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Transition metal-free strategies for the stereoselective construction of spirocyclopropyl oxindoles

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ABSTRACT

The spirocyclopropyl oxindole motif is an important architectural subunit as a well-established pharmacophore that is present in many biologically active natural products and small molecules with applications across a wide array of therapeutic areas. As a result, efforts toward the stereoselective assembly of this core framework have played a role in the recent resurgence of metal-free cycloaddition strategies. This review covers those recent transition metal-free approaches to the spirocyclopropyl oxindole framework proceeding with high levels of diastereoselectivity as classified into three reagent-based classifications: 1) cyclopropanations employing diazo compounds, 2) PL_3-mediated cyclopropanations, and 3) organocatalyzed formal [2 + 1]-cycloadditions.

Contents

1. Introduction

As a subset of the spirocyclic oxindole family, cyclopropyl spirooxindoles constitute a privileged molecular architecture, as they are prominent in a wide array of natural products and bioactive compounds [1]. For example, this motif is present in compounds that exhibit a diverse array of pharmacological effects, including the inhibition of NNRT-HIV1, anticancer activity, a treatment for diabetes and obesity, and vasopressin antagonists for the treatment of congestive heart failure, hyponatremia, and hypertension (Fig. 1a) [2]. In addition to their biological significance, they are also synthetically valuable intermediates in the construction of larger spirocyclic frameworks. For example, in 2000 and 2003 Carreira and coworkers completed the total syntheses of horsfiline and spirotryprostatin B, respectively, through the Lewis acid-mediated ring expansion of a spirocyclopropyl oxindole (Fig. 1b) [3]. Owing to its recognition as a potent and valuable pharmacophore, and in combination with the inherent challenge of constructing the quaternary spirocyclic center in a stereoselective fashion, the spirocyclopropyl oxindole core has inspired synthetic chemists to develop new strategies toward their assembly and design derivatives in search of new biologically active small molecules. In recent decades, numerous and distinctly different approaches have been published toward the construction of cyclopropyl spirooxindoles, comprised of both transition metal-catalyzed and metal-free protocols [1b,4].

While many efficient and elegant methods toward the transition

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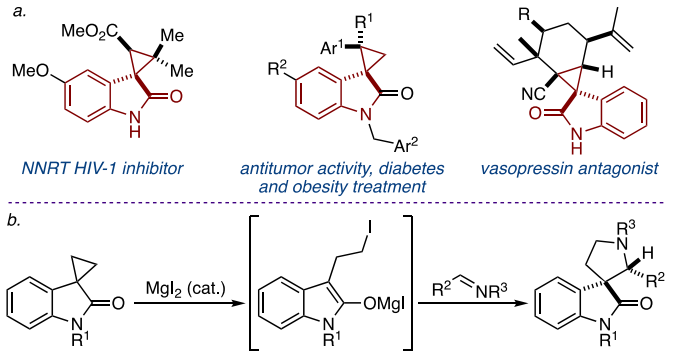


Fig. 1. Natural products inspired methods development: *a*. Selected biologically active cyclopropyl spirooxindoles. *b*. Carreira's MgI_2 mediated ring expansion towards the total syntheses of horsfiline and spirotryprostatin.

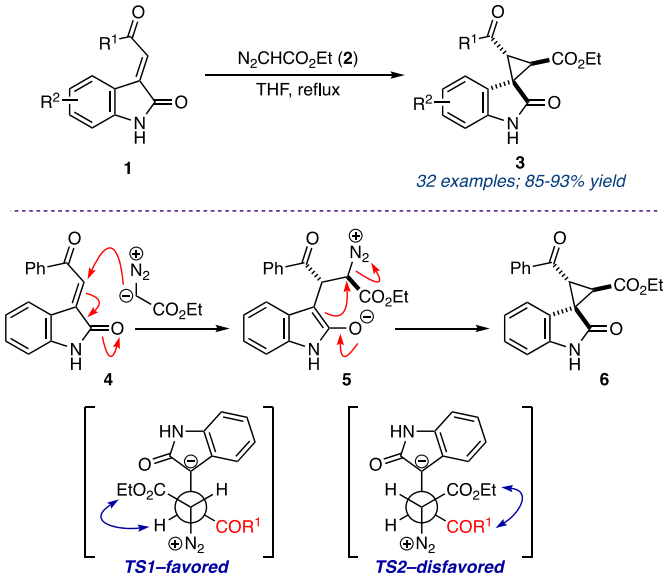
metal-catalyzed construction of cyclopropyl spirooxindoles exist [5], this review will focus on stereoselective, metal-free strategies.

Specifically highlighted are those [2 + 1] strategies that employ organocatalysts or stoichiometric organic-based reagents [6]. The cyclopropanation strategies herein are categorized into the following three reaction classifications: (1) metal-free cyclopropanations wherein diazo compounds are employed as the C1 component, (2) phosphorus-mediated, formal [2 + 1]-cycloadditions, and (3) organocatalyzed cyclopropanations.

2. Cyclopropanations employing diazo compounds

Diazo compounds are frequently employed as single carbon subunits in cycloadditions and cross coupling reactions [7]. These indispensable reagents in organic synthesis have effectively led to the formation of new C–C and C=C bonds with a diverse range of coupling partners. The generation of a stabilized carbenoid with transition metals such as Pd, Cu, Rh, Ni, Co, and Ir allows for efficient and controlled catalytic reactivity which is often rendered stereoselective through the utilization of chiral ligands. However, high levels of diastereoselectivity are achievable in the absence of expensive and often air-sensitive transition metal catalysts.

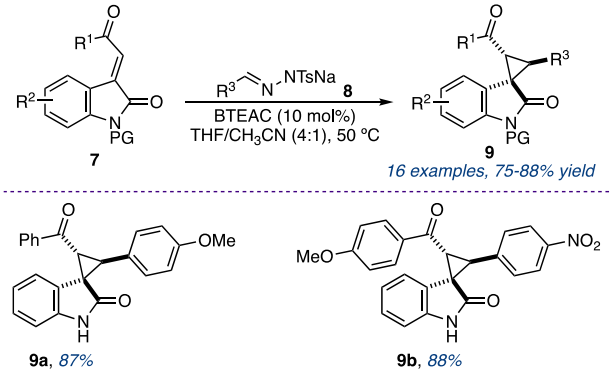
In 2014, Kamal and Maurya reported a catalyst-free cyclopropanation of electron deficient alkenes using ethyl diazoacetate [8]. Refluxing *E*-alkylidene oxindoles **1** with ethyl diazoacetate (**2**) in THF for 12 h resulted in the formation of exclusively the *anti*-cyclopropane **3** shown (Scheme 1). Several other cyclopropanes were synthesized in excellent yields (>85%) with comparable levels of diastereoselectivity. Substitution about the oxindole ring was well tolerated, with no significant change in product yield regardless of the presence of an electron donating or withdrawing group. Additionally, both alkyl esters and aryl ketone substituents on the oxindole alkylidene performed admirably in the formal [2 + 1]-cycloaddition. The high diastereoselectivity for this reaction is readily rationalized through the alleviation of steric interactions in the initial conjugate addition of diazoester **2** to the alkylidene in **1**. The addition of diazo **2** wherein the ester group orients *anti* to the carbonyl substituent on the alkylidene oxindole in **TS-1** avoids the unfavorable gauche interactions present in **TS-2** that would lead to the *cis* cyclopropane. Subsequent ring closure resulting from displacement of the diazonium through an intramolecular oxindole enolate addition provides the major *anti*-cyclopropane diastereomer **3** observed. In an attempt to broaden the applicability of this methodology, the ester/aryl group of the alkylidene was removed and replaced with an electron-neutral methyl group. Treatment of ethyl diazoacetate led to the anticipated *anti*-cyclopropane in 85% yield as a single stereoisomer. Interestingly, when



