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## Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks

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### 1. INTRODUCTION

Indoline-2,3-dione or indole-1*H*-2,3-dione (Figure 1), commonly known as isatin, is a well-known natural product found

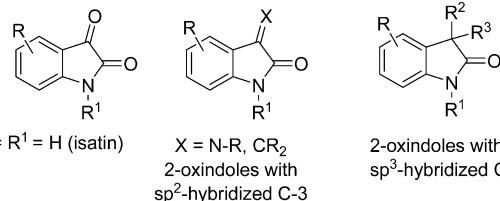


Figure 1. Structure of isatin and isatin-derived 2-oxindoles.

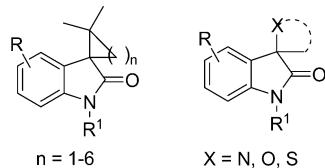
in plants of genus *Isatis* and in *Couropita guianensis aubl.*<sup>1,2</sup> It has also been isolated as a metabolic derivative of adrenaline in humans.<sup>3,4</sup> It was first obtained as an oxidation product of indigo in the early 19th century, and its current structure was proposed by Kekule.<sup>5</sup> Currently, isatin itself and many substituted isatins are commercially available at easily affordable prices. An extensive investigation on the synthesis and reactivity of isatins, possessing an indole motif with a ketone and a  $\gamma$ -lactam moiety, has unfolded many interesting aspects of organic reactions and mechanisms. It undergoes electrophilic aromatic substitution at positions C-5 and C-7 of the phenyl ring, *N*-substitutions, nucleophilic additions onto the C-3 carbonyl group, chemoselective reductions, oxidations, ring-expansions, and spiro-annulations, etc.<sup>1</sup> The unique potential of isatins to be used both as an electrophile and nucleophile and their easy availability have made them valuable building blocks in organic synthesis. Syntheses of several heterocyclic frameworks of biological significance such as pyrrolidines, quinolines, indoles,  $\beta$ -lactams, and 2-oxindoles, etc. have been developed using isatins as substrates. The chemistry of isatins was reviewed for the first time by Sumpter<sup>6</sup> and later updated by Popp<sup>7</sup> and by Silva et al.<sup>1</sup> Recent literature shows resurgence of interest in the chemistry and bioactivity of isatin derivatives leading to improvement in procedures of several already known reactions, development of stereoselective methodologies, and synthesis of isatin derivatives with various biological activities such as anticonvulsant,<sup>8</sup> antimicrobial,<sup>9</sup> antitumor,<sup>10</sup> antiviral,<sup>11</sup> anti-HIV,<sup>12</sup> and antitubercular.<sup>13,14</sup>

The most fascinating application of isatins in organic synthesis is undoubtedly due to the highly reactive C-3

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carbonyl group that is a prochiral center as well. The reactions of the C-3 carbonyl group of isatins, mostly by nucleophilic additions or spiroannulation, transform it into 2-oxindole derivatives (Figure 1). 2-Oxindoles, especially those which are spiro-fused to other cyclic frameworks (Figure 2), have drawn



**Figure 2.** Carbo- and heterocyclic frameworks spiro-fused to 2-oxindoles.

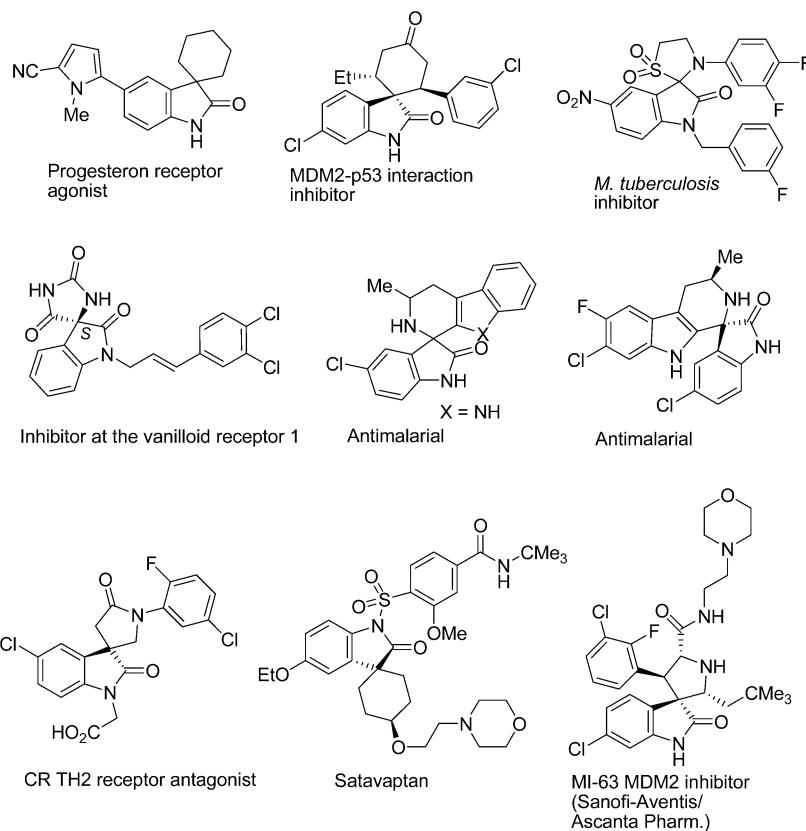
tremendous interest of researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide because they occur in many natural products such as spirotryprostins, horsfiline, gelsemine, gelseverine, rhynchophylline, and elacamine, etc. (see section 3) and have been reported to have various types of bioactivity (Figure 3)<sup>15</sup> such as progesterone receptor modulators,<sup>16</sup> anti-HIV,<sup>17</sup> anticancer,<sup>18</sup> antitubercular,<sup>19</sup> antimalarial,<sup>20,21</sup> and MDM2 inhibitor.<sup>22</sup>

The architecture of a spiro-cyclic framework has always been a challenging endeavor for synthetic organic chemists because it often requires synthetic design based on specific strategies. Due to steric strain, the presence of a spiro carbon atom induces easy rearrangements that can lead to different cyclic compounds. Under such a complex scenario, isatins constitute perhaps the single class of heterocyclic compounds which has been employed so extensively, either directly or via 3-

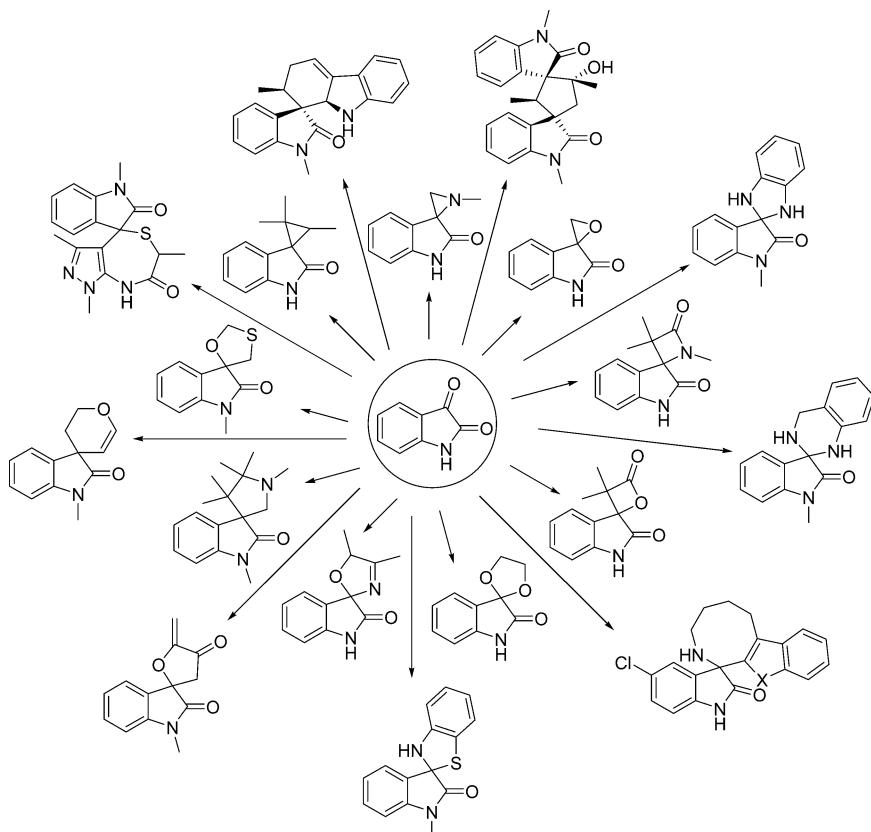
substituted 2-oxindoles, in design and synthesis of spiro-cyclic frameworks, both carbocyclic and heterocyclic, of diverse types (Figure 4). An extensive investigation on this aspect of isatins' chemistry during the past decade has led to successful design and synthesis of diverse types of heterocyclic and carbocyclic compounds with a spiro-fused 2-oxindole ring containing many stereocenters on one hand and discovery of many interesting facets of organic synthesis design on the other hand that need to be comprehensively reviewed.

Recent years have witnessed emergence of asymmetric synthetic methods employing chiral auxiliaries or chiral catalysts with good stereocontrol furnishing products containing spiro-fused rings with superb enantioselectivity. In many cases, simple chemical transformations of the initially formed spiro-oxindoles have been performed to achieve spiro-oxindoles with different functionality. Some review articles on asymmetric synthesis of C-3-functionalized oxindoles by asymmetric catalysis,<sup>15,23</sup> synthesis of 3,3-disubstituted oxindoles by transition metal-mediated cyclization of anilides,<sup>24</sup> synthesis of spiro-cyclopropane-2-oxindoles through enantioselective cyclopropanation of oxindoles,<sup>25</sup> and enantioselective methodologies for the synthesis of spiro compounds<sup>26</sup> have been published recently, but none of them focus on application of isatins in design and synthesis of different kinds of spiro-cyclic frameworks in detail.

This article aims to review for the first time the chemistry of isatins employed in design and synthesis of different types of compounds containing spiro-fused heterocyclic or carbocyclic rings with greater emphasis on recent literature. A brief overview of isatins' C-3 carbonyl group reactivity applicable to synthesis of substrates used in the construction of spiro-cyclic



**Figure 3.** Selected biologically important spiro-cyclic compounds possessing 2-oxindole motif.



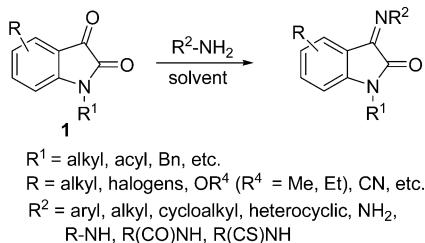
**Figure 4.** Selected spiro-fused heterocyclic and carbocyclic frameworks from isatin.

frameworks will be followed by applications of isatins and its derivatives in the synthesis (including asymmetric synthesis) of heterocyclic and cycloalkyl compounds spiro-fused to 2-oxindoles. The biological relevance of products will be emphasized wherever necessary.

## 2. AN OVERVIEW OF C-3 CARBONYL GROUP REACTIVITY

The synthetic endeavors to C-3 functionalized 2-oxindoles from isatins exploit the reactivity of the C-3 carbonyl group in isatins **1** with nucleophiles (Scheme 1). Some of the well-known

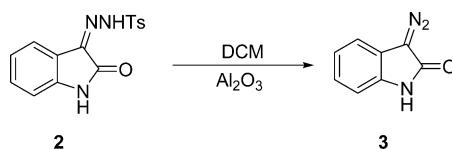
**Scheme 1**



reactions include the reactions of the ketone carbonyl group with nitrogen nucleophiles such as amines, hydrazines, semicarbazides, and thiosemicarbazides forming the imines,<sup>27</sup> hydrazones,<sup>28</sup> semicarbazones,<sup>29</sup> and thiosemicarbazones,<sup>30</sup> respectively. In many cases, isatins react with these nucleophiles even in the absence of any catalyst either at room temperature or by heating for a few hours. An efficient methodology for synthesis of isatin-3-oximes under Bronsted or Lewis acid catalysis in imidazolium-based ionic liquid solvent is reported.<sup>31</sup>

2-Oxindoles having azomethine linkage at its C-3 position are of special interest in the synthesis of spiro-frameworks as they can be easily transformed further into useful products that serve as substrates for spiro-cycle synthesis. For example, isatin-3-N-tosylhydrazone **2** is easily transformed to 3-diazoisatin **3** (Scheme 2),<sup>32</sup> that has been employed in several syntheses as

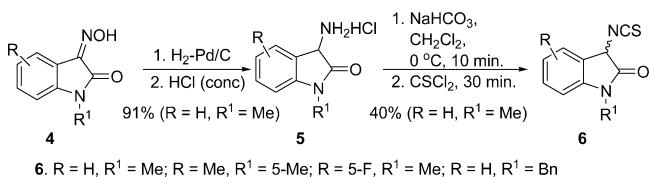
**Scheme 2**



carbene precursor via metal-carbenoids.<sup>11,33</sup> Isatin-3-oximes **4** are catalytically reduced to 3-amino-2-oxindole **5** which on treatment with thiophosgene leads to the formation of 3-isothiocyanato-2-oxindoles **6** (Scheme 3). The latter compounds have been employed diligently in asymmetric synthesis of spiro-heterocycles.<sup>34,35</sup>

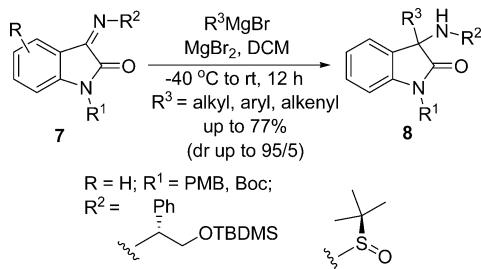
There are several recent reports on reactions of isatin imines leading to the formation of quaternary 3-amino-2-oxindoles.

**Scheme 3**



Isatin-3-imines and isatin-3-hydrazone are reported to furnish quaternary 3-aminooxindoles **8** by allylation and propargylation under the influence of indium and zinc catalysts, respectively, in aqueous media.<sup>36</sup> Some other methods for the synthesis of 3-substituted 3-amino-2-oxindoles involve triethylborane-induced intermolecular alkyl radical addition to *N*-methylisatin-3-hydrazone/imines<sup>37</sup> and the addition of the Grignard reagents to chiral *N*-protected isatin-3-imines **7** (Scheme 4).<sup>38</sup> The

Scheme 4

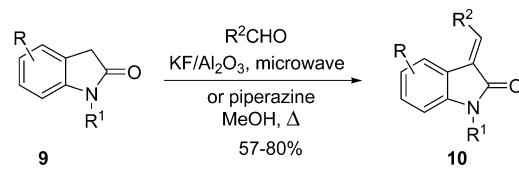


addition of alkynes to *N*-*tert*-butylsulfinylimine of isatins is also reported through dialkylzinc.<sup>39</sup> The Mannich reaction of *N*-protected isatin-3-imines with hydroxyacetone in the presence of a chiral primary amino acid catalyst is reported to yield 3-amino-2-oxindoles.<sup>40</sup> Both *anti*- and *syn*-Mannich adducts are obtained in high yields (up to 98%), good diastereoselectivities (dr: *anti/syn* = 90/10), and enantioselectivities (ee: 99% *anti*). A novel AgOAc-catalyzed vinylogous Mannich reaction between isatin imines and trimethylsilyloxyfuran is reported to yield the quaternary 3-amino-2-oxindoles in excellent yields and dr (94–99%, dr 99:1).<sup>41</sup> An enantioselective addition of 1,3-dicarbonyl compounds to *N*-alkoxycarbonyl ketimines of isatins is reported to occur in the presence of chiral thiourea bearing cinchona alkaloid moiety affording chiral 3-amino-2-oxindoles (up to >99% yield and up to 98% ee).<sup>42</sup> Feng and co-workers have reported the first asymmetric aza-Friedel-Crafts reaction of pyrroles and indoles with isatin-derived *N*-Boc ketimines catalyzed by chiral phosphoric acids to afford the 3-amino-2-oxindoles in high yields (up to 98%) and with excellent enantioselectivities (up to 98%).<sup>43</sup> These compounds would definitely be a valuable addition in the arsenal of building blocks for novel spiro-fused cyclic compounds.

The carbon analogs of the 3-azomethine-2-oxindoles, 3-alkylidene-2-oxindoles, frequently employed in the synthesis of spiro-fused cyclic frameworks, are synthesized by different methods. For example, the reaction of 2-oxindoles **9**, which in turn can be obtained by chemoselective reduction of isatins,<sup>44–46</sup> with aldehydes under basic conditions either in microwave<sup>47</sup> or by conventional heating in methanol affords 3-alkylidene-2-oxindoles **10** (Scheme 5).<sup>48</sup> Some more direct approaches to the synthesis of 3-alkylidene-2-oxindoles **12** are the Wittig reaction of isatins **1** with an appropriate Wittig reagent **11** (Scheme 6)<sup>49</sup> and reactions of isatins with active methylene compounds.<sup>50</sup>

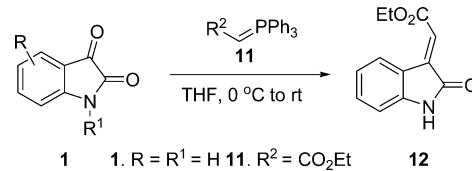
Besides 2-oxindoles bearing *sp*<sup>2</sup>-hybridized C-3 described in the preceding paragraphs, many 2-oxindoles with *sp*<sup>3</sup>-hybridized carbon at position-3 have been employed in the synthesis of spiro-fused cyclic frameworks. They are mostly synthesized by nucleophilic addition onto the C-3 carbonyl group. Like other ketones, isatins form acetals. The aldol reactions of isatins afford 3-substituted 3-hydroxy-2-oxindoles that are important synthetic intermediates for a variety of biologically active

Scheme 5



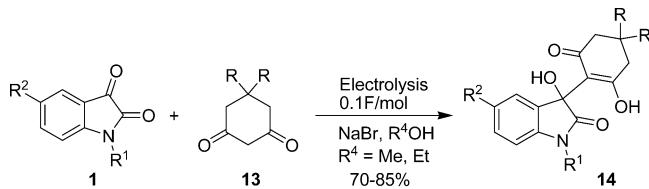
**10.** R = H, R<sup>1</sup> = H, R<sup>2</sup> = Ph; R = 6-Br, R<sup>1</sup> = H, R<sup>2</sup> = Ph;  
R = 6-CF<sub>3</sub>, R<sup>1</sup> = H, R<sup>2</sup> = Ph; R = Cl, R<sup>1</sup> = H, R<sup>2</sup> = Ph;  
R = 6-F, R<sup>1</sup> = H, R<sup>2</sup> = Ph; R = 6-Cl, R<sup>1</sup> = H, R<sup>2</sup> = 2-pyridinyl;  
R = 6-Cl, R<sup>1</sup> = H, R<sup>2</sup> = 2-thienyl; R = 6-Cl, R<sup>1</sup> = H, R<sup>2</sup> = 3-MeOPh

Scheme 6



alkaloids.<sup>51,52</sup> An electrochemical aldol reaction of isatins **1** with cyclic 1,3-diketones **13** in alcohol in an undivided cell results in the formation of 3-substituted 3-hydroxy-2-oxindoles **14** in 70–85% yields (Scheme 7).<sup>53</sup>

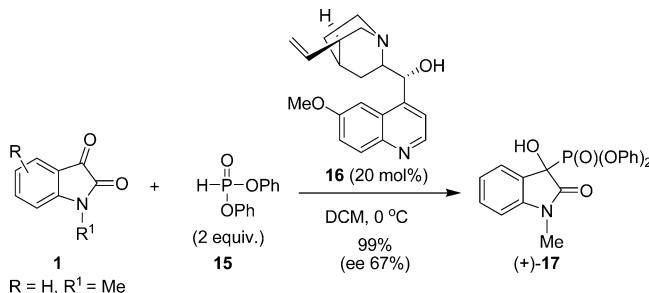
Scheme 7



**14.** R<sup>1</sup> = R<sup>2</sup> = R = H; R<sup>1</sup> = Me, R<sup>2</sup> = H, R = Me; R<sup>1</sup> = Bn, R<sup>2</sup> = H, R = Me;  
R<sup>1</sup> = Ac, R<sup>2</sup> = H, R = Me; R<sup>1</sup> = H, R<sup>2</sup> = Me, R = Me; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R = Me;  
R<sup>1</sup> = R<sup>2</sup> = H, R = Me; R<sup>1</sup> = Me, R<sup>2</sup> = H, R = H; R<sup>1</sup> = H, R<sup>2</sup> = Cl, R = H

The aldol reactions of isatins have stereochemical implications because they transform C-3 carbonyl carbon into a chiral center, and hence efforts have been made to carry out the reaction enantioselectively. There are many examples of enantioselective organocatalytic aldol reaction of isatins with inactivated carbonyl compounds.<sup>43,54–56</sup> A representative example is the reaction of *N*-methylisatin **1** with diphenylphosphite **15** catalyzed by commercially available cinchona alkaloid **16** resulting in a phospho-aldol addition forming adduct **17** in 99% yield but with moderate enantioselectivity (Scheme 8).<sup>48</sup> The authors have suggested the formation of a product through a possible transition state involving a ternary complex between

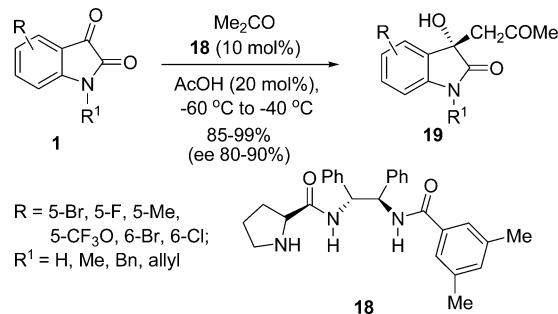
Scheme 8



1-methylisatin, diphenylphosphite, and the catalyst in which C=O (C-3) of isatin is activated by the hydroxyl group of the catalyst through H-bond interaction and the phosphite hydrogen is activated by another H-bond interaction with a nitrogen atom (in nonaromatic ring) of the catalyst.

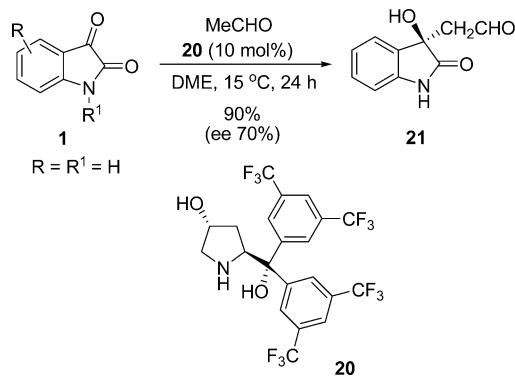
A direct catalytic asymmetric aldol reaction of ketones with isatin **1** using L-proline derived bifunctional organocatalyst **18** represents a general approach to 3-alkyl-3-hydroxyoxindoles **19** with a quaternary stereocenter. The products are obtained in excellent yields (up to 99%) and ee (up to 90%) with an optimized catalyst and under optimized reaction conditions (Scheme 9).<sup>57</sup> Isatin **1** also reacts with acetaldehyde in the

Scheme 9



presence of organocatalyst 4-hydroxy diaryl prolinol **20** to give aldol adduct **21** in almost quantitative yield but with moderate enantioselectivity (Scheme 10).<sup>46</sup>

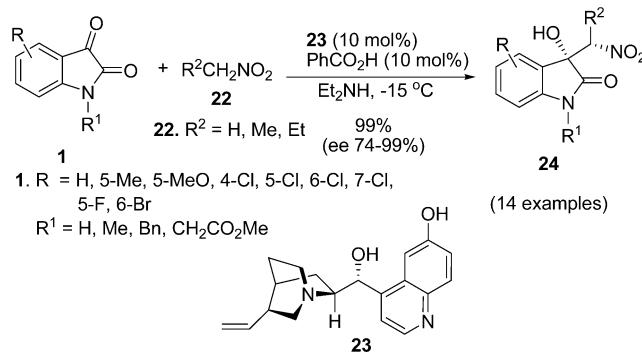
Scheme 10



Isatins **1** also undergo the nitro-aldol reaction, also known as the Henry reaction, with nitromethane **22** in the presence of diethylamine as a catalyst to form 3-hydroxy-3-nitromethyl-2-oxindoles.<sup>58</sup> These nitromethyl-adducts are privileged compounds and have been employed as building blocks in total synthesis of natural products and their analogues because the nitro functionality can be easily transformed into a variety of functional groups, such as amine, ketone, nitrile oxide, carboxylic acid, and so forth. An asymmetric version of this reaction is reported using cupreine **23** as an organocatalyst affording chiral 3-substituted 3-hydroxyoxindoles **24** in up to 99% ee (Scheme 11).<sup>44</sup> The use of an acidic additive benzoic acid was observed to increase the enantioselectivity of the reaction.

Isatins have been used as electrophilic components for the Morita-Baylis-Hillman reaction as well.<sup>59</sup> Isatin itself as well as N-substituted isatins **1** react with activated alkenes **25** in the

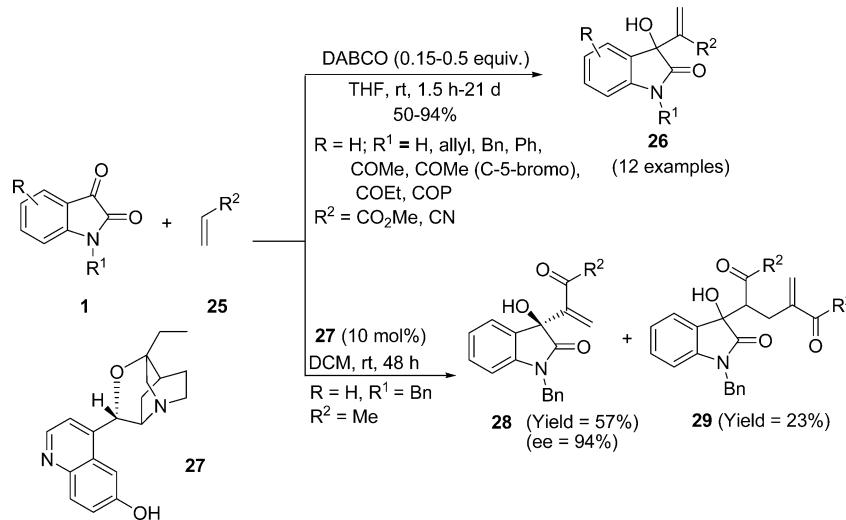
Scheme 11



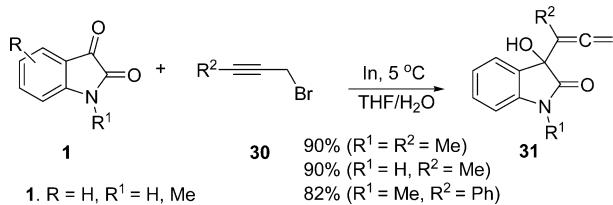
presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to yield an adduct **26** (Scheme 12).<sup>60,61</sup> In another example, isatin and its N-methyl or N-benzyl derivatives undergo the Morita-Baylis-Hillman coupling with chromene derivatives in methanolic trimethylamine to afford the corresponding adducts.<sup>62</sup> Guan and co-workers reported for the first time the reaction of N-benzylisatin with methyl vinyl ketone (MVK) in the presence of a chiral organocatalyst **27** affording the MBH-adduct **28** in 57% yield and 94% ee together with an 1:2 adduct **29** of isatin with MVK (Scheme 12).<sup>63</sup> Under the same reaction conditions, 1-naphthyl acrylate, however, reacted with various N-protected isatins to afford the corresponding MBH adduct as the sole product in excellent yields (70–99%) and enantioselectivities (87–94%) except in the case of 4-substituted N-benzylisatins where the reaction did not proceed due to steric hindrance. This catalyst has been employed in asymmetric MBH addition of isatins with acrolein<sup>64</sup> and with benzyl acrylate<sup>65</sup> also affording products in yields up to 97% and ee up to 99%. The C6'-OH group of the catalyst presumably facilitated the key proton transfer step in the MBH reaction, via an intramolecular proton relay process. Wang and Yu have employed N-(2-diphenylphosphino)cyclohexyl-N'-phenylthiourea as a catalyst in their study on asymmetric MBH addition of N-methylisatin to acrolein and to MVK.<sup>66</sup> Although the reaction offered yields of 82% and 42%, respectively, the enantioselectivities observed were only 13% and 20%, respectively. The asymmetric MBH addition of differently substituted isatins including N-unsubstituted isatins to different acrylates, however, occurred efficiently using the same phosphinothiourea catalyst affording products in up to 99% yield and ee up to 69%.

Alcaide and co-workers have reported indium-mediated Barbier-type carbonyl allylation, 1,3-butadien-2-ylation, and allenylation (using alkynyl bromides **30**) reactions of isatins in aqueous media to synthesize the 2-oxindoles bearing homoallylic alcohol, (1,3-butadien-2-yl)methanol, and  $\alpha$ -allenol groups **31** (Scheme 13), respectively, on its C-3 position that have been employed in the synthesis of spiro-heterocycles.<sup>67</sup> A palladium-catalyzed asymmetric allylation of isatins **1** using allyl alcohols **32** has been reported in the presence of a new class of phosphorimidite ligand **33** (Scheme 14).<sup>68</sup> The reaction, applicable to differently substituted isatins and allyl alcohols, afforded products **34** in excellent yields (74–99%) but moderate enantioselectivity (46–71%). An Ir-catalyzed transfer hydrogenation approach for allylation, crotylation, and reverse prenylation reactions of isatins is reported using allyl acetate reagents or 1,1-dimethylallene **35** as precursors for transient allyl-metal intermediates.<sup>69</sup> The reverse prenylation of isatins **1** with 1,1-dimethylallene **35** using the ligand **36** afforded

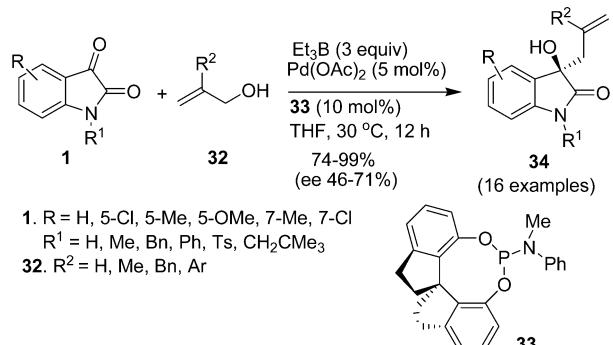
Scheme 12



Scheme 13



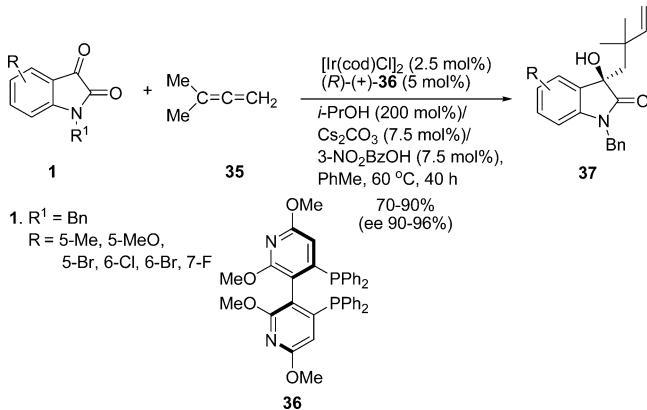
Scheme 14



products 37 in good yields and with good enantioselectivity (Scheme 15). This method does not necessarily require stoichiometric quantities of allyl metal reagents, but some complex mixtures of additives are required.

This brief section, in summary, showcases the significant reactions of C-3 carbonyl group in isatins leading to products that have applications in architecture of spiro-fused cyclic frameworks by multistep reactions of isatins. These reactions are mostly nucleophilic additions of nitrogen nucleophiles forming C-3 azomethines of different types. Many valuable substrates for spiro-oxindoles' synthesis such as 3-diazoisatin, 3-aminoisatins, and 3-isothiocyanatoisatins have been prepared through further transformations of 3-iminoisatins. Isatin-3-imines undergo aza-Friedel-Crafts reaction with pyrroles and indoles, alkyl radical addition, Mannich reaction, and addition of the Grignard reagents to afford the 3-substituted 3-amino-2-oxindoles. The Wittig reaction, reactions of isatins with active methylene compounds, aldol reaction, Henry reaction, MBH

Scheme 15

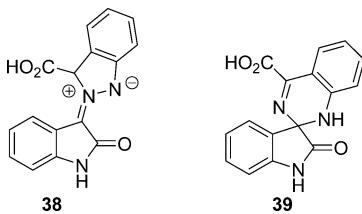


addition, and zinc- and indium-catalyzed allylations are important reactions that have been employed in gaining access to substrates required for the synthesis of spiro-cyclic compounds. The chiral catalysts such as cinchona alkaloids, proline derivatives, phosphinothiourea, and phosphines, etc. have been employed successfully in many of these reactions to achieve enantioselectivity in the reactions to obtain enantiopure products.

