spirooxindoles containing three-membered ring spirocycles.[46,47] Bencivenni and co-workers reported the first catalytic enantioselective synthesis of spirocyclopropaneoxindoles **78** using a Michael–alkylation cascade sequence with bromonitroalkanes **76** (Scheme 16). A bifunctional thiourea derivatized cinchona alkaloid **77b** was determined to be the optimal catalyst for high diastereo- and enantioselectivity up to 99% ee at 2 mol% catalyst loading. Notably, lower catalyst



Scheme 16 Synthesis of three membered spirooxindoles through organocatalytic strategies.

loading provided increased yields (99% yield for 2 mol% catalyst loading *vs.* 77% yield for 5 mol% catalyst loading). Thiourea catalysts with other tertiary amine motifs were also investigated, but lower enantioselectivity was observed. The use of Na_2CO_3 was necessary to provide enhanced reactivity and diastereocontrol, while other basic additives, such as triethylamine, led to reduced selectivity (*e.g.* 83 : 17 dr) due a to a competitive background reaction. Evaluating solvents demonstrated that methyl *tert*-butyl ether (MTBE) was optimal, while other more polar solvents afforded product **78** with reduced selectivity. With 1-bromonitroethane, excellent enantioselectivity (92–99% ee) was maintained, but lower diastereoselectivity (60 : 40 to 83 : 17 dr) was observed.

Gasperi and co-workers report an asymmetric epoxidation of alkylidene oxindole **2** using *tert*-butyl hydrogen peroxide (TBHP) in the presence of pyrrolidine catalyst **64b** to afford *trans*-epoxy-spirocycles **79** with enantioselectivity up to 88% ee (Scheme 16).[47,48] Using the methyl or silyl ether variant of the catalyst (*e.g.* **64a**) inverted diastereoselectivity and eroded enantioselectivity (Me = 37% ee, TMS = 58% ee) was observed, indicating formation of a hydrogen-bonding interaction between the catalyst and the TBHP. However, it was noted that electron-withdrawing aryl groups (*i.e.* Ar = 3,5-$(CF_3)_2C_6H_3$) on the catalyst did not improve enantioselectivity and led to longer reaction times (15 d *vs.* 3 d with the Ph variant). Other solvents and oxidizing agents proved to be less efficient for the epoxidation. Upon investigating the oxindole substrate scope, it was noted that 5- or 7-halosubstituted oxindoles afford the *cis*-epoxy-spirocycle **79**, while retaining moderate enantioselectivity (58% ee). The authors do not offer an explanation for this reversal in selectivity, but control experiments prove that *trans*-epoxy spirocycle **79** is not simply isomerizing under the reaction conditions.

Reactions with isatins

The second major strategy that has been widely utilized for the synthesis of spirooxindoles is the use of nucleophilic addition and annulation reactions for spirocyclization with isatin electrophiles. Isatins are cyclic electron-deficient dicarbonyl compounds that are often more reactive than benzaldehyde or acyclic

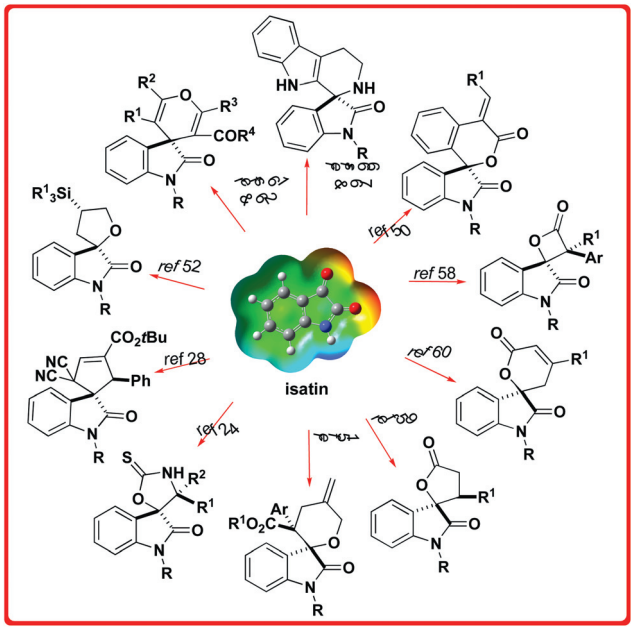
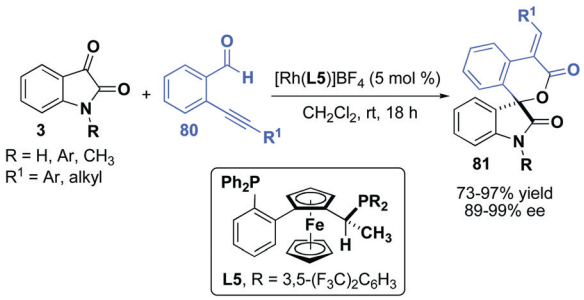


Fig. 6 Spirooxindoles synthesized from isatins.

dicarbonyl compounds such as beta-ketoesters.[48] The cisoid dicarbonyl is oriented for optimal binding to many chiral catalysts, which further activates the electrophile while inducing a chiral environment. Isatins (**3**) provide many complementary spirocyclic products compared to the spirocycles described previously resulting from alkylidene oxindoles (**2**). Many isatins are commercially-available, or can be efficiently synthesized, which further enhances their utility. As observed with alkylidene oxindoles, the protecting group on nitrogen has been shown to have a strong effect on the reactivity and selectivity in various nucleophilic addition and spirocyclization reactions (Fig. 6).