Scheme 1. Metal-free cyclopropanation of electron deficient alkylidene oxindoles with ethyl diazoacetate.

$Rh_2(OAc)_4$ was added to the reaction mixture, the authors observed uniformly lower yields and more limited structural diversity.

In 2014, Maurya and coworkers expanded upon this original study wherein readily available and bench stable hydrazone salts **8** were used in place of diazoesters to obtain the corresponding cyclopropanes (Scheme 2) [9]. Formation of the corresponding diazo compound *in situ* from the hydrazone yielded an operationally simpler protocol with a more widely accessible substrate scope. The reaction of alkylidene oxindole **7** with hydrazone salt **8** proceeded smoothly to afford *trans* cyclopropanes **9** in excellent yields (75–88%). Addition of benzyltriethylammonium chloride (BTEAC) increased the yield of the reaction by improving the solubility of the hydrazone salt under the reaction conditions. Mechanistically, the transformation is proposed to proceed through an initial [3 + 2]-



*IC_{50} (μM) of **10a** and **10b** against human cancer cell lines.*

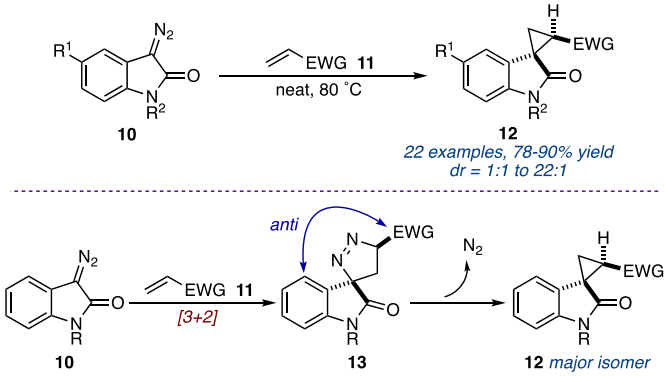
Compound	Hela	A549	DU-145
9a	9.332	20.12	8.709
9b	9.54	9.332	4.897
Doxorubicin	1.77	2.57	1.381

Scheme 2. Addition of hydrazone salts to alkylidene oxindoles.

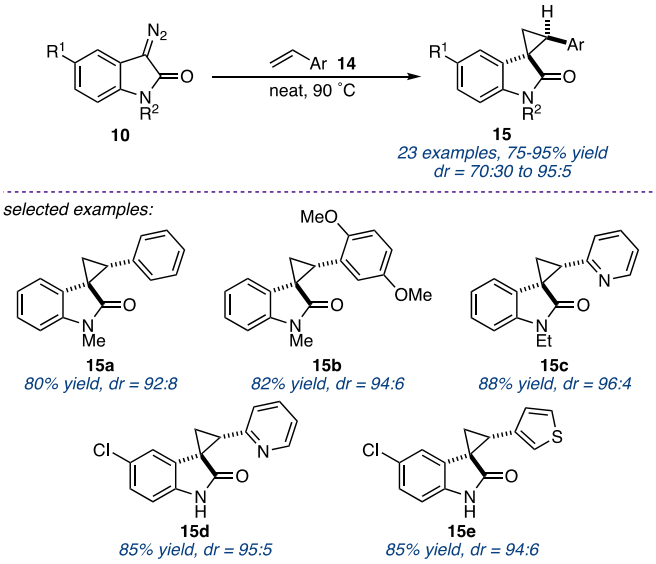
cycloaddition that leads to an intermediate pyrazoline. Subsequent loss of nitrogen with an overall net-retention of relative stereochemistry yields the diastereomerically enriched cyclopropane. Although not observed spectroscopically, a mechanism involving a pyrazoline intermediate is consistent with other comparable metal-free cyclopropanations [10]. *N*-Tosyl hydrazone salts of aromatic aldehydes bearing electron donating and withdrawing groups behaved well under the reaction conditions, while varying substitution patterns of oxindole **7** did not significantly impact product yields. All examples were obtained as diastereomerically pure compounds (*trans*) and were screened against three cancer cell lines: Hela (cervical cancer), A-549 (Lung cancer), and DU-145 (prostate cancer). Of those obtained, cyclopropanes **9a** and **9b** showed the most promising anticancer activity when compared against doxorubicin.

In 2014, Reddy published an efficient metal-free cyclopropanation of diazooxindoles with electron deficient alkenes in the absence of solvent (Scheme 3) [11]. Reactions of diazooxindole **10** with alkenes **11**, including acrylonitrile and methyl vinyl ketone, produced cyclopropanes **12** in 83–90% yields but comparatively low diastereoselectivities (dr = 1:1 to 3:1). The authors propose a mechanism that involves an initial [3 + 2]-cycloaddition between the diazo compound and alkene followed by a stereoretentive ring contraction driven by the expulsion of N_2. The selectivity of the reaction stems from a diastereoselective 1,3-dipole cycloaddition wherein sterics between the electron withdrawing substituent on alkene **11** and the arene of diazooxindole **10** are minimized. Various *N*-protecting groups on the diazooxindole, such as *N*-benzyl, *N*-Boc, and *N*-allyl, as well as bromo- and chloro-substituents at the C5 position, were well tolerated with no significant decrease in yield or diastereoselectivity. The reaction also proceeded with *N*-phenyl maleimides as electron-deficient cyclic alkenes to provide the corresponding highly substituted cyclopropanes in excellent yields (78–89%) and diastereoselectivities (>19:1 dr). Muthusamy and coworkers reported a similar approach to the cyclopropanation of diazooxindoles **10** with either mono-substituted or 1,2-disubstituted styrene derivatives **14** to yield aryl-substituted spirocyclopropyl oxindoles **15** in the absence of a transition metal catalyst (Scheme 4) [12]. Their work expanded the previously established substrate scope to include styrene and other heteroaromatic substituted alkenes with excellent yields and diastereoselectivities. They were able to leverage this method to establish a convergent route toward derivatives of cyclopropanes with known HIV-1 non-nucleoside reverse transcriptase inhibitor properties.