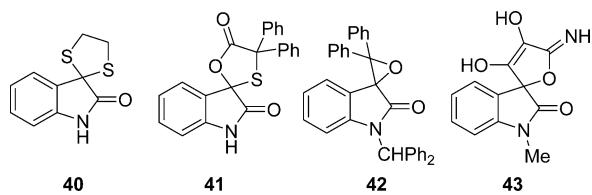
### 3. ISATIN-BASED SPIRO-CYCLIC FRAMEWORKS: HISTORICAL BACKGROUND

Although the isatins were well-known by the middle of the 19th century and their chemistry investigated extensively for over 100 years thereafter, only a few convincing reports were available on the formation of spiro-cyclic compounds from isatins until the middle of the 20th century. The investigations, in fact, were not focused on the synthesis of spiro-cyclic frameworks because of little or no knowledge about the significance of compounds with such frameworks. Among the first few reactions of isatins with possible formation of a spiro-cyclic product, one was its reaction with diazomethane. Arndt and co-workers reported the possibility of formation of a spiro-oxirane-oxindole in the reaction of isatins with diazomethane.<sup>70</sup> The structure of a compound called isamic acid with molecular formula C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>·H<sub>2</sub>O, obtained from the reaction of isatin with ammonia, was studied for some time,<sup>71</sup> and it was

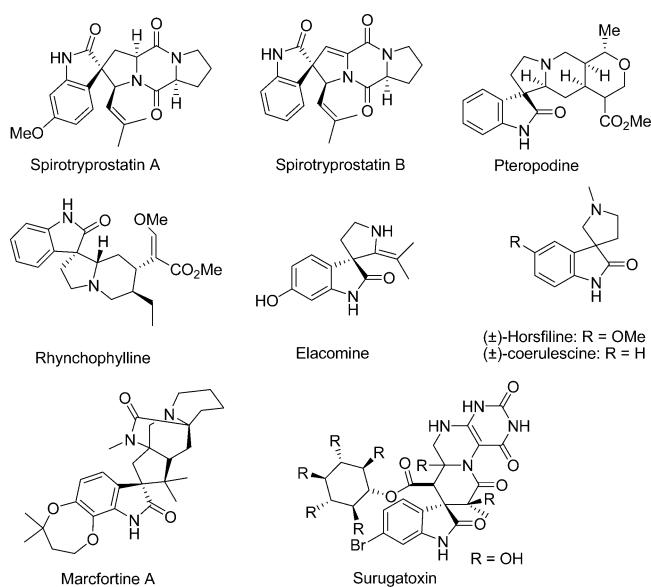
proposed as **38** in 1967.<sup>72</sup> This structure was later revised by Field who proposed a more reasonable structure, spiro-dihydroquinazoline-oxindole **39**.<sup>73</sup> In 1976, Cornforth further confirmed this structure for the product obtained from the reaction of isatin with two molar equivalents of ammonia.<sup>74</sup>



Some other examples of spiro-cycle formation included the formation of spiro-1,3-dithiolane-oxindole **40** from the reaction of isatin with ethane-1,2-dithiol,<sup>75</sup> formation of spiro-1,3-oxathiolan-4-one-oxindole **41** by a *p*-toluenesulfonic acid-catalyzed reaction of isatin with mercaptodiphenylacetic acid,<sup>76</sup> and a spiro-oxirane-oxindole **42** by reaction of *N*-benzhydrylisatin with an excess of diphenyldiazomethane.<sup>77</sup> The condensation of *N*-methylisatin, glyoxal bisulfate, and sodium cyanide in an aqueous sodium carbonate solution followed by neutralization was reported by Amiet and co-workers to give the spiro-dihydrofuran-oxindole **43**.<sup>78</sup>



The research on isatin-based spiro-cycles received increasingly more attention during the last quarter of the 20th century when investigations on phytochemistry of some bioactive natural resources led to isolation and structure elucidation of some natural products that contained this motif (Figure 5). Among a few to mention, one is the isolation and characterization of elacomine alkaloid, a spiro-pyrrolidine-oxindole, from



**Figure 5.** Selected examples of natural products with spiro-fused oxindoles motif.

the root bark of *Eleagnus commutata* by James and Williams in 1972.<sup>79</sup> Another alkaloid horsfliline with the same structural motif was isolated from the Malaysian medicinal plant *Horsfieldia superba* by Bodo and co-workers.<sup>80</sup> A powerful bioactive class of indole alkaloids, spirotryprostatin A and B, was isolated from the fermentation broth of *Aspergillus fumigatus* by Osada and co-workers.<sup>81</sup> Coerulescine was isolated from the blue canary grass *Phalaris coerulescens* by Anderton and co-workers.<sup>82</sup> An alkaloid rhynchophylline was isolated from a traditional Chinese medicinal herb *Uncaria rhynchophylla*.<sup>83</sup> Rhynchophylline has drawn extensive interest recently due to its antihypertensive, neuroprotective, and potassium ion channel activity.<sup>84</sup> A new alkaloid marcfortine A containing a spiro-cyclopentane-oxindole backbone was characterized from the fungus *Penicillium roqueforti*.<sup>85</sup> Surugatoxin, which depresses the orthodromic transmission reversibly and antagonizes the depolarizing effect of carbachol on isolated rat superior cervical ganglia, was isolated from the toxic Japanese ivory shell.<sup>86</sup> A pentacyclic oxindole alkaloid pteropodine, also known as uncarine C, was isolated from stem bark of *Uncaria tomentosa*, a medicinal plant known as cat's claw.<sup>87</sup>

The landmark achievements in the area of phytochemistry described in the preceding paragraph combined with discovery of potential anticancer activity in some synthetic analogs of horsfliline gave impetus to studies aimed toward the synthesis of spiro-cyclic oxindoles employing isatins and other methodologies. Most of these studies were, however, focused on development of appropriate methodology for the synthesis of natural products and not too many synthetic spiro-oxindoles were investigated. With further development in the area of stereochemistry and medicinal chemistry, it was realized that only a particular isomer was bioactive in many cases which encouraged researchers to develop stereoselective methodologies. This led to extensive investigation on the development of new synthetic methodologies and their stereoselective version for the synthesis of spiro-cyclic oxindoles during the past decade. Williams and co-workers and Carreira and co-workers led the research on the synthesis of these natural products employing isatins (section 4.5.3). Williams and co-workers employed chiral auxiliary in asymmetric synthesis of spirotryprostatin B. Carreira and co-workers reported the expansion of the cyclopropane ring into spiro-cyclopentane-oxindole. During the last five years, several enantioselective syntheses of spiro-cycloalkyl- and spiro-heterocyclic 2-oxindoles have emerged using the Lewis acid catalysts, Bronsted acid catalysts, and organocatalysts which will be discussed in detail in the appropriate sections.

#### 4. SYNTHESIS OF ISATIN-BASED SPIRO-FUSED HETEROCYCLIC FRAMEWORKS

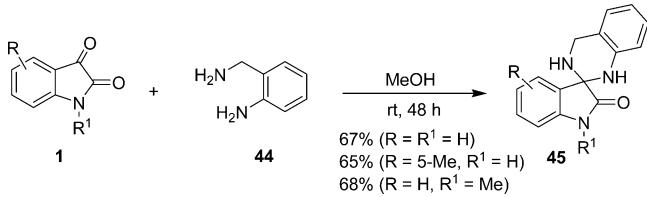
Isatins and its C-3 derivatives have been employed in the architecture of different types of spiro-heterocyclic moieties bearing 2-oxindoles. In many cases, such compounds are synthesized directly from isatins either by cyclocondensation or cycloaddition reactions with other reagents. Recently, multi-component cascade reactions of isatins have been employed which lead to an easy and convenient one-pot synthesis of spiro-heterocyclic frameworks. In many instances, the synthesis of the target spiro-heterocycle, however, is accomplished via a simple C-3 derivative of isatins such as alkylideneisatins, isatin imines, isatin hydrazones, Baylis-Hillman adducts of isatins, aldol-adducts of isatins, etc. Novel asymmetric syntheses using chiral metal-complexes, chiral organocatalysts, and chiral

auxiliaries furnishing complex molecules in an enantioselective manner have been developed.

#### 4.1. Synthesis Involving Two-Component Reactions of Isatin

**4.1.1. Cyclocondensation Reactions: Five- to Eight-Membered Heterocycles.** The reactions of ammonia, 1,2-diamines, and 1,3-diamines with isatins have been reported to furnish the five- or six-membered spiro-azaheterocycles. Cornforth, in 1976, established the formation of 2-oxindole spiro-fused to a 1,2-dihydroquinazoline ring by a 1:2 molar reaction of isatin with ammonia.<sup>66</sup> Bergman and co-workers have investigated the reactions of isatins with 1,2- and 1,3-diamines affording spiro-fused 2-oxindoles. The reaction of isatin with *N,N*-dimethylethylenediamine in water afforded the spiro-*N,N*-dimethylimidazolidine-oxindole.<sup>88</sup> The reaction of isatins **1** with 2-aminobenzylamine **44** in methanol at room temperature led to the formation of spiro-tetrahydroquinazoline-oxindoles products **45** (Scheme 16).<sup>89</sup> The condensation

Scheme 16

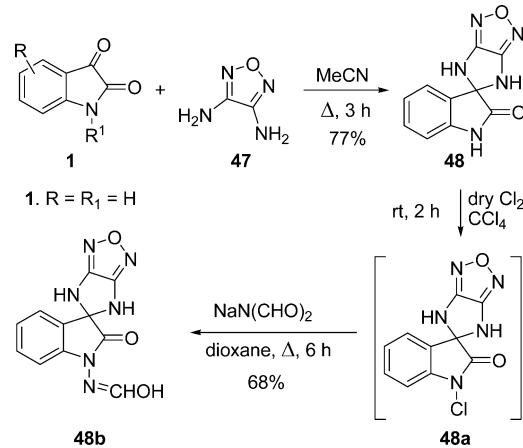


of isatins **1** with 2-aminobenzylamine **44** in acetic acid, however, afforded a spiro-fused 2-oxindole **46** as a result of 1:2 molar reaction between isatins and 2-aminobenzylamine. The product **46** was also obtained by the reaction of spiro-fused 2-oxindoles **45** with 2-aminobenzylamine **44** in acetic acid (Scheme 17).<sup>81</sup> The condensation of isatin **1** with *o*-phenylenediamine in refluxing methanol has been reported to afford the corresponding spiro-fused product only in trace amounts.<sup>90</sup> The formation of spiro-dihydroimidazole-oxindoles was reported by the reactions of *N*-acylisatins with *o*-phenylenediamine and 2,3-diaminopyridine in acetic acid and ethanol.<sup>91</sup>

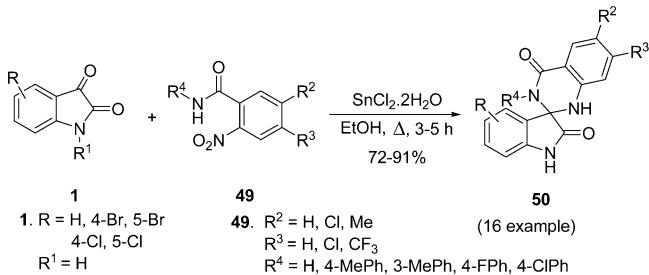
The cyclocondensation of isatin **1** with a heterocyclic 1,2-diamine, 3,4-diaminofurazane **47** on refluxing in acetonitrile afforded the spiro-1,2,5-oxadiazoloimidazolidine-oxindole **48** (Scheme 18).<sup>92</sup> A derivative of this compound was synthesized by treatment with dry chlorine resulting in the chlorination of oxindole nitrogen forming product **48a** and then treatment with sodium salt of *N*-formylformamide furnishing another spiro-fused 2-oxindole **48b**.

The reaction of isatins **1** with 2-nitrobenzamides **49** in the presence of tin(II) chloride is reported to afford the spiro-quinazolinone-oxindoles **50** (Scheme 19).<sup>93</sup> The tin(II) works

Scheme 18



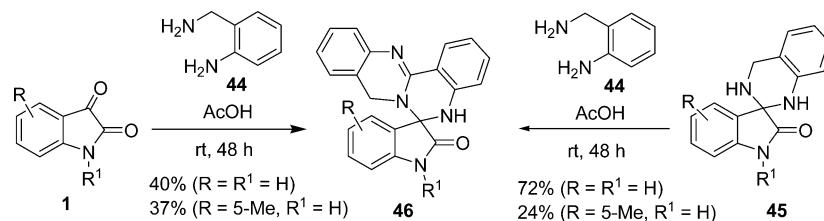
Scheme 19



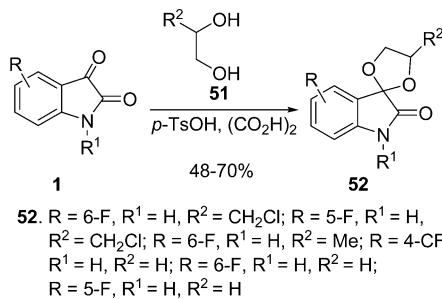
both as a reducing agent for transformation of the nitro group in amides to an amino group and, together with the oxidized tin(IV), as an activator of the C-3 carbonyl group of isatin. The isatin imine, formed initially, undergoes intramolecular cyclization with the amide to afford the final product. The reaction with different types of substituents on amides and on isatin afforded products in excellent yields. The methodology, however, remains unexplored for isatins bearing activating groups on the phenyl ring or for *N*-substituted isatins. It is worth mentioning here that formation of these products was reported earlier by a three-component reaction of isatins, amines, and isatoic anhydride.<sup>94</sup>

Analogous to reactions of isatins with 1,2-diamines the reaction of isatin **1** with ethylene glycols **51** has been reported to form the spiro-dioxolane-oxindoles **52** under both homogeneous (Scheme 20)<sup>95</sup> and heterogeneous catalysis employing the strongly acidic resin Dowex 50X-X<sub>2</sub>.<sup>96</sup> However, the use of heterogeneous catalyst is preferred because an eco-friendly transformation may be achieved without using more solvent.<sup>97</sup> The solvent-free preparations of spiro-dioxolane-oxindoles in high yields from isatin and 5-chloroisatin using the Keggin's heteropolyacids, namely, heteropolyphosphotungstic

Scheme 17



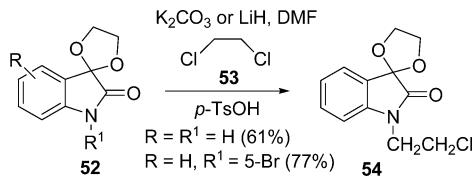
Scheme 20



acid (HPW), HPW/SiO<sub>2</sub>, and Cs<sub>2</sub>HPW are reported.<sup>98</sup> The reaction of ethylene-1,2-thiol with isatin results in formation of spiro-dithiolane-oxindole.<sup>99</sup>

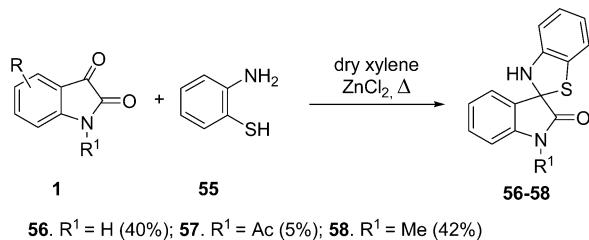
The reactivity of the nitrogen atom in the oxindole ring of spiro-dioxolane-oxindoles has been explored for the synthesis of N-substituted spiro-dioxolane-oxindoles.<sup>100</sup> The reaction of compounds **52** with 1,2-dichloroethane **53** using K<sub>2</sub>CO<sub>3</sub> or LiH as a base in dimethylformamide afforded the corresponding N-(2-chloroethyl)isatin-3-acetals **54** (Scheme 21).

Scheme 21



The reactions of isatins **1** with 2-aminothiophenol **55** have been observed to afford the spiro-benzothiazoline-oxindoles **56–58** in varying yields depending on the substituent at the isatin ring nitrogen and on reaction conditions.<sup>101–103</sup> N-Methylisatin reacted with 2-aminothiophenol only at reflux temperature to afford the spiro-benzothiazoline-oxindole **58** as a sole product in 42% yield (Scheme 22). The isatin and N-

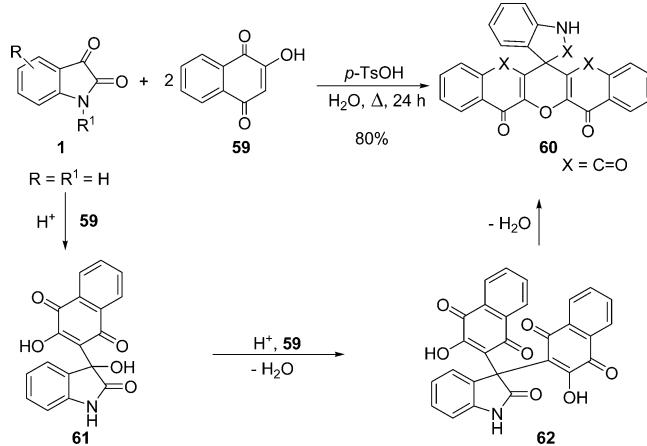
Scheme 22



acetylisatin under the same conditions afforded the spiro-fused products **56** and **57**, respectively, together with two other products in 35% and 70% overall yields, respectively. The reactions of isatin and N-acetylisatin occurred at room temperature as well, but the products were obtained in very low yields.

A 2:1 molar reaction of 2-hydroxynaphthalene-1,4-dione **59** and isatin **1** in the presence of a catalytic amount of *p*-TsOH proceeded smoothly in water under refluxing for 24 h to furnish the spiro[dibenzo[b,i]-xanthene-1,3,3'-indoline]-2',5,7,12,14-pentaone **60** in 80% yield (Scheme 23).<sup>104</sup> A series of such compounds in good yields (75–82%) have been synthesized from the reactions of N-methylisatin, N-benzylisatin, 5-

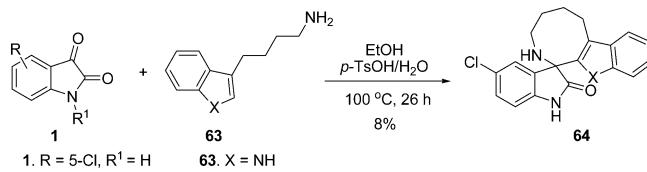
Scheme 23



bromoisatin, 5-nitroisatin, and *N*-bromo-5-methylisatin with compound **59**. The formation of products has been explained by an initial addition of 2-hydroxynaphthalene-1,4-dione to isatin generating intermediate **61** which reacts further with compound **59** to afford the product **62**. The latter compound cyclizes finally to give product **60**. Jadidi and co-workers have reported a *p*-TsOH-catalyzed cyclocondensation of isatins with two molar equivalents of 2,6-diaminopyrimidine(3*H*)-4-one resulting in the formation of spiro-pyridodipyrimidine-oxindole derivatives.<sup>105</sup>

The condensation of  $\beta$ -arylethylamines such as tryptamine with aldehydes under acidic conditions followed by cyclization of the resulting imines to afford the  $\beta$ -tetrahydrocarbolines is well-known as the Pictet-Spengler reaction.<sup>106</sup> The use of isatins in this reaction as the carbonyl component, however, switches the cyclization to the C-3 position of isatins furnishing spiro-azaheterocyclic compounds such as spiro- $\beta$ -tetrahydrocarboline-oxindoles.<sup>20</sup> Furthermore, an increase in amine chain-length allows access to seven- and eight-membered spiro-azaheterocycles such as spiro-tetrahydroazepine-oxindoles and spiro-hexahydroazocene-oxindoles though in diminished yields. For example, the reaction of 5-chloroisatin **1** with 4-indol-(3-yl)-1-butanimine **63** affords the spiro-hexahydroazocene-oxindole **64** in 8% yield (Scheme 24).

Scheme 24

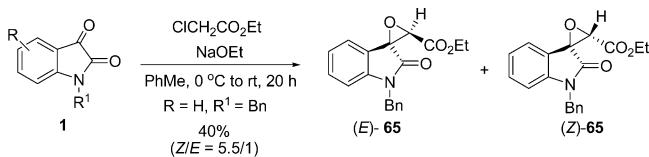


**4.1.2. Cycloaddition and Cyclization Reactions.** Next to cyclocondensations, the most common direct approaches to spiro-fused oxindoles are either 1,3-dipolar cycloadditions or different types of cyclization reactions. Cyclizations by the Darzens reaction and the reaction of a sulfur ylide afford spiro-cyclooxirane. The 1,3-dipolar cycloadditions to isatins result in formation of five-membered spiro-heterocycles. A [4+2]-cycloaddition leads to the formation of six-membered spiro-heterocycles. The diastereo- and/or enantioselective versions of many of these reactions are reported by employing different types of catalysts. Such reactions are described separately in

section 4.1.3 in which the literature, though not separated, is arranged according to the type of catalyst used because the outcome of the reaction depends principally on the nature of catalyst.

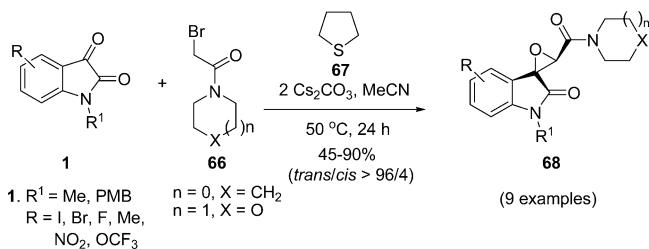
**4.1.2.1. Three-Membered Heterocycles.** The Darzens reaction, a cyclization reaction through chloride displacement, of isatin **1** was reported by Baiocchi and Giannangeli to afford the isomeric spiro-oxirane-oxindoles **65**.<sup>107</sup> The reaction of isatin **1** with ethylchloroacetate in the presence of sodium ethoxide afforded the isomeric products (Scheme 25). In a

Scheme 25

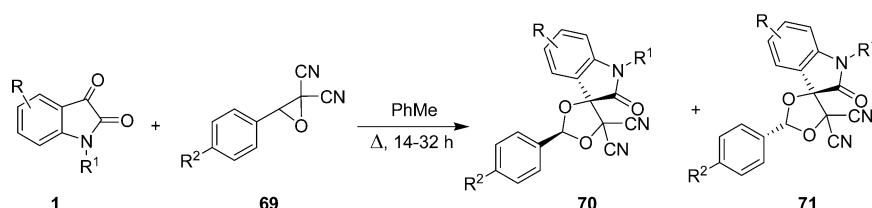


recent report, the reaction of isatin and *N*-methylisatin with other alkylating agents having an acidic methylene, phenacyl iodides, in the presence of a strong base such as sodium ethoxide is reported to yield the spiro-oxirane-oxindoles.<sup>108</sup> The reaction was observed to be dependent on polarity of the solvents at reflux temperature. The products were obtained in reasonable yields between 40 and 52% in lesser polarity solvents benzene or chloroform at reflux temperature, but at room temperature the reaction was independent of solvent and afforded the product in up to 90% yield. The spiro-oxiranes are a scarce class of compounds because of complexity involved in structure due to i) spiro-carbon and ii) instability due to ring-strain. These compounds can, however, serve as important building blocks in organic synthesis because the instability inherent from ring-strain can be exploited in the synthesis of large ring heterocycles. The reaction of sulfur ylides, generated from  $\alpha$ -bromoamides **66** and thiolane **67**, with isatins **1** is reported to form the spiro-oxirane-oxindoles **68** diastereoselectively (Scheme 26).<sup>109</sup> The presence of a morpholine ring in the bromoamide component diminished the yield to 45%.

Scheme 26



Scheme 27



**4.1.2.2. Five- and Six-Membered Heterocycles.** A domino reaction of 3-aryloxirane-2,2-carbonitriles **69** with isatins **1** afforded the *cis*- and *trans*-spiro-1,3-dioxolane-oxindoles **70** and **71**, respectively, with the *cis*-isomer being the major product in most cases (Scheme 27).<sup>110</sup> The reactions were carried out either in refluxing toluene or by microwave irradiation without solvent. The *cis*-products were marginally high in the case of oxiranes with phenyl and 4-methoxyphenyl groups (entries 1 and 3), but its ratio was very high in the case of oxirane with the 4-chlorophenyl group (entry 2) (Table 1). The presence of a

Table 1. Synthesis of *cis*- and *trans*-Spiro-1,3-Dioxolane-Oxindoles **70** and **71**

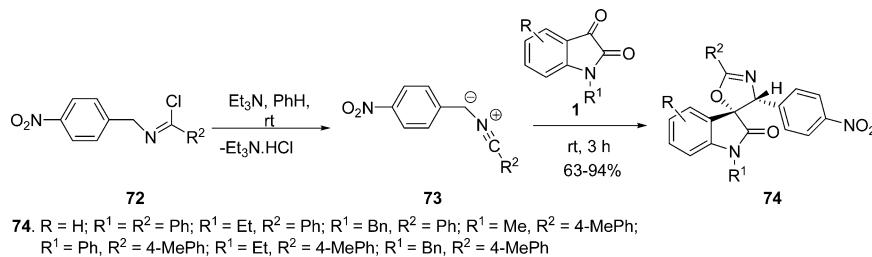
entry	R <sup>2</sup>	R <sup>1</sup> , R	R	70:71 <sup>a,b</sup>	ratio 70:71 <sup>a,c</sup>	isolated yield (%) 70	isolated yield (%) 71
1	H	H	H	57:43	55:45	42 <sup>b</sup>	
2	Cl	H	H	75:25	54:46	66 <sup>b</sup>	
3	OMe	H	H	55:45	33:65	49 <sup>b</sup>	
4	H	Me	H	73:27	-	72	
5	Cl	Me	H	74:26	-	73	
6	OMe	Me	H	63:37	-		30
7	H	H	S-Cl	59:41	-	52	28
8	Cl	H	S-Cl	71:29	-	59	25
9	OMe	H	S-Cl	58:42	-	49	

<sup>a</sup>Yields calculated from <sup>1</sup>H NMR. <sup>b</sup>Reaction carried out in refluxing toluene. <sup>c</sup>Reactions carried out by microwave irradiation (285 W, 180 °C) under solvent-free condition.

methyl group on isatin nitrogen too favored the formation of *cis*-isomers (entries 4–6). This domino process comprises of two consecutive processes: i. thermal decomposition of oxiranes generating an ylide and ii. [2+3]-cycloaddition of isatins to the ylide. The two processes have been studied theoretically by DFT calculations. Analysis of the reactivity indexes indicated that the large electrophilicity of the carbonyl ylide accounted for the nucleophilic attack of isatin onto ylide. The analysis of the Fukui function indicated that more favorable electronic interaction took place between the carbonyl oxygen atom of the isatin, the more nucleophilic center, and the phenyl-substituted carbon atom of the carbonyl ylide, the more electrophilic one, which explained the experimentally observed regio- and chemoselectivity.

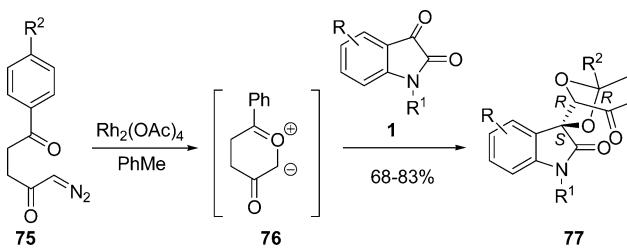
Nair and co-workers have reported the synthesis of various spiro-heterocyclic frameworks by [2+3]-annulations of isatins. The [2+3]-cycloaddition of nitrile ylides **73**, generated by the base-catalyzed reaction of imidoyl chloride **72**, with *N*-substituted isatins **1** has led to the formation of spiro-1,3-oxazoline-oxindoles **74** (Scheme 28).<sup>111</sup> The reaction proceeded smoothly in benzene at room temperature with *N*-

Scheme 28



methyl-, *N*-ethyl-, *N*-benzyl- and *N*-phenylisatins affording the products in 63–94% yields. The Huisgen addition of azomethine ylide to isatins afforded the spiro-1,3-oxazolidine-oxindoles.<sup>112</sup> The reactions of isatins with allyl silanes in the presence of  $\text{SnCl}_4$  as a catalyst led to the formation of spiro-tetrahydrofuran-oxindole in very good yields (62–91%).<sup>113</sup> Furthermore, this group has reported the [2+3]-cycloaddition reaction of cyclic carbonyl ylide 76, generated from the Rh(II)-catalyzed decomposition of 5-diazo-1-arylpentane-1,4-diones 75, with isatins 1 forming spiro-fused 2-oxindoles 77 (Scheme 29).<sup>114</sup>

Scheme 29

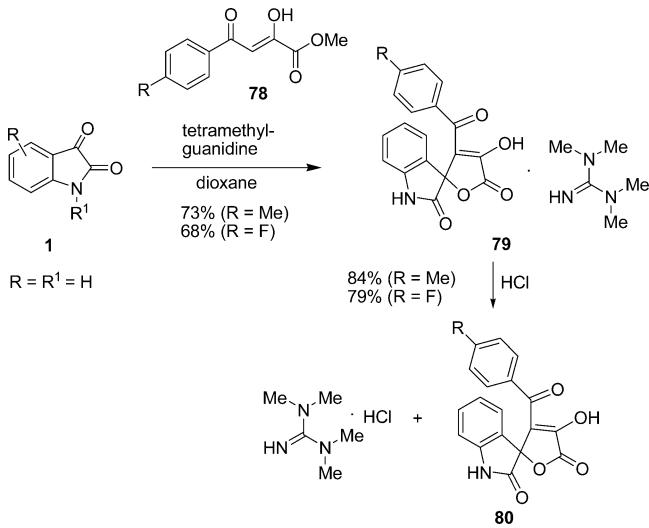


Liu and co-workers have reported the 1,3-dipolar cycloaddition reaction of azomethine ylide, generated by treatment of Ni(II)  $\beta$ -formyl-*meso*-tetraphenylporphyrins with sarcosine, with the C-3 carbonyl group of isatin forming spiro-porphyrin-oxindoles.<sup>115</sup> It is worth mentioning that porphyrin derivatives have diverse applications in the scientific field. Besides being helpful in understanding the crucial biological processes, they have the potential for applications in catalysis of organic reactions,<sup>116</sup> supramolecular chemistry,<sup>117</sup> and photodynamic therapy.<sup>118</sup>

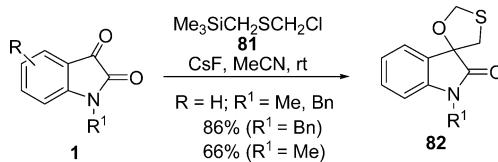
An equimolar reaction of isatin 1 with methyl benzoylpyruvates 78 in the presence of *N,N,N',N'*-tetramethylguanidine in dioxane results in spiroannulation forming the spiro-oxindolyl guanidinium salts 79 (Scheme 30).<sup>119</sup> An acidic hydrolysis of the salts 79 liberated the 3'-*aro*yl-4'-hydroxyspiro[indole-3,2'-furan]-2,5'-(1*H*)-diones 80. The reactions of isatins with trialkylphosphates are reported to yield the bis-spiro-oxindole-phospholanes in 35–80% yields.<sup>120</sup>

The reaction of *N*-substituted isatins 1 with chloromethyl trimethylsilyl sulfide 81 with the aid of cesium fluoride affording spiro-1,3-oxathiolane-oxindoles 82 was reported by Hosomi and co-workers (Scheme 31).<sup>121</sup> Although there were no sufficient mechanistic studies, the results were considered compatible with a [3+2]-cycloaddition of the *in situ* generated thiocarbonyl ylide.

Scheme 30

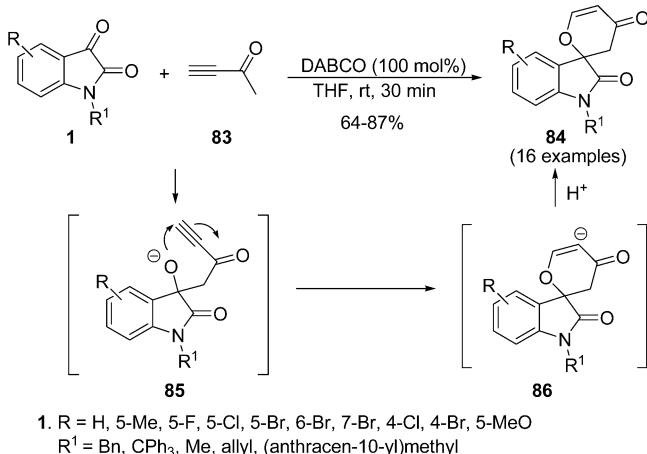


Scheme 31

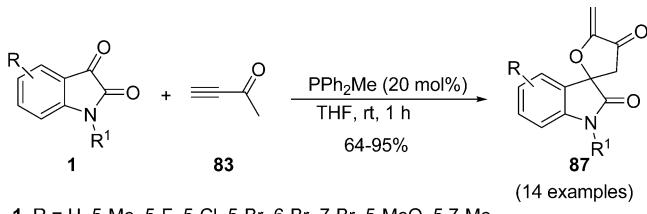


Lian and Shi have reported [4+2]-annulations of *N*-protected isatins 1 with but-3-yn-2-one 83 in the presence of a stoichiometric amount of the Bronsted base DABCO in THF at room temperature to afford the spiro-pyanone-oxindoles 84 (Scheme 32).<sup>122</sup> The method was independent of electronic factors on the phenyl ring and was employed smoothly with various *N*-protecting groups such as benzyl, allyl, methyl, (trifluoromethyl)phenyl, and (anthracen-10-yl)methyl as well. The formation of products has been explained by a nucleophilic attack of enolates, generated by the abstraction of proton from alkynes by DABCO, on the C-3 carbonyl group of the isatins. An intramolecular nucleophilic attack of the  $\text{O}^-$  anion in intermediate 85 at the terminal carbon of the alkyne moiety followed by protonation of intermediate 86 leads to the formation of the final product. Interestingly, the change of nitrogen catalyst DABCO by a phosphorus catalyst,  $\text{PPh}_2\text{Me}$ , changed the course of reaction and afforded the [3+2]-annulation products, spiro-furanone-oxindoles 87 (Scheme 33), rather unstable compounds which started decomposing during purification. The use of water as an additive further accelerated the reaction. The [3+2]-annulation is proposed to proceed through the enolates 89, generated through a 1,3-hydrogen shift in zwitterionic intermediate 88 obtained by reaction of the

Scheme 32

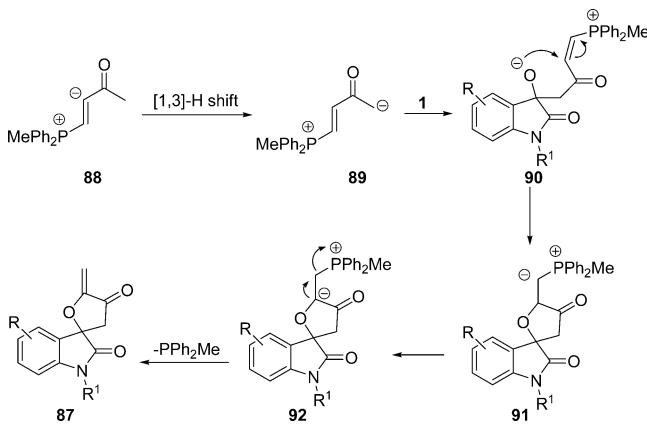


Scheme 33



catalyst PPh<sub>2</sub>Me with enynone 83 (Scheme 34). The nucleophilic attack of enolate 89 onto the isatins' C-3 carbonyl

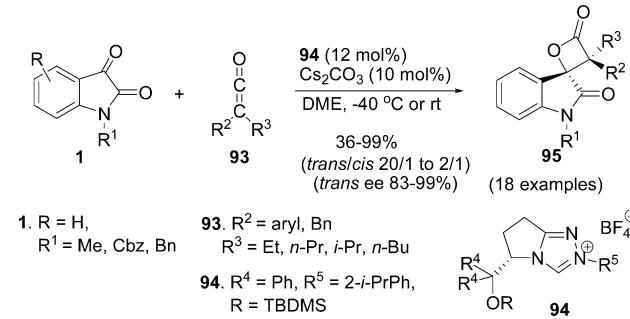
Scheme 34



group gives an intermediate 90 which cyclizes to generate initially the ylide-type intermediate 91 which undergo a 1,2-hydrogen shift to form another intermediate 92. The elimination of catalyst then affords the final product. Deuterium exchange studies supported a stepwise mechanism for this reaction.

**4.1.3. Stereoselective Methodologies: Four- to Six-Membered Heterocycles.** An interesting [2+2]-cycloaddition of *N*-substituted isatins 1 and disubstituted ketenes 93 to afford the spiro-β-lactone-oxindoles 95 constitutes perhaps the first example of [2+2]-cycloaddition of isatins.<sup>123</sup> The reaction is catalyzed by the *N*-heterocyclic carbene (NHCs) at -40 °C to room temperature affording products in good yields and with good diastereo- and enantioselectivities (Scheme 35). An

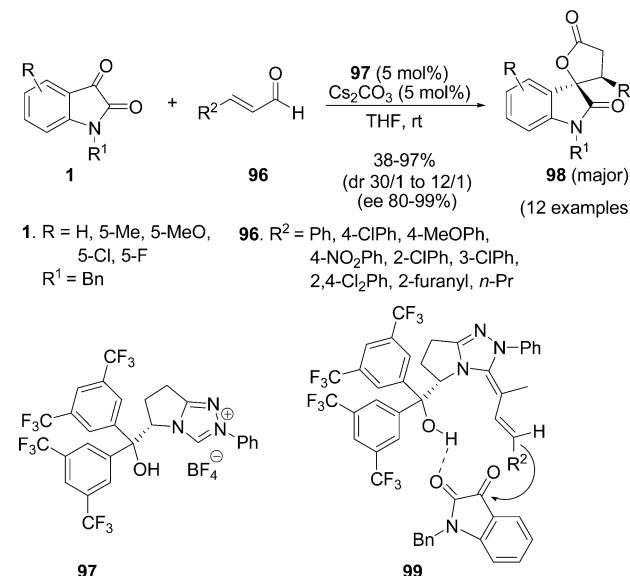
Scheme 35



investigation of a series of freshly prepared NHCs by treatment of L-pyroglutamic acids (12 mol %) with Cs<sub>2</sub>O<sub>3</sub> (10 mol %) at room temperature for 1 h led to the discovery of catalyst from precursor 94 as the model catalyst in terms of yields and stereoselectivity. A variety of aryl(alkyl)ketenes with electron-donating and electron-withdrawing groups have been observed to undergo cycloaddition efficiently. Ketenes with sterically hindered aryl groups (2-chlorophenyl, 2-naphthyl), however, either did not work or reacted sluggishly. Also, ketenes with longer alkyl chains such as (*n*-Pr, *n*-Bu) or a branched chain (*i*-Pr) worked but afforded low yields which is understandable due to electronic and steric factors.