Spirocyclic-tetrahydrofurans and pyrans

Pyrans and tetrahydrofurans are present in many natural products and prevalent pharmacophores for drug discovery.[49] Spirocyclic pyrans represent a challenge for synthetic chemistry and several examples with distinct strategies have been recently reported. Metal-catalyzed spirocyclization reactions with isatin **3** demonstrate the efficient access to spirocyclic oxindole pyrans such as **81** and **83**. In 2008, Tanaka and co-workers reported a rhodium (I)-catalyzed intermolecular [4 + 2] annulation reaction between 2-alkynylbenzaldehydes **80** and isatins to access spirocyclic benzopyranones **81** in excellent yield (up to 97%) and enantioselectivity (up to 99% ee) (Scheme 17).[50] The reaction uses a cationic rhodium catalyst with a bisphosphine (*R*,*R*)-walphos ligand (**L5**) to achieve the desired reactivity and selectivity. Other common bisphosphine ligands were also screened (using benzaldehyde instead of *N*-methylisatin), but these ligands all afforded dramatically lower yields and enantioselectivity. Once an optimal ligand was identified, the authors demonstrate the scope of the process for various alkynylaldehydes with *N*-methylisatin. Consistently higher yields and enantioselectivity were observed for the initial cross-[4 + 2] annulation in all cases relative to benzaldehyde. The *N*-phenyl and N–H isatins also proceeded efficiently with



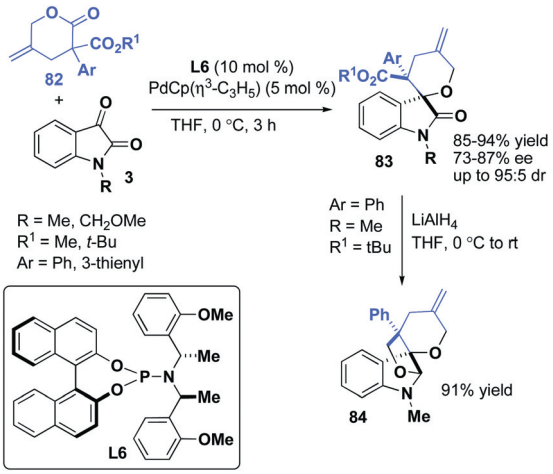
Scheme 17 Synthesis of tetracyclic spirooxindoles using a [4 + 2] annulation strategy.

high yields and enantioselectivity (92 and 89% ee, respectively). Despite poor solubility, acenaphthenequinone was also successful in this reaction, though 10 mol% of the cationic rhodium(I) catalyst was utilized to maintain efficient conversion.

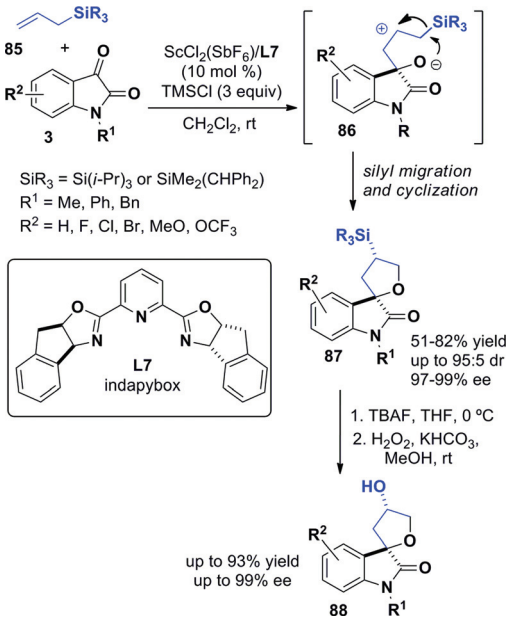
In 2009, Hayashi and co-workers reported an asymmetric palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones **82** with isatins to access unique spirocyclic oxindole pyrans **83** (Scheme 18).[51] The reaction was optimized with *P*,*N*-ligands, where ligand **L6** afforded the highest yield and enantioselectivity. The reaction proceeds with the highest enantioselectivity (87% ee) when the lactone contains a methyl ester; however, the reaction also proceeds with higher diastereoselectivity (95 : 5 dr *vs.* 88 : 12 dr) when the *tert*-butyl ester is used, albeit with reduced enantioselectivity (73% ee). The product can be further transformed upon treatment with $LiAlH_4$ to obtain spirotetracycle **84** containing an *N*,*O*-acetal functionality.

Franz and co-workers recently reported the first enantioselective [3 + 2] allylsilane annulation reaction, accessing spirooxindoles **87** in high diastereo- and enantioselectivity (Scheme 19).[52] This reaction utilizes a cationic scandium(III) complex with pybox ligand **L7** to overcome the competing formation of the Hosomi–Sakurai addition (allylation) product while providing excellent enantiocontrol.[53] The role of the scandium salt (triflate *vs.* chloride), counterion, and solvent were optimized to favor formation of the annulation product, which likely play a role in stabilizing the β-silyl carbocation **86** formed in this reaction. Importantly, TMSCl was identified as an essential promoter for the reaction. Using the allyldimethylbenzhydrylsilane provides silyl spirocyclic oxindole products that can be further transformed upon oxidation of the C–Si bond to afford the hydroxy-spirocyclic oxindole **88** in high yield with retention of configuration. Other bulky allylsilanes with aryl groups capable of undergoing oxidative cleavage were also investigated, but afforded a lower ratio of annulation product relative to the competing allylation product (52 : 48).

Since Wanzlick's first synthesis of *N*-heterocyclic carbenes (NHCs) in the 1960's,[54,55] NHC catalysts have found diverse applications in synthetic methodology due to their unique ability to provide umpolung type reactivity.[56,57] Ye and co-workers have reported that these NHC catalysts are effective for the enantioselective synthesis of spirocyclic oxindole lactones (Scheme 20). Ye first reported the use of NHC catalysts in the synthesis of spirocyclic oxindole-β-lactones **91** in a [2 + 2] cycloaddition between ketenes **89** and isatins **3**.[58] Initial catalyst screening was performed using *N*-methyl isatin and phenyl ethyl