Employing an oxidative strategy to the *in situ* generation of diazo compounds from trifluoroethyl ammonium chloride **16**, Lu and Xiao reported the cyclopropanation of alkylidene oxindoles **7**

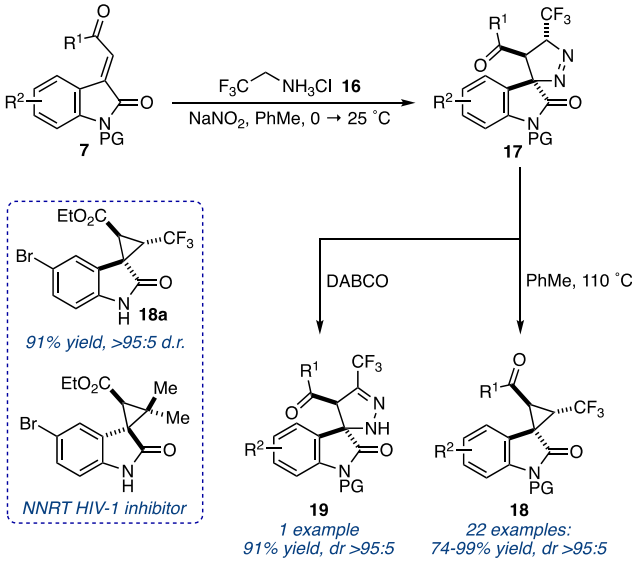


Scheme 3. Cyclopropanations of electron deficient alkenes with diazooxindoles.



Scheme 4. Diazooxindole cyclopropanation of styrenyl derivatives.

via a similar cycloaddition/ring contraction sequence (Scheme 5) [10b]. Formation of the corresponding cyclopropanes **17** proceeded with exceptional diastereoselectivity (≥95:5) in yields ranging from 79 to 99%. Halogen substitution about the oxindole ring was well tolerated and provided a functional handle for further synthetic manipulations. This protocol allows for operationally simple, metal-free access to medicinally relevant CF_3-substituted cyclopropanes **18**, which previously required the use of expensive transition metal complexes derived from rhodium, cobalt, and iron [13]. Incorporation of a CF_3 group onto carbocyclic and heterocyclic scaffolds often leads to improved lipophilicity, binding selectivity, and metabolic stability when compared to the non-CF_3 substituted analogs [14]. The authors leveraged this method in the synthesis of the CF_3-substituted cyclopropane **18a**, analog of a known HIV-1 NNRT inhibitor, in one step from commercially available materials. Interestingly, during their optimization studies, the authors noted an unusual 1,3-H shift from the intermediate [3 + 2]-cycloadduct when DABCO was used as the base to provide the CF_3-



Scheme 5. Incorporation of CF_3-substituted spirooxindole cyclopropanes.

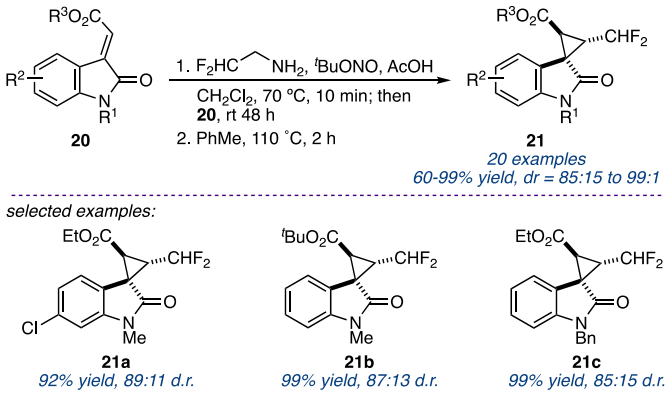
substituted spiropyrazoline oxindole **19**. This observation provides complimentary reactivity, allowing for the synthesis of oxindoles bearing either a spirocyclopropane or spiropyrazoline.

Han and Chen reported a comparable approach toward the synthesis of cyclopropanes **21** bearing difluoromethyl substituents via the oxidative *in situ* generation of the corresponding diazo compound derived from readily available $F_2HCCH_2NH_2$ (Scheme 6) [15]. The resulting difluoromethyl-substituted cyclopropanes **21** are of medicinal relevance as the acidic F_2C—H bond serves as a bioisostere of functional groups, such as alcohols and thiols [16]. The biological relevance of the products obtained was demonstrated through a preliminary evaluation of their activity against human prostate cancer cells (PC-3) and lung cancer cells (A549). While cyclopropane **21b** showed comparable activity to *cis*-platin against PC-3 (IC_{50}: 25.7 μM vs 23.7 μM), several others exhibited moderate activity, thereby highlighting the potential of this scaffold for the development of new anticancer therapeutics.

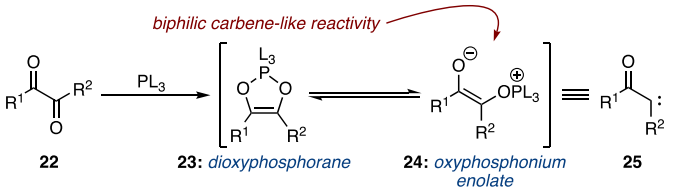
3. Phosphorus-mediated cyclopropanations

One biphilic C1 carbene surrogate that has drawn considerable interest recently arises from the addition of a phosphorus(III) reagent to a 1,2-dicarbonyl compound. Since its discovery in the 1960s, Kukhtin-Rameriz reactivity has become an indispensable tool in organic synthesis. The addition of a trivalent phosphorus compound to a 1,2-dicarbonyl **22** results in the formation of a penta-coordinate dioxaphosphorane adduct **23**, which exists in equilibrium with the corresponding phosphonium enolate **24** (Scheme 7) [17]. The equilibrium shifts from the closed phosphorane to the more reactive oxyphosphonium enolate with the use of sterically bulky ligands on phosphorus in more polar solvents [17f,18]. The biphilic reactivity of phosphorus adducts **23** and **24** mirrors that of an acyl carbene (**25**), which has been leveraged in the assembly of highly substituted cyclopropanes.