Recently, the Ye group extended this study to the synthesis of spiro-γ-lactone-oxindoles.<sup>124</sup> In this study, the authors have investigated the reactions of *N*-benzylisatins 1, with α,β-unsaturated aldehydes 96 in the presence of L-pyroglutamic acids-derived *N*-heterocyclic carbene 97 to synthesize the spiro-γ-lactone-oxindoles 98 with very good diastereoselectivity and enantioselectivity (Scheme 36). The substituents at the phenyl

Scheme 36

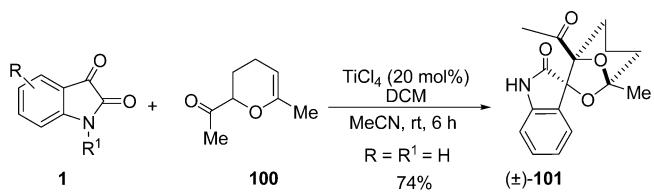


ring of isatin or the phenyl ring of enals had no significant effect on the outcome of the reaction. An enal with a β-alkyl substituent (*n*-propyl) offered the desired product with dr 20:1 and ee 86% albeit in only 38% yield. The scope of this reaction for the synthesis of spiro-oxindole rings with differently substituted nitrogen atom other than the benzyl group remains to be explored. It was observed that the presence of the

hydroxyl group in the catalyst played a crucial role in enhancing the diastereo- and enantioselectivities of the reactions. Taking into consideration these observations and stereochemistry of products, the transition-state **99** has been proposed responsible for formation of products.

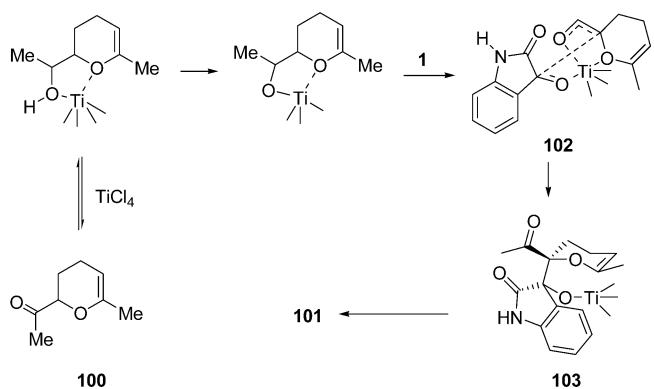
A  $\text{TiCl}_4$ -catalyzed coupling of 2-acetyl-6-methyl-2,3-dihydro-4H-pyran **100** with isatin **1** results in tandem C–C and C–O bonds formations offering a simple methodology for the stereoselective synthesis of [(1-acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane)-7-spiro-3'-(2-oxindole)] **101** (Scheme 37).<sup>125</sup> The reaction has been carried out with isatin,

Scheme 37



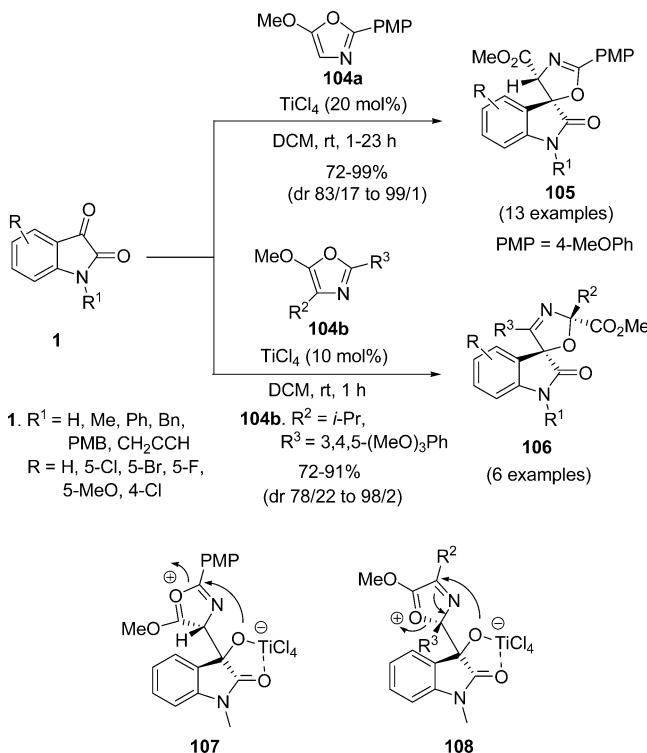
*N*-alkylisatins, *N*-phenylisatin, 5-nitroisatin, and some 1,5-disubstituted isatins in the presence of 20 mol % of catalyst at room temperature to afford the products in 44–74% yields. The formation of product has been explained by initial coordination of pyran with titanium and then formation of transition state **102** which can selectively lead to *S,S,S* (Scheme 38) and *R,R,R* products via intermediate **103**.

Scheme 38



Franz and co-workers have developed a titanium-catalyzed regio- and stereoselective spiroannulation of isatins **1** with 2-aryl-5-methoxyoxazoles **104** for synthesis of spiro-oxazoline-oxindoles **105** and **106** (Scheme 39).<sup>126</sup> The substitution at the C-4 position of the oxazole was observed to control the nucleophilic attack leading to the formation of either 2- or 3-oxazoline spiro-heterocycles with excellent regiocontrol (>99%). Some other Lewis acids such as  $\text{In}(\text{OTf})_3$ ,  $\text{Zn}(\text{OTf})_2$ ,  $\text{ZnBr}_2$ ,  $\text{CuCl}_2$ ,  $\text{Cu}(\text{OTf})_2$ ,  $\text{MgCl}_2$ , and  $\text{BF}_3\text{-Et}_2\text{O}$  were also investigated as catalysts in this study but showed either no reaction or poor conversion (<20%). The reaction was extremely successful with both *N*-substituted and *N*-unprotected isatins with different electronic environments on the phenyl ring. The reaction of 4-chloro-1-methyl- and 4-chloroisatins afforded excellent diastereoselectivity (99/1); though they reacted sluggishly (15–23 h). Isatin with an electron-donating methoxy group on C-5 gave slightly reduced diastereoselectivity (86/14). The major product was charac-

Scheme 39

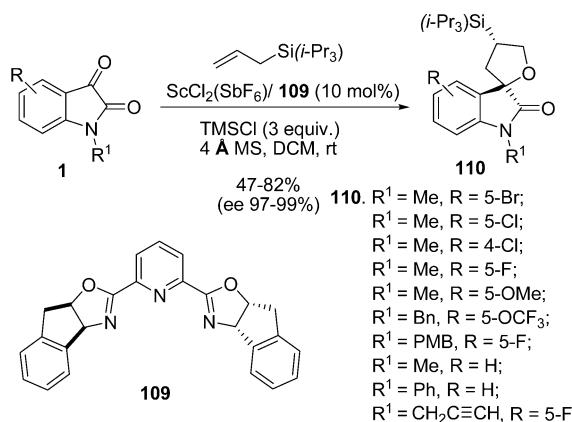


terized as *cis* that is the kinetically controlled product and could be epimerized to *trans* by treatment with DBU. The reaction is proposed to be initiated by titanium(IV) activation of the isatin dicarbonyl to accelerate a nucleophilic attack by oxazole producing intermediates **107** and **108** which may lead to the formation of products **105** and **106**, respectively.

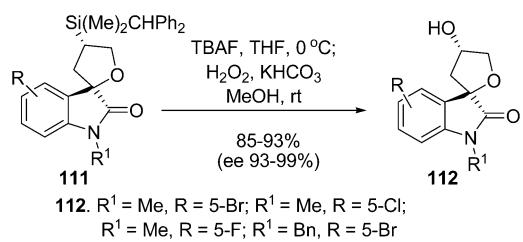
A catalytic asymmetric [3+2]-spiroannulation of isatins **1** with allylsilanes is reported recently to form the spiro-tetrahydrofuran-oxindoles **110** having a silyl group on a tetrahydrofuran ring.<sup>127</sup> A wide variety of the chiral Lewis acid metal complexes ( $\text{Pd}$ ,  $\text{Cu}$ ,  $\text{Ti}$ ,  $\text{Sc}$ ,  $\text{In}$ , etc.) were investigated under different conditions to optimize the reaction conditions. Finally, the use of chiral cationic  $\text{ScCl}_2(\text{SbF}_6)$ -pybox (**109**) complex in the presence of trimethylsilyl chloride as an essential activator in the reactions of various isatins **1** with allylsilane led to an exclusive formation of the desired product at room temperature in good yields and excellent enantioselectivity (Scheme 40). Transformation of the silyl group containing spiro-oxindoles **111** by oxidation of the Si–C bond led to the formation of the spiro-products **112** having a hydroxyl group on the tetrahydrofuran ring (Scheme 41).

A chiral phosphoric acid-catalyzed Pictet-Spengler type reaction upon addition of tryptamines to isatins leading to an enantioselective synthesis of functionalized spiro-tetrahydro- $\beta$ -carboline-oxindoles has been reported by Bencivenni and co-workers<sup>128</sup> and Franz and co-workers.<sup>129</sup> The former group optimized the procedure employing phosphoric acid (*S*)-**114b** bearing 2,4,6-triisopropylphenyl moiety in DMF at 40 °C. Franz and co-workers, after investigating many chiral bis-oxazolines, bifunctional thioureas, and phosphoric acids, identified phosphoric acid (*R*)-**114a** bearing an anthracenyl moiety (not studied by the Bencivenni group) as the optimized catalyst in dichloromethane besides (*S*)-**114b** in DMF offering high enantioselectivity and affording (*S*)-enantiomer of **115**

Scheme 40



Scheme 41



(Scheme 42, Table 2) characterized on the basis of X-ray crystallography analysis.<sup>129</sup>

Scheme 42

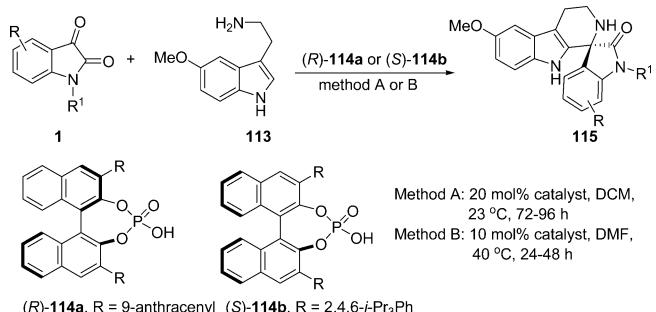


Table 2. Synthesis of Spiro-Tetrahydro-β-Carboline-Oxindoles 115

$R^1$	$R$	115 yields (%) method A (method B)	er method A (method B)
Me	5-Br	99 (70)	91/9 (82/18)
Me	5-Cl	99 (90)	92/8 (88/12)
Me	H	99 (99)	88/12 (95/5)
Me	5-OMe	99 (79)	58/42 (70/30)
Bn	H	99 (95)	82/18 (97/3)
PMB	H	72 (87)	87/13 (93/7)
PMB	5-Br	86 (81)	87/13 (75/25)
$\text{CH}_2\text{CCH}$	F	60 (86)	92/8 (92/8)
Ph	H	99 (44)	85/15 (97/3)
Ac	H	87 (53)	-
H	H	66 (99)	94/6 (94/6)
H	5-Cl	99 (88)	84/16 (80/20)
H	5-OMe	84 (92)	97/3 (96/4)

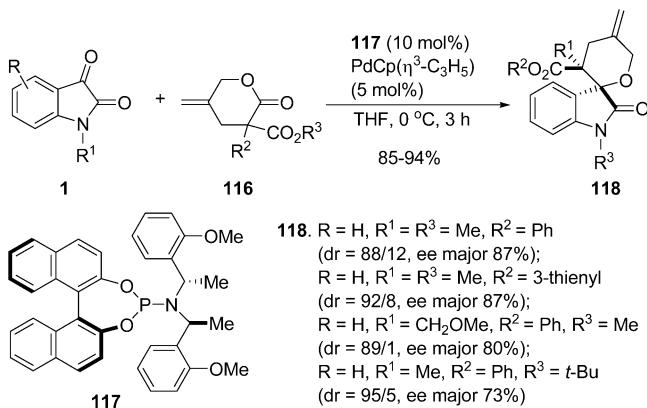
Although a variety of *N*-alkylated and NH-isatins and tryptamines are well-tolerated in the reaction with moderate to high enantioselectivity for both catalytic systems, their substituents also affected the yields and enantioselectivity. It was observed that the reactions of unsubstituted tryptamine or S-methoxytryptamine proceeded with high yields and moderate to high enantioselectivity, but other substituents or even the change in position of the methoxy group, such as from C-5 to C-6, deteriorated the enantioselectivity of the spiro-cyclization. Among isatins, halogen substitution at the C-5 of *N*-methylisatin led to an erosion of selectivity in comparison to the *N*-methylisatin with no substituent.

The authors observed that both (*R*)-114a and (*S*)-114b catalysts (in DMF), besides having opposite configurations of axial chirality, afforded the same (*S*)-enantiomer of the spiro-products 115 indicating that the substituents on the binaphthyl system (e.g., 9-anthracenyl vs 2,4,6-tri-*i*-Pr-phenyl) directed the sense of stereoinduction. The catalyst (*S*)-114b in DMF worked best in NH isatins presumably due to solubility reasons, whereas the catalyst (*R*)-114a worked best for halogen-substituted isatins. Bencivenni and co-workers also identified the catalyst (*S*)-114b under the same conditions as the most efficient catalyst and synthesized several spiro-tetrahydrocarboline-oxindoles in 68–97% yields and 71–95% ee using different isatins and tryptamines.<sup>128</sup> It is noteworthy to mention here that Yeung and co-workers have designed some compounds of this class that have been observed to exhibit potential antiplasmodial activity.<sup>20</sup> This group employed the Pictet-Spengler reaction specifically using 5-chloroisatin to synthesize the spiro-tetrahydrocarboline-oxindoles which showed potential antiplasmodial activity. In order to synthesize an enantiomerically pure product, the authors exploited the diastereoselective nature of the Pictet-Spengler reaction and used enantiomerically pure (*R*)- and (*S*)- $\alpha$ -methylindoleamines as substrates.

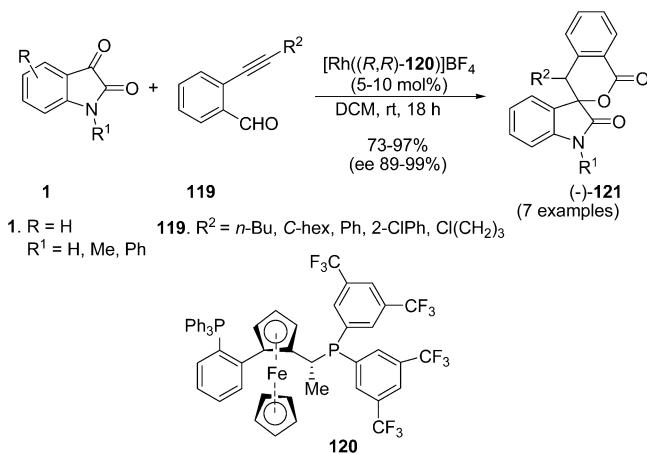
Hayashi and co-workers have reported a palladium-catalyzed decarboxylative cyclization of  $\gamma$ -methylidene- $\delta$ -valerolactones with isatins in the presence of a phosphoramidite ligand furnishing spiro-pyran-oxindoles with excellent diastereoselectivity (95/5 or even more).<sup>130</sup> The use of a *tert*-butyl group on ester in lactones and a newly prepared phosphorimidite bearing bis(diphenylmethyl)amino group on phosphorus enhanced the diastereoselectivity up to 97/3. Aryl-substituted and *N*-substituted isatins also undergo this reaction. The methodology has been extended to carry out an enantioselective synthesis of the products using chiral phosphoramidite 117 as a ligand. The reactions of *N*-methyl- and *N*-methoxymethylisatins 1 with lactones 116 proceeded smoothly at 0 °C to give the corresponding spiro-pyran-oxindoles 118 with promising stereoselectivity (dr = 88/12 to 92/8, major 73–87% ee) (Scheme 43). Further transformation of the products with LiAlH<sub>4</sub> afforded complex tetracyclic products with *N*,*O*-acetal functionality. A cationic Rh-catalyzed intermolecular [4+2]-annulation between isatins 1 and 2-alkynylbenzaldehydes 119 in the presence of [Rh((*R,R*)-120)]BF<sub>4</sub> has been developed by Tanaka and co-workers to access the corresponding spiro-benzopyranone-oxindoles 121 in excellent yields and enantioselectivity (up to 99%) (Scheme 44).<sup>131</sup>

List and co-workers have carried out a Bronsted acid-catalyzed model reaction between isatin 1 and 2-amino-benzamide 122 during their investigation on enantioselective synthesis of antihypertensive drugs.<sup>132</sup> After investigating several catalysts for optimization, the catalyst 114 was identified

Scheme 43

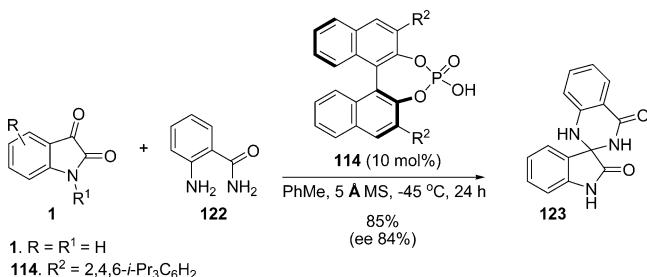


Scheme 44



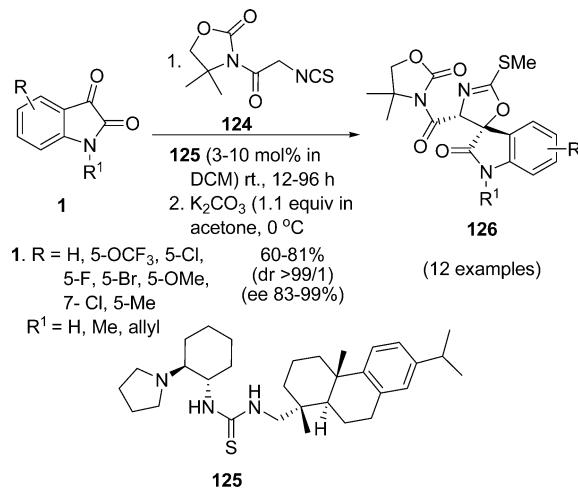
as the most efficient catalyst furnishing the product **123** in 85% yield and 84% ee (Scheme 45).

Scheme 45

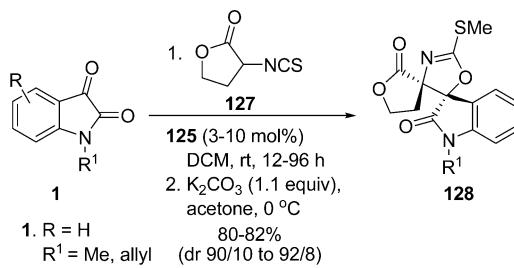


The reactions of isatins **1** with some acyclic- and cyclic-isothiocyanates **124** and **127** in the presence of chiral thiourea catalyst **125** result in the formation of novel spiro-oxazoline-oxindoles **126** and **128**, respectively (Schemes 46, 47) via thiocarbamates formed by the asymmetric aldol reaction.<sup>133</sup> A wide range of isatins including *N*-unsubstituted isatins have been employed in the study directed toward development of new antipyretic agents. The preliminary biological evaluation of the products using a model of acute neuroinflammation revealed promising antipyretic activity in many compounds which may serve as lead compounds in this area. The reaction of *N*-unsubstituted isatins **1** with *N*-protected 3-isothiocyanato-2-oxindoles **6** in the presence of triethylamine occurs under

Scheme 46

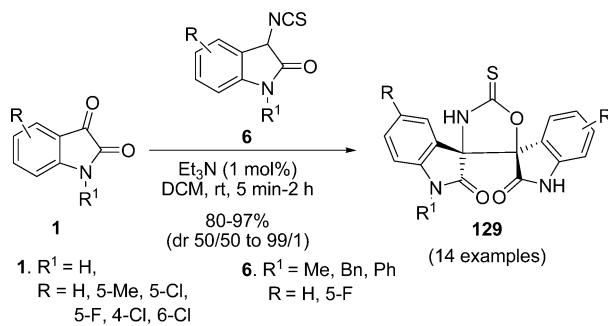


Scheme 47



mild conditions to afford the dispiro-oxazolidine-2-thione-bis(oxindoles) in a stereoselective manner **129** (Scheme 48).<sup>134</sup>

Scheme 48



The isomers were easily separable by simple column chromatography, and a single diastereomer could be obtained. The products were obtained in very high yields and diastereoselectivity with diverse types of isothiocyanates and isatins with exception of 4-chloroisatin where two diastereomers were obtained in equal amounts. Methylation and carboxylation of nitrogen atoms in one of the products were performed to get a spiro-compound with all nitrogen atoms protected.

The reactions of isatins directly with another component by cyclocondensation or cycloaddition, thus, have been employed in the synthesis of a number of spiro-heterocyclic frameworks. These include three- to eight-membered heterocycles bearing usually one or two heteroatoms. The cyclocondensation of isatins with 1,2-diamines affords the five-membered heterocycle imidazoline, whereas the similar reaction with 1,3-diamines

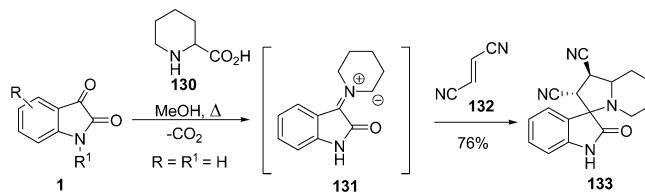
affords the six-membered heterocycle tetrahydroquinazolines. Analogous reactions with ethylene glycol and 2-amino-thiophenol are reported to form the spiro-dioxolane and spiro-thiazolidine, respectively. The 1,3-dipolar cycloadditions of isatins to oxygen ylides and nitrogen ylides have been employed in the synthesis of spiro-dioxolanes and spiro-oxazolines, respectively. The Darzens reaction of isatin and cycloaddition of isatins to ylide from  $\alpha$ -bromoamide and thiolane afford the scarce class of heterocyclic compounds spiro-cyclooxirane-oxindoles. The applications of catalysts such as the simple Lewis base triethylamine, Lewis acids ( $TiCl_4$ ), Bronsted acids such as phosphoric acid derivatives, metal-complexes, and chiral organocatalysts especially bifunctional thioureas have made it possible to synthesize most of these heterocycles diastereoselectively and enantioselectively. As a result of extensive optimization studies with regard to catalysts, solvents, and reaction conditions, excellent enantioselective methodologies have been developed for the synthesis of tetrahydroquinazolinones, oxazolines, 2-methylene- and 3-methylenepyrans, tetrahydrocarbolines, and oxolanes. A unique example of [2+2]-cycloaddition of isatins to disubstituted ketenes, catalyzed by a heterocyclic carbene, is reported to form the spiro- $\beta$ -lactones. A heterocyclic carbene, derived from L-pyroglutamic acid, also serves as an efficient asymmetric organocatalyst in the synthesis of spiro- $\gamma$ -lactone-oxindoles by [3+2]-annulation of isatins with  $\alpha,\beta$ -unsaturated aldehydes. Apart from these two-component reactions, isatins have been employed in three- and four-component-reactions forming spiro-heterocyclic frameworks that will be discussed in the next section.

#### 4.4. Synthesis Involving Three- or Four-Component Reactions of Isatins

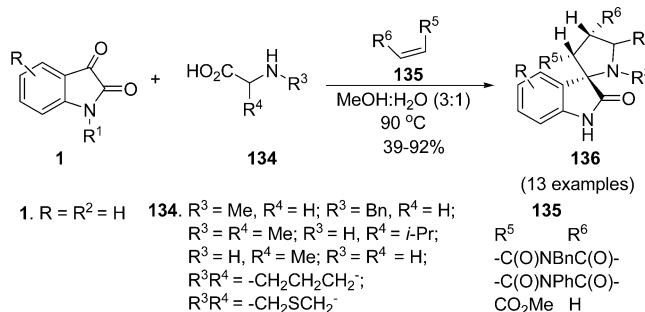
The design of reactions involving more than two components, usually referred to as multicomponent reactions (MCRs), for synthesizing molecules with complex structures has become an important area of research in organic, medicinal, and combinatorial chemistry.<sup>135–137</sup> Such strategies reduce the number of steps in schemes, thus avoiding the complicated purification procedures and allowing saving of both solvents and reagents. Three- and four-component reactions of isatins have been employed in the synthesis of five- to seven-membered spiro-heterocycles with one or more heteroatoms.

**4.4.1. Five-Membered Heterocycles.** Among five-membered spiro-heterocycles, the synthesis of spiro-pyrrolidine-oxindoles has been extensively investigated due to their occurrence in many natural products (Figure 5).<sup>138</sup> The 1,3-dipolar cycloaddition of azomethine ylides, generated from the decarboxylative condensation of isatins with  $\alpha$ -amino acids, to activated olefins represents an efficient method for construction of pyrrolidine structural unit spiro-fused to 2-oxindoles. In the early 1980s, a stereospecific 1,3-dipolar cycloaddition of fumeronitrile **132** to azomethine ylide **131**, generated from isatin **1** and picolic acid **131**, was reported to afford the spiro-pyrrolidine-oxindole (Scheme 49).<sup>139</sup> Later on, similar reactions were reported by employing proline and some other  $\alpha$ -amino acids to generate the azomethine ylides and methyl acrylate and some other  $\alpha,\beta$ -unsaturated ketones as dipolarophiles forming spiro-pyrrolidine-oxindoles.<sup>140</sup> Rehn and co-workers have reported the three-component reactions of isatin **1**,  $\alpha$ -amino acids **134**, and dipolarophiles **135** forming spiro-pyrrolidine-oxindoles **136** (Scheme 50).<sup>141</sup> Both *N*-unsubstituted and *N*-substituted  $\alpha$ -amino acids have been

Scheme 49



Scheme 50

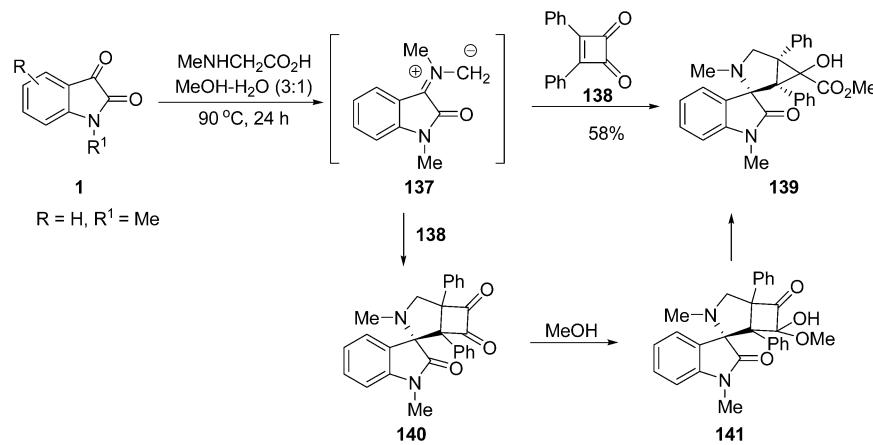


employed in the study. Shi and co-workers have reported the cycloaddition of ylides, generated from *N*-methylglycine and isatins, to acryloyl pyran-2-ones with excellent regioselectivity (99/1) to synthesize the spiro-pyrrolidine-oxindoles in excellent yields (87–97%).<sup>128</sup>

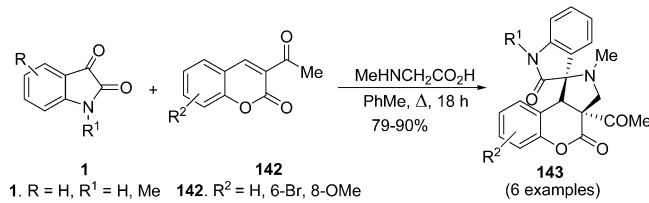
There are several reports in the literature on cycloadditions of alkenes to azomethine ylides, generated *in situ* by decarboxylative condensation of isatins with an  $\alpha$ -amino acid, sarcosine ( $MeNHCH_2CO_2H$ ), forming spiro-pyrrolidine-oxindoles. The cycloaddition of ylide **137** from *N*-methylisatin **1** and sarcosine to 3,4-diphenylcyclobutene-1,2-dione **138** proceeded smoothly to afford the product **139** (Scheme 51).<sup>142</sup> The formation of product was explained by methanol-initiated ring-contraction of the cyclobutane-dione ring in the initial cycloadducts **140** and **141**. Gandhi and co-workers have reported the reactions of isatins **1** with 3-acetyl-2*H*-chromen-2-ones **142** in the presence of sarcosine leading to the formation of spiro-pyrrolidine-oxindoles **143** in very good yields (Scheme 52).<sup>143</sup> Some other dipolarophiles employed in reaction of this ylide forming spiro-pyrrolidine-oxindoles involve 2-arylidene-1,3-indanediones<sup>144</sup> and 2-(2-oxindolin-3-ylidene)-malononitrile.<sup>145</sup> More recently, Raghunathan and co-workers have employed unsaturated sugar lactones,<sup>146</sup> steroid ketones,<sup>147</sup> and ferrocene-containing ketones<sup>148</sup> as dipolarophiles in 1,3-dipolar cycloaddition to azomethine ylides, generated from isatins and a range of acyclic and cyclic amino acids, affording spiro-pyrrolidine-oxindoles containing sugar, steroid, and ferrocene moieties, respectively. This group has also reported a solvent-free microwave-assisted protocol for diastereoselective synthesis of spiro-pyrrolidine-oxindoles.<sup>149,150</sup>

A 1,3-dipolar cycloaddition of (*E*)-3-aryl-1-(thiophen-2-yl)prop-2-en-1-ones **146** to azomethine ylide **145**, generated from isatin **1** and L-proline **144**, has been reported to form the 1'-aryl-2'-(2-thienylcarbonyl)-spiro[3*H*-indole-3,3'-[3*H*]-pyrrolizin]-2-ones **147** (Scheme 53).<sup>151</sup> Ganguly and co-workers have used *N*-phenylisatin **1**, proline **144**/sarcosine, and a chiral  $\alpha,\beta$ -unsaturated heterocyclic amide **148** having an oxazolidinone ring, prepared using the Evans chemistry from (*S*)-alanilol, to develop both solution- and solid-phase

Scheme 51



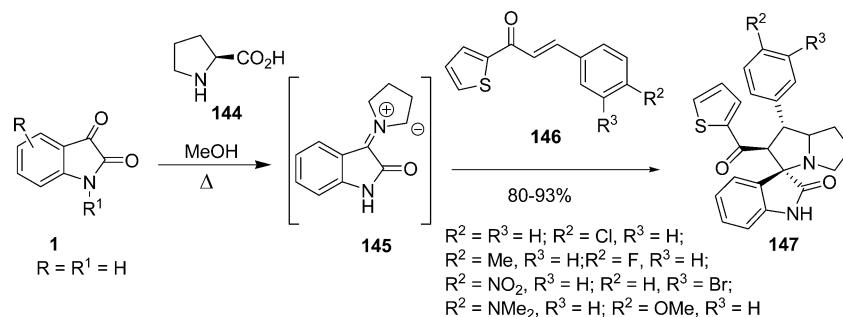
Scheme 52



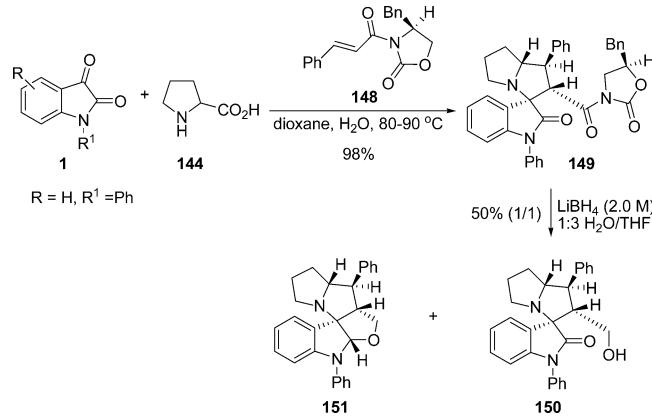
enantioselective methodology for the synthesis of spiro-pyrrolidine-oxindole 149.<sup>152</sup> Treatment of the single diastereomer 149, obtained from this reaction, with lithium borohydride afforded the enantiomerically pure spiro-pyrrolidine-oxindole 150 together with a fused-pentacyclic product 151 in equal yields (Scheme 54). The solid-phase synthesis was carried out with another chiral dipolarophile that was bound to Merrifield resin.

There are many reports in the literature on formation of bis-spiro-pyrrolidine-oxindoles by reaction of azomethine ylides, generated from sarcosine and isatins, with compounds having carbonyl groups. The reactions of cycloalkanones 152, benzocyclohexanone 154, and *N*-substituted piperidin-4-ones 156 with isatins in the presence of sarcosine result in the synthesis of bis-spiro-fused 2-oxindoles 153, 155, and 157, respectively (Scheme 55).<sup>153,154</sup> Using 3-[*(E*)-2-oxo-2-arylethylidene]-2-oxindoles as dipolarophiles, the bis-spiro-pyrrolidines bearing two 2-oxindole moieties have been synthesized.<sup>155</sup> The ylides, generated from isatins and *N*-methylglycine,<sup>128</sup> undergo cycloaddition with isatylidene malononitriles to furnish the dispiro-pyrrolidine-bisspiro-oxindoles.<sup>156</sup>

Scheme 53

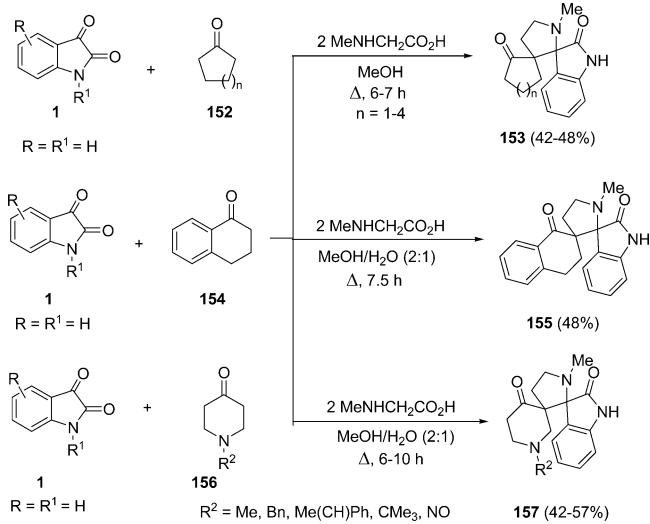


Scheme 54



The reaction of mercaptoacetic acid 159, instead of an amino acid, isatin 1, and 4-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-ylsulfonyl)aniline 158 leads to the synthesis of spiro-thiazolidinone-oxindole 160 (Scheme 56).<sup>157</sup> The aldol condensation of D-glucose 161 and 4-chlorobenzaldehyde to 4-thiazolidinone ring of 160 have led to formation of the corresponding 4-alkylidene derivatives 162 and 163. The spiro-fused 2-oxindole 163 has been further transformed into spiro-thiazoline-oxindoles by reactions with thiourea, hydrazine hydrate/phenyl hydrazine, ethylcyanoactate, and malononitrile forming differently functionalized spiro-thiazoline-oxindoles 164–167 (Scheme 57). Hu and Feng have reported the [2+3]-cycloaddition of azomethine ylide 168, generated from isatin 1 and sarcosine, onto the arylmethylene moiety present in 5-aryl-2,10-bis(aryl methylene)-2,3,6,7,8,9-hexahydro-5*H*,10*H*-

Scheme 55



cycloheptano[1,2-d]thiazolo-[3,2-a]pyrimidine-3-ones **169** forming novel spiro-2-oxindoles **170** in a regioselective manner (Scheme 58).<sup>158</sup> The three-component reactions of isatin/S-chloroisatin/5-nitroisatin **1**, 2-arylmethylene-1-indanones **171**, and 1,3-thiazolidine-4-carboxylic acid **172**, however, have been reported to give bis-spiro-thiazolidinopyrrolidine-dioxindoles **173** (Scheme 59) that have shown significant antitubercular activity.<sup>159</sup>

A three-component reaction of several isatins **1**, phthalhydrazide **174** malononitriles, or cyanoacetic ester **175** catalyzed by nickel chloride in polyethylene glycol 600 (PEG 600) constitutes an efficient one-pot procedure for the synthesis of spiro-pyrazolophthalazine-oxindoles **176** in good to excellent yields (Scheme 60).<sup>160</sup> A sequence of the Knoevenagel reaction between isatins and nitriles, the aza-Michael addition of phthalhydrazide to the Knoevenagel-adducts, cycloaddition, and isomerization has been proposed to furnish the product. The role of nickel chloride is assumed to be the Lewis acid for activation of nitriles to be transformed into amines.