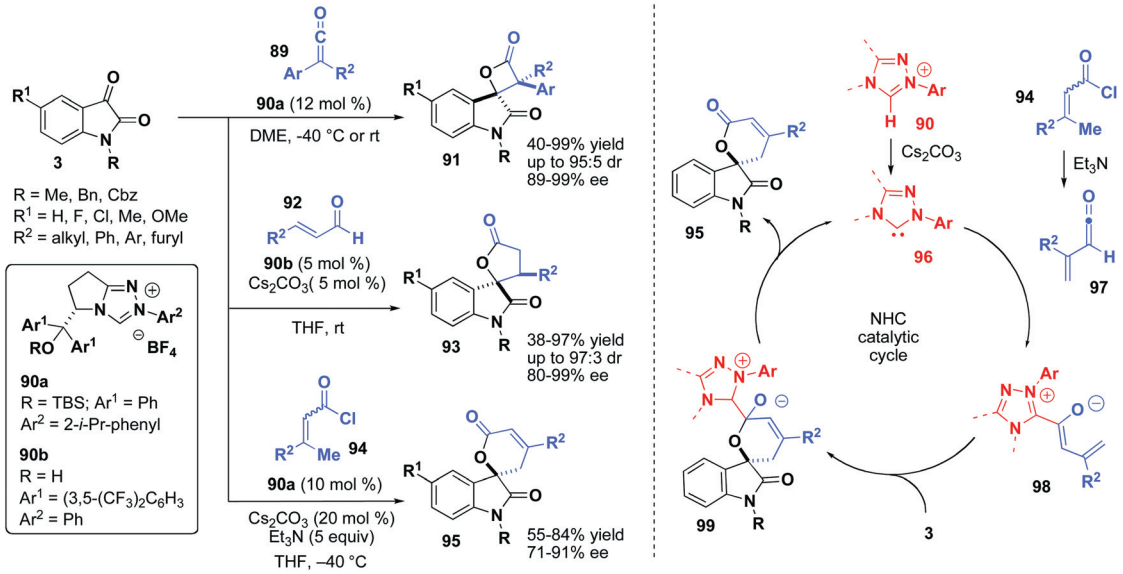


Scheme 18 Palladium-catalyzed strategy to access spirocyclic oxindole pyrans.

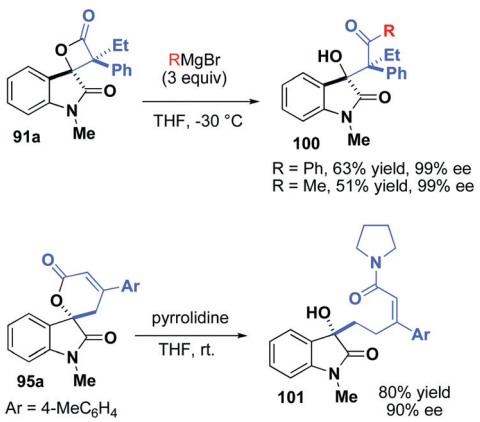


Scheme 19 Synthesis of spirooxindoles using an allylsilane annulation strategy.

ketene **89**, where the TBS protected NHC catalyst **90a** was demonstrated to be optimal, affording 75 : 25 diastereoselectivity in favor of the *trans*-lactone with excellent yield (95%) and enantioselectivity (99% ee). It was noted that the TMS and hydroxy variants of the catalysts exhibited dramatically lower catalytic activity. The reaction is sensitive to steric effects, providing lower yield or no reaction when more sterically-hindered ketenes are used. For example, the 2-naphthyl ethyl ketene afforded low yield (40%) and poor diastereomeric ratio (64 : 33 dr), although the enantioselectivity of the trans (major) isomer was still excellent (99% ee). In the case of the 2-chlorophenyl ketene, the reaction was inhibited completely. The scope of *N*-protecting groups on the isatin was demonstrated with *N*-benzyl and *N*-Cbz substrates, each affording comparable yields and selectivities; the use of N–H isatins was not reported. Further



Scheme 20 Strategies for the asymmetric synthesis of spirocyclic lactones using NHC catalysts.



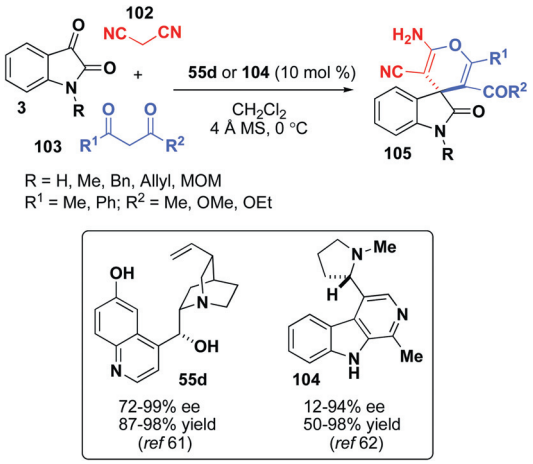
Scheme 21 Further transformations of spirocyclic lactones.

synthetic transformations were performed to demonstrate that β-lactone **91a** can be ring-opened with phenyl or methyl Grignard reagents to reveal the 3-hydroxy ketone oxindole **100** with excellent retention of enantioselectivity (Scheme 21).

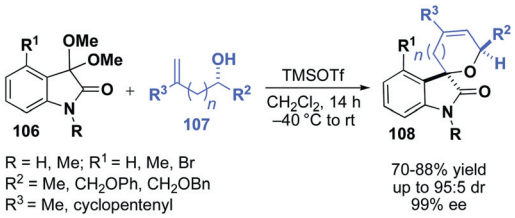
In a subsequent report, Ye and co-workers described an NHC-catalyzed [3 + 2] annulation strategy for the synthesis of spirocyclic oxindole-γ-butyrolactones **93** using enals **92** with isatins (Scheme 20).[59] This strategy employs umpolung reactivity of the homoenolate formed by the addition of the NHC catalyst to enals. Several NHC catalysts were evaluated and in this case, hydroxy NHC catalyst **90b** was optimal while the silyl ether catalyst **90a** demonstrated no reactivity, indicating that the hydrogen-bonding capability of the free hydroxy must be important for catalytic activity. Evaluation of the conditions utilized to generate the NHC catalyst revealed that 20 mol% of Cs_2CO_3 in toluene afforded the highest diastereo- and enantioselectivity and catalyst loading could be reduced to 5 mol% with no loss in reactivity. This strategy was then further expanded using acyl chlorides **94** to provide access to spirocyclic oxindole dihydropyranones **95**.[60] Comparing performance of the previously successful NHC catalysts showed that the use of the silyl ether NHC catalyst **90a** is optimal for reactivity in this system, in contrast to the previous case. Here the reaction requires the addition of triethylamine and therefore likely proceeds through ketene intermediate **97** as shown in the representative catalyst cycle for this class of reactions (Scheme 20). Notably, no N–H isatins were shown in any paper involving NHC catalysis. Further transformations were investigated and it was demonstrated that the spirocyclic lactone **95a** could be subjected to aminolysis with pyrrolidine to afford the corresponding 3-hydroxyoxindoles **101** while maintaining enantiopurity (Scheme 21).