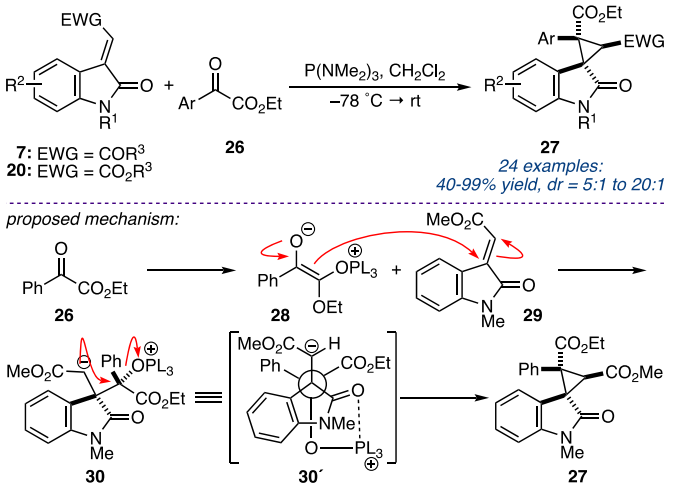
He and Ashfeld in 2014 independently reported the exploitation of the inherent biphilic reactivity of 1,2-dicarbonyls in the presence of phosphoramides in the synthesis of cyclopropyl spirooxindoles [19]. He and coworkers described the efficient and diastereoselective cyclopropanation of α-keto esters **26** or α-keto amides with $P(NMe_2)_3$ and an acyl alkylidene oxindoles **7/20** (Scheme 8) [19a]. The corresponding cyclopropanes **27** were obtained in moderate to high yields (40–99%) and diastereoselectivities (dr = 5:1 to 20:1). The authors proposed that the spirocyclic core is formed from a sequential conjugate addition/intramolecular S_N2 reaction, resulting in a *cis*-orientation of the aryl rings across the cyclopropane. The favored *cis* configuration is due to the minimization of steric interactions between the phosphonium cation and



Scheme 6. Installation of CHF_2-substituted cyclopropanes.



Scheme 7. Formal [4 + 1]-cycloadditions between PL_3 and 1,2-dicarbonyls.

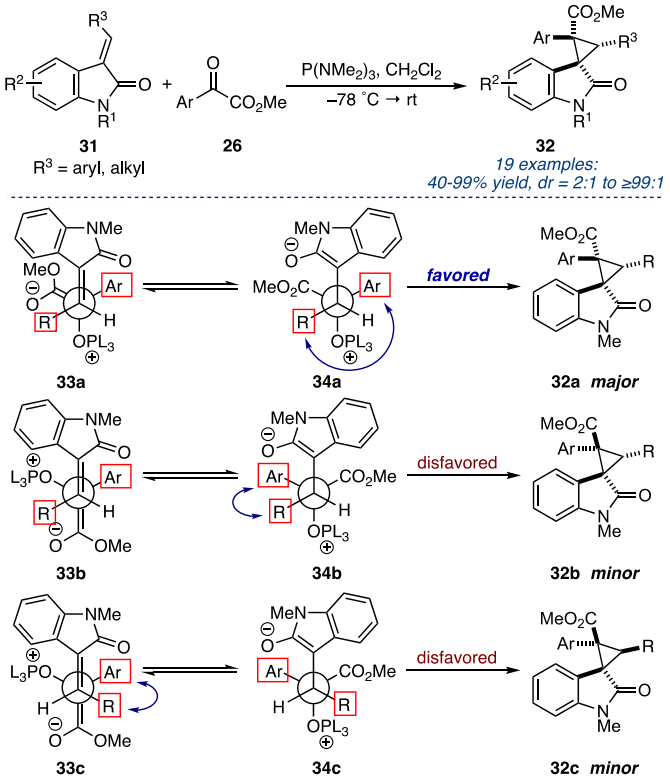


Scheme 8. $P(NMe_2)_3$-mediated alkylidene oxindole cyclopropanations employing α-keto esters.

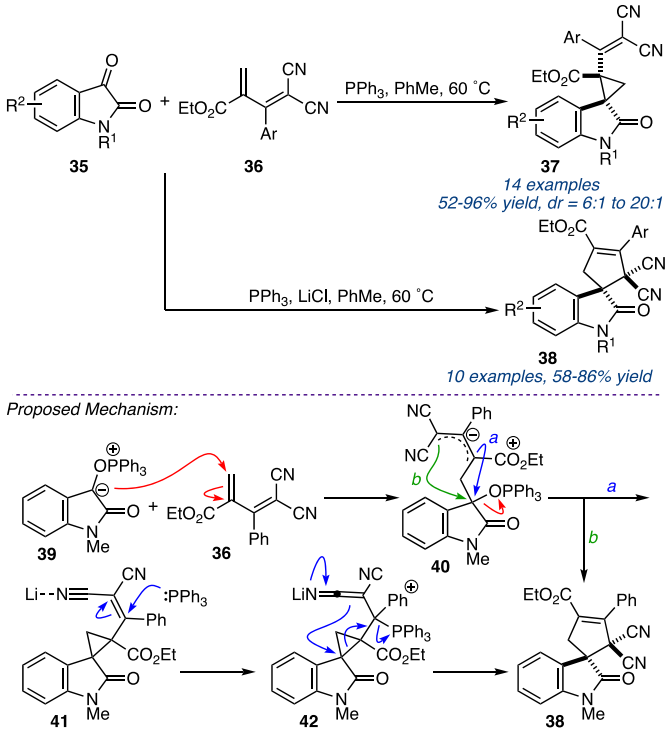
carbonyl oxygen of the oxindole in the subsequent S_N2 displacement as shown in transition state **30′**. In an effort to evaluate the utility of this method over conventional Rh(II)-catalyzed cyclopropanations, the authors compared the cyclopropanation of electron poor alkenes with methyl phenyl diazo ester and $Rh_2(OAc)_4$. Not surprisingly, the reactions routinely produced a complex mixture of products, indicating that the phosphorus-mediated approach showed considerable promise to promote the cyclopropanation of this challenging class of substrates.

Subsequently, work from our lab revealed that the generation of dioxaphospholenes from 1,2-dicarbonyls and $P(NMe_2)_3$ resulted in the efficient cyclopropanation of aryl *E*-alkylidene oxindoles **31** without the need for an additional electron withdrawing β-ester substituent (Scheme 9) [19b]. The corresponding cyclopropanes **32** were obtained in modest to excellent yields and diastereoselectivities (up to 98:2). A variety of functional groups substituting the oxindole arene ring were well tolerated. In contrast to the diastereoselectivities observed by He and coworkers, the presence of a β-aryl substituent in place of an alkyl ester on the *E*-alkylidene oxindole resulted in formation of an epimeric major diastereomer **32** wherein the oxindole arene and β-aryl groups reside in an *anti*-orientation of the aryl rings across the cyclopropane. The stereochemical outcome of the cyclopropanation proved heavily dependent on the starting geometry of the alkylidene oxindole. For example, when the corresponding *Z*-alkylidene was employed, the major diastereomer was found to be the *syn*-cyclopropane with respect to the 1,2-dicarbonyl aryl substituent and the arene of the oxindole.

This complementary stereochemical outcome is likely due to the chemoselectivity of the initial conjugate addition of the oxyphosphonium enolate to the alkylidene oxindole. He proposed that in the presence of an alkylidene β-ester substituent, nucleophilic attack occurs in a stereoselective 1,4-fashion to the alkyl ester at C3



Scheme 9. $P(NMe_2)_3$-mediated cyclopropanations of β-aryl substituted alkylidene oxindoles.