The reaction of *N*-substituted isatins **1**, aryl-/alkylisocyanides **177**, and allenoates **178** is reported recently to furnish the spiro-butanolide-oxindoles **179** (Scheme 61).<sup>161</sup> The cyclohexyl- and other alkyl isocyanides offered better yields (68–83%) than aromatic isocyanides especially those with electron-

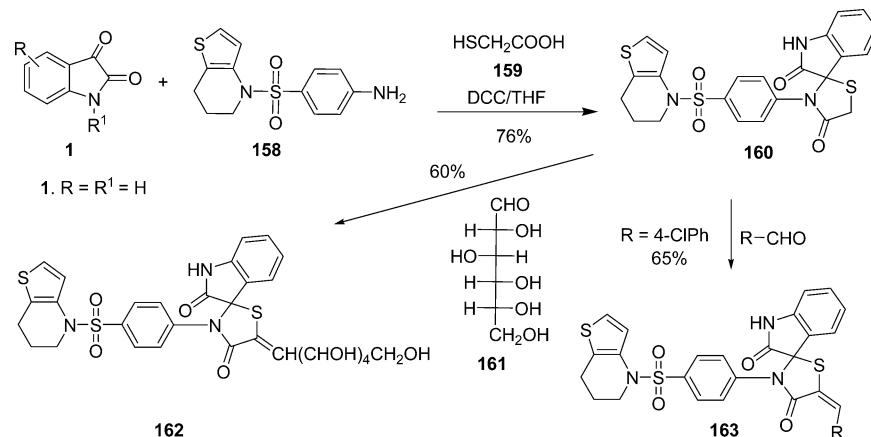
withdrawing groups such as chloro- or bromo groups which furnished products in 38–39% yields. Both electron-donating and electron-withdrawing groups on different positions of the phenyl ring of isatin also offered excellent yields (67–91%) except the sterically demanding isatins bearing chloro group(s) at C-4 or C-4,6 positions which afforded products in 52% and 47% yields, respectively. The reaction has been successfully extended to  $\alpha$ - and  $\gamma$ -substituted allenoates.

The formation of products has been suggested to be initiated by formation of zwitterionic intermediates **180** from isocyanides **177** and allenoates **178** followed by its trapping by the C-3 carbonyl group of isatin **1** forming the spiro-products **181** which isomerize through enolization to the final products **179** (Scheme 62). The potential of this methodology for synthesis of spiro- $\gamma$ -lactone-oxindoles has been demonstrated by transformation of C=N linkage in compounds **179** to the C=O bond as a result of chemoselective acidic hydrolysis.

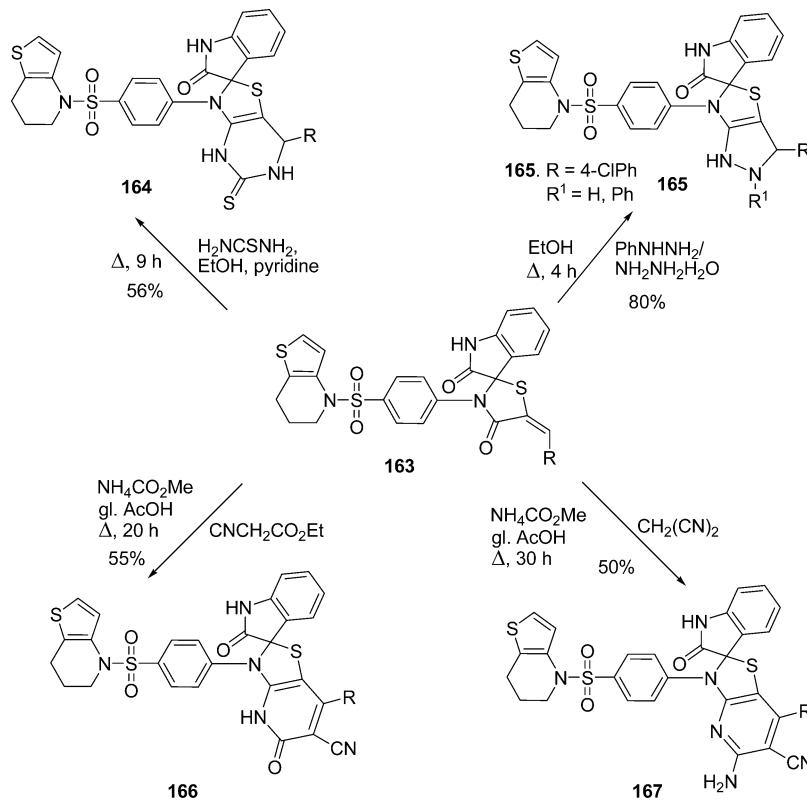
The *N*-heterocyclic carbenes (NHC)-mediated reactions of isatins have been employed in the synthesis of spiro- $\gamma$ -lactone-oxindoles.<sup>162</sup> The reaction of isatins **1** and cinnamaldehydes **96** (2.5 equiv of **1**) in the presence of a NHC-precursor **182** (6 mol %) and DBU (12 mol %) as a base resulted in the formation of two easily separable diastereomers of the spiro- $\gamma$ -lactone-oxindoles **183** (Scheme 63) in excellent yields (up to 98%) at room temperature. The reaction, which proceeded through carbene-aldehyde enol-adduct, was successfully carried out with *N*-methyl/allyl/*n*-propyl isatins bearing a strong electron-withdrawing group such as bromo or an electron-donating group such as methoxy on the C-5 position.

**4.4.2. Six-Membered Heterocycles.** Chen and Shi have developed an efficient method for the synthesis of spiro-pyridine-oxindoles by reactions of isatin, 5-amino-3-methylpyrazole, and 1,3-dicarbonyl compounds in aqueous medium using cerium(IV) ammonium nitrate (10 mL%) as a catalyst.<sup>163</sup> The products were obtained in up to 90% yields by heating the reaction mixture at 80 °C for 6–12 h. The authors have discussed the mechanistic details to confirm the order of nucleophilic additions and proposed a reaction route proceeding through a 3-hydroxy-2-oxindole intermediate. Quiroga and co-workers investigated this reaction of isatin by taking several  $\beta$ -diketones and three pyrazoles, 3-methyl-1-phenyl-5-aminopyrazole, 3-phenyl-5-aminopyrazole, and 3-methyl-5-aminopyrazole.<sup>164</sup> The reaction of isatin **1**, 3-methyl-1-phenyl-5-aminopyrazole **184**, and diketones **185**

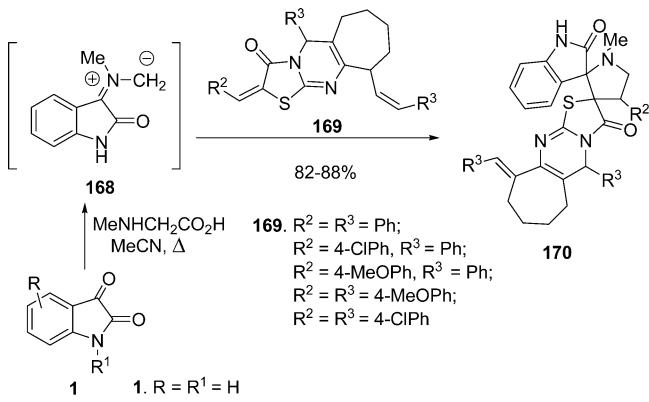
Scheme 56



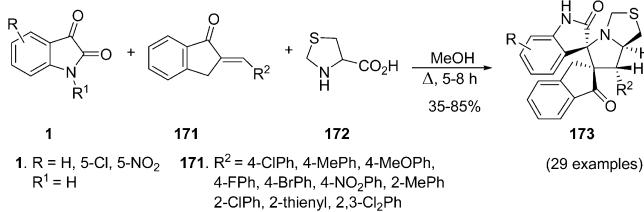
Scheme 57



Scheme 58

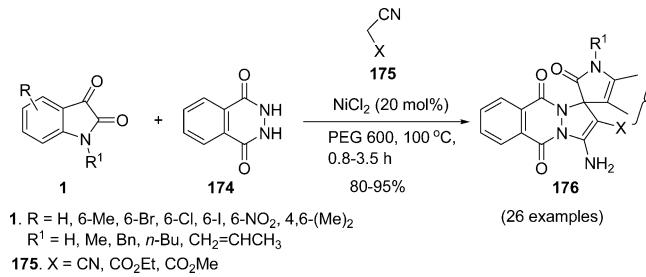


Scheme 59

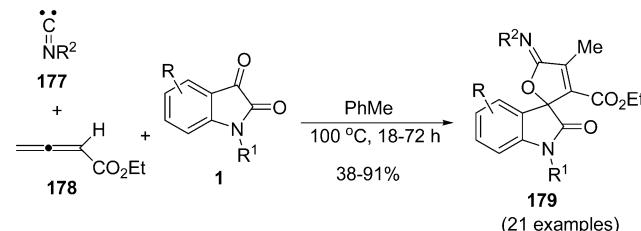


afforded the spiro-pyrazolo[3,4-b]pyridine-oxindoles **186** (Scheme 64). There could be two possible products **188** and **189** from the latter two *N*-unsubstituted pyrazoles **187** due to the presence of an additional nitrogen nucleophilic center, but the reaction was completely regioselective and afforded product **188** (Scheme 65) exclusively. The authors considered this outcome of the reaction due to the high nucleophilicity of the

Scheme 60



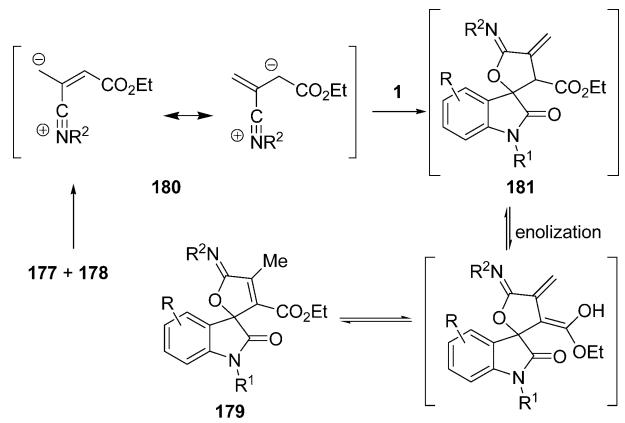
Scheme 61



C-4 in comparison to *N*-1 in 3-phenyl- and 3-methyl-5-aminopyrazoles.

According to the proposed mechanism, isatin **1** first reacted with  $\beta$ -diketones **185** to give the condensation product **190** which underwent a Michael-type addition of 5-aminopyrazoles **187** followed by cyclocondensation of the intermediate adduct **191** to give the final products **188** (Scheme 66). A similar

Scheme 62

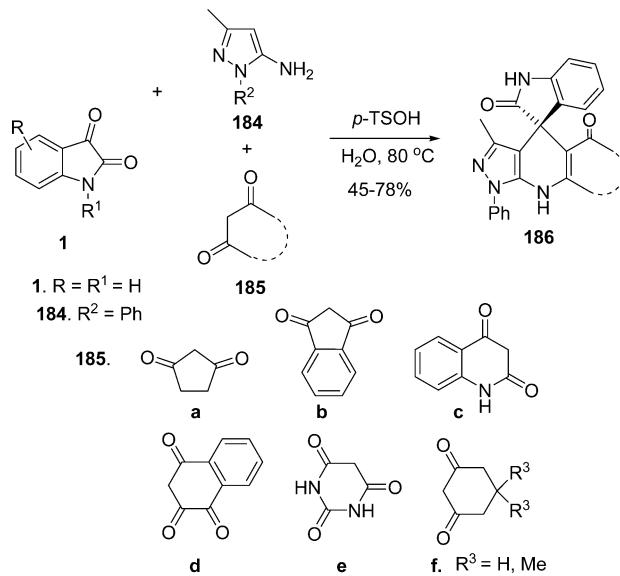


mechanism was proposed earlier by Bazgir and co-workers in their report on reactions of isatins, amines, and indane-1,3-dione/acenaphthenone producing spiro-dihydropyridine-oxindoles.<sup>165</sup> In this case, however, the reaction was performed by grinding all three components of the reaction and the catalyst in an agate mortar for 5–10 min affording products in very good yields (80–91%). The yield, in the absence of the catalyst, diminished significantly (<40%) even on grinding for a longer time; perhaps this is why the authors have described the methodology as “pseudo four-component reaction”. More recently an ionic liquid *N,N,N,N*-tetramethylguanidinium triflate has been used as a catalyst in the three-component reactions of isatins, (2*H*)-indene-1,3-dione, and 1- or 2-naphthyl amine forming spiro-dihydropyridine-oxindoles.<sup>166</sup>

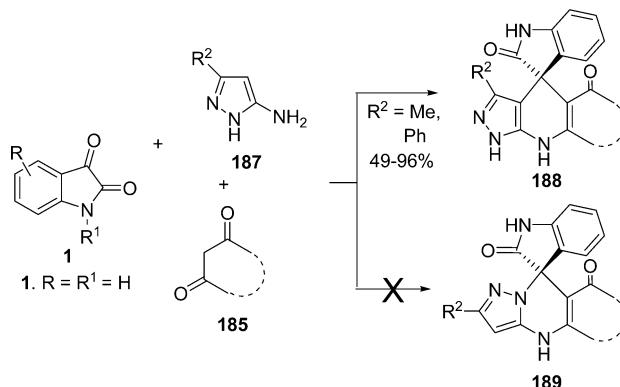
Zhu and co-workers reported a simple and clean procedure for the synthesis of spiro-pyran-oxindoles in 2007.<sup>167</sup> The procedure involved a reaction between isatin, active methylene reagents such as malononitrile or methyl cyanoacetate, and cyclohexane-1,3-diones, mediated by the surfactant triethylbenzylammonium chloride (TEBA) in water. This report was followed by several other papers reporting the synthesis of spiro-pyran-oxindoles using similar methodologies. For example, a three-component reaction of isatins, malononitrile, and 1,3-diketones was reported to form the spiro-pyran-oxindole derivatives via a domino Knoevenagel/Michael/cyclization sequence.<sup>168</sup> In another communication, a three-component reaction of isatins **1**, ethylcyanoacetate or malononitrile, and 3-methylpyrazol-5-one **192** in the presence of triethanolamine was reported to furnish the spiro-pyran-oxindoles **193** or **194** in reasonable yields (Scheme 67).<sup>169</sup> The reaction of malononitriles occurred in boiling ethanol but of ethyl cyanoacetate occurred at room temperature.

The three-component reactions of isatins, malononitrile, and 3-methylpyrazol-5-one have been investigated by Elinson and co-workers using electrochemical means.<sup>170</sup> The reactions in

Scheme 64



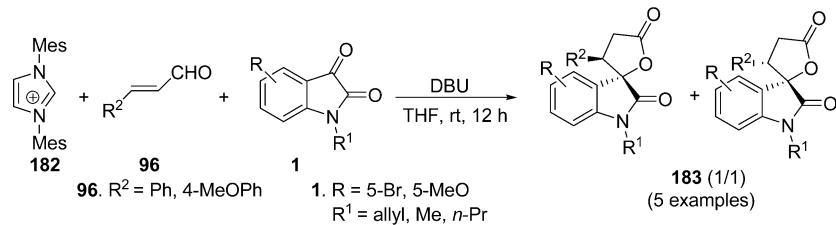
Scheme 65



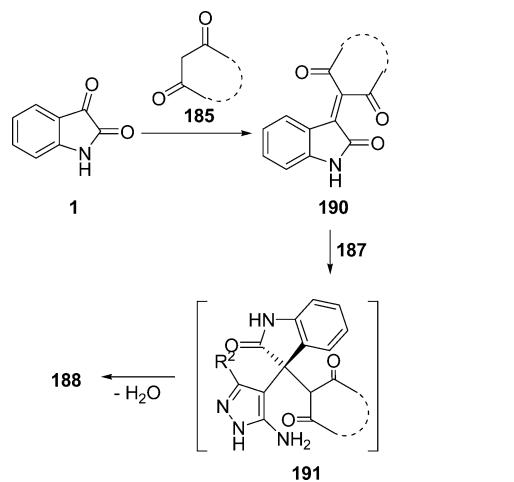
ethanol in an undivided cell using NaBr as an electrolyte afforded the spiro-products in 78–91% yields. Shanthi and Perumal have used isatins, malononitrile, and phthalhydrazide as substrates in this reaction using L-proline as a catalyst in ethanol affording pyrazolophthalazinyl spiro-oxindoles in excellent yields.<sup>171</sup> Hari and Lee have used cyclohexane-1,3-diones in an aqueous medium using ethylenediamine as a catalyst.<sup>172</sup> Zhao and co-workers have carried out this reaction with a variety of 1,3-diketones in an aqueous medium under catalyst-free conditions.<sup>173</sup> Recently, a biocatalytic method has been developed using lipase from porcine pancreas (PPL) to get products in up to 95% yield.<sup>174</sup>

A four-component combinatorial synthesis of several spiro-pyran-oxindoles was reported using isatins, malononitrile, ethyl

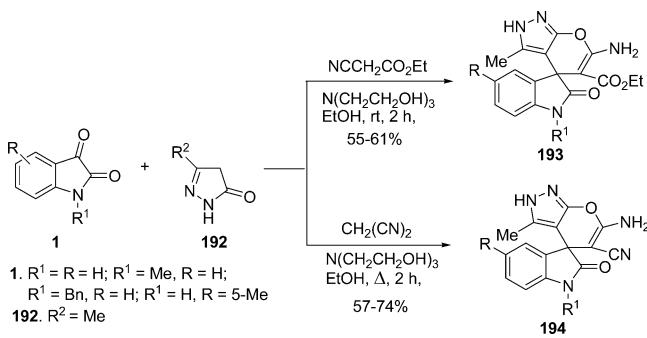
Scheme 63



Scheme 66



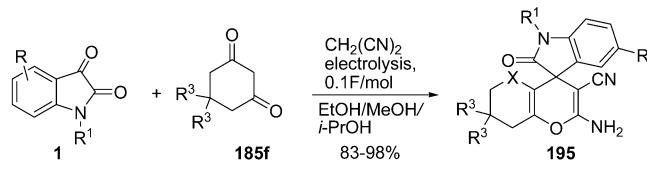
Scheme 67



acetoacetate, and hydrazine hydrate in the presence of triethylamine in refluxing ethanol.<sup>129</sup> Recently, this reaction has been observed to be accelerated by ultrasonic irradiation.<sup>175</sup> The four component reaction of isatins,  $\beta$ -ketoesters, malononitrile or ethyl cyanoacetate, and hydrazine hydrate is catalyzed by piperidine under ultrasonic irradiation to afford the spiro products in 69–93% yields. The key steps in the reaction involve the condensation of hydrazines with  $\beta$ -ketoesters to give a pyrazolone intermediate and the Michael addition of this intermediate with alkylidene isatins obtained by the Knoevenagel reaction of isatins with nitriles.

Elinson and co-workers have synthesized spiro-pyran-oxindoles 195 by electrocatalytic reactions of isatins 1, cyclohexanones 185f, and malononitrile under neutral and mild conditions in an undivided cell in alcoholic solvents in the presence of sodium bromide as an electrolyte (Scheme 68).<sup>176</sup> The electrochemical reaction of isatins and malononitrile has also been reported recently in the presence of 4-hydroxyquino-

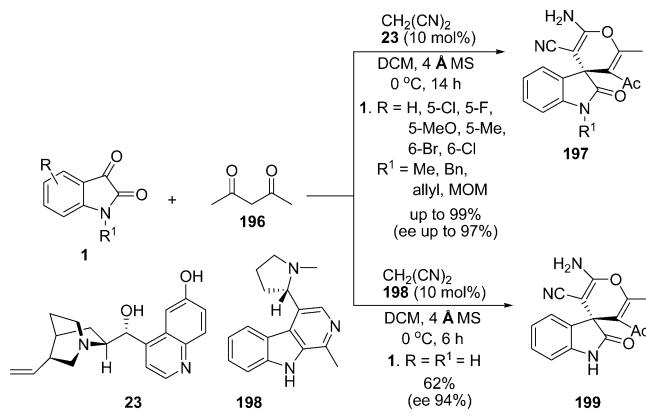
Scheme 68



line-2(1*H*)-one resulting in the formation of spiro-oxindoles with fused functionalized indole-3,4'-pyrano[3,2-*c*]quinoline scaffold in 75–91% yields.<sup>177</sup> Li and co-workers have also reported a similar MCR catalyzed by L-proline, but no enantioselectivity was observed in this reaction.<sup>178</sup>

The first enantioselective example of the above sequence was developed by asymmetric organocatalysis using cupreine as a catalyst.<sup>179</sup> Optically active spiro-4*H*-pyran-oxindoles 197 were obtained in excellent yields (up to 99%) with good to excellent enantioselectivity (up to 97%) in the reaction of isatins 1, pentane-2,4-dione 196, and malononitrile in the presence of cupreine 23 (Scheme 69). A similar asymmetric organocatalytic

Scheme 69

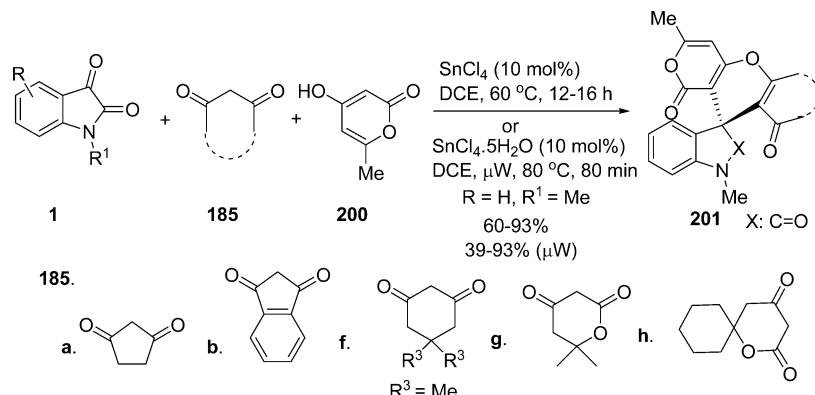


reaction of isatin/*N*-benzylisatin, malononitrile, and ethyl acetoacetate/pentane-2,4-dione has been investigated recently in the presence of cinchonine, cinchonidine, and (*S*)-brevicolline 198.<sup>180</sup> Although the former two catalysts gave better yields (60–98%) of spiro-pyran-oxindoles, the latter catalyst, a natural product isolated from plant *Carex brevicollis*, offered better enantioselectivity. The reaction of isatin 1, malononitrile, and pentane-2,4-dione 196 catalyzed by (*S*)-brevicolline 198 afforded the product 199 in 62% yield and 94% ee (Scheme 69).

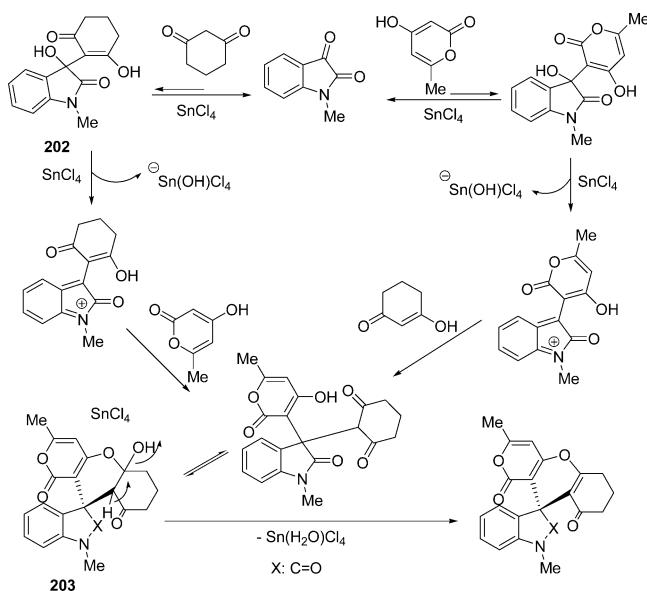
Stephenson and co-workers have employed the Lewis acid catalyst tin(IV) chloride in the three-component reaction of *N*-methylisatin 1 with two  $pK_a$ -differentiated 1,3-dicarbonyl compounds forming spiro-pyran-oxindoles.<sup>181</sup> The reactions were carried out under conventional heating and microwave irradiation; the latter taking much lower time as usual. In one set of investigation, the *N*-methylisatin and cyclohexane-1,3-dione were reacted with some acyclic and cyclic ketones and in another set *N*-methylisatin 1 and 4-hydroxy-6-methyl-2-pyrone 200 were reacted with some cyclic 1,3-diketones 185 (Scheme 70) to afford the spiro-products 201 with comparatively higher yields in the latter set. The authors have proposed the mechanism of formation of product via aldol condensation and involvement of an indolenium ion derived from the isatin and one 1,3-dicarbonyl compound in two different ways (Scheme 71). Two of the intermediates 202 and 203 were prepared independently and converted into the spiro-product under the reaction conditions.

A four-component reaction of isatin 1, 1-phenyl-2-(1,1,1-triphenyl- $\lambda^5$ -phosphorylidene)-1-ethanone 11, benzylamine 204, and methyl acetoacetate 205 in dry methanol under reflux has been reported as an effective route to synthesize the spiro-dihydropyridine-oxindole 206 (Scheme 72).<sup>182</sup> The

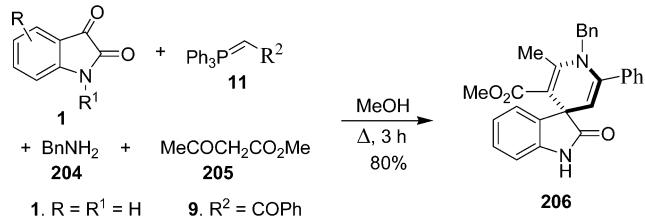
Scheme 70



Scheme 71



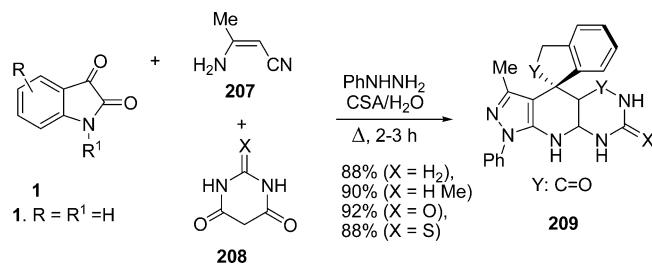
Scheme 72



reaction has been extended to substituted benzylamines, allylamine, *n*-propylamine, *iso*-butylamine, and *p*-anisidine either in the presence of methyl- or ethylcarboxylate affording the products in 74–85% yields. The formation of the products has been explained by a reaction between isatin and the Wittig reagent forming 3-alkylideneisatins and a reaction between amines and the methyl acetoacetate forming the condensation product. Finally, this condensation product reacts with 3-alkylideneisatins to afford the final product. A four-component reaction of isatins, aromatic amines, dimethyl acetylenedicarboxylate, and cyclohexane-1,3-dione is reported to occur in acetic acid at room temperature to afford the spiro-dihydropyridine-oxindoles.<sup>183</sup>

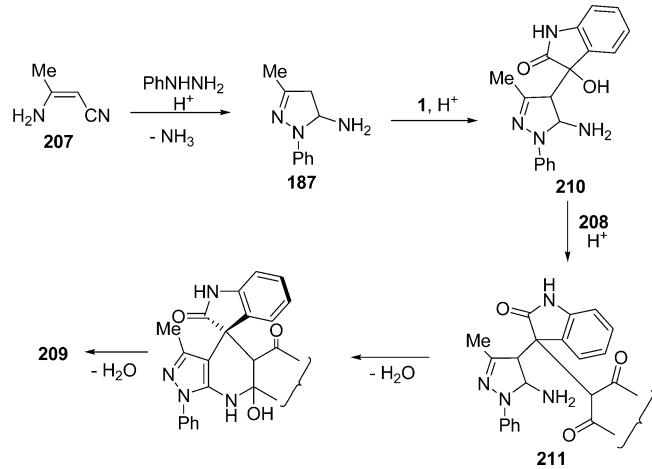
A four-component domino reaction of isatin **1**, phenylhydrazine, 3-aminocrotononitrile **207**, and cyclic  $\beta$ -diketones/amide/thioamide **208** in an aqueous medium in the presence of ( $\pm$ )-camphor-10-sulfonic acid on heating at 100 °C for 2–3 h afforded the spiro-fused 2-oxindoles **209** (Scheme 73).<sup>184</sup> The

Scheme 73



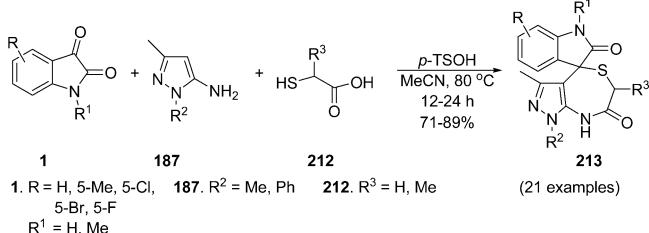
reaction was successfully extended to 5-chloro- and 5-nitroisatins. According to the proposed mechanism, an acid-catalyzed reaction of phenylhydrazine with nitrile **207** affords the 5-amino-3-methyl-1-phenyl pyrazole **187** which adds onto the isatin carbonyl group furnishing an intermediate product **210**. The acid-catalyzed reaction of this intermediate, which has been isolated, with carbonyl compounds **208** affords another intermediate compound **211** which affords the final products **209** by cyclodehydration and subsequent dehydration (Scheme 74).

Scheme 74



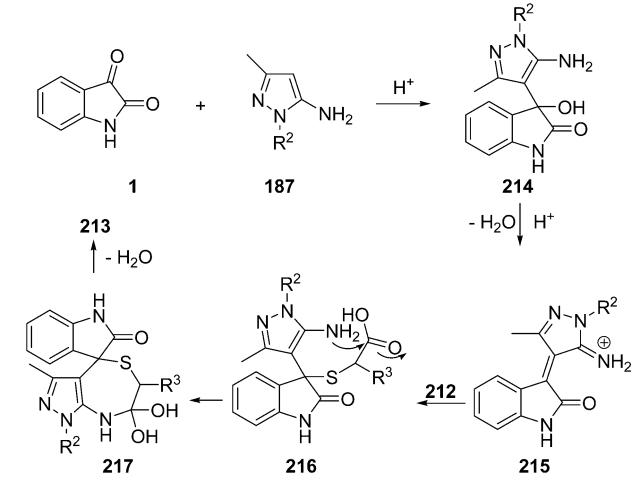
**4.4.3. Seven-Membered Heterocycles.** A three-component reaction of isatins **1**, 1-phenyl/methyl-3-methyl-5-amino-pyrazoles **187**, and mercaptoacetic acids **212** in the presence of *p*-toluenesulfonic acid as a catalyst is reported to afford the spiro-thiazepinone-oxindoles **213** (Scheme 75).<sup>185</sup> The reac-

Scheme 75



tion is proposed to occur through the nucleophilic addition of pyrazoles to isatin forming the Baylis-Hillman type adduct **214** (Scheme 76) which undergoes protonation of the hydroxyl

Scheme 76



group followed by dehydration affording another intermediate **215**. The Michael addition of mercaptoacetic acids to intermediate **215** forming an intermediate product **216** followed by cyclization to the spiro-fused heterocycle **217** and dehydration in it leads to the formation of final product **213**. In order to confirm the mechanism, the initial adduct **214** was isolated by carrying out the reaction under controlled conditions.

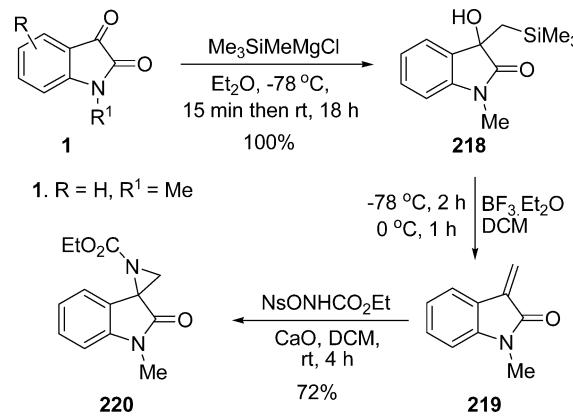
The literature review on multicomponent reactions of isatins reveals three- and four-component reactions employed in the synthesis of five- to seven-membered spiro-heterocycles; the most common being spiro-pyrrolidines and spiro-pyrans. The 1,3-dipolar cycloadditions of azomethine ylides, generated from decarboxylative condensation of isatins with  $\alpha$ -amino acids, to different types of dipolarophiles constitute a common method for the synthesis of diverse types of spiro-pyrrolidine framework. Another extensively investigated protocol is the reactions of isatins, malononitrile, or ethyl cyanoacetate and different types of carbonyl compounds furnishing spiro-pyrans. On a promising note, asymmetric version of this reaction is also reported employing chiral organocatalysts such as cupreine and (*S*)-brevicolline. The spiro-pyrans, however, have also been synthesized by a Lewis acid-catalyzed reaction of isatins with

two different carbonyl compounds in one pot. Only a few four-component reactions involving isatins are reported; these reactions lead to the formation of six-membered spiro-azaheterocycles and spiro-oxaheterocycles. A *p*-toluenesulfonic acid-catalyzed three-component reaction of isatins, mercaptoacetic acids, and 5-aminopyrazoles represents a novel method for constructing the seven-membered ring spiro-thiazepinones. It is interesting to note that many reactions have been performed in an aqueous medium using nonconventional techniques such as microwave and ultrasonic irradiations with greatly reduced reaction times. The stereochemical control, however, remains a challenging endeavor in MCRs. There are many synthetic procedures in which isatins, instead of being used directly in two- to four-component reactions, are first transformed into appropriate 3-functionalized 2-oxindoles that are used as precursors for spiro-fused cyclic compounds.