Yuan and co-workers have reported access to spirocyclic oxindole pyrans **105** in high yield and enantiopurity utilizing a three-component domino Knovenagel/Michael/cyclization sequence catalyzed by a cinchona alkaloid, cupreine **55d** (Scheme 22).[61] This reaction also proceeds starting directly from an isatylidene malononitrile. While enantioselectivity is generally high, using N–H isatins or cyclic 1,3-diones led to lower enantioselectivity (78% ee or 8% ee, respectively). It is a disadvantage that this reaction requires extremely dilute conditions (0.1–0.005 M) and thus large amounts of solvent are employed. Macaev and co-workers subsequently reported the use of (−)-(*S*)-brevicolline **104** as an alternate catalyst for the domino Knovenagel/Michael/cyclization, affording the same spirooxindole pyrans **105** with up to 94% ee.[62] In general, the enantioselectivities are low and yields are modest relative to Yuan's method using cupreine as a catalyst. Several racemic examples of this reaction have also been reported previously.[63,64]

In an alternate approach to spirocyclic oxindole pyrans, Porco and co-workers have reported a TMSOTf-catalyzed diastereoselective synthesis of spirocyclic pyrans **108** using a Prins cyclization strategy with isatin ketals **106** and homoallylic alcohols **107** (Scheme 23).[65] Although racemization often occurs during



Scheme 22 MCR strategies in the synthesis of spirooxindoles.

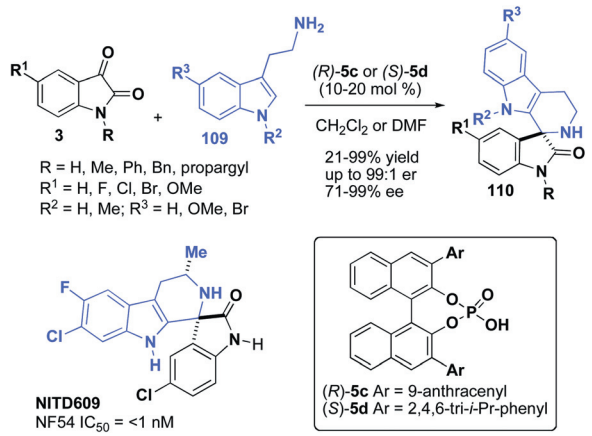


Scheme 23 Stereoselective TMSOTf-catalyzed strategy synthesis of spirocyclic pyrans.

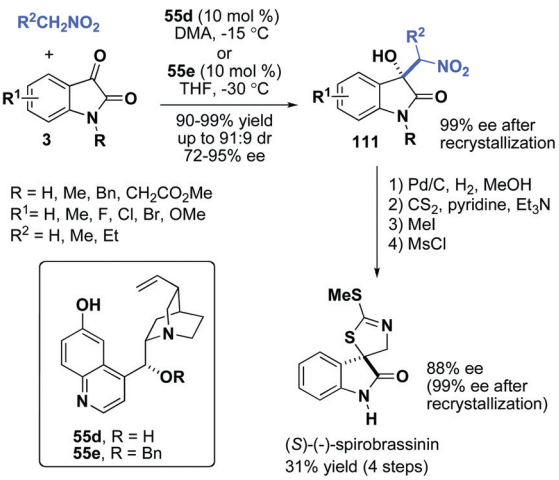
Prins cyclizations, no erosion of enantiopurity was observed under these conditions.

Spirocyclic *N*-heterocycles

Franz and Bencivenni both reported the enantioselective synthesis of spirocyclic tetrahydro-β-carbolines **110** (spiroindolones) using a Pictet–Spengler strategy with isatins and tryptamines **109** (Scheme 24).[66,67] Spiroindolones represent an important synthetic target due to promising anti-malaria activity. For example, **NITD609** is a lead compound that has been shown to have single dose efficacy for the treatment of malaria in a mouse model, with one enantiomer demonstrating >80-fold potency relative to other stereoisomers.[8,68] Franz and co-workers evaluated the catalytic activity of various chiral Lewis acid complexes, thioureas and phosphoric acids for the enantioselective synthesis of spiroindolones using a Pictet–Spengler reaction with 5-methoxy-tryptamine. While scandium(III) and tin(II) complexes provide excellent activity to catalyze spiroindolone formation, only racemic products were observed. Similarly, excellent yields were observed with thiourea catalysts (up to 99%) but only poor enantioselectivities (≤52% ee). Ultimately, the 9-anthracenyl phosphoric acid catalyst **5c** was determined to be an optimal catalyst (in CH_2Cl_2) for the spirocyclization of 5-methoxy-tryptamine with various substituted isatins, where both electron-donating and withdrawing groups gave comparable results (up to 99% yield, up to 94% ee). Using 5-methoxy-isatin provided excellent enantioselectivity (94% ee); however, the 5-methoxy-*N*-methyl isatin proceeded with poor enantioselectivity (16% ee).



Scheme 24 Synthesis of spiroindolones using a Pictet–Spengler-type strategy.



Scheme 25 Access to substituted oxindoles and the synthesis of spirobrassinin using a Henry reaction.

Bencivenni and co-workers performed parallel optimization studies and identified that the (*S*)-TRIP catalyst **5d** in DMF was optimal for the enantioselective Pictet–Spengler reactions, with enantioselectivity up to 95% ee. Substituted tryptamines such as 5-bromo-tryptamine or *N*-methyl tryptamine also required higher temperatures and/or longer reaction times with this system, and resulted in lower enantioselectivity (73% ee and 71% ee, respectively).