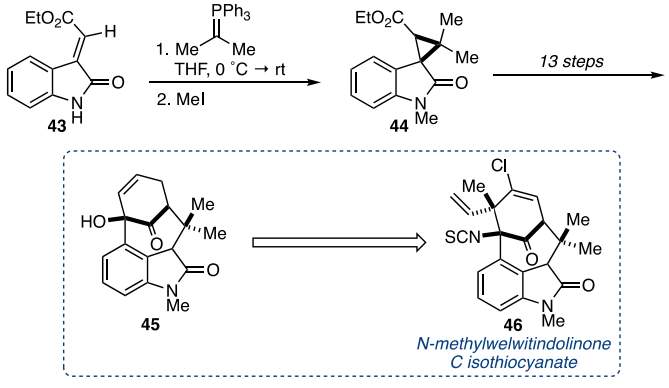


Scheme 10. PPh_3-mediated cyclopropanations employing isatins.

of the oxindole. In contrast, alkylidene oxindole **31** with an aryl substituent at R^3 undergoes 1,4-addition at the exocyclic β-position resulting in oxindole enolates **34a-34c** via the three most likely transition states **33a-c**, in which the initial C–C bond formation event has a direct impact on the stereoselectivity of the cyclopropanation. Gauche interactions are minimized in transition state **33a** and subsequent intermediate **34a** compared to those present in transition states **33b**/**34b** and **33c**/**34c**, leading to a preferential formation of the *trans* cyclopropane **32a** over **32b/c**. Minimization of unfavorable steric interactions between β-alkylidene oxindole substituent and aryl group on the 1,2-dicarbonyl appear to govern the diastereoselectivity observed.

In 2017, Xu reported a triphenylphosphine-mediated cyclopropanation between isatins **35** and electron deficient dienes **36** (Scheme 10) [20]. Xu and coworkers exploited the embedded α-keto amide framework of isatin derivatives and combined it with an electron deficient alkene. A wide array of isatins were employed that provided the desired cyclopropanes **37** in good to excellent yields (52–96%) and diastereoselectivities ranging from 6:1 to >20:1. However, it is notable that the cyclopropanation event proved sensitive to varying electronic substitution patterns across the electrophilic alkene **36**. For example, while electron rich aryl substituents afforded products in high yields, the corresponding electron poor aryl substitution underwent cyclopropanation in diminished yields. During optimization studies, the authors noted that the addition of excess LiCl led to exclusive formation of cyclopentene **38** in good to excellent yields. Cyclopropane **37** is proposed to arise from an initial conjugate addition of oxyphosphonium enolate **39** to the α,β-unsaturated ester **36** followed by ring closure of the ester enolate **40** via the indicated path *a*. However, Lewis acid activation of the cyano groups in **41** promotes a second conjugate addition event by excess PPh_3 that then enables the resulting nitrile enolate **42** to undergo an intramolecular nucleophilic addition to the spirocyclopropyl oxindole, with concomitant phosphonium cation displacement, to form the spirocyclpentenyl oxindole **43**. Alternatively, further stabilization of the allyl anion in **40** by the Lewis acidic Li^+ may promote a thermodynamically controlled cyclopentane formation directly via path *b*.

The welwitindolinone alkaloids, known for their wide range of biological activity, have challenged synthetic chemists for decades in the construction of their highly functionalized tetracyclic scaffold, characterized by the bicyclo[4.3.1]decane ring system. *En* route to **45**, a precursor of *N*-methylwelwitindolinone C isothiocyanate that bears the natural product's entire carbon skeleton, Wood and coworkers treated enoate **43** with isopropyl triphenylphoshorane and methyl iodide to cleanly and selectively furnish cyclopropane **44** (Scheme 11) [21]. Saponification of the ester with LiOH followed by an acidic work up provided the corresponding acid in 79% yield over four steps.

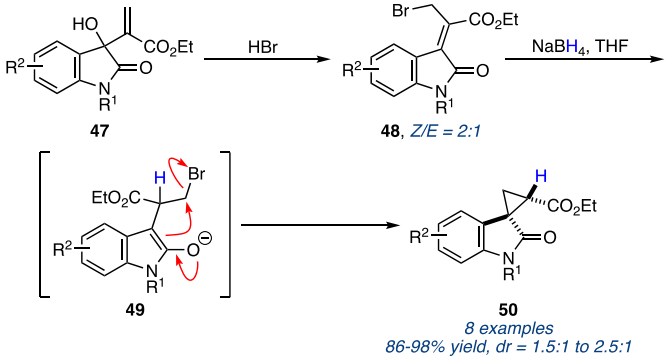


Scheme 11. Cyclopropanation of enoate **43** towards the synthesis of **45**.