#### 4.5. Multistep Synthesis from Isatins via C-3 Functionalization

**4.5.1. Three-Membered Heterocycles.** Loreta and co-workers have studied the synthesis of spiro-aziridine-oxindoles and spiro-oxirane-oxindoles by aziridination and epoxidation, respectively, of isatin-3-alkylidene derivatives.<sup>186–188</sup> As a model 2-oxindole for aziridination, this group synthesized 1-methyl-3-methylene-2-oxindole **219**<sup>152</sup> by Peterson's olefination of *N*-methylisatin, proposed by Rossiter for the preparation of 3-methylene-2-oxindole itself.<sup>189</sup> In this protocol, the reaction of (trimethylsilyl)methylmagnesium chloride with *N*-methylisatin **1** afforded the corresponding alcohol **218** which underwent dehydration in  $\text{BF}_3\text{-Et}_2\text{O}$  to afford the oxindole **219** which on aziridination with ethyl [(4-nitrophenyl)sulfonyl]oxy carbamate,  $\text{NsONHCO}_2\text{Et}$ , afforded the spiro-aziridine-oxindole **220** (Scheme 77). The aziridination was extended to

Scheme 77



the synthesis of spiro-aziridine-oxindoles from 3-methylene-2-oxindoles, and from an alkoxy carbonyl group bearing 3-methylene-2-oxindoles, obtained from isatin itself and other *N*-substituted isatins by Horner-Wadsworth-Emmons reaction<sup>190</sup> with trialkyl phosphonoacetates.<sup>178</sup> Most recently, the Wadsworth-Emmons reaction of mono- and disubstituted isatins **1** with tetraethyl methylenebis(phosphonate) **221** has been reported to afford the 3-(phosphoromethylene)-2-oxindoles **222** which on epoxidation with hydrogen peroxide led to the formation of spiro-oxirane-oxindoles **223** (Scheme 78, Table 3) while on aziridination with  $\text{NsONHCO}_2\text{Et}$  yielded the spiro-aziridine-oxindoles.<sup>179</sup> It is noteworthy to mention that the synthesis of aziridines remains a challenging endeavor

Scheme 78

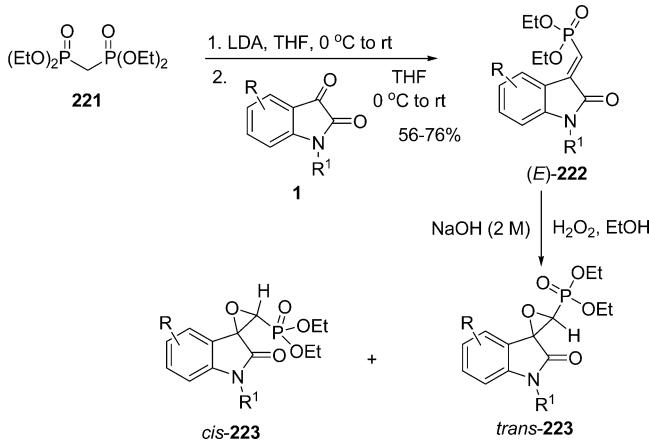


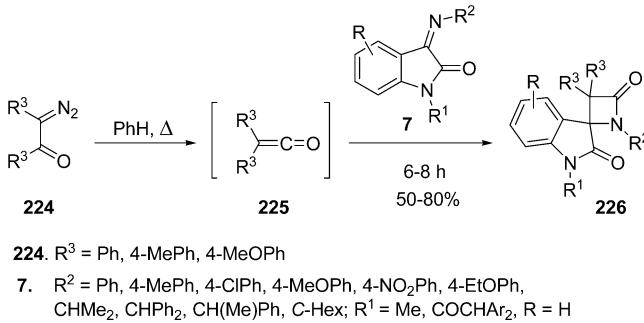
Table 3. Synthesis of Spiro-Oxirane-Oxindoles 223

R <sup>1</sup>	R	223 yields (%)	cis:trans
Me	H	80	78:22
Ph	H	78	80:20
-CH <sub>2</sub> -(2,4-(Cl) <sub>2</sub> )Ph	H	89	75:25
Bn	H	80	85:15
Bn	5-OMe	96	83:17
Bn	5-i-Pr	92	92:8

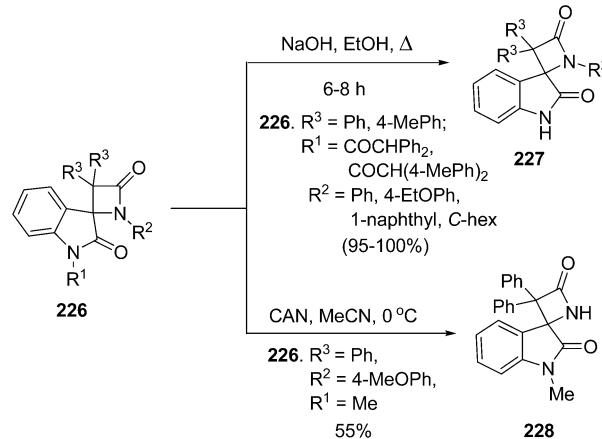
due to ring-strain associated with it. Many of them, even though, occur in nature and are biologically important compounds.<sup>191</sup>

**4.5.2. Four-Membered Heterocycles.** In the recent past, the synthesis, reactivity, and structures of 2-azetidinones spiro-fused to 2-oxindoles have been studied by many groups including ours.<sup>192</sup> The most common methods for synthesis of spiro-fused 2-azetidinones are the same as for the synthesis of monocyclic 2-azetidinones such as the Staudinger's ketene-imine cycloadditions and cyclization of  $\beta$ -amino acids.<sup>193</sup> For creating a spiro- $\beta$ -lactam framework by the Staudinger ketene-imine cycloaddition, however, any one component of the reaction must be cyclic. The ketenes are generated either by thermal or photochemical decomposition of  $\alpha$ -diazoketones followed by the Wolff-rearrangement<sup>194</sup> of the resulting  $\alpha$ -ketocarbenes or from dehydrochlorination of acid chlorides using a tertiary amine base. Our group reported for the first time the synthesis of 2-azetidinones spiro-fused to C-3 of 2-oxindoles by reaction of 2-diazo-1,2-diphenylethanone with N-methylisatin-3-imines.<sup>195</sup> Since then, the reactions of diphenylketene, di-p-tolylketene, and di-p-anisylketene, generated from the corresponding 2-diazo-1,2-diarylethanones, with isatin 3-imines have been reported to form several spiro-azetidinone-oxindoles.<sup>196,197</sup> Recently, the reactions of diarylketenes 225, generated *in situ* from 2-diazo-1,2-diarylethanones 224, with 3-alkylimino-N-methylindolin-2-ones 7 have been reported to yield spiro-fused 2-azetidinones 226 in good yields (Scheme 79) but with poor-to-moderate antibacterial activity.<sup>198</sup> Simple transformations of compounds 226 to 1-unsubstituted spiro-fused oxindoles 227 and 1'-unsubstituted spiro-fused oxindole 228 have been achieved by chemoselective removal of groups attached to these nitrogen atoms using ethanolic NaOH<sup>199</sup> and CAN, respectively (Scheme 80).<sup>200</sup> The free NH group in these compounds can be utilized for introduction of various other groups including heterocyclic motifs of desired biologic interest.

Scheme 79

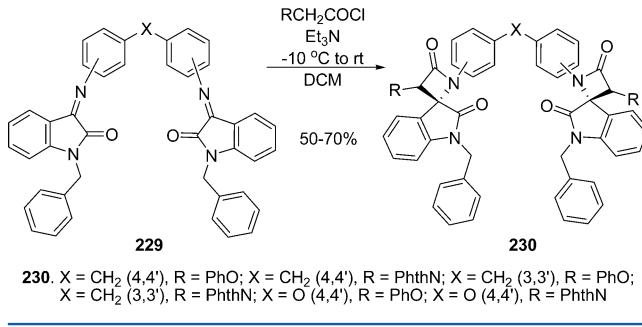


Scheme 80



The synthesis of isatin imines-derived mono- and bis-spiro-azetidinone-oxindoles using the Staudinger ketene-imine cycloaddition has been reported by Jarrahpour and Khalili as well.<sup>201</sup> Bisimines 229, obtained from the reaction of N-benzylisatin with various diamines, were treated with different acyl chlorides in the presence of triethylamine to give the bis-spiro-azetidinone-oxindoles 230 in reasonable yields (Scheme 81). The reactions of 3-arylimino-1-methyl-2-oxindoles have

Scheme 81

230. X = CH<sub>2</sub> (4,4'), R = PhO; X = CH<sub>2</sub> (4,4'), R = PhthN; X = CH<sub>2</sub> (3,3'), R = PhO; X = CH<sub>2</sub> (3,3'), R = PhthN; X = O (4,4'), R = PhO; X = O (4,4'), R = PhthN

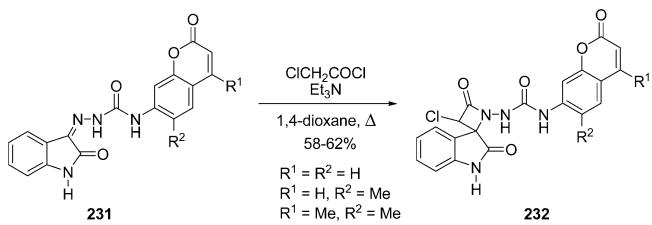
also been carried out with dichloroketene to synthesize the corresponding spiro-azetidinone-oxindoles.<sup>202</sup> The Staudinger ketene-imine cycloaddition of isatin-3-semicarbazone 231 containing coumarin moiety with chloroacetyl chloride in the presence of triethylamine has been reported to form the spiro-azetidinone-oxindoles 232 (Scheme 82) having a chloro group at the C-4 position of the azetidinone ring that exhibit significant antibacterial activity.<sup>203</sup>

Nishikawa and co-workers during their synthetic endeavor toward the chartelline bearing spiro-azetidinone-indole moiety

6127

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Scheme 82



have reported the synthesis of spiro-azetidinone-oxindoles **239** by cyclization of 2-oxindole-tethered  $\beta$ -amino acids **235–237** (Scheme 83).<sup>204</sup> The reaction of 3-N-(4-methoxyphenylimino)-2-oxindole **226** with ketene silyl acetal **233** of ethyl acetate in  $\text{BF}_3\text{-Et}_2\text{O}$  afforded the corresponding  $\beta$ -amino ester **234**. The latter compound was transformed to  $\beta$ -amino acids **235–237** by routine methods such as deprotection of the PMP group followed by hydrolysis for compound **235**, straightforward hydrolysis of the ester group for compound **236**, and *N*-methylation followed by deprotection of the PMP group for compound **237**. The cyclization of  $\beta$ -amino acids **235–237** in the presence of tris(2-oxo-3-benzoxazolinyl)phosphine oxide **238** and triethylamine led to formation of spiro-azetidinone-oxindoles **239**. The yield depended greatly on the electronic environment of the substrates. The highest yield of 70% was obtained from the substrate **237** having *N*-methyl-2-oxindole and a free amino group, whereas the lowest yield of 26% was obtained from the substrate **236** having NH-oxindole but PMP-substituted amine. The substrate **235** having both NH-oxindole and a free amino group afforded the product in 39% yield.

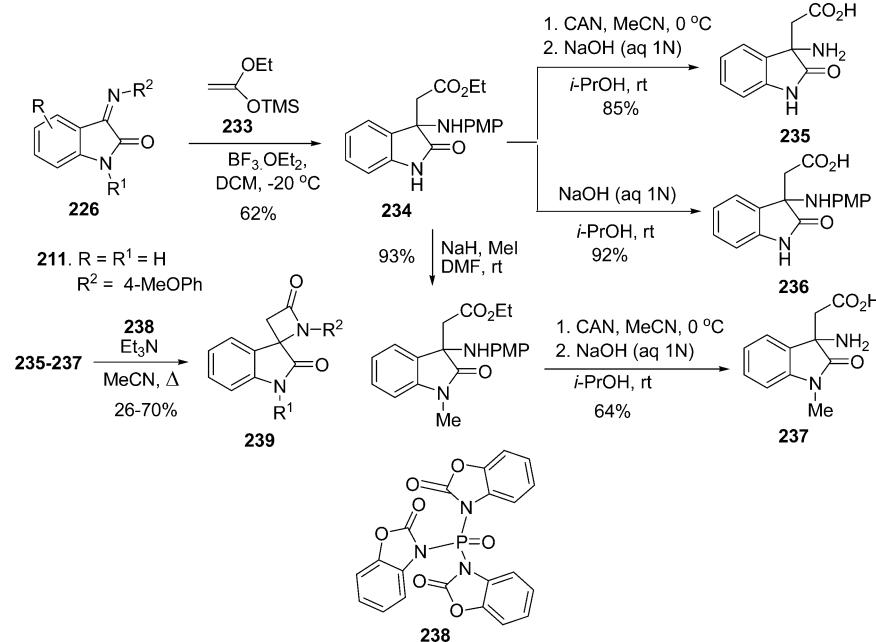
Shibasaki and co-workers have reported the synthesis of a spiro-azetidinone-oxindole **245** starting from a chiral bimetallic Ni-Schiff base complex **242**-catalyzed asymmetric amination of methyl 2-(*N*-Boc-2-oxindolin-3-yl)acetate **240** with di-*tert*-butylazadicarboxylate **241**.<sup>205</sup> The accessibility of substrate **240** in this case, however, could not be confirmed from isatin. The reductive cleavage of the ester group from hydrazine **243**

forming compound **244** followed by cyclization of the product **244** led to the spiro-azetidinone-oxindole **245** with an unsubstituted nitrogen atom in both rings (Scheme 84).

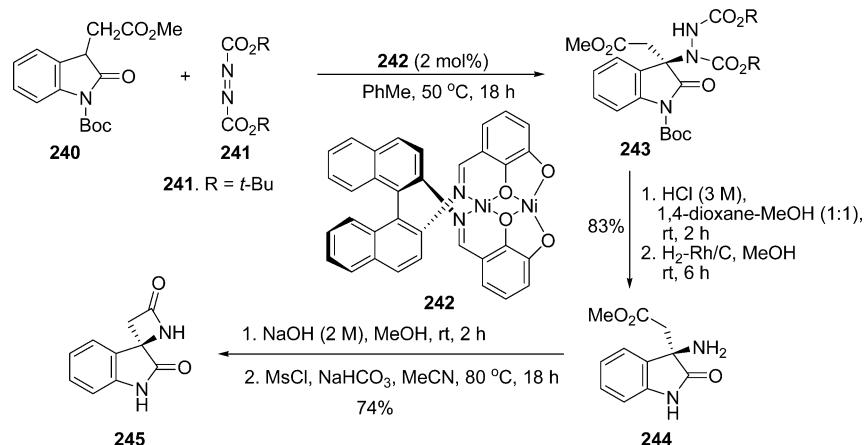
**4.5.3. Five-Membered Heterocycles.** Among five-membered spiro-heterocyclic 2-oxindoles, as in MCRs, design of the spiro-pyrrolidine ring is broadly investigated obviously because it occurs in many natural products<sup>130</sup> (Figure 5) and constitutes core structure in many biologically important 2-oxindoles. A p53-MDM2 interaction inhibitor MI-219 containing the spiro-pyrrolidine-oxindole backbone is about to enter phase I clinical trials as an anticancer agent.<sup>206</sup> A novel approach to synthesize the spiro-pyrrolidine-oxindoles **248** was developed by the  $\text{MgI}_2$ -catalyzed ring-expansion of a cyclopropane ring in *N*-benzylspiro[2-oxindole-3,1'-cyclopropane] **246** in the presence of aldimines **247** (Scheme 85).<sup>207</sup> The reactions of *N*-benzylspiro[2-oxindole-3,1'-cyclopropane] **246** with *N*-*p*-tolylsulfonylisocyanate in the presence of  $\text{MgI}_2$  also furnished spiro[oxindole-3,3'-pyrrolidines]. The Lewis acidity of the metal center  $\text{Mg}^{2+}$  and nucleophilicity of the counterion  $\text{I}^-$  appeared to operate in synergy in this reaction. Three mechanistic pathways were postulated which differed in the sequence of C–N and C–C bond formations (Scheme 86). The methodology was later employed in the total synthesis of alkaloids ( $\pm$ )-strychnofoline<sup>208</sup> and ( $\pm$ )-horsfiline.<sup>209</sup> Later on the group led by Carreira synthesized the spiro-cyclopropane-oxindole **250** by cyclopropanation of pyperilene **249** using carbenoid, generated from a Rh(II)-catalyzed decomposition of 3-diazoisatin 3, and carried out ring-expansion using imine **251** to obtain the spiro-pyrrolidine-oxindole **252** that was employed in the synthesis of spirotryprostatin B (Figure 3) (Scheme 87).<sup>210</sup>

The multicomponent reactions carried out employing isatins as one of the substrates are also reported using 3-alkylidene-2-oxindoles as one of the substrates in place of isatins. For example, the reactions of azomethine ylide **255** with (*E*)-ethyl 2-(2-oxindolinyl-3-ylidene)acetate **12** have been investigated for asymmetric synthesis of spiro-pyrrolidine-oxindoles. Wil-

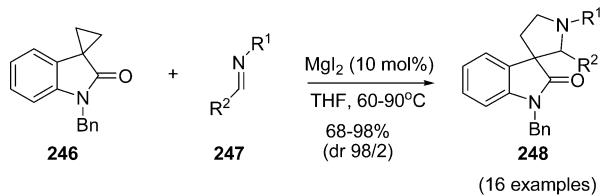
Scheme 83



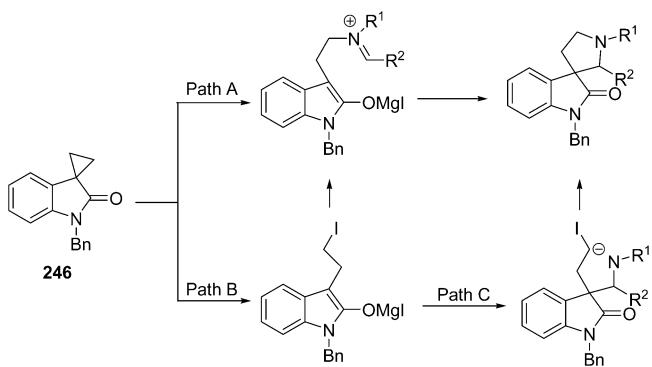
Scheme 84



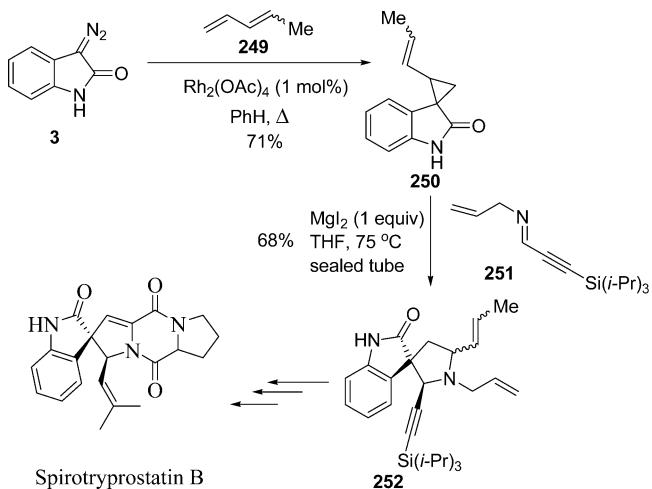
Scheme 85



Scheme 86



Scheme 87



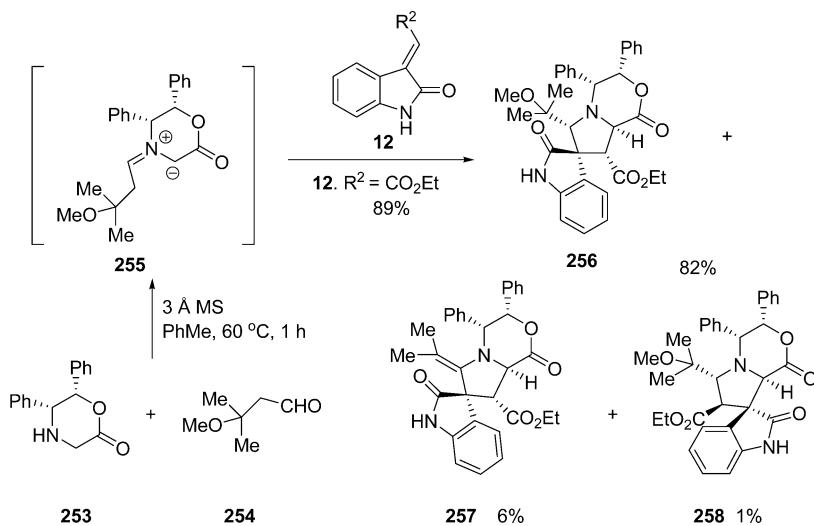
Liams and co-workers have employed this methodology in the synthesis of spirotryprostatin B. This group has used (*S*,*R*,*S*)-

5,6-diphenylmorpholin-2-one 253 as a chiral auxiliary.<sup>211–213</sup> For example, the reaction of chiral azomethine ylide 255, obtained from (*S*,*R*,*S*)-5,6-diphenylmorpholin-2-one 253 and 3-methoxy-3-methylbutanal 254 with 2-oxindol-3-ylidene 12, leads to the formation of three cycloadducts 256–258 in 89% overall yield with 256 as the predominant one in 82% yield (Scheme 88). The same chiral auxiliary was used later by Wang and co-workers in the reactions of 3-arylidene-2-oxindoles 10 with aldehydes.<sup>214</sup> The products 259, obtained in these reactions, however, were characterized on the basis of single crystal X-ray studies as having a different configuration (2'*R*, 3*S*, 4'*R*, 5'*R*) from the product 256 (2'*S*, 3*S*, 4'*R*, 5'*R*) reported by Williams' group. The chiral auxiliary in the product 259 was removed by hydrolysis of the morpholinone ring with dimethylamine forming spiro-product 260 followed by oxidation to afford spiro-2'-alkyl-4'-arylpyrrolidine-oxindoles 261 (Scheme 89, Table 4).

The first catalytic asymmetric synthesis of spiro-pyrrolidine-oxindole derivatives using a MCR was reported by Gong and co-workers.<sup>215</sup> The reactions of 3-alkylidene-2-oxindoles 10, aldehydes, and diethyl 2-aminomalonate 262 in the presence of a chiral phosphoric acid catalyst 263 led to the formation of densely functionalized spiro-products 264 (Scheme 90) in very good yields with high regioselectivity and excellent enantioselective excess. In contrast to the *N*-unsubstituted isatins that are typically used in auxiliary-induced reactions, the *N*-acyl group on isatins was essential for high yields and regioselectivity that was observed independent of the electronic effects. The formation of products was explained by 1,3-dipolar addition of 2-oxindoles 10 on azomethine ylide, generated *in situ* from the reaction of aldehydes with malonate 262. In order to get an insight into the regioselectivity and enantioselectivity, the mechanism was studied theoretically, and a transition state 265 was proposed in which both the azomethine ylide and oxindole were H-bonded to phosphoric acid. The unusual regioselectivity was proposed to result from a favorable π–π stacking interaction between the oxindole ring and the conjugated ester.

Liu and co-workers have reported recently the first asymmetric 1,3-dipolar cycloaddition of *N*-unsubstituted 3-alkylidene-2-oxindoles 10 as dipolarophiles to azomethine ylides from imino-esters 266 for the synthesis of spiro-pyrrolidine-oxindoles 268 having four contiguous stereocenters (Scheme 91).<sup>216</sup> A new catalytic system, the complex of AgOAc/TF-Biphosphos 267, has been employed in the reaction affording products in high yields and excellent

Scheme 88



Scheme 89

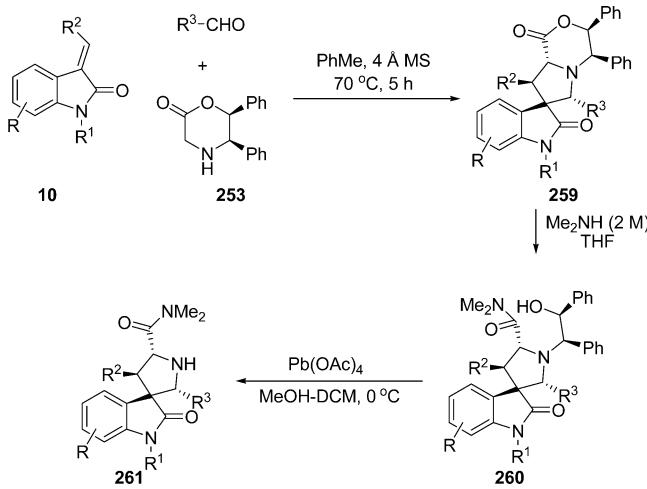
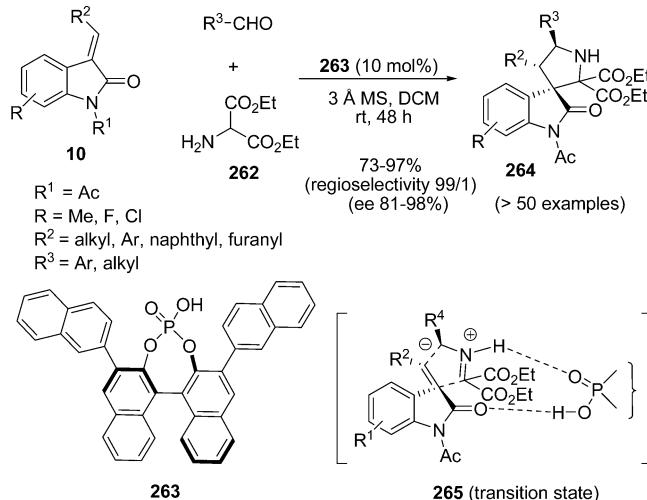


Table 4. Asymmetric Synthesis of Spiro-Pyrrolidine-Oxindoles 260 and 261 Using Chiral Auxiliary

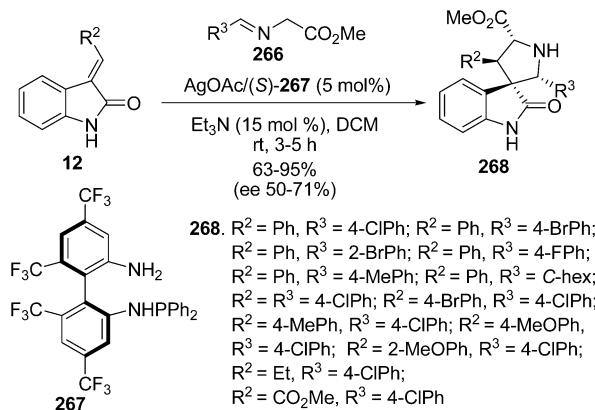
R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	260 yields (%)	261 yields (%)
H	H	Ph	i-Bu	70	55
6-Br	H	Ph	i-Bu	75	62
6-CF <sub>3</sub>	H	Ph	i-Bu	75	59
6-Cl	H	Ph	i-Bu	68	60
6-F	H	Ph	i-Bu	73	58
6-Cl	H	2-pyridinyl	2,2-dimethylpropyl	60	59
6-Cl	H	2-thienyl	2,2-dimethylpropyl	65	63
6-Cl	H	3-MeOPh	2,2-dimethylpropyl	75	65
6-Cl	H	Ph	2,2-dimethylpropyl	80	63
6-Cl	H	Ph	2-dimethylbutyl	78	60
6-Cl	H	Ph	n-propyl	77	59

diastereoselectivity but moderate enantioselectivity. Similar reactions in the presence of a chiral catalyst, formed by a N<sub>3</sub>P-ferrocenyl ligand and Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub>, has been reported by Waldmann and co-workers affording spiro-pyrrolidine-

Scheme 90



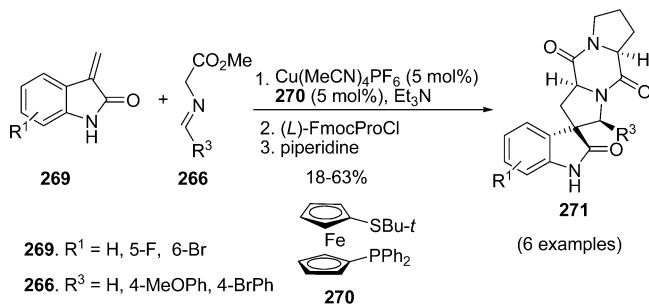
Scheme 91



oxindoles in up to 97% yield and 98% ee (17 examples).<sup>217</sup> This group has recently reported the organocatalytic asymmetric cycloaddition of 3-methylene-2-oxindoles to azomethine ylides from glycyl imine methyl esters resulting in the synthesis of pentacyclic spirotryprostatin A scaffold with an all carbon quaternary stereocenter.<sup>218</sup> The 1,3-dipolar cyclo-

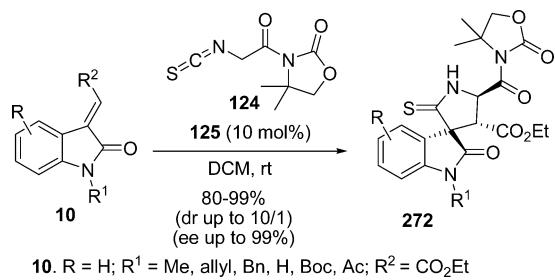
addition of a variety of mono- and polysubstituted glycyl imine esters **266** and *N*-unsubstituted 3-methylene-2-oxindoles **269** bearing electron-withdrawing and electron-donating groups, catalyzed efficiently by a ferrocene-based ligand **270** and  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$  (5 mol %) at ambient temperature, followed by *N*-acylation afforded the spiro-*N*-acylpyrrolidine-oxindole products in good yields and enantiomeric excess. Except for *ortho*-substituted azomethine ylides, the diastereoselectivity was high. Acylation of the amino group in the spiro-pyrrolidine ring, however, with (*L*)-Fmoc-ProCl and deprotection of the Fmoc group resulted in an immediate triggering of the diketopiperazine cyclization to form the pentacyclic scaffold **271** of spirotryprostatin A (Scheme 92). The presence of an electron-withdrawing group on both substrates led to a decrease in yields (18–21%) of the products.

Scheme 92



An asymmetric organocatalytic Michael addition/cyclization reaction between *N*-substituted 3-alkylideneisatins **10** and  $\alpha$ -isothiocyanato imides **124** in the presence of a bifunctional thiourea catalyst **125**, used earlier in the similar reactions of isatins (Scheme 46), results in a highly enantioselective synthesis of spiro-pyrrolidinethione-oxindoles **272** with three contiguous stereocenters (Scheme 93).<sup>219</sup> The stereochemistry

Scheme 93



of the product has been explained by activation of electron-deficient methylideneisatins by H-bonds involving the carbonyl group in oxindole and the thiourea hydrogen atoms and enolization of  $\alpha$ -isothiocyanato imides by deprotonation at its  $\alpha$ -carbon atom by the tertiary amine. The *Re* face of the enolate is exposed to methylideneisatins and the *Si* face of the Michael acceptor is approached by the incoming nucleophile. Subsequent nucleophilic attack of the stabilized carbanion onto the electron-deficient carbon atom of the  $\alpha$ -isothiocyanato imides leads to the formation of 3*R*,4'*R*,5'*R*-configured products **272**.

One of the compounds **272** was further transformed first by conversion of the imide to ester by treatment with MeMgI forming **273** followed by oxidation of this product with  $\text{H}_2\text{O}_2$

or catalytic reduction to afford the spiro-products **274** and **275** (Scheme 94), respectively, without any loss of diastereoselectivity or enantioselectivity.

More recently, Barbas III and co-workers have investigated the reactions of differently substituted alkylideneoxindoles **10** and isothiocyanato imides **124** in a range of quinine catalysts.<sup>220</sup> The cinchona alkaloid-based thiourea catalyst **277**, observed as the most efficient catalyst, afforded products **278** in good yields and enantioselectivity up to 97% (Scheme 95). The substrates with different electronic effects were tolerated in the reaction affording the products in 86–95% yields. In the proposed mechanism, the authors have suggested simultaneous activation of both the substrates by the catalyst. Further synthetic utility of the methodology has been demonstrated by replacement of the pyrazolyl group with a methoxy group by simple methanolysis.

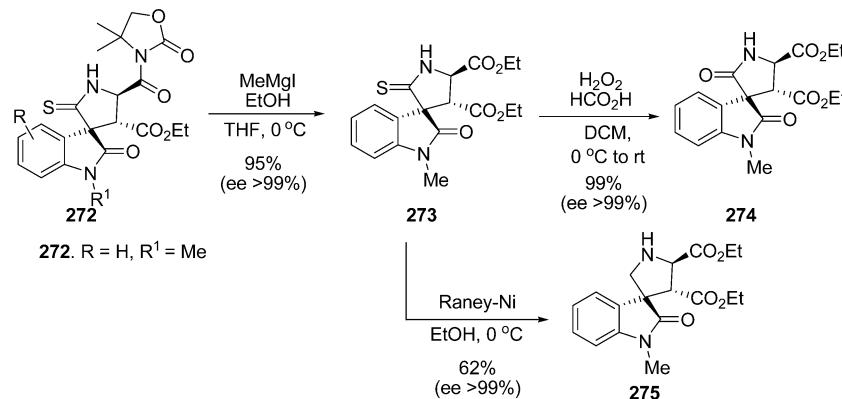
Junjappa and co-workers have reported the synthesis of dl-coerulescine and dl-horsfliline from 3-[bis(methylthio)-methylene]-2-oxindoles **279**.<sup>221</sup> Treatment of the latter compounds with aziridine **280** to form the 3-[aziridin-1-yl(methylthio)methylene]-2-oxindoles **281** and subsequent iodide ion induced rearrangement leads to the formation of spiro-dihydropyrrole-oxindoles **282** (Scheme 96). A reductive dethiomethylation-*N*-methylation of these products affords the natural products, dl-coerulescine and dl-horsfliline.

Silvani and co-workers have reported the Strecker type reaction of isatin-derived chiral ketimines **283** with trimethylsilyl cyanide (TMSCN) in the presence of Lewis acids such as  $\text{ZnCl}_2$ ,  $\text{SnCl}_4$ ,  $\text{MgBr}_2$ ,  $\text{BF}_3\text{-Et}_2\text{O}$ , etc.<sup>222</sup> The product,  $\alpha$ -amino nitriles **284**, was obtained in good yields but moderate diastereoselectivity. Further transformation of the cyanide group in a model compound by treatment with chlorosulfonyl cyanate allowed the preparation of a spiro-hydantoin-oxindole **285** (Scheme 97). Treatment of the major diastereomer **285a** that was separated from the mixture by recrystallization with *n*-hexane-EtOAc, with methylsulfonic acid led to the removal of the chiral auxiliary furnishing oxindole-based peptidomimetic and a pharmaceutically relevant spiro-hydantoin **286** that was developed by AstraZeneca for potential use in the treatment of pain.<sup>223</sup>

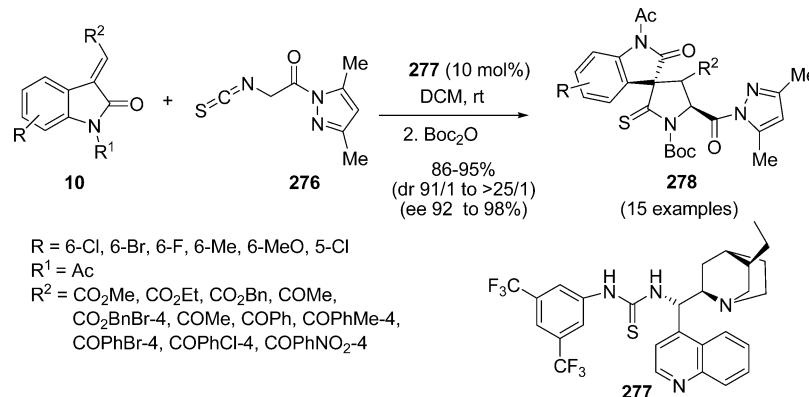
Contrary to five-membered spiro-azaheterocycles, there are only a few studies reported toward the synthesis of five-membered spiro-oxaheterocycles. Nair and co-workers have employed 3-alkylidene-2-oxindols **10** as dipolarophiles in [2+3]-cycloaddition of six-membered cyclic carbonyl ylides **288**, generated from Rh(II)-catalyzed decomposition of 5-diazo-1-phenyl/(2-thienyl)pentane-1,4-diones **287**, and a five-membered cyclic carbonyl ylide generated in the same manner from 1-(1-acetylpropyl)-2-diazoethanone.<sup>224</sup> The cycloaddition to six-membered cyclic ylides **288** occurred in a regioselective manner affording *endo*- and *exo*-products **289** and **290** (Scheme 98), while to a methyl-substituted five-membered carbonyl ylide it occurred almost regiorandomly affording all four possible isomers. The *endo* to *exo* ratio was observed as 2:1 except in the reaction of *N*-benzylisatin with 5-diazo-1-(thiophen-2-yl)pentane-1,4-dione in which the *endo* to *exo* ratio was 1.1: 1.