3,3′-Disubstituted oxindoles

Wang and co-workers reported the first asymmetric nitroaldol (Henry) reactions with isatins catalyzed by cupreine **55d** with high yields and excellent enantioselectivities (up to 95% ee) (Scheme 25).[69] Several bifunctional cinchona alkaloid catalysts were investigated and the authors demonstrate that both the 6′- and 9-OH groups are critical for stereocontrol. The highest enantioselectivities are obtained using dimethylacetamide (DMA) at −15 °C, with the addition of 10 mol% benzoic acid as a co-catalyst. For practical utility, it was noted that the hydroxy-oxindole

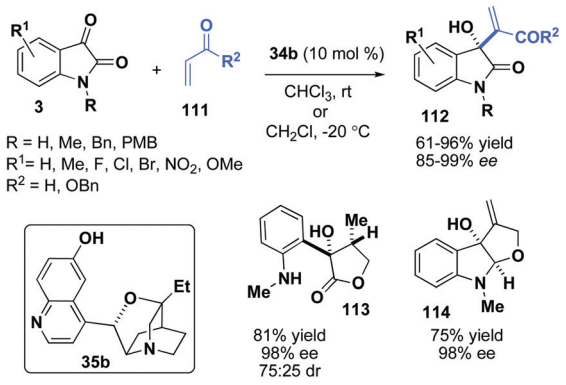
products **111** can be readily isolated and purified without column chromatography using trituration (or recrystallization) with CH_2Cl_2, which afforded enantioselectivity up to 99% ee. A broad scope of nitroalkanes was demonstrated and the reaction proceeds in quantitative yield for both electron-donating and withdrawing groups. Various isatins are also well-tolerated and recrystallization can be used to enhance enantiomeric excess (up to 99% ee) for substrates proceeding with lower enantioselectivity. Reactions with nitroethane and nitropropane create two new stereocenters, proceeding with moderate to high diastereoselectivity (75 : 25 to 91 : 9 dr), which can be further improved by recrystallization or trituration (up to 96 : 4 dr). The synthetic utility of these products is showcased in the first enantioselective synthesis of (*S*)-(−)-spirobrassinin (31% yield over 4 steps, 99% ee after recrystallization), which is performed without the need for any protecting groups. A subsequent report describes alternate conditions using a C9-OBn cupreine derivative **55e**, in THF at −30 °C without an acid additive.[70] The reaction is equally successful with similar yields and enantioselectivities. Although different catalyst variations and conditions are utilized, both authors propose a similar stereochemical model involving dual activation through hydrogen bonding interactions and nucleophile direction by the quinuclidine.

While several examples of organocatalytic asymmetric Morita–Baylis–Hillman reactions have been reported with alkylidene oxindoles as described above, there are only two examples reported with isatins (Scheme 26). Zhou and co-workers reported the first example of a catalytic asymmetric MBH reaction for the synthesis of 3-hydroxy-2-oxindoles **112** from isatins and acrolein.[71] The authors discovered that cinchona alkaloid **35b** (10 mol%) affords optimal reactivity and selectivity in CH_2Cl_2 at −20 °C. The use of *N*-protected isatins (either *N*-methyl or *N*-benzyl) was important for high conversion; unprotected N–H isatins generally proceeded with low yields, likely due to poor solubility in CH_2Cl_2. The fully unsubstituted isatin was an exception, proceeding with good yield (79%) and excellent enantioselectivity (98% ee). In general, both electron-donating and withdrawing groups are well-tolerated in the reaction. Ethyl acrylate proceeded in 50% yield and 96% ee with 5,7-dibromoisatin, in the presence of 20 mol% of **35b**. Further synthetic transformations were demonstrated with the hydroxy-oxindole products by treatment with $NaBH_4$ to afford lactone **113** in 75% yield and 75 : 25 dr. Treatment with $LiAlH_4$ afforded the hydroxyfuroindoline **114** as a single diastereomer (75% yield).

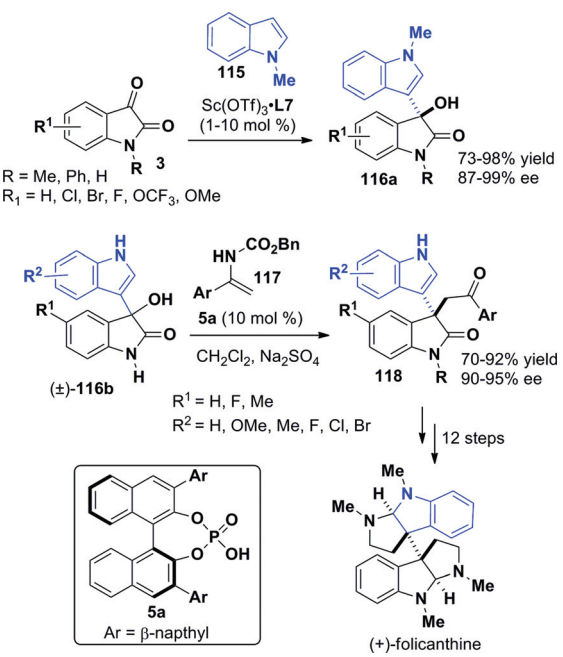
A subsequent report by Lu and co-workers also employs 10 mol% of cinchona alkaloid **35b** for the addition of acrylates to isatins, obtaining similar results for a reaction in $CHCl_3$ at room temperature.[72] Here, it was also observed that N–H isatins afford poor results, with the unsubstituted isatin proceeding in 26% yield with 33% ee. In general, isatins with electron-donating groups required longer reaction times (72 h *vs.* 48 h) and higher catalyst loading (up to 20 mol%). The mechanism of the reaction was studied and the authors conclude that the C6′-OH plays an important role in a key intramolecular proton transfer which aids in directing enantioselectivity.