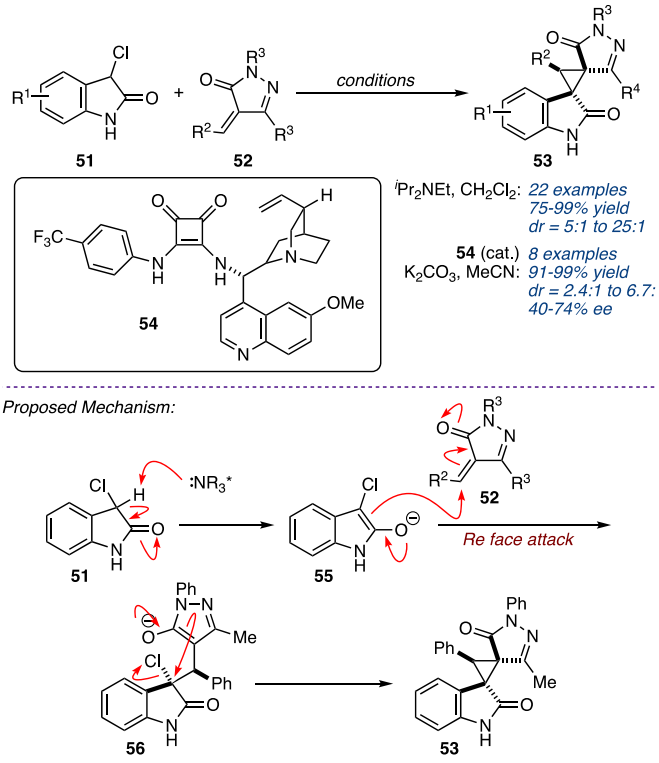
4. Organocatalyzed cyclopropanations

The development of organocatalyzed reaction processes for the synthesis of complex molecules continues to be an area of interest and growth as more organocatalysts that enable the ready generation of optically enriched small molecules of therapeutic value become commercially available [22]. As a result, it is not surprising that many groups have sought to develop enantioselective, organocatalyzed strategies for the formation of cyclopropyl oxindoles in an effort to avoid the use of more expensive and potentially toxic chiral transition metal complexes. To that end, Shanmugam and coworkers demonstrated in 2006 the utility of isatin derived Morita-Baylis-Hillman adducts **47** to undergo reductive cyclizations to provide spirocyclopropyl oxindoles **50** (Scheme 12) [23]. Addition of methyl acrylate to *N*-methyl isatin in the presence of catalytic DABCO resulted in formation of allyl alcohol **47**, which underwent ionization and subsequent net S_N2' bromination in the presence of HBr to give alkylidene oxindole **48** as a mixture of *Z*/*E* isomers in a 2:1 ratio. Treatment of this mixture with $NaBH_4$ provided cyclopropane **50**, also in a 2:1 ratio of diastereomers. The diastereoselectivity of the reductive cyclization event proved independent of the starting olefin geometry of **48**. The observation that the same ratio of cyclopropane diastereomers was produced regardless of which alkene isomer was subjected to the reductive cyclization would indicate the common mechanistic intermediate **49**. This method effectively promoted cyclopropane formation in excellent yields (86–98%) from *N*-benzyl and *N*-propargyl isatins and acrylonitrile Morita-Baylis-Hillman adducts of isatin. However, a notable limitation of this strategy is the reliance on the use of isatin derivatives to provide the corresponding cyclopropanes as Morita-Baylis-Hillman adducts derived from aryl aldehydes failed to undergo cyclopropanation.

Subsequently, Du and coworkers employed oxindole derivatives, namely 3-chlorooxindoles **51**, as the nucleophilic component in a cascade conjugate addition/alkylation cyclopropanation of arylidene pyrazolones **53** (Scheme 13) [24]. Upon exposure to base, the resulting 3-chlorooxindole enolate **55** underwent a *re*-face selective addition to pyrazolone **52**. A subsequent intramolecular displacement of chloride in intermediate **56** provided the cyclopropane diastereomer **53** in diastereoselectivities ranging from 5:1 to 25:1. The pyrazolone scaffold was targeted as it is an important motif exhibiting significant anti-inflammatory, antiviral, antitumor, and antibacterial properties [25]. The reaction tolerates various aryl-substituted pyrazolones and electron deficient isatin derivatives to give the desired cyclopropanes in 75–99% yield. An enantioselective variant of this strategy was developed that employed bifunctional squaramide catalyst **54**. Treatment of chlorooxindoles **51** and arylidene pyrazolones **52** with



Scheme 12. Reductive cyclization of oxindole allyl bromides.

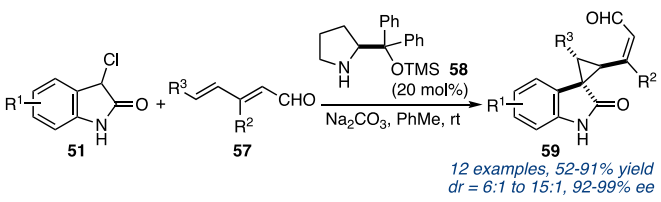


Scheme 13. Synthesis of pyrazolone spirooxindole cyclopropanes.

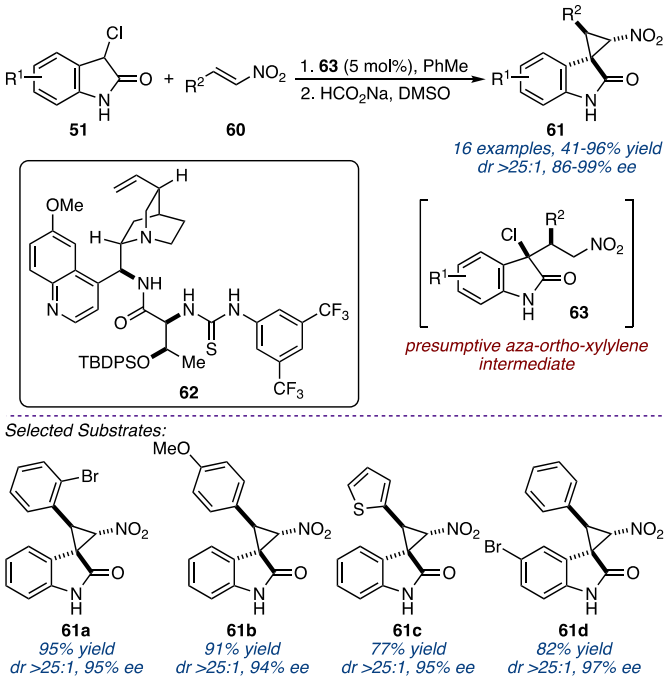
squaramide catalyst **54** and K_2CO_3 led to formation of cyclopropanes **53** bearing three contiguous stereocenters, including two vicinal quaternary centers, with modest levels of enantioinduction (≤74% *ee*), excellent yields (91–99%), and modest diastereoselectivity (dr ≤ 6.7:1).

Melchiorre and coworkers exploited a comparable cascade process with 3-chlorooxindoles **51** and dienals **57** catalyzed by proline derivative **58** (Scheme 14) [26]. This method is a rare example of a highly selective, asymmetric 1,6-addition to 2,4-dienals. The exclusive ∂-site selectivity of this addition is controlled by the presence of a directing group at the β-dienal position. Various arene substitutions on the 3-chlorooxindole **51** were well tolerated, as were variations at the R^2 position of the 2,4-dienal **57**, giving cyclopropanes **59** in good to excellent yields of 52–91%, d.r. from 6:1–13:1, and excellent enantioselectivies between 92 and 99% *ee*.

Similarly, Lu and coworkers showed that the addition of 3-chlorooxindoles **51** to nitroolefins **60** in the presence of the bifunctional chiral Bronsted acid/base catalyst **62** efficiently led to formation of optically enriched nitro-substituted cyclopropanes **61** after treatment with sodium formate (Scheme 15) [27]. An initial conjugate addition of the C3-oxindole anion to **60** presumably leads to formation of the aza-*ortho*-xylylene intermediate **63** that then undergoes chloride displacement to provide the desired



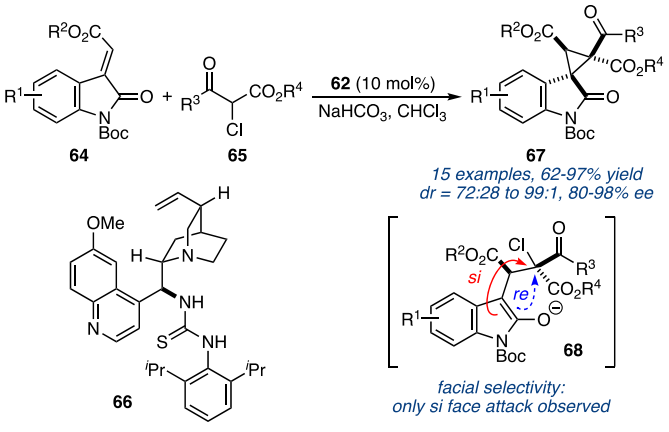
Scheme 14. Cyclopropanations of 2,4-dienals.