In another approach to synthesize the spiro-oxaheterocycles, MBH adducts **26** of isatins have been employed in the synthesis of spiro- $\alpha$ -methylene- $\gamma$ -butyrolactone-oxindoles **293** (Table S).<sup>225</sup> The products were obtained in excellent yields by a sequence of three reactions (Scheme 99): i) isomerization of the MBH-isatins adducts with trimethyl orthoformate using

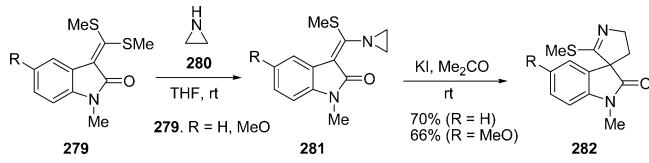
Scheme 94



Scheme 95



Scheme 96

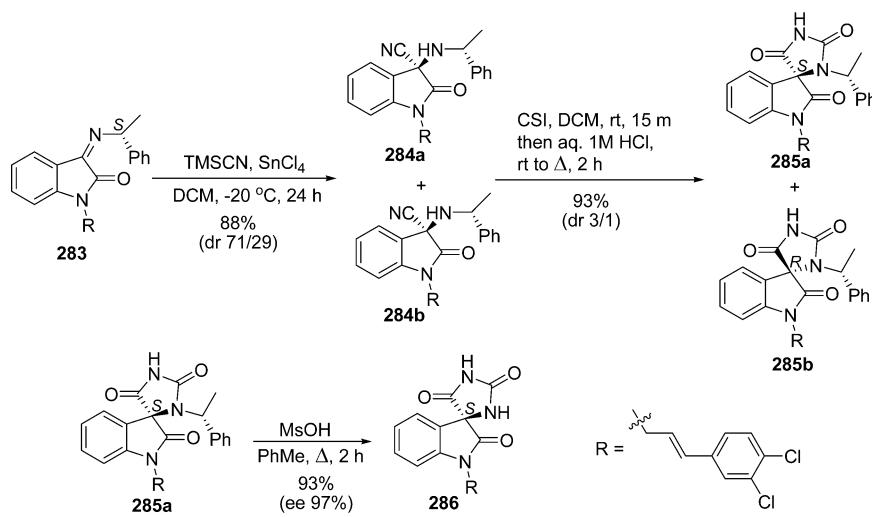


Montmorillonite K10 clay catalyst forming products **291**, ii) a second MBH reaction with formaldehyde affording products

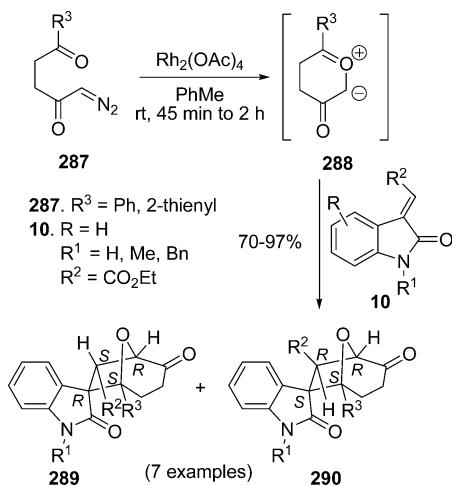
**292**, and finally, iii) an acid-catalyzed lactonization. In some cases, spiro-dihydrofuran-oxindole was obtained as a minor product. The second step of the reaction – the second MBH was successful only with formaldehyde and not with aromatic aldehydes such as benzaldehyde, 4-chlorobenzaldehyde, and 4-nitrobenzaldehyde or some aliphatic aldehydes such as acetaldehyde, heptanal, and (*E*)-crotonaldehyde.

Melchiorre and Bergonzine<sup>226</sup> have published their results recently on the investigation of nucleophilic addition of  $\alpha,\beta$ -unsaturated aldehydes to 3-hydroxy-2-oxindoles, easily acces-

Scheme 97

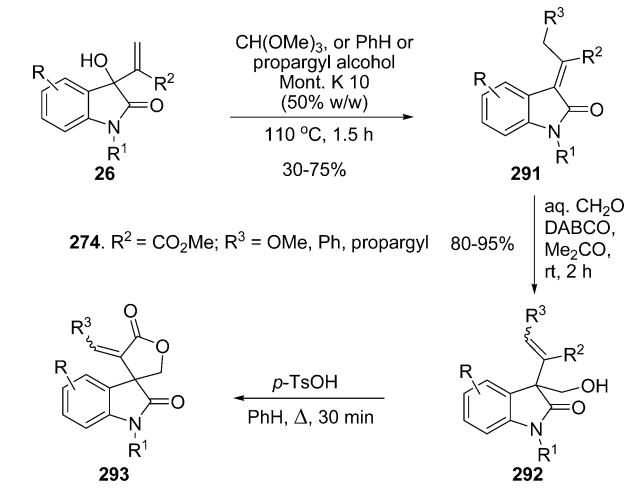


Scheme 98

Table 5. Synthesis of Spiro- $\alpha$ -Methylene- $\gamma$ -Butyrolactone-Oxindoles 293

$R^1$	$R$	$R^3$	293 yields (%)	Z:E
Et	H	OMe	90	2:1
propargyl	H	OMe	80	5:1
Bn	H	OMe	95	
Bn	5-Br	OMe	70	10:3
allyl	H	OMe	77	10:7
$\text{CO}_2\text{Me}$	H	OMe	67	2:1
Me	H	propargyl	84	2:1
Me	H	Ph	97	5:3

Scheme 99



sible from isatins by simple reduction, en route to asymmetric synthesis of maremycin A, a 3-substituted 3-hydroxy-2-oxindole. A wide range of  $\beta$ -substituted enals including differently substituted aryl groups, heteroaryl groups, and alkyl- and alkenyl groups react with 3-hydroxy-2-oxindoles in the presence of secondary amine chiral catalyst 295 to afford the hemiacetals. The direct oxidation of crude mixture with pyridine chlorochromate (PCC) affords the corresponding spiro- $\gamma$ -butyrolactone-oxindoles with high optical purity. Application of 2-fluorobenzoic acid as a cocatalyst led to dramatic acceleration of the Michael addition and reduced the formation of a dimer isatylide, obtained through an alternative

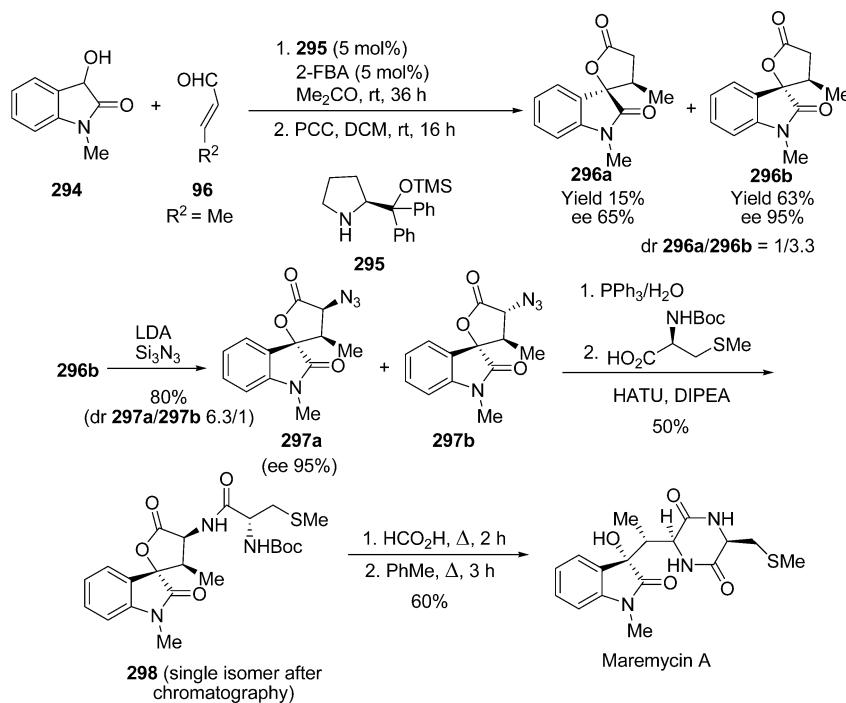
oxidative pathway. A representative example of the reaction between *N*-methyl-3-hydroxy-2-oxindole 294 and 2-butenal 96 forming products 296 that has been employed in the synthesis of maremycin A via other spiro- $\gamma$ -butyrolactone-oxindoles 297 and 298 is depicted in Scheme 100.

Alcaide and co-workers have reported the silver-, palladium-, and ruthenium-mediated cyclization of 2-oxindole-tethered  $\alpha$ -allenols 31, allylic alcohols, and ethers 302, in the synthesis of diverse functionalized spiro-dihydrofurans 299–301 (Scheme 101) and 304 (Scheme 102). The cyclization of substrate 302 containing an OH group in  $\text{Ag}_2\text{O}$  and iodine afforded the spiro-tetrahydrofuran-oxindole 303 (Scheme 102).<sup>227</sup> A possible mechanism for the formation of spiro compound 301 involved the initial formation of a ( $\pi$ -allyl)palladium species 305 (Scheme 103). The allenepalladium complex, formed initially, suffered a nucleophilic attack by the bromide to produce a  $\sigma$ -allylpalladium species, which rapidly equilibrated with the corresponding ( $\pi$ -allyl)palladium intermediate 306 which underwent intramolecular cycloetherification to afford the product 301. The formation of product 300 has been explained by initial Pd(II) coordination followed by an intramolecular cyclization with the hydroxyl group creating a palladadihydron furan moiety. The latter reacted with allyl bromide to give a product which underwent debromopalladation to afford the product.

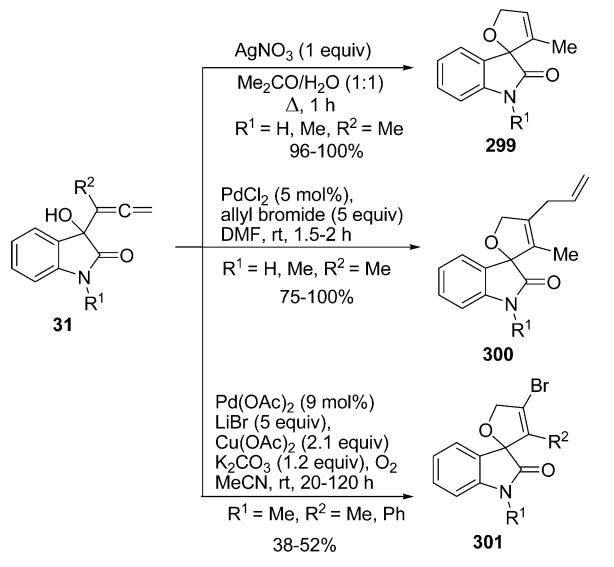
Shanmugam and co-workers have reported the reactions of sulfur- and nitrogen ylides, generated from the Morita-Baylis-Hillman adducts of isatins, for the synthesis of spiro-azaheterocycles containing one or two nitrogen atoms in the ring. The reaction of bromo-isomerized Morita-Baylis-Hillman adducts 307 with pyridines 308 generates pyridinium ylides 309 which undergo a 1,5-electrocyclization to give the spiro-dihydroindolizine-oxindoles 310 in a diastereoselective manner (Scheme 104).<sup>228</sup> It is noteworthy to mention that indolizines constitute a class of biologically important compounds,<sup>229</sup> and spiro-indolizine scaffolds occur as main structural features in many yohimbane alkaloid natural products.<sup>230</sup> The synthesis of spiro-pyrazoline-oxindoles 311 has been reported by cycloaddition of sulfur ylides, generated *in situ* from the reaction of *E*- and *Z*-isomers of 3-bromoallyl derivatives 307 of the Morita-Baylis-Hillman-isatin adducts with dimethylsulfide, with azadicarboxylates 241 (Scheme 105).<sup>231</sup> An introduction of electron-withdrawing groups such as formyl and fluorine at the C-5 position of the phenyl ring in bromoallyl derivatives (entries 4–6) (Table 6) resulted in a reduction of the reaction time and better yields of the products in comparison to those with electron-releasing groups (entry 3) indicating that the [3+2]-annulations were favored by the presence of electron-withdrawing groups in substrates 307. Furthermore, the reaction of nitrile MBH derivatives (entries 2, 6, 8, 10) took a shorter reaction time and afforded better yields than the ester MBH adduct derivatives (entries 1, 5, 7, 9).

An aldol-addition of acetophenones 312 to isatin 1 affords 3-hydroxy-3-phenacyloxindoles 313 which undergoes dehydration forming 3-phenacylidene-2-oxindoles 314 in quantitative yields that have been employed in the synthesis of spiro-dihydropyrimidinethione-oxindole 315 and spiro-pyrazoline-oxindoles 316–317.<sup>232,233</sup> The reaction of compound 314 with phenylthiourea afforded the product 315, whereas the reactions with phenylhydrazine and with hydrazine resulted in the formation of *N*-phenylpyrazoline 316 and pyrazoline 317, respectively, spiro-fused to 2-oxindole (Scheme 106).

Scheme 100

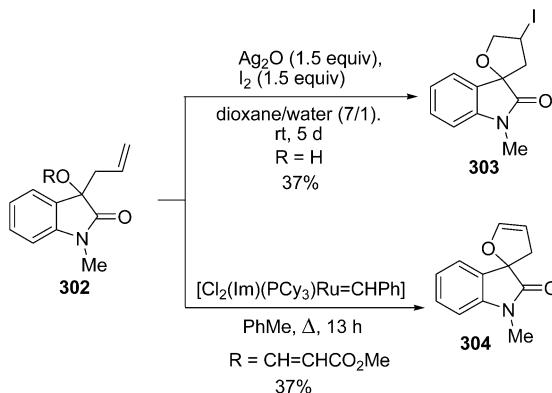


Scheme 101

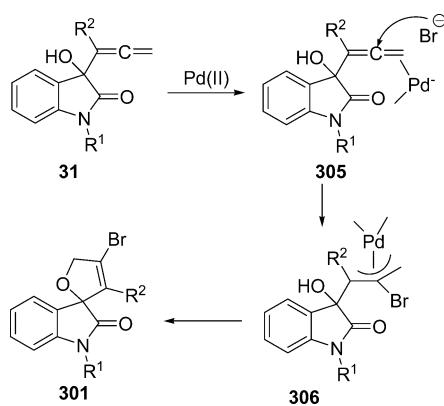


Yuan and co-workers have reported an organocatalytic asymmetric aldol reaction of 3-isothiocyanato-2-oxindoles forming directly the spiro-heterocyclic products bearing two highly congested contiguous quaternary carbon stereocenters.<sup>31</sup> The reaction of isothiocyanates 6, prepared via isatin-3-oximes, with ketones 312 is catalyzed by a bifunctional thiourea-tertiary amine catalyst 318 to afford the spiro-oxazolidinethione-oxindoles 319 in excellent yields and stereoselectivity (Scheme 107). A variety of acetophenones, acetonaphthones, and also cyclohexanone (not shown in scheme) were employed as ketones. The synthetic utility of the products has been demonstrated by simple conversions (Scheme 108) employing *N*-protection and oxidation of the thiolactone group in 319 to lactone forming spiro-product 321, *S*-benzylolation to spiro-oxazoline 320 and *S*-methylation to spiro-oxazoline 324. The

Scheme 102

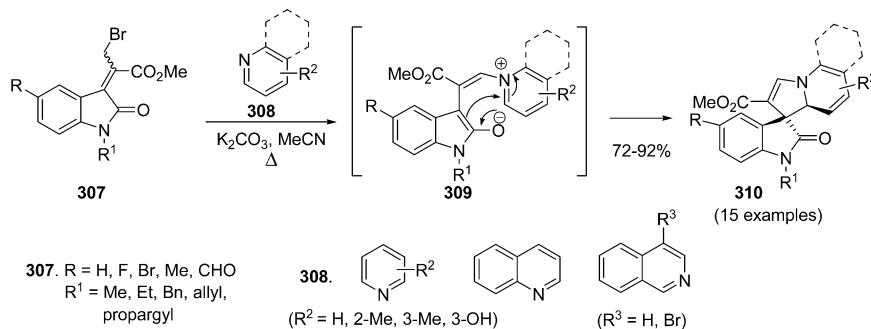


Scheme 103



cyclization of compound 320 was achieved with anthranilic acid 322 to *N*-Boc-spiro-oxazolidine 323. The spiro-oxazolidinone-oxindole 325 was synthesized either directly from compound

Scheme 104



Scheme 105

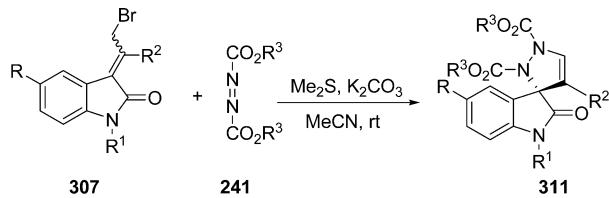


Table 6. Synthesis of Spiro-Pyrazoline-Oxindoles 311

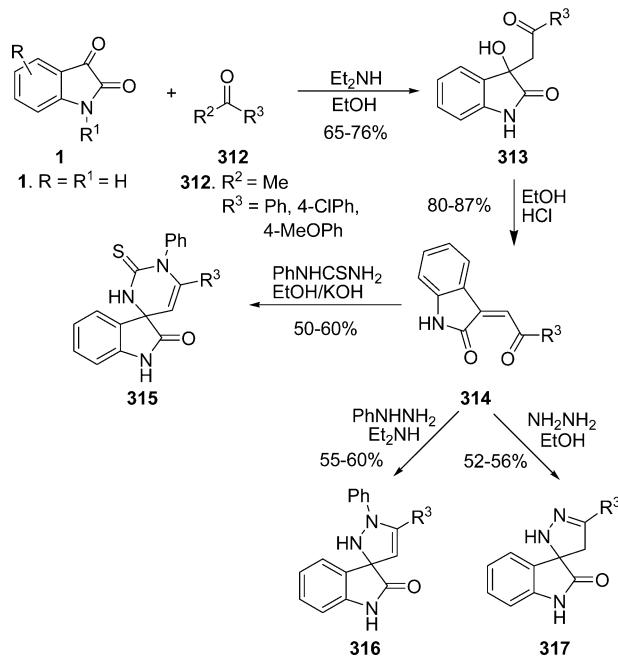
entry	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	t (h)	311 yields (%)
1	H	Me	CO <sub>2</sub> Me	Et	9	73
2	H	Me	CN	Et	6	89
3	Me	Me	CO <sub>2</sub> Me	Et	26	66
4	CHO	Me	CO <sub>2</sub> Me	Et	4	74
5	F	Me	CO <sub>2</sub> Me	Et	4	79
6	F	Me	CN	Et	3	86
7	H	propargyl	CO <sub>2</sub> Me	Et	8	66
8	H	propargyl	CN	Et	5	79
9	H	Bn	CO <sub>2</sub> Me	Et	8	87
10	H	Bn	CN	Et	4	91
11	H	Bn	CO <sub>2</sub> Me	i-Pr	8	83
12	H	Me	CO <sub>2</sub> Me	i-Pr	9	79
13	H	Me	CO <sub>2</sub> Me	t-Bu	8	86

319 by oxidation of thiolactone to lactone (Path A) or from compound 321 by N-deprotection (Path B).

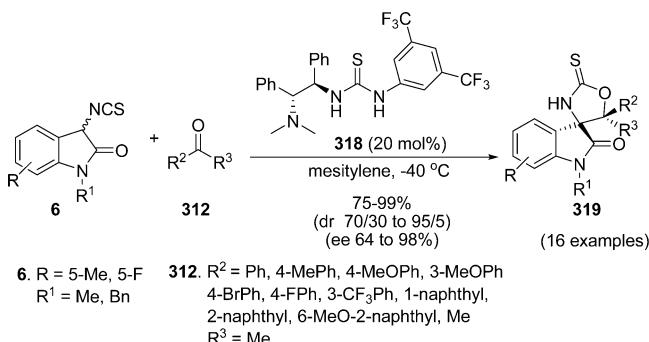
Isatins, through its 3-alkylidene derivatives, find a new application in the synthesis of a scarce class of spiro-heterocyclic framework spiro-isooxazoline-oxindoles.<sup>234</sup> A 1,3-dipolar cycloaddition of 3-alkylidene-2-oxindoles 10 with chlorooximes 326 in the presence of triethylamine or zinc led to the formation of spiro-heterocyclic products 327 containing an ester group at C-4 and an aromatic or ester group at C-3 of the isooxazoline ring in yields ranging from 71% to 94% (Scheme 109). The structures of products have been unambiguously established by single crystal X-ray crystallography of a model compound from the series. In a preliminary communication, the authors have studied the reactions of NH- and N-methyl-substituted 2-oxindoles containing either a methyl- or ethyl carboxylate group at the end of olefinic carbon chain. This study has a further scope in the form of the effect of substituents on the phenyl rings of both 2-oxindole and chlorooxime. On a different note, this study reports for the first time the use of zinc as a dehydrochlorinating agent in 1,3-dipolar cycloaddition reactions.

(S)-(-)-Spirobrassinin 330, a natural product isolated from *Pseudomonas cichorii* inoculated Chinese cabbages and Japanese

Scheme 106



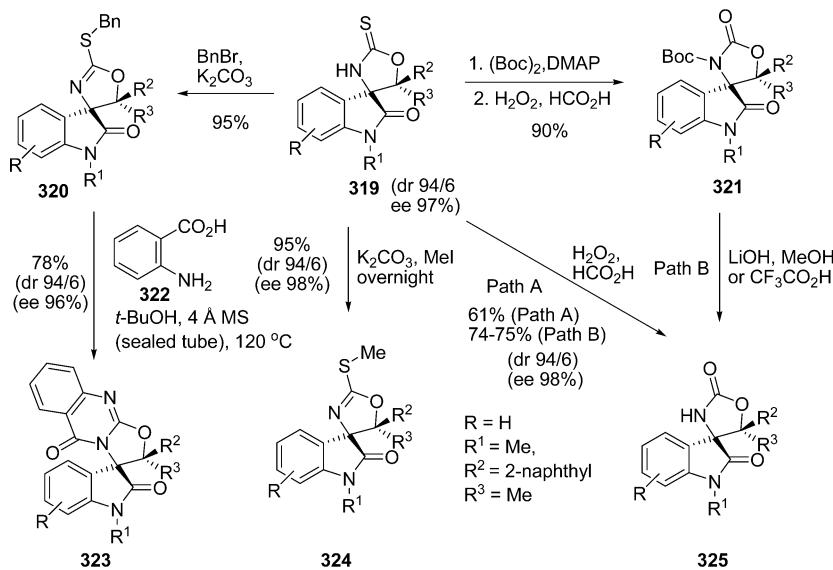
Scheme 107



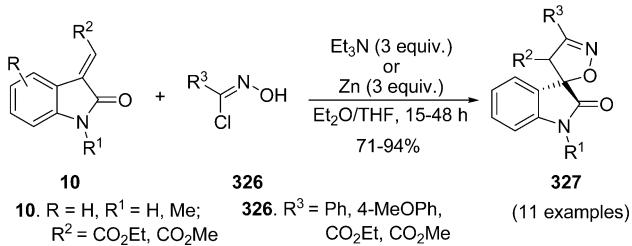
radishes, has been synthesized using enantiopure isatin-nitromethane adduct 24 as a substrate (Scheme 110).<sup>44</sup> The catalytic reduction of the adduct 24 leads to the formation of the corresponding aminomethane 328. The transformation of compound 328 to a dithiocarbamate, (+)-dioxibrassinin 329 followed by treatment with methylsulfonyl chloride affords 330. This compound is reported to display biological properties such as plant defense<sup>235</sup> and antifungal<sup>236</sup> and antitumor activities.<sup>237</sup>

There are several reports in the literature on the reactions of different isatin-3-imines<sup>238–242</sup> and isatin-3-hydrazones<sup>243</sup> with

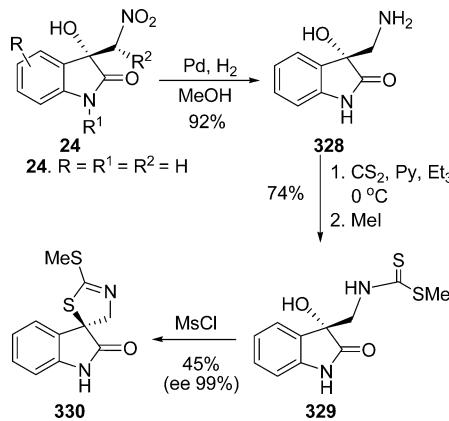
Scheme 108



Scheme 109



Scheme 110



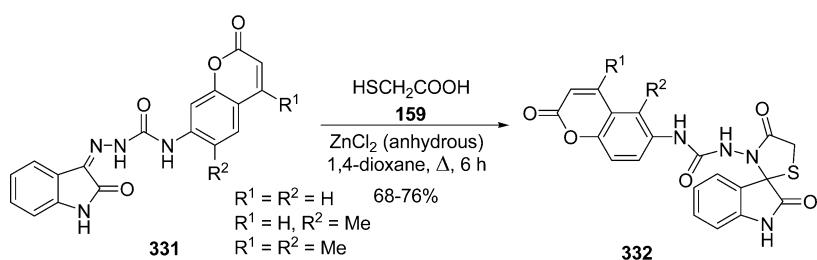
mercaptoacetic acid forming spiro-thiazolidine-oxindoles. Recently, Vintonyak and co-workers have employed this reaction in design and synthesis of several spiro-thiazolidinone-oxindoles as potential selective inhibitors of *Mycobacterium* protein tyrosine phosphatase B.<sup>244</sup> Mulwad and Mir have reported the reaction of isatin-3-semicarbazones 331 with mercaptoacetic acid 159 forming *N*-(coumarin-6-yl)-spiro[thiazolidine-2-oxindole] derivatives 332 (Scheme 111) with significant antibacterial activity.<sup>203</sup>

The reactivity of the nitrogen atom in the 2-oxindole ring of compounds 333, synthesized from the reaction of isatin-3-imines with mercaptoacetic acid, has been further explored to synthesize products with a spiro-fused 2-oxindole ring.<sup>230</sup> The reactions of compounds 333 with ethyl chloroacetate in the presence of NaH/DMF yielded the *N*-substituted products 334 which afforded compounds 335 on treatment with hydrazine hydrate (Scheme 112). These products, on further condensation with azalactone 336, furnished the spiro-cyclic compounds 337.

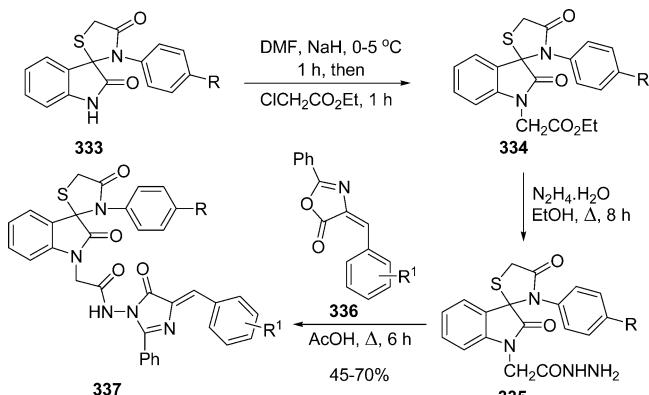
One of the spiro-azetidinones 226 synthesized by our group employing the Staudinger's ketene-imine cycloaddition (Scheme 80) underwent an unprecedented ring-enlargement of the 2-azetidinone ring during attempted deprotection of the *N'*-benzhydryl group in 226 using CAN resulting in the formation of the spiro-oxazolidinone-oxindole 338 (Scheme 113).<sup>200</sup> The C3'-C4' bond of the azetidinone ring suffered a hydrolytic cleavage that was followed by oxidative ring-closure.

The reactions of 3-isothiocyanato-2-oxindoles with isatins, described in section 4.3, have also been investigated with 3-

Scheme 111

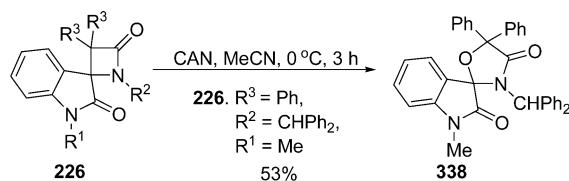


Scheme 112



**337.** R = R<sup>1</sup> = H; R = H, R<sup>1</sup> = 4-Me; R = H, R<sup>1</sup> = 4-MeO; R = H, R<sup>1</sup> = 4-Cl; R = H, R<sup>1</sup> = 3-NO<sub>2</sub>; R = H, R<sup>1</sup> = 4-NMe<sub>2</sub>; R = OMe, R<sup>1</sup> = H; R = OMe, R<sup>1</sup> = 4-Me; R = OMe, R<sup>1</sup> = 4-Me; R = OMe, R<sup>1</sup> = 4-MeO; R = OMe, R<sup>1</sup> = 4-NMe<sub>2</sub>; R = OMe, R<sup>1</sup> = 3-NO<sub>2</sub>

Scheme 113



imino-2-oxindoles.<sup>134</sup> The reactions of 3-isothiocyanato-2-oxindoles 6 with various 3-N-(4-methoxyphenyl)imino-2-oxindoles 339 in triethylamine occurred smoothly to afford the spiro-imidazolidine-2-thione-oxindoles 340 in high yields (84–95%) and diastereoselectivity up to 99/1. The authors have explored the potential of asymmetric induction using imines containing an O-TBDMS (*R*-phenylglycinol chiral auxiliary. Optically active isomeric products (Scheme 114),

Scheme 114

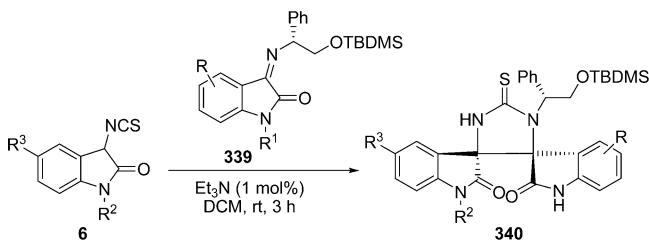


Table 7) were separated by simple column chromatography. The catalytic asymmetric Mannich-type reaction of *N*-substituted 3-isothiocyanato-2-oxindoles with some aldimines using a Sr-Schiff base complex as a catalyst affords spiro-

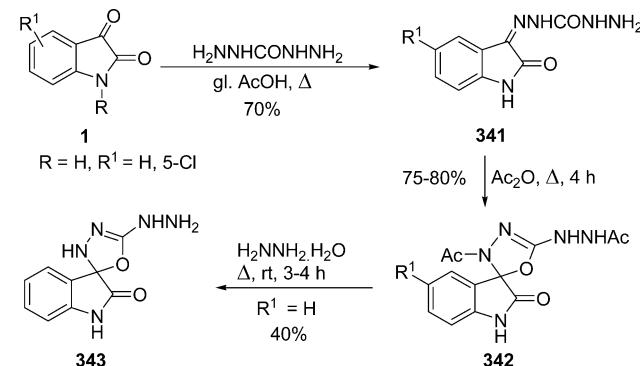
Table 7. Synthesis of Dispiro-Imidazolidine-2-Thione-Oxindoles 340

R <sup>2</sup>	R <sup>3</sup>	R	R <sup>1</sup>	dr	340 yield (%)
Bn	H	H	H	23:4:73:0	92
Ph	H	H	H	67:33:0:0	90
Me	F	5-Cl	H	50:50:0:0	92
Ph	H	H	H	75:6:19:0	90

imidazolidine-2-thione-oxindoles in excellent yields (88–98%) and enantioselectivity (93–99%).<sup>35</sup>

The reactions of isatins via semicarbazones have been employed in constructing a spiro-heterocycle with three heteroatoms in the ring – one oxygen atom and two nitrogen atoms.<sup>245</sup> The reaction of isatins 1 with carbohydrazide in glacial acetic acid afforded the 3-carbohydrazone 341, which underwent oxidative cyclization to yield the spiro-1,3,4-oxadiazoline-oxindole 342 (Scheme 115). The hydrazinolysis

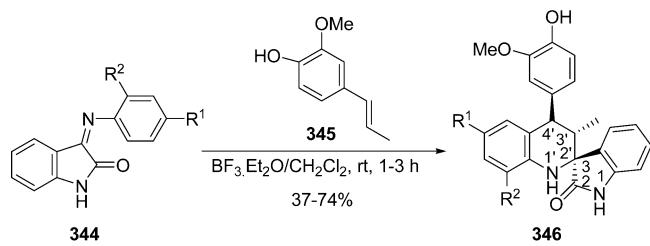
Scheme 115



of the product 342 afforded the spiro-fused product 343. A study of the cytotoxic effect of compounds 342 on brine shrimp showed that the compound containing a chlorine atom exhibited significant cytotoxicity in comparison to the compound with no chlorine atom. Somogyi has reported the formation of 1,3,4-oxadiazolines spiro-fused to 2-oxindole at its C-3 position during *N*-acylation of hydrazone moiety in isatin-3-hydrazones.<sup>246</sup>

**4.5.4. Six-Membered Heterocycles.** Isatin-3-imines serve as useful substrates for the synthesis of six-membered spiro-azaheterocycle-oxindoles. 3-*N*-Arylimino-2-oxindoles 344 undergo the BF<sub>3</sub>·Et<sub>2</sub>O-promoted aza-Diels–Alder reaction, known as the Povarov reaction, with *trans*-isoeugenol 345 offering a straightforward methodology for the synthesis of spiro-dihydroquinoline-oxindoles 346 (Scheme 116).<sup>247</sup> The

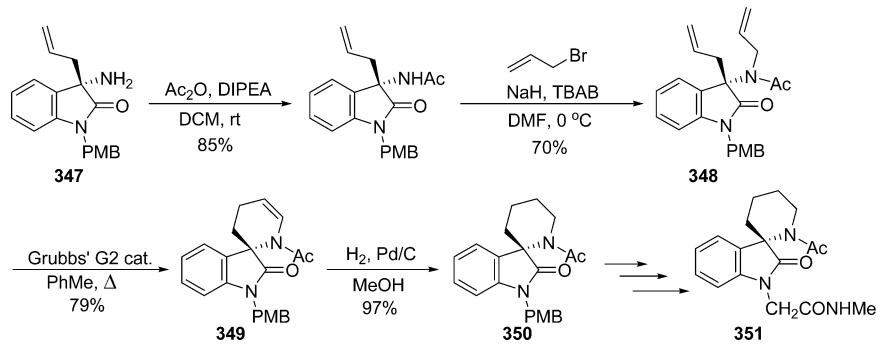
Scheme 116



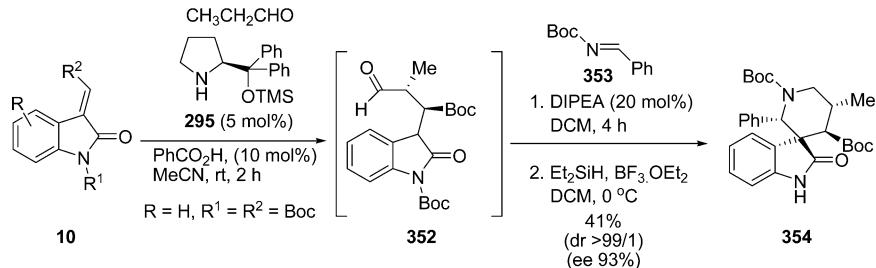
**346.** R<sup>1</sup> = R<sup>2</sup> = H; R<sup>1</sup> = H, R<sup>2</sup> = Me; R<sup>1</sup> = H, R<sup>2</sup> = OMe; R<sup>1</sup> = Me, R<sup>2</sup> = H; R<sup>1</sup> = Et, R<sup>2</sup> = H; R<sup>1</sup> = H, R<sup>2</sup> = Et; R<sup>1</sup> = Cl, R<sup>2</sup> = H; R<sup>1</sup> = Br, R<sup>2</sup> = H

reaction occurs at room temperature in 1 to 3 h in anhydrous dichloromethane. The NMR studies indicated the C-3' methyl group in the major diastereomer (*trans*-3'*e*,4'*e*) present *trans* to aromatic ring at C-4' and *cis* to the oxindole carbonyl. An enantiopure 3-allyl-3-amino-2-oxindole 347, accessed through the Grignard addition to isatin-3-imine, has been employed in the synthesis of spiro-piperidine-oxindole 350.<sup>248</sup> An *N*-acylation followed by *N*-allylation led to the formation of 3-allyl-3-(*N*-acyl-*N*-allyl)amino-2-oxindole 348 (Scheme 117).