Several methods for the enantioselective addition of indoles **115** to isatins have now been reported,[73–75] providing access to important 3-indolyl-oxindoles core structures found in alkaloid natural products (Scheme 27). Franz and co-workers reported the first catalytic asymmetric synthesis of 3-indolyl-3-hydroxyoxindole **116a** using chiral scandium and indium complexes.[74] Previous reports describe the formation of the 3,3′-bisindolyl oxindole, but here the metal–ligand complex controls the enantioselectivity and favors formation of the 3-hydoxy oxindole product. A broad scope of isatins and arene nucleophiles, including N–H isatins and N–H indoles, proceed with high yields and enantioselectivities. The authors also demonstrate that the scandium catalyst is broadly applicable for other nucleophilic addition reactions, including allylation and Mukiayama aldol reactions, while the indium catalyst is necessary for regioselective pyrrole addition reactions.[76] Other catalysts reported for the enantioselective addition of indoles to isatins include reactions catalyzed by cupreine derivatives.[73,75]

Gong and co-workers recently reported an enantioselective nucleophilic substitution reaction utilizing racemic 3-hydroxyoxindoles **116b** with enecarbamates **117** catalyzed by chiral



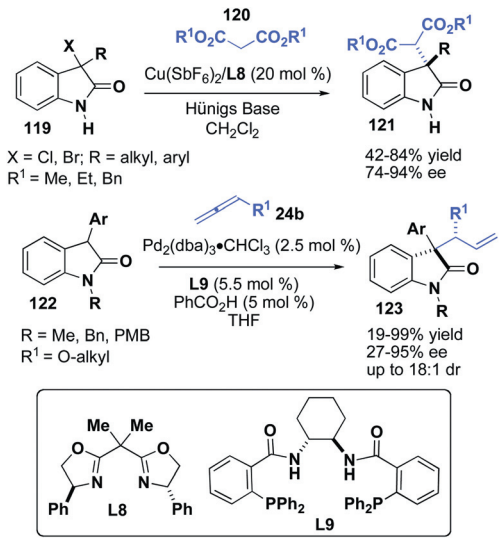
Scheme 26 MBH reaction strategy for the enantioselective synthesis of substituted oxindoles.



Scheme 27 Strategies for the synthesis of indolyloxindoles.

phosphoric acid **5a** (Scheme 27).[77] This stereoablative strategy provides access to 3,3′-disubstituted oxindoles **118** containing a quaternary stereocenter with high enantioselectivity. The reaction proceeds through a vinylogous iminium intermediate generated upon dehydration. The authors use this methodology to synthesize the bispyrrolo[2,3-*b*]indole natural product (+)-folicanthine in 12 steps with 3.7% overall yield.

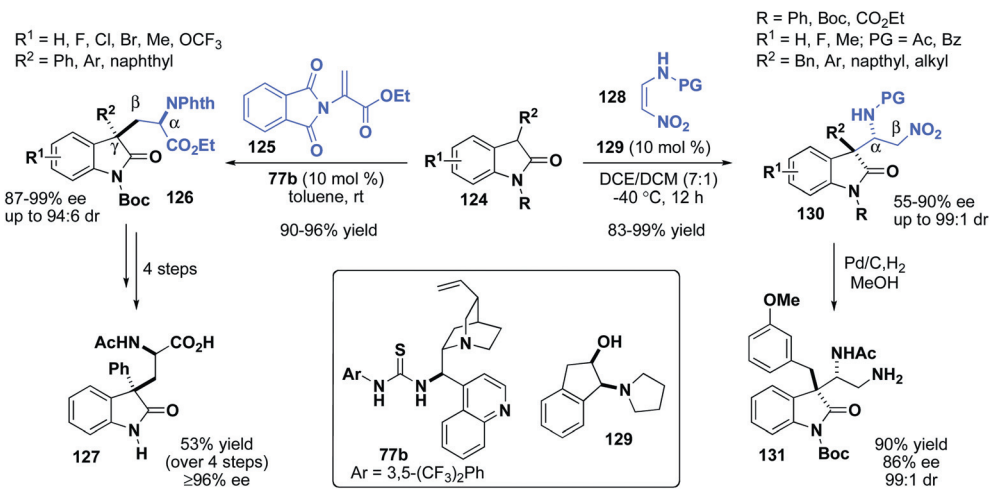
An alternate strategy to 3,3′-disubstituted oxindoles utilizes 3-substituted oxindoles in various asymmetric addition strategies. Stoltz and co-workers have reported a stereoablative strategy for the synthesis of 3,3′-disubstituted oxindoles starting with 3-halooxindoles **119** using a chiral cationic copper complex for the catalytic asymmetric addition of malonate esters (Scheme 28).[78] Variations to the copper complex were investigated and the reaction proceeds with the highest enantioselectivity and yield using a chiral bisoxazoline ligand **L8** with a SbF_6^- counterion. Trost and co-workers access 3,3′-disubstituted oxindoles **123** by harnessing chiral Pd-allyl electrophiles in combination with nucleophilic anionic 3-substituted oxindoles.[79] Focusing on atom economy, allenes **24b** were used to generate the Pd allyl species *in situ*, eliminating byproducts, and affording a cleaner and more environmentally benign reaction.



Scheme 28 Synthesis of 3,3′-disubstituted oxindoles using metal catalyzed reaction strategies.

The synthesis of 3,3′-disubstituted oxindoles with amines incorporated at the α and β positions are especially appealing based on their functional similarities to alkaloid natural products. Xiao and co-workers have developed a synthesis for enantioenriched C^{γ}-tetrasubstituted α-amino acid derivatives using an asymmetric nucleophilic addition–protonation cascade reaction of 3-substituted oxindoles **124** and ethyl 2-phthalimidoacrylates **125**.[32,80] The cinchonine-derived thiourea **77b** was determined to be the optimal catalyst, with the quinuclidine nitrogen being sufficiently basic to enolize 3-phenyl oxindole, and the thiourea proving indispensable for activation of the ethyl 2-phthalimidoacrylate. The scope of oxindole was investigated and the enantioselectivities are excellent (93–99% ee) with high diastereoselectivities (89 : 11 to 94 : 6 dr). The 3-benzyl oxindole affords the corresponding C^{γ}-tetrasubstituted α-amino acid derivative **126** in 90% yield with good enantioselectivity (87% ee), albeit with poor diastereoselectivity (52 : 48 dr). The utility of these structures was demonstrated by the synthesis of C^{γ}-tetrasubstituted α-amino acid **127** in 99% yield and 96% ee. The opposite enantiomer of the amino ester can be readily obtained by using the cinchonidine analogue (a diastereomer of cinchonine).