Scheme 15. Synthesis of nitro cyclopropyl oxindoles.

spirocyclopropyl oxindoles **61** in modest to excellent yields (41–96%), excellent diastereoselectivity (>25:1) and high levels of enantiocontrol stereocontrol (86–99% *ee*). Variations in the electronics of the nitroolefin, including both electron donating and withdrawing groups and heteroaromatic rings, were well tolerated. Halogen substitution at the 5- and 6-positions of the oxindole also provided the spirocyclopropanes in good yields and stereoselectivity. Impressively, this methodology is the first report of an intramolecular trapping of an aza-*ortho*-xylylene intermediate, whereas previous reports employed external carbon or heteroatom nucleophiles.

Employing alkylidene oxindoles **64**, Malkov demonstrated that impressive levels of stereocontrol could be obtained in the formation of cyclopropanes **67** with ethyl 2-chloroacetoacetates **65** by employing the quinine-derived thiourea catalyst **66** (Scheme 16) [28]. Various substitution patterns on the oxindole arene of **64** were well tolerated to provide adducts **67** in excellent yields (82–97%),

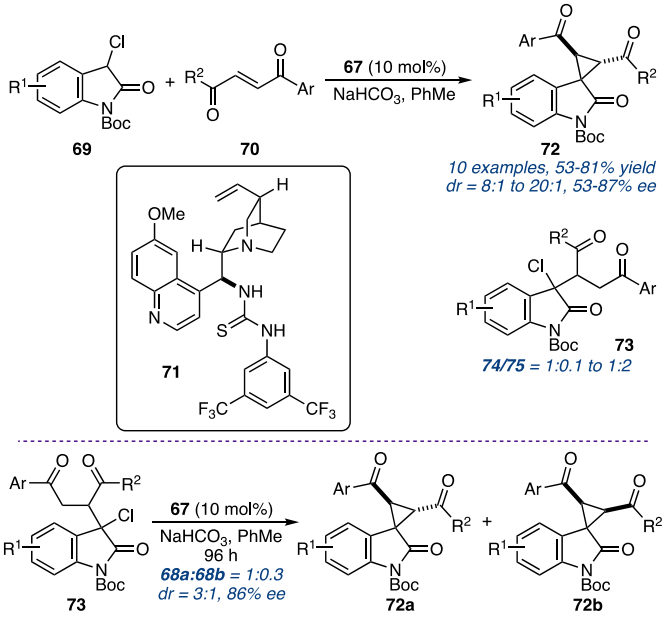


Scheme 16. α-Chloroketones as single carbon components in the cyclopropanation of alkylidene oxindoles.

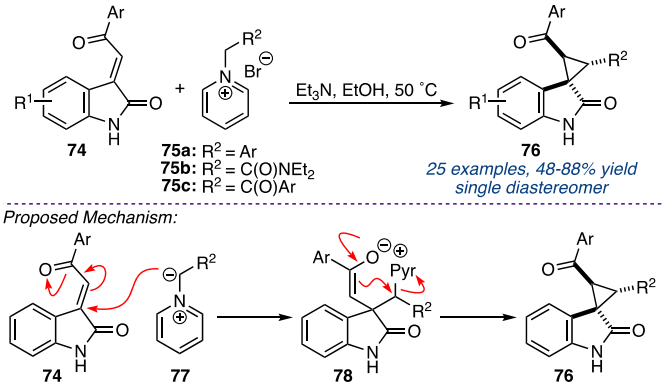
diastereoselectivity (91:9–97:3), and enantioselectivities (87–97% *ee*). The reaction mechanism follows a familiar path that includes an initial conjugate addition of the enolate derived from **65** to exocyclic β-carbon of alkylidene oxindole **64**, generating two stereogenic centers in intermediate **68**, which is followed by a stereoselective, intramolecular chloride displacement. The authors propose that the catalyst **66** favors *si* facial attack through a well-defined transition state characterized by thiourea H-bond donation to the oxindole *N*-acyl group, while the pendant quinuclidine deprotonates the β-dicarbonyl nucleophile.

In 2014, Kanger and coworkers reported an enantioselective cyclopropanation of *N*-Boc protected 3-chlorooxindoles **69** employing an unsaturated 1,4-diketone **70** in the presence of chiral thiourea catalyst **71** (Scheme 17) [29]. In a mechanistically similar fashion to that proposed by Malkov, chlorooxindole **69** undergoes a conjugate addition to unsaturated 1,4-diketone **70**, followed by an intramolecular nucleophilic chloride displacement to provide cyclopropane **72**. With *symmetrical* 1,4-diketones, a mixture of the spirocyclopropyl oxindole **72** and uncyclized Michael adduct **73** were observed, although the desired spirocyclopropane was the major product. However, *unsymmetrical*, unsaturated 1,4-diketones led to formation of a single regioisomer. In each case, the desired cyclopropanes **72** were obtained in good yields (58–81%), diastereoselectivity (dr = 8:1 to 20:1), and enantioselectivity (≤87% *ee*). Uncyclized products **73** could be converted to a mixture of cyclopropane diastereomers **72a**/**b** in the presence of catalyst **71** and base, albeit sluggishly, indicating the importance catalyst/substrate interactions during the cascade reaction.

Pyridinium salts **75** as precursors to pyridinium ylides **77** were used in conjunction with 3-phenacylidendoxindoles **74** to synthesize *anti*-cyclopropanes **76** by Yan and coworkers in 2013 (Scheme 18) [30]. Both *p*-nitrobenzyl pyridinium (**75a**) and *N*-diethylcarbamoylmethyl pyridinium bromides (**75b**) proceeded to give the corresponding diastereomerically pure cyclopropanes in good to excellent yields (54–88%). A conjugate addition of the pyridinium ylide **77** to the 3-position of the 3-phenylacylideneoxindole **74** preceded an intramolecular C-alkylation of the resulting enolate **78** to provide the anticipated cyclopropane **76**. Interestingly, when *N*-phenacyl pyridinium bromides



Scheme 17. Cyclopropanations of 3-chlorooxindoles.

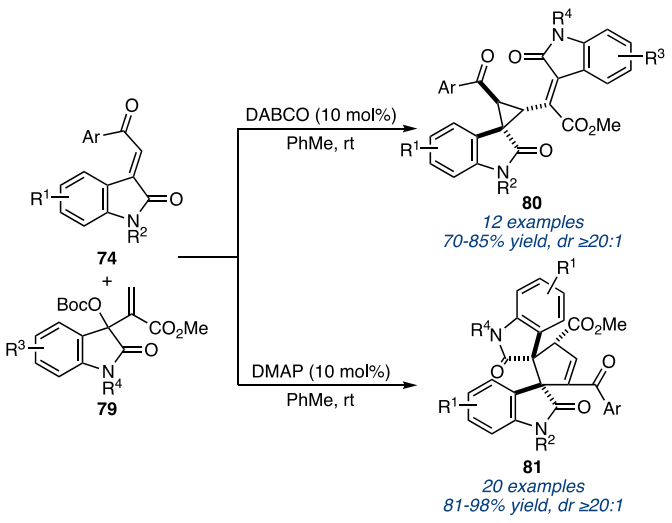


Scheme 18. Pyridinium ylide-mediated cyclopropanations.