Scheme 117



Scheme 118



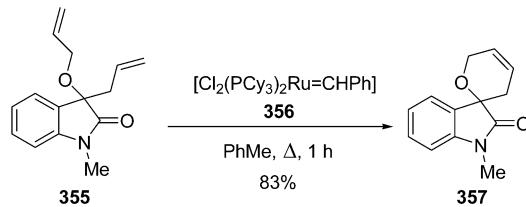
This compound was subjected to a ring-closing metathesis (RCM) reaction with the Grubbs' second generation catalyst in refluxing toluene to afford the spiro-tetrahydropyridine-oxindole **349** which underwent catalytic reduction to furnish the spiro-piperidine-oxindole **350**. This product was further subjected to simple chemical transformations to synthesize another spiro-piperidine-oxindole **351** that adopted a type II  $\beta$ -turn conformation in solution as assessed by computer-assisted modeling and spectroscopic studies.

Chen and co-workers have developed a tandem organocatalytic [2+2+2]-annulation using chiral amine catalyst to construct the spiro-cyclic systems – both heterocyclic and carbocyclic. For example, the reaction of 3-alkylideneisatin **10**, propanal, and *N*-Boc-substituted imine **353** in the presence of pyrrolidine derivative **295** led to the formation of spiro-piperidine-oxindole **354** through the adduct **352** (Scheme 118).<sup>249</sup>

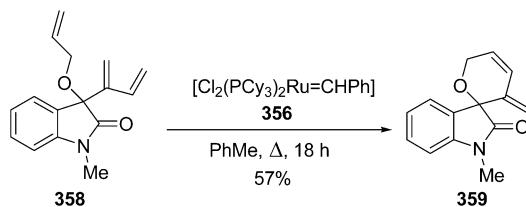
The synthesis of six-membered spiro-oxaheterocycle-oxindoles has been achieved by a similar procedure as described earlier for the synthesis of spiro-oxolanes.<sup>227</sup> The 2-oxindole-tethered diene **355** and triene **358** having an ether functionality undergo cyclization in the presence of the Grubbs' ruthenium-based catalyst **356** forming spiro-dihydropyran-oxindole **357** and spiro-methylenedihydropyran-oxindole **359**, respectively (Schemes 119 and 120), whereas a diene **360** with an embedded ester affords spiro-dihydropyranone-oxindole **361** (Scheme 121).

The reaction of *N*-substituted/unsubstituted isatin dimethyl acetals **362** with enantiopure homoallylic alcohols **363** in the presence of trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a catalyst results in the Prins cyclization of alcohols to afford the spiro-pyran/oxepene-oxindoles **364** in a stereoselective manner (Scheme 122).<sup>250</sup> Although the Prins cyclizations are reported to occur with racemization,<sup>251</sup> no reduction in enantiopurity was obtained in this case, and the products were retained up to 99% ee. Introduction of a bulky bromine substituent on the C-4 of isatin acetals resulted in an

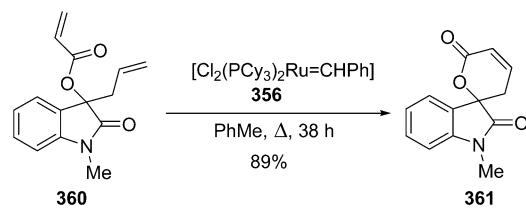
Scheme 119



Scheme 120

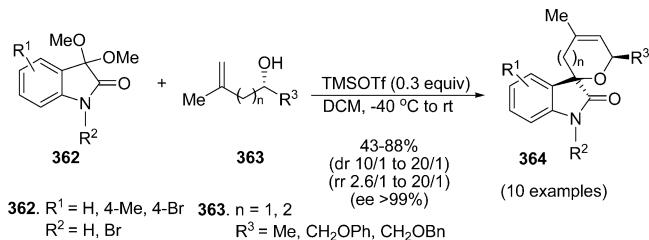


Scheme 121

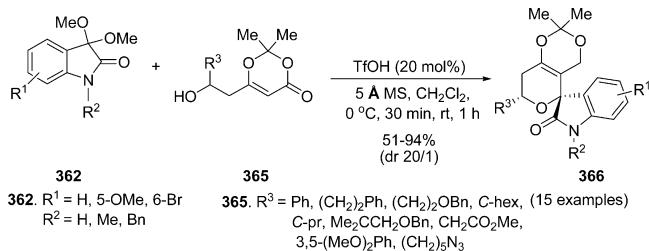


increased diastereoselectivity and regioselectivity. A similar reaction of isatin dimethyl acetals<sup>252</sup> with hydroxyl dioxinone **365** in the presence of trifluorosulfonic acid has been reported to result in a Prins-type cyclization sequence leading to the formation of spiro-pyran-oxindoles **366** in excellent yields and with high diastereoselectivity (Scheme 123).<sup>253</sup> The substituents at C-5 and C-6 positions of *N*-methyl- and *N*-benzylisatins were well tolerated, but the sterically demanding 4-bromoisatin

Scheme 122



Scheme 123

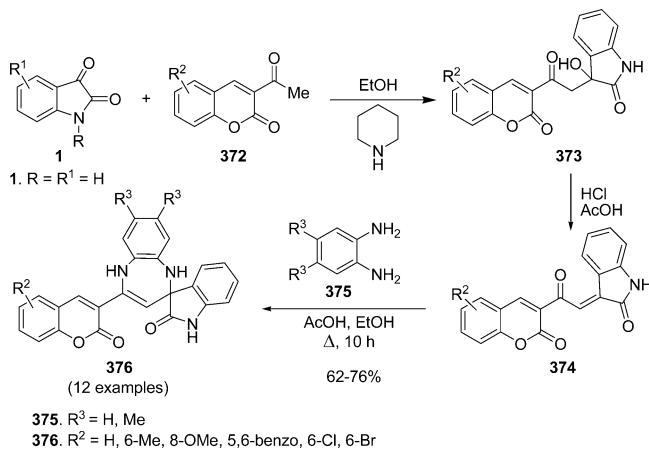


did not react. Further transformations of compound 366 have been achieved via reactions of an acyl ketene intermediate 367, generated by thermally initiated retro[4+2]-cycloaddition of 366, producing novel spiro-pyran-oxindoles 368–371 (Scheme 124). The synthesis of optically active spiro-4*H*-pyran-oxindoles 197 described earlier (Scheme 69) by three-component reactions of isatins 1, pentane-2,4-dione 196, and malononitrile in the presence of cupreine 23 has also been accomplished by a two-component reaction between isatyldiene malononitrile derivatives and 1,3-dicarbonyl compounds in the presence of cupreine.<sup>179</sup>

**4.5.5. Seven-Membered Heterocycles.** The aldol-adducts 373 of isatin and coumarins 372 have been employed in the synthesis of spiro-benzodiazepine-oxindoles.<sup>254</sup> The dehydration of adducts 373 affords the  $\alpha,\beta$ -unsaturated ketones 374. The cyclocondensation of compounds 374 with *o*-phenylenediamines 375 affords the spiro-benzodiazepine-oxindoles 376 (Scheme 125).

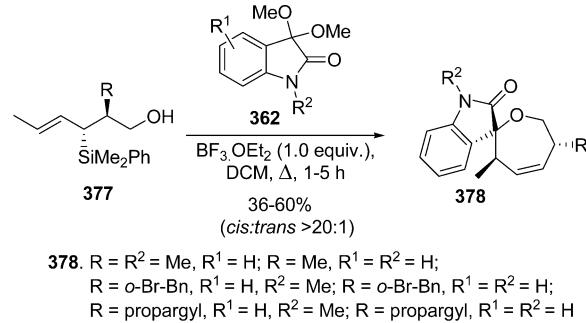
The Lewis acid-promoted [5+2]-annulations of chiral crotylsilanes 377 containing the primary alcohol functionality

Scheme 125



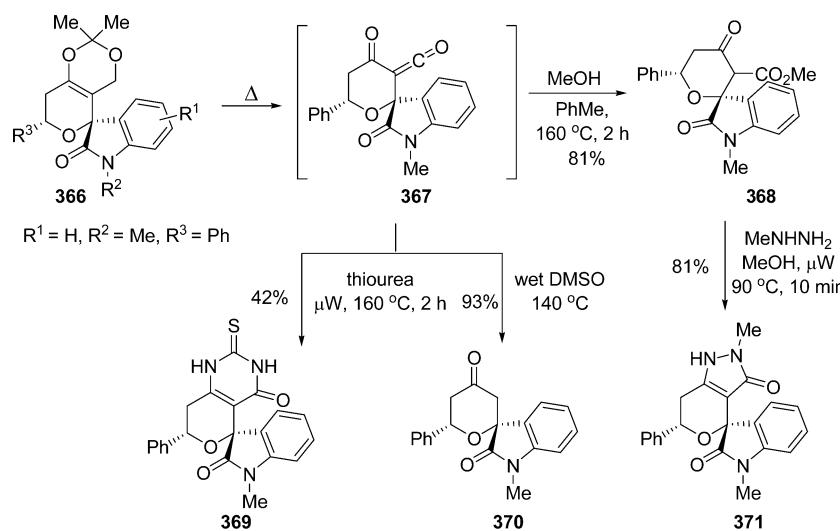
with isatin dimethyl acetals 362 result in an enantioselective synthesis of spiro-tetrahydrooxepene-oxindoles 378 (Scheme 126).<sup>255</sup> The products with complex structures have been

Scheme 126



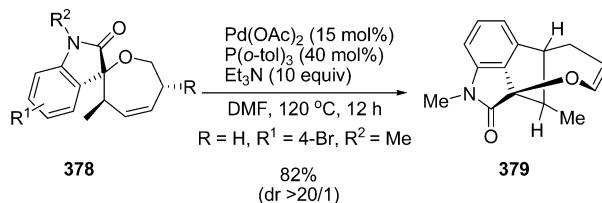
synthesized employing different combinations of functionalized silyl alcohols or substituted isatin partners. Initially the authors obtained *cis*- and *trans*-products; the latter due to epimerization of the former. Under optimized conditions,  $BF_3\text{-OEt}_2$  was used in refluxing dichloromethane to provide the desired product as a single diastereomer. The use of 4-bromo-isatin or bromosilyl

Scheme 124



alcohol yielded products capable of further transformation into the fused polycyclic ring system **379** through a Pd-catalyzed intramolecular Heck reaction (Scheme 127).

Scheme 127



The literature review on design and synthesis of spiro-fused heterocyclic frameworks involving C-3-isatin derivatives reveals applications of isatin-3-imines, isatin-3-hydrazone, 3-amino-2-oxindoles, 3-alkylidene-2-oxindoles, aldol-adducts, nitro-aldol-adducts, the MBH adducts, 2-oxindole-tethered homoallylic alcohols and  $\alpha$ -allenols, and 3,3-dimethylacetals of isatins as powerful substrates.

Aziridination and epoxidation of carbon–carbon double bonds in 3-alkylidene-2-oxindoles have been employed for constructing spiro-aziridine and spiro-oxirane frameworks, respectively. The Staudinger [2+2]-ketene–imine cycloaddition and cyclization of  $\beta$ -amino acids lead to the synthesis of spiro-azetidinone-oxindoles.

The synthesis of spiro-pyrrolidine skeleton has been investigated most extensively because it occurs in many natural products of biological importance. The 1,3-dipolar cycloaddition to azomethine ylides represents the most common approach for the synthesis of spiro-pyrrolidine-oxindoles. The problem of enantioselectivity in the synthesis of such compounds has been addressed either by employing chiral auxiliary or chiral catalysts. The use of Lewis acids, chiral metal complexes, and some amines and thioureas as catalysts is reported to afford the product either diastereo- or enantioselectively or both.

The Diels–Alder reaction and organocatalytic asymmetric [2+2+2]-annulations have been employed in the synthesis of spiro-piperidine-oxindoles. The Prins cyclization of isatin dimethylacetals with homoallylic alcohols constitutes an excellent method for the synthesis of spiro-pyrans/oxepenes. Silver-, palladium-, and ruthenium-mediated ring closing metathesis of oxindole-tethered homoallylic alcohols and  $\alpha$ -allenols has also been employed in the synthesis of spiro-oxolanes and spiro-pyrans. The seven-membered spiro-heterocyclics such as spiro-benzodiazepine-oxindoles and spiro-tetrahydrooxepene-oxindoles have been synthesized by

the cyclocondensation of *o*-phenylenediamine with aldol condensation products of isatins and the Lewis acid-promoted [S+2]-annulation of chiral crotylsilanes bearing a primary alcohol with isatin dimethyl acetals, respectively.

In this way, the synthesis of three- to seven-membered spiro-heterocyclic frameworks with one to three heteroatoms in the ring, and bearing a 2-oxindole moiety, has been accomplished starting from simple C-3-functionalized isatins. In general, there are fewer reports on spiro-oxaheterocycles in comparison to spiro-azaheterocycles and hence there is a wide scope for research on the former class of compounds. Isatins, besides being employed in the synthesis of the spiro-heterocyclic frameworks, have found application in construction of complex spiro-carbocyclic frameworks as well that will be discussed in the succeeding section.

## 5. SYNTHESIS OF ISATIN-BASED SPIRO-FUSED CARBOCYCLIC FRAMEWORKS

Although the synthetic approaches to spiro-fused heterocyclic frameworks containing 2-oxindoles have been widely investigated, the spiro-fused carbocyclic frameworks with 2-oxindoles are not uncommon either. Specially, spiro-cyclopentane-oxindole motifs are embodied in natural alkaloids such as marcfortines (Figure 5), citrinadins,<sup>256</sup> cirinalins A, cyclopamines (Figure 6), notoamides, and versicolamides,<sup>257</sup> etc. The spiro-cycloalkane-oxindoles have been recognized as compounds of biological interest. For example, spiro-cyclopropane-oxindoles are known to have inotropic and herbicidal properties.<sup>258,259</sup> Apart from their recognition as potential bioactive compounds in medicinal chemistry, spiro-cyclopropane-oxindoles have been used as building blocks in the synthesis of more complex spiro-oxindoles. Wood and co-workers have reported a protocol for construction of the carbon skeleton of a rare class of marine natural product welwitindolinone C using the spiro-cyclopropyl oxindole.<sup>49</sup> It is worth mentioning here that the total synthesis of welwitindolinones has been a challenging endeavor for synthetic organic chemists due to the complexities involved in its skeleton.

A rare spiro-cyclobutane-oxindole scaffold occurs in alkaloid welwitindolinone A isonitrile (Figure 6), isolated from a blue-green algae.<sup>260</sup> This compound has been observed responsible for antifungal activity of lipophilic extract from *Hapalosiphon welwitschii*. A spiro-cyclohexane-2-oxindole bearing *N*-methyl-pyrrole-2-carbonitrile-5-yl group on the C-5 position of the 2-oxindole ring has been discovered as a potential progesterone receptor agonist with an EC<sub>50</sub> value of 2.3 nM.<sup>16</sup>

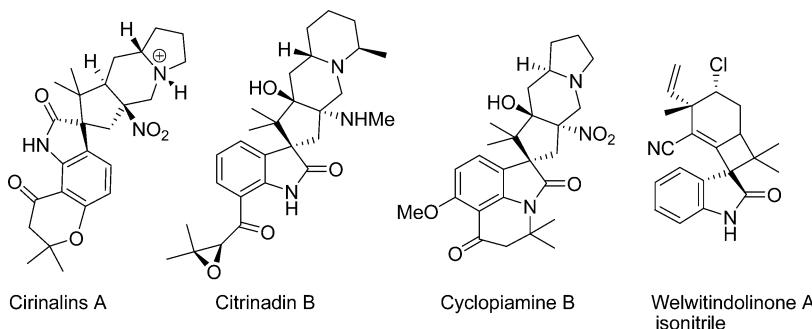


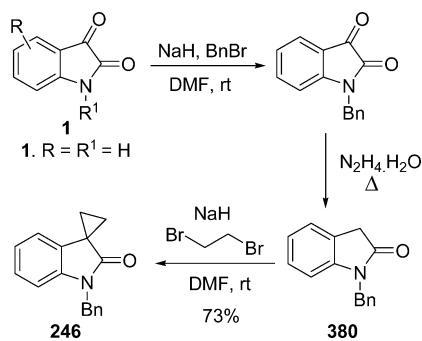
Figure 6. Some naturally occurring spiro-fused cycloalkanes.

Recent years have witnessed considerable interest of researchers in organic and medicinal chemistry in the synthesis and biological evaluation of spiro-carbocyclic oxindoles.<sup>261</sup> Some novel enantioselective methodologies have been developed by application of newly designed novel chiral catalysts. This section reviews the synthesis of spiro-carbocyclic oxindoles; the literature is arranged according to the size of the carbocyclic rings.

### 5.1. Spiro-Cyclopropanes

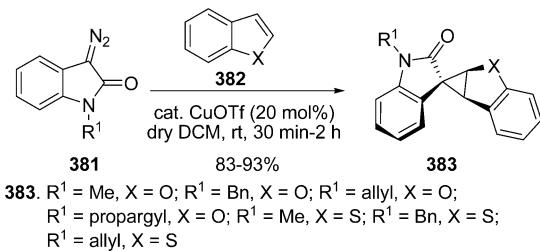
The Carreira group has developed methodologies for the synthesis of spiro-cyclopropane-oxindoles employing metal-carbenoids and other reactions. The synthesis of spiro-alkylidene-2-oxindole **250** through cyclopropanation of alkene **249** with carbene, generated from Rh(II)-catalyzed decomposition of the 3-diazoisatin **3**, has been described in section 4.5.3 (Scheme 87).<sup>210</sup> This group has also synthesized 1-benzyl-spiro[cyclopropane-1',3-indolin]-2-one **246** using isatin as a substrate via *N*-benzylisatin and 2-oxindole **380** (Scheme 128).<sup>207,262</sup> The application of these products in the synthesis of spiro[pyrrolidine-oxindoles] has been described previously (section 4.5.3).

**Scheme 128**



Recently, the cyclopropanation of an olefinic linkage in cyclic systems such as benzofuran and benzothiophene **382** by carbenoids, generated from a copper-catalyzed decomposition of 3-diazoisatins **381**, has been reported to furnish strained spiro-cyclopropane-oxindoles **383** (Scheme 129).<sup>263,264</sup> Mu-

**Scheme 129**

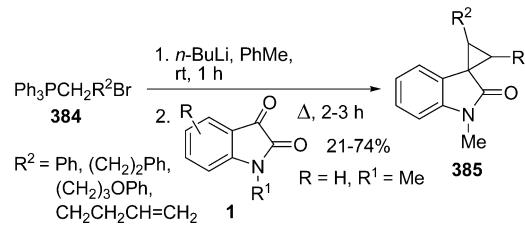


thusamy and co-workers reported CuOTf as an efficient catalyst in comparison to Rh<sub>2</sub>(OAc)<sub>4</sub>; the reaction in the former catalyst was fast and afforded high yields of the products.<sup>263</sup> The reaction has been successfully carried out in a diastereoselective manner with indene, dihydronaphthalene, benzofuran, and benzothiophene. In reaction with *N*-substituted indoles, the spiro-cyclopropane underwent ring-opening to afford 3-(indol-3-yl)-2-oxindoles. Singh and co-workers have reported cyclopropanation of alkenes employing

the Rh-carbenoids, generated from Rh<sub>2</sub>OAc<sub>4</sub>-catalyzed decomposition of 5-substituted 3-diazoisatins.<sup>264</sup> The spiro-cyclopropane-oxindoles with a *trans*-relationship between the lactam carbonyl group and the substituent on the cyclopropane ring were obtained as the major products. The synthesis of spiro-oxindolyl sugar derivatives has been accomplished by cyclopropanation of glycals with rhodium-carbenoids from *N*-substituted 3-diazo-2-oxindoles.<sup>265</sup>

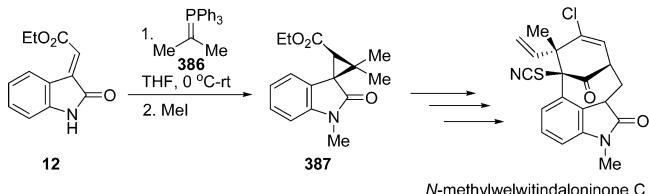
The reaction of *N*-methylisatin with ylides, generated by treatment of alkyl triphenylphosphonium bromides **384** with *n*-BuLi, has been reported to form the diastereoisomeric spiro-cyclopropane-oxindoles **385** as a result of the reaction of *N*-methylisatin **1** with two molar equivalents of the Wittig reagents (Scheme 130).<sup>266</sup> Wood and co-workers have

**Scheme 130**



synthesized the spiro-cyclopropane-oxindole **387** from the reaction of 3-alkylidene-2-oxindole **12** with the Wittig reagent **386** (Scheme 131) and employed them in construction of the

**Scheme 131**

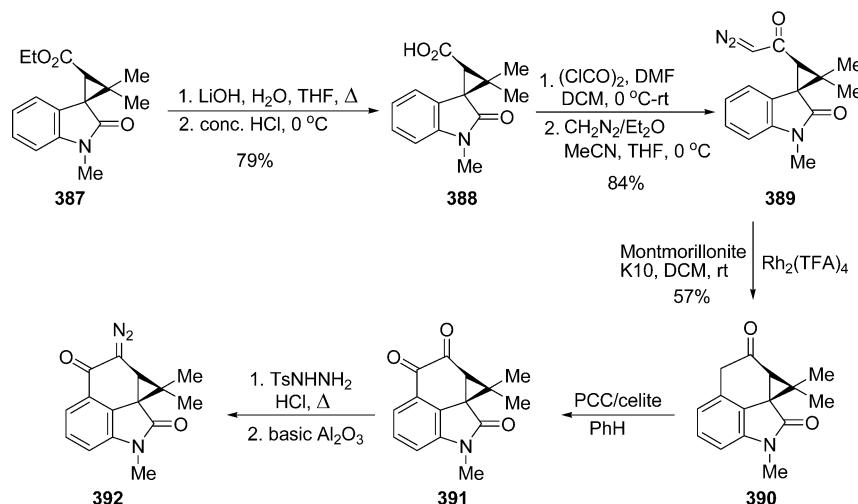


carbon skeleton of welwitindolinone C.<sup>49</sup> Along this 15-step route for the synthesis of welwitindolinone C, the spiro-cyclopropane-oxindole **387** is transformed into several other derivatives (**388–392**) (Scheme 132). The reaction of 3-alkylidene-2-oxindole **12** with diazomethane results in 1,3-dipolar cycloaddition forming spiro-pyrazoline-oxindole **393** which undergoes extrusion of nitrogen on heating resulting in ring-contraction to spiro-cyclopropane-oxindole **394** (Scheme 133).<sup>267</sup>

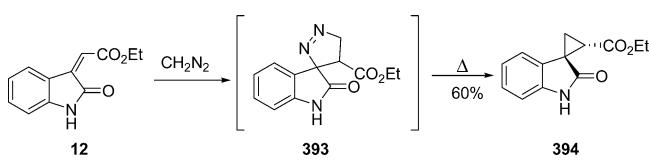
The reactions of isatins **1** with bromomalononitrile in isopropanol followed by treatment with an aqueous solution of NaI results in the cyclopropanation furnishing 2'-oxo-1',2'-dihydrospiro[cyclopropane-1',3'-indole]-2,2,3,3-tetracarbonitriles **397** (Scheme 134).<sup>268</sup> The mechanism of this reaction involves formation of an intermediate adduct **395** and dicyanomethylene derivatives **396**. The addition of bromomalononitrile onto the compound **396** followed by elimination of HBr affords the products **397**.

Shanmugam and co-workers have reported a diastereoselective synthesis of spiro-cyclopropane-oxindoles **399** and **400** by reductive cyclization of isomerized bromo derivatives **398** of the Morita-Baylis-Hillman adducts **26** of *N*-substituted isatins with sodium borohydride (Scheme 135).<sup>269</sup> To get insight into the mechanism, the authors separated the isomeric bromo

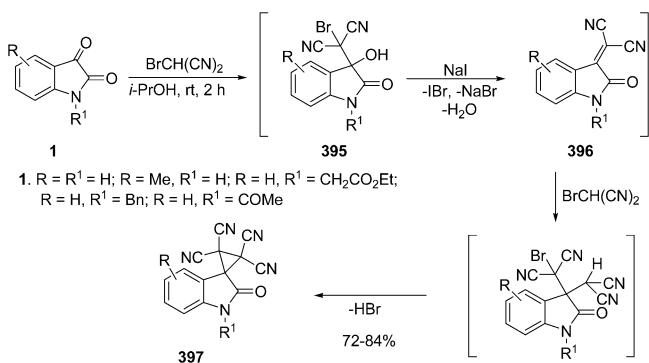
Scheme 132



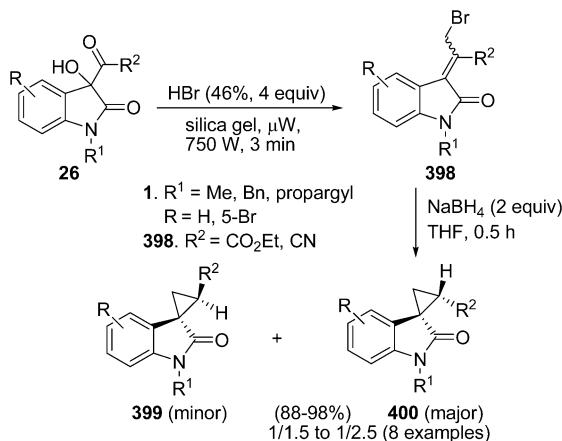
Scheme 133



Scheme 134



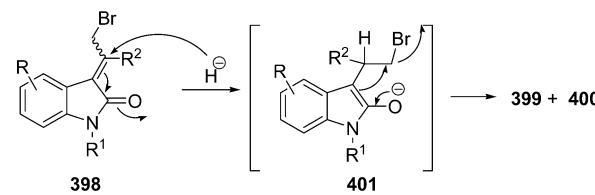
Scheme 135



derivatives and performed reductive cyclization on each of them which resulted in the formation of the same isomers of spirocyclopropane-oxindoles in the same ratio as obtained from the

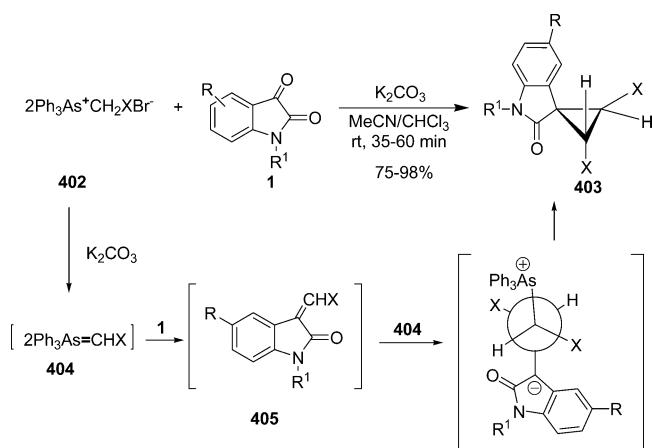
mixture of isomeric bromo derivatives. This observation led us to believe that there was a common intermediate 401 (Scheme 136), formed from a hydride ion attack on the olefinic double bond, leading to formation of both the isomers of spirocyclopropane-oxindoles.

Scheme 136

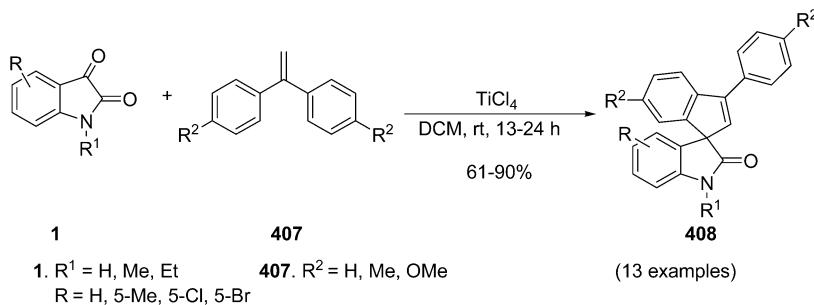


The reaction of isatins 1 with arsonium salts 402 in the presence of K<sub>2</sub>CO<sub>3</sub> constitutes a one-pot approach for a highly stereoselective synthesis of spirocyclopropane-oxindoles 403 (Scheme 137).<sup>270</sup> First, the Wittig reaction of isatins 1 and arsonium ylide 404, derived from arsonium salt 402, presumably generated 3-alkylideneisatins 405. The ylide 404

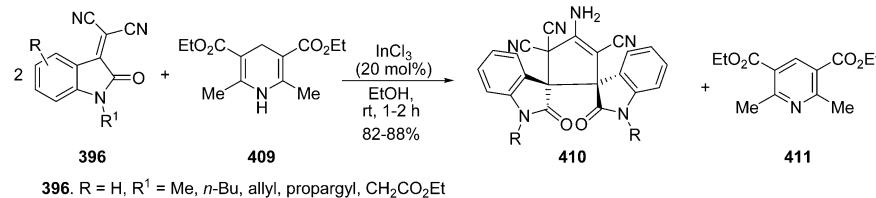
Scheme 137



Scheme 138



Scheme 139



then may add onto the exocyclic carbon–carbon double bond in **405** to afford the product **403** through intermediate **406**.

### 5.2. Spiro-Cyclopentanes and Spiro-Cyclopentenes

The synthesis of spiro-cyclopentene-oxindoles has been accomplished by the Lewis acid-mediated reactions of isatins. A simple protocol for the synthesis of spiroindene-oxindoles **408** via a  $\text{TiCl}_4$ -mediated reaction of 1,1-diarylethylenes **407** and isatins **1** involving formation of two C–C bonds through the tandem Prins and intramolecular Friedel–Crafts reactions (Scheme 138) is reported.<sup>271</sup> An In(III)-catalyzed reductive cyclization of isatidylidene malononitriles **396** using the Hantzsch ester **409** has been reported to afford the novel bis-spirocyclopentene-bisoxindoles **410** and the oxidized pyridine derivative **411** (Scheme 139).<sup>272</sup>

The chemistry of isatin derivatives as phosphorus ylides **412** has been explored leading to a facile, short, and efficient synthesis of spiro-cyclopentene-oxindoles **414** (Scheme 140, Table 8).<sup>231</sup> The reactions of ylides **412** from *E*- and *Z*-isomers of bromo derivatives **398** of the Morita-Baylis-Hillman adducts of *N*-substituted isatins **1** with  $\text{Ph}_3\text{P}/\text{activated alkenes}/\text{K}_2\text{CO}_3$  have resulted in the formation of products **414** by [3+2]-

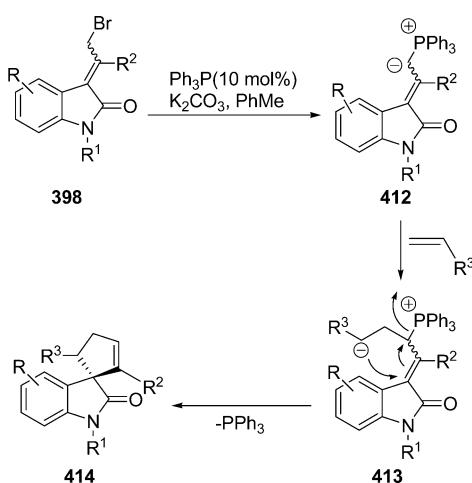
Table 8. Synthesis of Spiro-Cyclopentene-Oxindoles **414**

R	$R^1$	$R^2$	$R^3$	temp (°C)	time (h)	<b>414</b> yield (%)
H	Me	$\text{CO}_2\text{Me}$	$\text{CO}_2\text{Me}$	80	12	65
H	Me	CN	$\text{CO}_2\text{Me}$	60	5	74
H	Bn	$\text{CO}_2\text{Me}$	$\text{CO}_2\text{Me}$	80	12	63
H	Bn	$\text{CO}_2\text{Me}$	$\text{CO}_2\text{Me}$	60	2	48
H	Bn	CN	$\text{CO}_2\text{Me}$	60	6	77
H	Me	$\text{CO}_2\text{Me}$	$\text{C}_{10}\text{H}_7\text{O}_2\text{N}$	60	4	51
H	propargyl	CN	$\text{CO}_2\text{Me}$	60	6	66

annulation through an intermediate **413**. A cyclic dipolarophile *N*-phenylmaleimide was also used in the study successfully to afford the spiro-oxindole. This method created three consecutive stereocenters in one step, and in all cases a single diastereomer was observed among the various possible diastereomers.

Although there are many reports on enantioselective methodologies for the synthesis of spiro-pyrrolidine-oxindoles, there are only a few reports on enantioselective synthesis of its carbocyclic analog, spiro-cyclopentane-oxindoles. The approaches toward the enantioselective synthesis of spiro-cyclopentane-oxindoles include some palladium- and phosphine-catalyzed processes. Marinetti and co-workers have reported the first phosphine-mediated asymmetric organocatalytic process for enantioselective synthesis of spiro-cyclopentene-oxindoles.<sup>273</sup> After a series of studies on [3+2]-cycloaddition reactions of *N*-substituted 3-alkylideneisatins **10** and ethyl 2,3-butadienoate **415** in the presence of triphenylphosphine, (*R*)-BINAP, (*S*)-PHENPHOS, (*S*)-*tert*-butyl-Binepin **416**, and (*S,S*)-FerroPhane **419**, etc., this group identified the former catalyst as the most efficient catalyst and *N*-acyl-3-alkylideneisatins as the model substrates affording regiosomeric products **417** and **418** (Scheme 141) in very good yields and enantioselectivity (Table 9) with only a few exceptions (entries 4, 10, 12) in which the use of the catalyst **419** (entries 13–15) provided much better yields though with slightly reduced enantioselectivity. The reaction has been employed in the synthesis of spiro-oxindoles with phosphonate function. Thus, the organocatalytic [3+2]-cycloaddition of allenylphosphonate

Scheme 140



Scheme 141

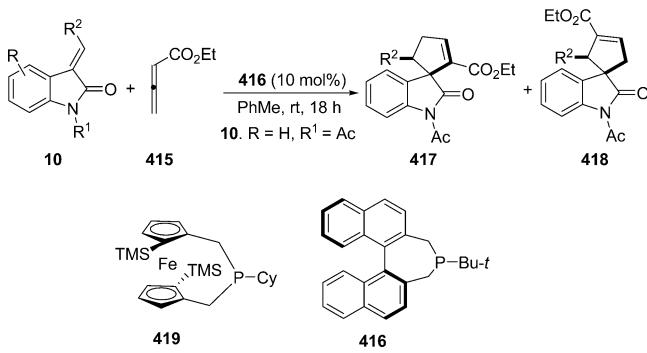
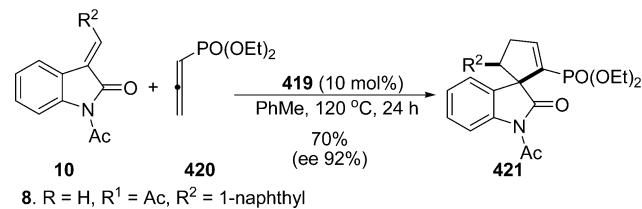


Table 9. Synthesis of Spiro-Cyclopentene-Oxindoles 417 and 418

entry	R <sup>2</sup>	catalyst	417 + 418 yield (%)	417/418 ratio	ee (%)
1	Ph	416	95	>95/5	>99
2	1-naphthyl	416	98	>95/5	>99
3	2-naphthyl	416	92	>95/5	99
4	4-Ph-Ph	416	20	90/10	99
5	4-CF <sub>3</sub> Ph	416	62	85/15	99
6	4-BrPh	416	63	90/10	>99
7	4-ClPh	416	80	92/8	>99
8	3-BrPh	416	82	85/15	>99
9	4-MePh	416	99	88/12	>99
10	2-furyl	416	25	76/24	97
11	2-quinolinyl	416	75	90/10	97
12	1-heptynyl	416	38	74/26	97
13	4-Ph-Ph	419	61	92/8	92
14	2-furyl	419	80	77/23	90
15	1-heptynyl	419	56	80/20	86

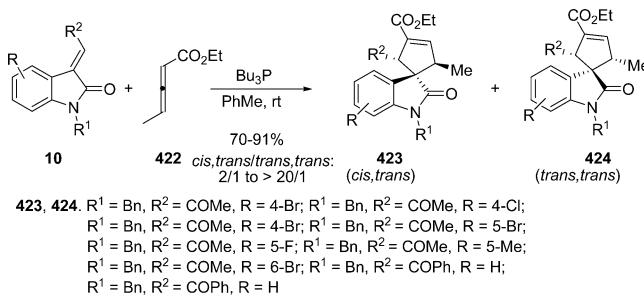
420 and 3-alkylideneisatin 10 using (S,S)-FerroPhane 419 as a catalyst afforded the phosphonate-functionalized spiro-pentene 421 (Scheme 142).