Yuan and co-workers have reported an asymmetric Michael addition with 3-substituted oxindoles **124** and protected 2-amino-1-nitroethanes **128** for the synthesis of 3,3′-disubstituted oxindoles **130** containing an α,β-diamino functionality (Scheme 29).[81] Several catalysts were screened for this transformation, including cinchona alkaloids and thioureas. Ultimately, it was determined that a simple indanol derivative **129** was the optimal catalyst using a 7 : 1 mixture of DCE/DCM at −40 °C. In general *N*-Boc-3-benzyl derivatives proved to be most effective, affording excellent yields and diastereoselectivities (up to 99% yield, up to 99 : 1 dr) with good enantioselectivity (78–90% ee). Various substitution is tolerated, but a single



Scheme 29 Strategies for the synthesis of amine-substituted oxindoles.

example suggests that 3-aryl substitution provides low enantioselectivity (55% ee), although the yield and diastereoselectivity again are excellent (92% yield, 99 : 1 dr). The nitro group can be reduced with Pd/C to reveal the β-primary amine **131** in 90% yield, with 99 : 1 dr, and 86% ee.

Conclusion

The strategies and catalyst systems described here highlight recent advances for the enantioselective synthesis of spirooxindoles and related 3,3′-disubstituted oxindoles. Challenges remain to design and develop efficient catalysts with low catalyst loading, provide synthetic methods that allow selective access to all stereoisomers while maintaining high enantioselectivity, incorporate polar groups and heterocycles, and determine the effects of additives and co-catalysts for both metal- and organocatalyzed reactions. Additional notable examples and strategies continue to be reported, for example, several interesting examples were reported during the review of this manuscript.[82–85] The ongoing development of synthetic methods for these targets is expected to have important applications for the synthesis of complex natural products and the design of new pharmaceutical compounds.

References

1 A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735.
2 S. M. Rajesh, S. Perumal, J. C. Menendez, P. Yogeeswari and D. Sriram, *Med. Chem. Commun.*, 2011, **2**, 626.
3 J. Schonhaber and T. J. J. Muller, *Org. Biomol. Chem.*, 2011, **9**, 6196.
4 C.-B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **52**, 12651.
5 C.-B. Cui, H. Kakeya and H. Osada, *J. Antibiot.*, 1996, **49**, 832.
6 H. Conroy and J. K. Chakrabarti, *Tetrahedron Lett.*, 1959, **1**, 6.
7 F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Lett.*, 1959, **1**, 1.
8 B. K. S. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E. K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E. A. Winzeler, F. Petersen, R. Brun, V. Dartois, T. T. Diagana and T. H. Keller, *J. Med. Chem.*, 2010, **53**, 5155.
9 V. V. Vintonyak, K. Warburg, H. Kruse, S. Grimme, K. Hübel, D. Rauh and H. Waldmann, *Angew. Chem., Int. Ed.*, 2010, **49**, 5902.
10 T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.*, 2001, **44**, 4641.
11 References for this graph were accumulated by performing a scifinder substructure search of spirooxindoles with ring sizes of 3–7 with saturated and unsaturated rings accounted for, and spirooxindoles ring systems of any atoms accounted for. Duplicates were removed to determine the final number of publications.
12 F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381.
13 J. J. Badillo, N. V. Hanhan and A. K. Franz, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 758.
14 C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748.
15 B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003.
16 M. Presset, K. Mohanan, M. Hamann, Y. Coquerel and J. Rodriguez, *Org. Lett.*, 2011, **13**, 4124.
17 M. M. C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 16077.
18 X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819.
19 T.-L. Liu, Z.-Y. Xue, H.-Y. Tao and C.-J. Wang, *Org. Biomol. Chem.*, 2011, **9**, 1980.
20 C.-J. Wang, F. Gao and G. Liang, *Org. Lett.*, 2008, **10**, 4711.
21 W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2011, **13**, 2472.
22 T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 17082.
23 Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang and R. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 9124.
24 X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen and R. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 15328.
25 B. M. Trost, N. Cramer and S. M. Silverman, *J. Am. Chem. Soc.*, 2007, **129**, 12396.
26 A. Voituriez, N. Pinto, M. Neel, P. Retailleau and A. Marinetti, *Chem.–Eur. J.*, 2010, **16**, 12541.
27 B. Tan, N. R. Candeias and C. F. Barbas, *J. Am. Chem. Soc.*, 2011, **133**, 4672.
28 F. Zhong, X. Han, Y. Wang and Y. Lu, *Angew. Chem., Int. Ed.*, 2011, **50**, 7837.
29 J. Peng, X. Huang, L. Jiang, H.-L. Cui and Y.-C. Chen, *Org. Lett.*, 2011, **13**, 4584.
30 B. Tan, N. R. Candeias and C. F. Barbas, *Nat. Chem.*, 2011, **3**, 473.
31 X. Li, Y.-M. Li, F.-Z. Peng, S.-T. Wu, Z.-Q. Li, Z.-W. Sun, H.-B. Zhang and Z.-H. Shao, *Org. Lett.*, 2011, **13**, 6160.
32 T. Bui, S. Syed and C. F. Barbas, *J. Am. Chem. Soc.*, 2009, **131**, 8758.
33 Y.-M. Li, X. Li, F.-Z. Peng, Z.-Q. Li, S.-T. Wu, Z.-W. Sun, H.-B. Zhang and Z.-H. Shao, *Org. Lett.*, 2011, **13**, 6200.
34 G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200.
35 Z. Z. Liu, *Patent PCT Int. Appl.*, WO2008055812, 2008, (Hoffmann-La Roche AG), Spiroindolinone derivatives.
36 Y.-B. Lan, H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao and X.-W. Wang, *Org. Lett.*, 2011, **13**, 4866.
37 Q. Wei and L.-Z. Gong, *Org. Lett.*, 2010, **12**, 1008.
38 L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu and L.-X. Wang, *Chem. Commun.*, 2010, **46**, 8064.
39 K. Jiang, Z.-J. Jia, S. Chen, L. Wu and Y.-C. Chen, *Chem.–Eur. J.*, 2010, **16**, 2852.
40 Y. Liu, M. Nappi, E. Arceo, S. Vera and P. Melchiorre, *J. Am. Chem. Soc.*, 2011, **133**, 15212.
41 K. Jiang, Z.-J. Jia, X. Yin, L. Wu and Y.-C. Chen, *Org. Lett.*, 2010, **12**, 2766.
42 P. Magnus, T. Gallagher, P. Brown and P. Pappalardo, *Acc. Chem. Res.*, 1984, **17**, 35.
43 T. Gallagher and P. Magnus, *Tetrahedron*, 1981, **37**, 3889.
44 X. Companyo, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano and R. Rios, *Chem. Commun.*, 2010, **46**, 6953.
45 B. Tan, G. Hernández-Torres and C. F. Barbas, *J. Am. Chem. Soc.*, 2011, **133**, 12354.
46 F. Pesciaioli, P. Righi, A. Mazzanti, G. Bartoli and G. Bencivenni, *Chem.–Eur. J.*, 2011, **17**, 2842.
47 C. Palumbo, G. Mazzeo, A. Mazziotta, A. Gambacorta, M. A. Loreto, A. Migliorini, S. Superchi, D. Tofani and T. Gasperi, *Org. Lett.*, 2011, **13**, 6248.
48 T. Gasperi, M. A. Loreto, A. Migliorini and C. Ventura, *Eur. J. Org. Chem.*, 2011, 385.
49 A. K. Ghosh, P. Ramu Sridhar, N. Kumaragurubaran, Y. Koh, I. T. Weber and H. Mitsuya, *ChemMedChem*, 2006, **1**, 939.
50 D. Hojo, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem., Int. Ed.*, 2008, **47**, 5820.
51 R. Shintani, S.-y. Hayashi, M. Murakami, M. Takeda and T. Hayashi, *Org. Lett.*, 2009, **11**, 3754.
52 N. V. Hanhan, N. R. Ball-Jones, N. T. Tran and A. K. Franz, *Angew. Chem., Int. Ed.*, 2012, **51**, 989.
53 S. M. Hande, M. Nakajima, H. Kamisaki, C. Tsukano and Y. Takemoto, *Org. Lett.*, 2011, **13**, 1828.
54 H. W. Wanzlick, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 75.
55 H. W. Wanzlick and H. J. Schönherr, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 141.
56 D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606.
57 E. M. Phillips, A. Chan and K. A. Scheidt, *Aldrichimica Acta*, 2009, **42**, 55.
58 X.-N. Wang, Y.-Y. Zhang and S. Ye, *Adv. Synth. Catal.*, 2010, **352**, 1892.
59 L.-H. Sun, L.-T. Shen and S. Ye, *Chem. Commun.*, 2011, **47**, 10136.
60 L.-T. Shen, P.-L. Shao and S. Ye, *Adv. Synth. Catal.*, 2011, **353**, 1943.
61 W.-B. Chen, Z.-J. Wu, Q.-L. Pei, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2010, **12**, 3132.