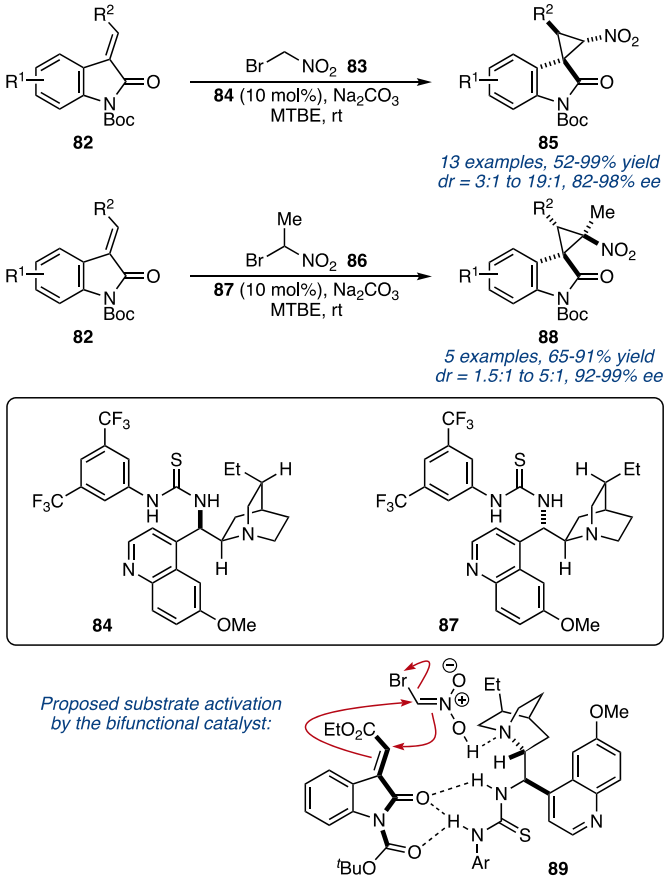
75c were employed, 3-(2-hydroxyfuran-3(2H)-ylidene)oxindoles were produced as significant byproducts. The formation of these furanyl oxindoles likely proceeds via initial conjugate addition of the pyridinium ylide to the exocyclic carbon atom of the 3-phenacylideneoxindole that then initiates sequential pyridine elimination of pyridine and carbonium ion ring closure to form the C=C bond. Similar reactivity has been seen in the addition of malonitrile to the exo-methylene atom of 3- phenacylideneoxindoles, as reported by Otomasu [31].

In 2018, Bhat reported an intriguing catalyst-controlled annulation reaction between 3-methyleneoxindoles **74** and isatin-derived Morita-Baylis-Hillman carbonates **79**, resulting in a formal [2 + 1]-cycloaddition in the presence of DABCO or [3 + 2] adducts with DMAP to access two architecturally distinct spirooxindole frameworks (Scheme 19) [32]. Both conditions afforded the corresponding spirocyclopropyl oxindole **80** or cyclopentenyl bis-spirooxindoles **81**, respectively, in excellent yields (70–98%) and diastereoselectivity (>20:1). The reaction is proposed to proceed via an allylic displacement of BocO by the nucleophilic amine in an S_N2' fashion on **79** followed by nitrogen ylide formation and a conjugate addition to enone **74**. At this stage, an intramolecular C-alkylation provides cyclopropane **80**, whereas the cyclopentenyl bis-spirooxindole **81** undergoes an additional intramolecular Michael addition, followed by a 1,3-proton shift leading to product after catalyst release. The cause for this catalyst dependent regioselective alkylation is unknown at present and constitutes an additional avenue of exploration into this intriguing cyclization event. However, the conditions were quite tolerant to mild electronic perturbations about the oxindole core, which also had no observable impact on the resulting diastereoselectivities.

Bartoli and Bencivenni reported a chiral base-mediated tandem conjugate addition/alkylation sequence for the one-step synthesis of enantioenriched cyclopropyl spirooxindoles **85** and **88** with three contiguous stereocenters from nitroalkanes and *N*-acyl-alkylidene oxindoles **82** (Scheme 20). The bifunctional nature of catalysts **84** and **87** employed was critical to achieving high levels of stereoselectivity and product yields by simultaneously activating the *N*-acyl oxindole via hydrogen bonding, as shown in transition state **89**, while the tertiary amine activated the halonitroalkanes **83** and **86** as nucleophiles in the conjugate addition step. The reaction of alkylidene oxindole **82** with bromonitromethane (**83**) led to formation of cyclopropane **85** in moderate to excellent yields (52–99%), good to excellent diastereoselectivities (dr = 3:1 to >19:1), and impressive enantiocontrol (≤98% *ee*). Notably, the opposite enantiomer of **85** could be obtained by utilizing catalyst **87**, the pseudo-enantiomeric form of **84**. In contrast, employing bromonitroethane (**86**) led to the formation of highly substituted cyclopropanes **88** in high yields (65–91%) and optical purity (92–99% *ee*) with moderate diastereoselectivity (dr = 1.5:1 to 5:1) for the assembly of two adjacent stereocenters in a single operation.



Scheme 19. Divergent synthesis of spirocyclopropyl oxindoles and cyclopentenyl bis-spirooxindoles.



Scheme 20. Construction of nitro-bearing cyclopropanes via a bifunctional activation modality.

5. Conclusion

The pharmaceutical potential of spirooxindole frameworks, specifically those bearing a spirocyclopropyl ring, has led to a dramatic increase in the number of methods to stereoselectively assemble these motifs in recent years. This review covers those transition metal-free synthetic approaches that include cyclopropanations starting from diazo compounds, phosphorus-mediated cycloannulations, and organocatalyzed strategies. Despite the absence of a well-defined transition metal complex, the methods highlighted here provide the desired cyclopropane bearing scaffolds with significant diastereoselectivity, and in those cases that employ a chiral organocatalyst, enantioselectively. The ready availability of many starting materials, employment of mild reaction conditions, and modest operational cost of these methods should result in an increase in both academic and industrial use of these approaches to access high-value spirooxindole cyclopropanes. Despite incredible advances over a relatively short period of time, opportunities for future work in this area include outstanding complications in product distribution and substrate diversification outside specific well-tolerated aryl and alkyl substitution patterns. Given the translational relevance of cyclopropyl sprirooxindoles, the development of new and complementary strategies for the stereoselective assembly of highly functionalized adducts will likely draw the attention of synthetic chemists for years to come.

Acknowledgments

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