62 F. Macaev, N. Sucman, F. Shepeli, M. Zveaghintseva and V. Pogrebnoi, *Symmetry*, 2011, **3**, 165.
63 G. Shanthi, G. Subbulakshmi and P. T. Perumal, *Tetrahedron*, 2007, **63**, 2057.
64 S.-L. Zhu, S.-J. Ji and Y. Zhang, *Tetrahedron*, 2007, **63**, 9365.
65 M. P. Castaldi, D. M. Troast and J. A. Porco, *Org. Lett.*, 2009, **11**, 3362.
66 J. J. Badillo, A. Silva-Garcia, B. H. Shupe, J. C. Fettinger and A. K. Franz, *Tetrahedron Lett.*, 2011, **52**, 5550.
67 S. Duce, F. Pesciaioli, L. Gramigna, L. Bernardi, A. Mazzanti, A. Ricci, G. Bartoli and G. Bencivenni, *Adv. Synth. Catal.*, 2011, **353**, 860.
68 M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175.
69 L. Liu, S. Zhang, F. Xue, G. Lou, H. Zhang, S. Ma, W. Duan and W. Wang, *Chem.–Eur. J.*, 2011, **17**, 7791.
70 M.-Q. Li, J.-X. Zhang, X.-F. Huang, B. Wu, Z.-M. Liu, J. Chen, X.-D. Li and X.-W. Wang, *Eur. J. Org. Chem.*, 2011, 5237.
71 Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2011, **132**, 15176.
72 F. Zhong, G.-Y. Chen and Y. Lu, *Org. Lett.*, 2011, **13**, 82.
73 J. Deng, S. Zhang, P. Ding, H. Jiang, W. Wang and J. Li, *Adv. Synth. Catal.*, 2010, **352**, 833.
74 N. V. Hanhan, A. H. Sahin, T. W. Chang, J. C. Fettinger and A. K. Franz, *Angew. Chem., Int. Ed.*, 2010, **49**, 744.
75 P. Chauhan and S. S. Chimni, *Chem.–Eur. J.*, 2010, **16**, 7709.
76 E. G. Gutierrez, C. J. Wong, A. H. Sahin and A. K. Franz, *Org. Lett.*, 2011, **13**, 5754.
77 C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2011, **50**, 1046.
78 S. Ma, X. Han, S. Krishnan, S. C. Virgil and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2009, **48**, 8037.
79 B. M. Trost, J. Xie and J. D. Sieber, *J. Am. Chem. Soc.*, 2011, **133**, 20611.
80 S.-W. Duan, J. An, J.-R. Chen and W.-J. Xiao, *Org. Lett.*, 2011, **13**, 2290.
81 X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.*, 2011, **76**, 4008.
82 F. Zhong, X. Han, Y. Wang and Y. Lu, *Chem. Sci.*, 2012, **3**, 1231.
83 T. Cao, J. Deitch, E. C. Linton and M. C. Kozlowski, *Angew. Chem., Int. Ed.*, 2012, **50**, 2448.
84 B. Tan, X. Zeng, W. W. Y. Leong, Z. Shi, C. F. Barbas and G. Zhong, *Chem.–Eur. J.*, 2012, **18**, 63.
85 J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2012, **51**, DOI: 10.1002/anie.201201643.