Scheme 142



Shi and co-workers have reported annulation of isatylidene malononitrile with the MBH carbonates<sup>274</sup> and isatin-derived electron-deficient alkenes with allenotes<sup>275,276</sup> in the presence of phosphanes. A phosphine-catalyzed highly diastereoselective [3+2]-cycloaddition of isatin-derived  $\alpha,\beta$ -unsaturated ketones 10 with  $\alpha$ -allenic esters 422 has been reported to furnish functionalized spiro-cyclopentenes 423 and 424 (Scheme 143).<sup>266</sup> The effects of catalyst, solvents, and substituents on the isatin moiety have been investigated. Among the triarylphosphines, Bu<sub>3</sub>P gave the best result in Bu<sub>2</sub>O or toluene as the solvent. The product was a diastereomeric mixture of *cis*, *trans* and *trans*,*trans* with the former as the major product. No regioisomer was obtained in the reaction as observed in the case of 3-alkylideneisatins.<sup>273</sup> Among the

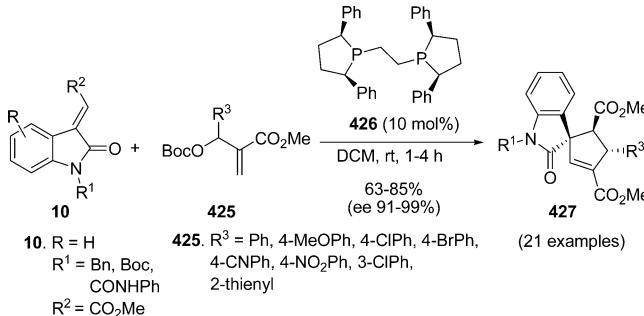
Scheme 143



triarylphosphines investigated, (4-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P has been observed as the most efficient catalyst using dioxane as the solvent affording products in good yields with excellent diastereoselectivity. The major diastereomer in this case, however, was *trans*,*trans*. An investigation into the effect of substituents on the phenyl ring of the *N*-benzylisatin in the presence of Bu<sub>3</sub>P and of (4-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P revealed that both electron-donating and electron-withdrawing substituents at the C-4, C-5, or C-6 position were well-tolerated in the reaction as the corresponding spiro-cyclopentene-oxindoles were obtained in good total yields (up to 90%); the major diastereomer being *cis*,*trans* in the presence of Bu<sub>3</sub>P and *trans*,*trans* in the presence of (4-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P, unambiguously established by single crystal X-ray analysis. The position of substituents were also observed to have an effect on diastereoselectivity of the reaction as a substituent at the C-4 position of the *N*-benzylisatin afforded the *cis*,*trans* diastereomer as the major product in both Bu<sub>3</sub>P and (4-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P-catalyzed reactions.

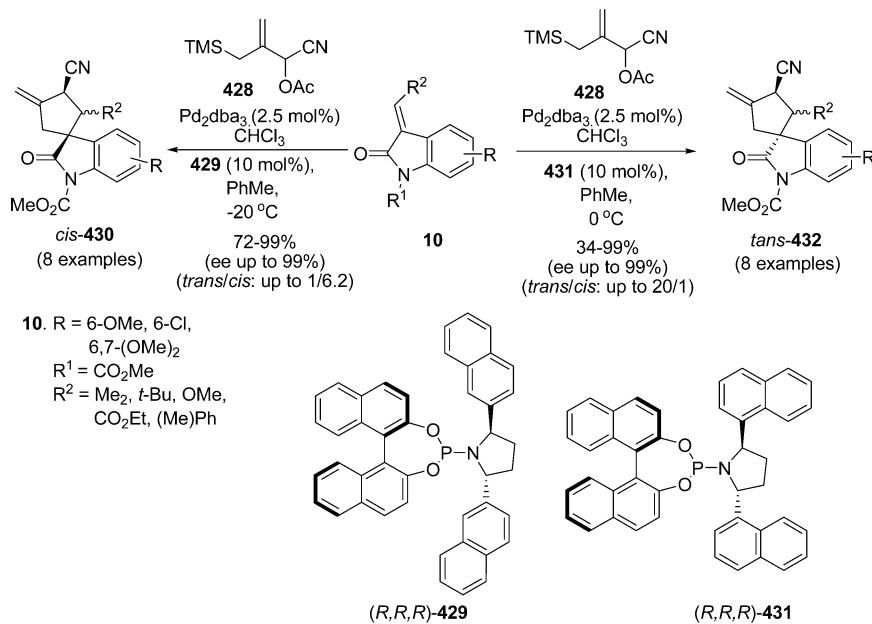
Barbas III and co-workers have investigated the organocatalytic asymmetric [3+2]-cycloaddition of *N*-protected methyldieneisatins 10 with the Morita-Baylis-Hillman adducts 425 in the presence of triarylphosphine (*R*)-BINAP, diphenylphosphine catalysts (DIOP), some biphosphines (DuPhos), and trialkylphosphine moiety-bearing catalysts (+)-Et-BPE and (+)-Ph-BPE 426.<sup>277</sup> Several spiro-cyclopentene-oxindoles 427 have been synthesized in good yields (63–85%) with excellent enantioselectivity (91–99%) using the (+)-Ph-BPE 426 as a model catalyst for this reaction (Scheme 144). The position and electronic properties of

Scheme 144



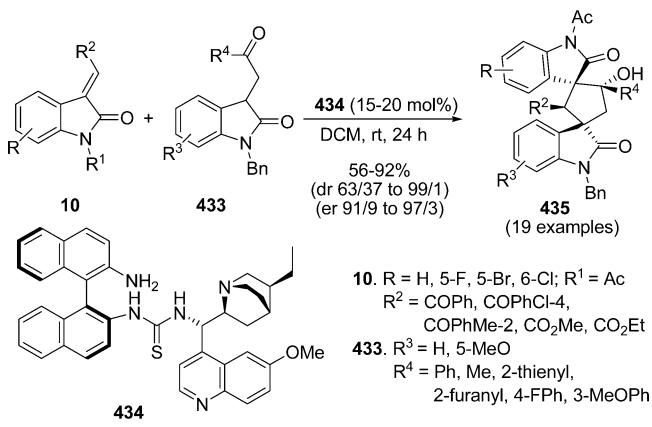
substituents were observed to have very little or no role on stereoselectivity. Only the methyl Morita-Baylis-Hillman carbonate failed to react efficiently and yielded the product in only 47% yield with low enantioselectivity (46%). The amide deprotection in spiro-oxindole moiety has been achieved using KOH on silica gel which enhances the further synthetic utility of the spiro-product.

Scheme 145



Trost and co-workers have reported the first enantioselective synthesis of spiro-cyclopentane-oxindole scaffold bearing three adjacent stereocenters by Pd-catalyzed asymmetric [3+2]-cycloaddition of cyano-substituted trimethylenemethane from precursor **428** with 3-alkylidene-2-oxindoles **10** (Scheme 145).<sup>278</sup> The chiral ligands controlled both the diastereo- and enantioselectivity as isomeric chiral ligands **429** and **431** furnished different isomers **430** and **432**, respectively, of spiro-cyclopentane-oxindoles. An organocatalytic asymmetric domino Michael-aldol reaction between *N*-acyl-3-alkylidene-2-oxindoles **10** and 3-substituted *N*-benzyl-2-oxindoles **433** affords the bis-spiro-oxindoles **435** spiro-fused to cyclopentane (Scheme 146).<sup>279</sup> The reaction is catalyzed by a newly designed

Scheme 146



multifunctional cinchona alkaloid catalyst **434** bearing a binaphthyl primary amine, a tertiary amine, and a thiourea functions to activate the substrates simultaneously, providing extraordinary stereocontrol over four stereocenters, three of which are quaternary carbon stereocenters. A chemoselective deprotection of the *N*-acyl group in the product, achieved by an acidic treatment, further enhances the scope of product for synthetic purposes.

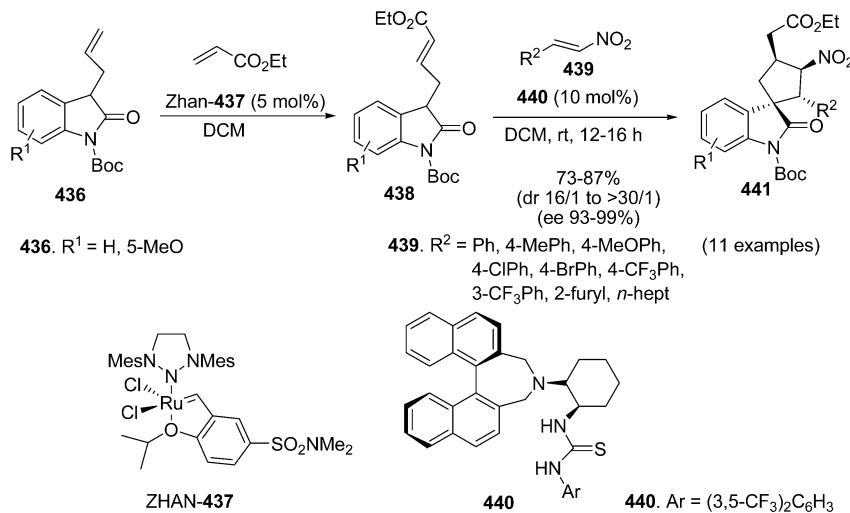
Shao and co-workers have reported a highly enantioselective one-pot synthesis of spiro-cyclopentane-oxindoles containing an oxime group on the cyclopentane ring by the reaction of *N*-Boc-3-allyloxindoles with nitroolefins using a bifunctional thiourea catalyst **440** bearing central and axial chiral elements.<sup>280</sup> The reaction involved an organocatalyzed asymmetric Michael addition/ISOC/fragmentation sequence affording products in up to 85% yield and up to 99% ee. Later on, this group extended the study to cross-metathesis of *N*-Boc-3-allyloxindoles **436** with vinyl ester in the presence of a Ru-catalyst Zhan-437 providing the novel Michael donor–acceptor synthons **438** (Scheme 147) that were employed in the synthesis of spiro-cyclopentane-oxindoles **441** bearing a nitro group on the cyclopentane ring.<sup>281</sup> A double Michael addition cascade of these newly designed synthons **438** with nitroolefins **439** in the presence of catalyst **440** furnished synthetically challenging products **441** with four contiguous stereocenters in good yields with excellent diastereo- and enantioselectivity.

On the basis of study with several other cinchona alkaloid and  $\alpha$ -amino acid-derived thioureas, it was observed that the diamine scaffolds of the catalysts had a significant impact on both diastereo- and enantioselectivity, and notably the axial chiral binaphthyl moiety of the catalyst played an important role in the stereocontrol of this reaction. The reactions tolerated diverse types of nitroolefins such as aromatic nitroolefins with various substituents on the aromatic ring, heteroaromatic- and aliphatic nitroolefins. The reactions were also successfully carried out with different substituents on the phenyl ring of 2-oxinole. The synthetic utility of the reaction was further demonstrated by transformation of the compound **441** to a tetracyclic molecule **442** possessing indolinol, pyrrolidin-2-one, and fused [5.5]-bicyclic lactam by a simple reduction reaction (Scheme 148).

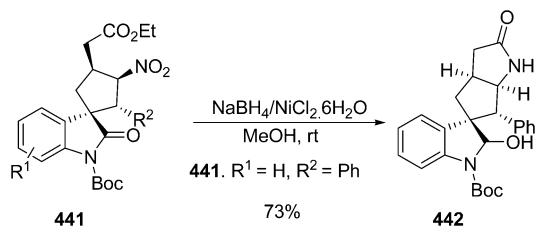
### 5.3. Spiro-Cyclohexanes, Spiro-Cyclohexenes, and Spiro-Cyclohexadienes

The vinylogous Michael addition of vinylmalononitriles on isatylidene malononitriles **396**, which is followed by a tandem reaction, affords spiro-cyclohexene-oxindoles and spiro-cyclohexadiene-oxindoles.<sup>282</sup> The reaction depends on the electronic

Scheme 147

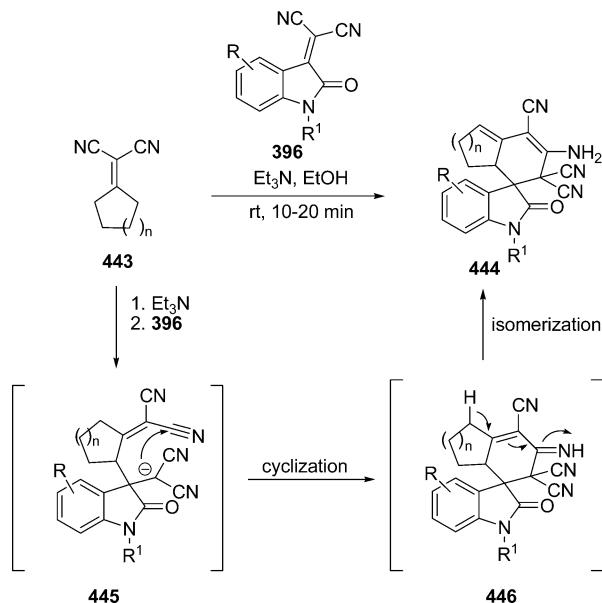


Scheme 148



environment of isatylidene malononitriles and nature of vinylmalononitriles. The reactions of isatylidene malononitriles **396** with cycloalkylenemalononitriles **443** afforded the spirocyclohexene-oxindoles **444** (Scheme 149, Table 10). The reaction with acyclic vinylnitriles **447**, however, afforded either spirocyclohexadiene-oxindole **448** as a sole product or a mixture of spirocyclohexene-oxindole **449** and spirocyclohexadiene-oxindole **450** (Scheme 150) depending on the substituent on vinylnitrile **447**. The reaction occurred quickly at

Scheme 149

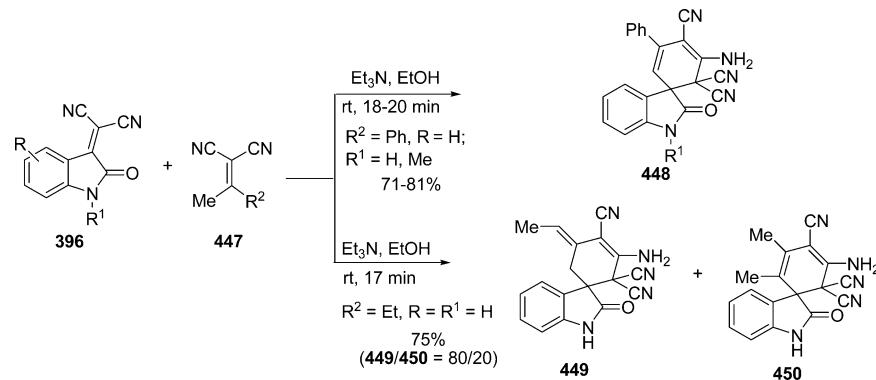
Table 10. Synthesis of Spiro-Cyclohexene-Oxindoles **444**

entry	R	R <sup>1</sup>	n	t (min)	<b>444</b> yields (%)
1	H	H	2	10	90
2	H	Me	2	12	92
3	H	allyl	2	15	90
4	H	propargyl	2	13	92
5	H	Bn	2	12	90
6	5-Br	H	2	20	85
7	5-NO <sub>2</sub>	H	2	22	83
8	H	H	1	15	90
9	H	Me	1	13	90
10	H	allyl	1	15	88
11	H	propargyl	1	13	91
12	Br	H	1	19	84

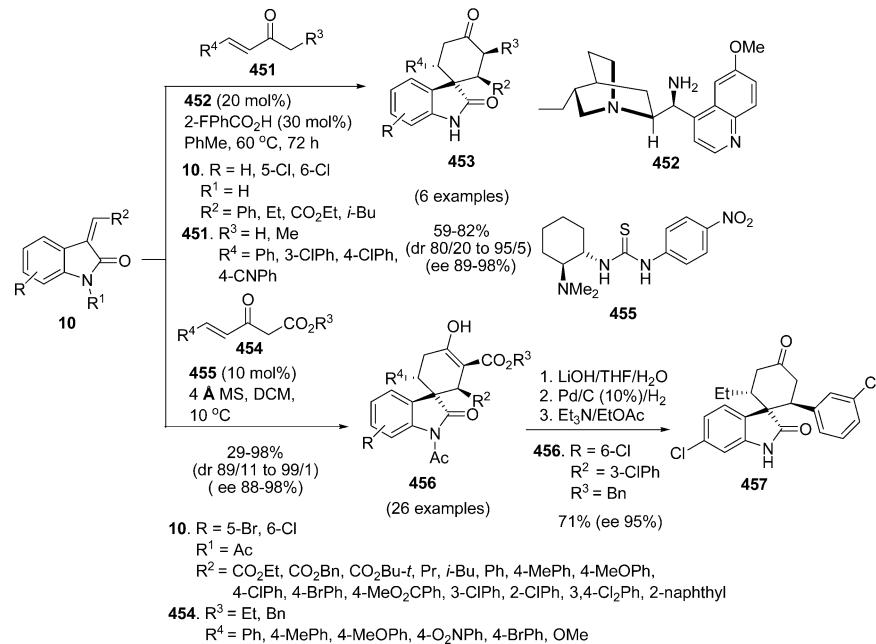
room temperature and was catalyzed by inexpensive base triethylamine. The reactions of 5-substituted isatylidenemalononitriles **396** with cycloalkylenemalononitriles **443** occurred quite slowly (Table 10) (entries 6, 7, 12) compared to unsubstituted or *N*-substituted substrates **396**. Further, the reaction of vinyl malononitrile with ethyl cyanoacetate-isatin adduct afforded a mixture of inseparable products. It was observed that the reactions of cycloalkylenemalononitriles **443** furnished an exocyclic double bond (Scheme 149) in the products **444**, whereas the acyclic vinyl malononitriles **447** furnished an endocyclic double bond in the products **448-450**. A plausible mechanism of formation of products involved the nucleophilic attack of the vinylogous carbanion, generated by abstraction of proton from compound **443** by triethylamine, onto the C-3 carbonyl group of isatylidenemalononitriles **396** and subsequent cyclization of the resulting intermediate **445** by intramolecular nucleophilic attack on the nitrile group and subsequent isomerization of the product **446** (Scheme 149).

There are many reports emerging in recent years on design of chiral organocatalysts for asymmetric synthesis of spirocyclohexane-oxindoles. Melchiorre and co-workers exploited the catalytic ability of the cinchona alkaloid catalyst 9-amino(9-deoxy)*epi*-hydroquinine **452** in an enamine-iminium activation strategy in the Michael addition of 3-alkylidene-2-oxindoles **10** with  $\alpha,\beta$ -unsaturated ketones **451** forming spirocyclohexane-oxindoles **453** (Scheme 139).<sup>283</sup> The products, obtained in good yields with variable diastereomeric ratio up to 98%

Scheme 150



Scheme 151

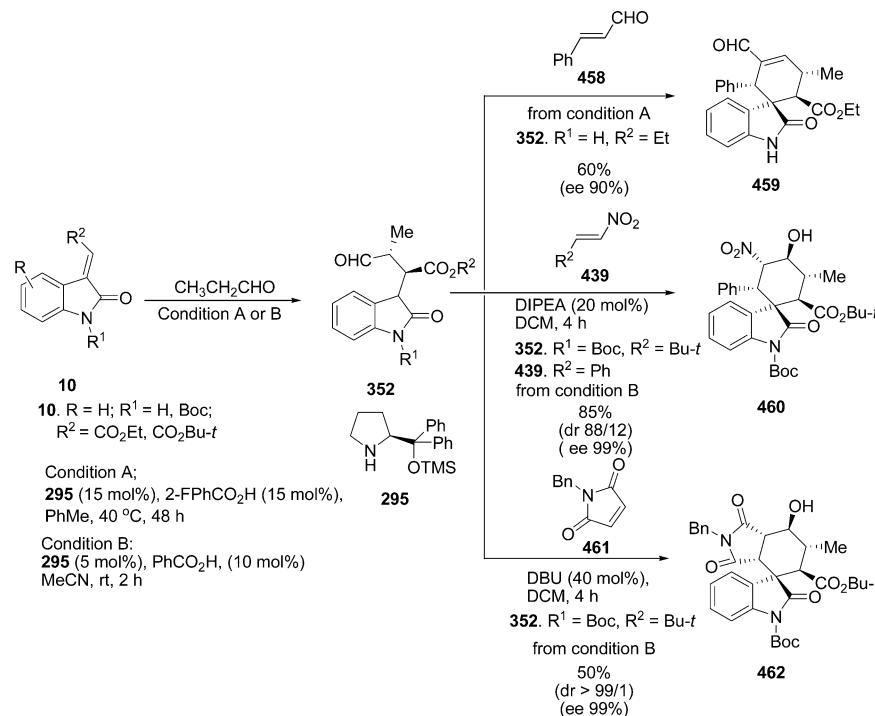


ee, were having four new stereocenters. A similar tandem double Michael addition was reported subsequently by Gong and co-workers in the presence of a chiral thiourea catalyst **455**. The reaction of *N*-acetyl-3-alkylidene-2-oxindoles **10** with  $\gamma,\delta$ -unsaturated  $\beta$ -ketoesters **454** provided access to spiro-cyclohexene-oxindoles **456** with three new chiral centers in high yields and selectivity (Scheme 151).<sup>284</sup> The bifunctional thiourea catalyst has been proposed to activate both the substrates through H-bonding interaction. During optimization studies on catalysts, it was observed that the minor structural features of thioureas had a significant effect on the yield (from 6 to 91%) and enantioselectivity (from 49 to 91%), but the diastereoselectivity was consistently high. Overall, the more acidic thiourea catalyst provided higher conversions and better selectivity. Further transformation of the product **456** by a three-step reaction sequence led to the formation of the spiro-cyclohexanone-oxindole **457** (Scheme 151) which has been identified as a potent inhibitor of the MDM2-p53 interaction.<sup>285</sup> Wang and co-workers later reported the synthesis of spiro-cyclohexanone-oxindoles in very good yields and enantioselectivities employing 3-unsubstituted *N*-protected-2-oxindoles in double Michael addition with 1,4-pentadien-3-ones

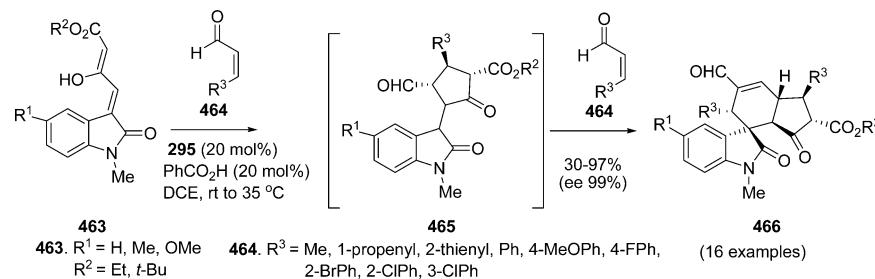
possessing various aromatic substituents on C-1 and C-5 in the presence of a cinchona-based primary amine catalyst.<sup>286</sup>

Chen and co-workers have employed the chiral pyrrolidine catalyst **295** in several multicomponent cascade reactions of 3-alkylidene-2-oxindoles **10**. An oxindole-propanal adduct **352** reacts with cinnamaldehyde **458**, with nitroolefin **439**, and with maleimide **461** forming spiro-cyclohexene-oxindole **459** and spiro-cyclohexane-oxindoles **460** and **462**, respectively (Scheme 152).<sup>249</sup> The reaction was extended successfully to diversely substituted cinnamaldehydes and nitroolefins affording products in good yields (50–84%) and enantioselectivity. Melchiorre and co-workers had reported this reaction earlier<sup>283</sup> using similar nitroolefins and cinnamaldehydes but 2-oxindoles with free NH instead of *N*-Boc-protected oxindoles used by Chen and co-workers. In the reactions of NH-unprotected 2-oxindoles, 2-fluorobenzoic acid was used as an acidic catalyst, but benzoic acid was used as an acidic catalyst in most reactions of *N*-Boc-protected oxindoles. Although the reactions of NH-unprotected 2-oxindoles, aldehydes, and  $\alpha,\beta$ -unsaturated carbonyl compounds offered moderate yields (35–74%, the lowest with *p*-nitrocinnamaldehyde), excellent enantioselectivity (>99%) and diastereoselectivity (19/1) were observed.

Scheme 152



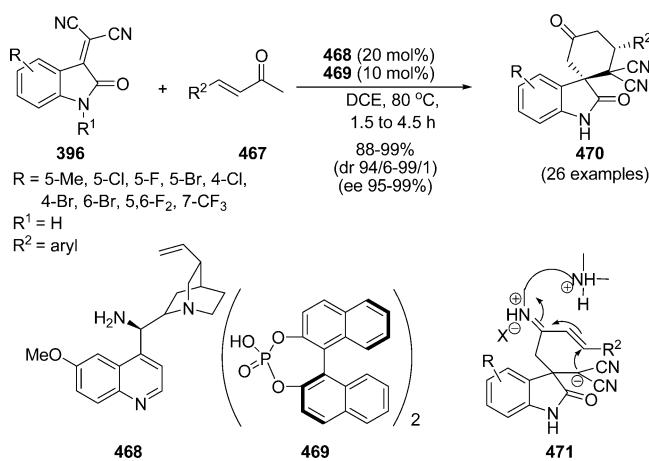
Scheme 153



In another cascade process, the reaction of (*E*)-4-(1-methyl-2-oxindolin-3-ylidene)-3-oxabutanoates **463** with  $\alpha,\beta$ -unsaturated aldehydes **464** (Scheme 153) or with nitroolefins **439** in the presence of amine **295** led to the synthesis of enantioenriched spiro-hydroindane-oxindoles **466**.<sup>287</sup> The reaction proceeded via a quadruple iminium-enamine-iminium-enamine catalysis to furnish compounds through intermediate product **465**. The products containing six to eight contiguous stereocenters were obtained with excellent enantiomeric excess but in low to moderate yields in most reactions.

Wang and co-workers have reported the combination of a cinchona-based chiral primary amine **468** and a BINOL-phosphoric acid **469** as a powerful and synergistic catalytic system for the double Michael addition of isatylidene malononitriles with  $\alpha,\beta$ -unsaturated ketones affording optically pure spiro-cyclohexanone-oxindoles **470**.<sup>288</sup> The reaction of *N*-unsubstituted isatylidene malononitriles **396** with  $\alpha,\beta$ -unsaturated ketones **467** having electron-donating and electron-withdrawing groups on the phenyl ring occurred smoothly in the presence of this catalyst to afford spiro-cyclohexanone-oxindoles in excellent yields, diastereo- and enantioselectivity (Scheme 154). Like in many other reports, C-4 substituted malononitriles reacted very sluggishly (36 h). It is worth

Scheme 154



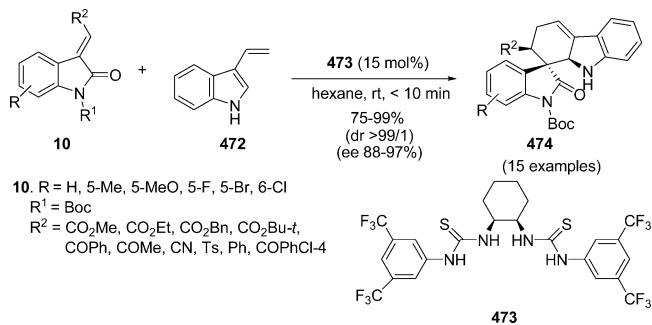
mentioning here that in these products the ketone functionality was present at C-3' instead of C-4', as in the products reported by Melchiorre's<sup>283</sup> and Gong's groups.<sup>284</sup>

The authors envisioned isatylidene malononitriles both as an acceptor and latent donor in a double Michael addition sequence. They proposed activation of  $\alpha,\beta$ -unsaturated ketones

by condensation with the chiral primary amine catalyst assisted by protic acid forming a chiral nucleophilic dienamine intermediate that would stereoselectively attack the C-3 of oxindole moiety. The regioselectivity here would be determined by more electron-withdrawing cyano groups. The resulting Michael adduct may lead to the formation of final product by an iminium ion-catalyzed intramolecular conjugate addition. The chiral counteranion in the catalytic system provided additional stereodiscrimination in the transition state **471** that was responsible for excellent diastereo- and enantioselectivity.

Recently, an extremely rapid and efficient organocatalytic asymmetric Diels–Alder cycloaddition of *N*-Boc-3-alkylidene-2-oxindoles **10** and 3-vinylindole **472** is reported to afford the spiro-carbazole-oxindoles **474** containing three or four stereocenters, including one spiro quaternary chiral carbon (Scheme 155).<sup>289</sup> A simple bisthiourea **473** has been used as a catalyst in

Scheme 155



this reaction furnishing structurally diverse products in almost quantitative yields and with excellent stereoselectivity (dr >99/1, ee up to 99%). Moreover, both the catalyst and solvent could be easily recycled. The reaction also occurs efficiently with differently substituted vinyl indoles with same ease. The formation of the products has been explained by activation of alkylideneoxindoles through H-bonding interactions with bisthiourea. Further transformations of an *N*-Boc protected product were achieved by deprotection of the *N*-Boc group in trifluoroacetic acid and by a 1,3-hydrogen shift, also in acidic medium, without affecting the ester functionalities and enantioselectivity forming other spiro-carbazole-oxindoles **475** and **476**, respectively (Scheme 156).

The literature review on spiro-cycloalkyl oxindoles reveals direct application of isatins either through the Wittig reaction or through the Lewis acid-catalyzed reactions in the synthesis of spiro-cyclopropanes and spiro-cyclopentanes. Most syntheses of spiro-carbocyclic compounds are through isatin derivatives such as rhodium-carbenoids from 3-diazoisatins, 3-alkylidene-isatins, isatin-malononitrile adducts, and isatin-MBH adducts. The development of enantioselective methodologies for the synthesis of spiro-carbocyclic frameworks bearing 2-oxindoles is the area of current interest which is evident from many

publications in the area in recent years. Some novel phosphines and thioureas containing binaphthyl moiety and cinchona alkaloids, respectively, have been designed to achieve diastereo- and enantioselective synthesis of spiro-cyclopentane framework. The Michael addition followed by cyclization and the Diels–Alder reaction using 3-alkylideneisatins are general protocols for the synthesis of spiro-cyclohexanes. Enantioselective syntheses of spiro-cyclohexanes are reported by asymmetric organocatalysis using a chiral bifunctional thiourea and a chiral pyrrolidine as the catalysts.

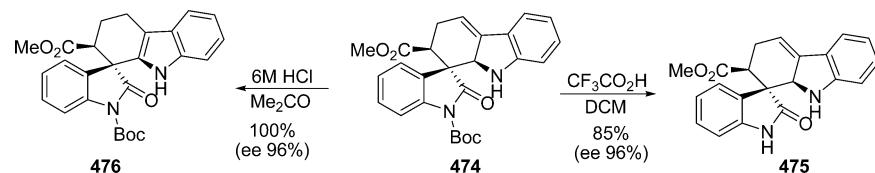
## 6. CONCLUDING REMARKS

Isatins and its C-3 functionalized derivatives occupy a prominent place in organic synthesis and medicinal chemistry. The most significant applications of isatins in organic synthesis are due to high reactivity of its C-3 carbonyl group. Recent years have witnessed many fascinating applications of isatins in design and synthesis of spiro-fused cyclic frameworks, both heterocyclic and carbocyclic, of complex nature from the synthetic point of view. Many of these spiro-cyclic compounds are natural products of biological importance. Many synthetic spiro-cyclic compounds bearing a 2-oxindole moiety also exhibit potential antimalarial, anticancer, and antimicrobial activities. Isatin itself, *N*-substituted isatins, and isatins with different substituents on a phenyl ring have been employed in two-, three-, and four-component reactions leading to the formation of three- to eight-membered spiro-heterocyclic frameworks and three- and five-membered spiro-carbocyclic frameworks bearing a 2-oxindole moiety.

Isatins are reported to undergo cyclocondensation with nitrogen, oxygen, and sulfur nucleophiles forming spiro-imidazolines, spiro-tetrahydroquinazolines, spiro-dioxolanes, and spiro-thiazolidines. The 1,3-dipolar cycloadditions of isatins to oxygen ylides and to nitrogen ylides have been employed in the synthesis of spiro-dioxolanes and spiro-oxazolines, respectively. The Darzens reaction of isatin is known to afford spiro-oxiranes. The cycloaddition of isatins to ylide from  $\alpha$ -bromoamide and thiolane affords spiro-oxiranes as well. The three-component reactions of isatins through azomethine ylides, generated from its decarboxylative condensation with  $\alpha$ -amino acids, constitute a common approach for the synthesis of spiro-pyrrolidine-oxindoles. Another commonly investigated MCR is the reactions of isatins, active methylene compounds such as malononitrile, ethyl cyanoacetate, etc., and various types of carbonyl compounds, furnishing spiro-pyrans. A *p*-TsOH-catalyzed three-component reaction of isatins, mercaptoacetic acids, and 5-aminopyrazoles represents a novel method for constructing seven-membered ring spiro-thiazepinones. Only a few four-component reactions involving isatins are reported; these reactions lead to the formation of six-membered spiro-azaheterocycles.

There are many synthetic procedures employing isatins-derived 3-functionalized 2-oxindoles as substrates for spiro-products. The most commonly used isatin derivatives employed

Scheme 156



in design of the spiro-cyclic frameworks include 3-alkylideneisatins, 3-iminoisatins, isatin-3-hydrazone, 3-aminoisatins, 3-diazoisatins, isatin-aldol adducts, and isatin-MBH adducts, etc. The application of these compounds has led to the development of methodologies for the synthesis of aziridines, oxiranes,  $\beta$ -lactams, oxazolines, oxadiazolines, piperidines, oxolanes, pyrans, and oxepenes, etc., spiro-fused to 2-oxindoles.

Isatins and its derivatives have been employed in design and synthesis of spiro-fused carbocyclic frameworks of potential biological importance. Isatins are directly employed in the synthesis of spiro-cyclopropanes and spiro-cyclopentanes involving either the Wittig reaction or the Lewis acid-catalyzed reactions. Most syntheses of spiro-carbocyclic compounds such as spiro-cyclopropanes, spiro-cyclopentanes, and spiro-cyclohexanes, however, are reported through isatin derivatives such as rhodium-carbenoids from 3-diazoisatins, 3-alkylideneisatins, isatilydenemalononitrile, and isatin-MBH adducts. The Michael addition followed by cyclization and the Diels–Alder reaction using alkylideneisatins are general protocols for the synthesis of spiro-cyclohexanes.

The development of diastereo- and enantioselective methodologies for the synthesis of spiro-fused cyclic frameworks containing two to four stereocenters is the area of current interest which is evident from several publications in this area recently. Although there are some reports on the use of chiral auxiliary, recent research is dominated by application of asymmetric catalysis. The Lewis acids such as  $TiCl_4$  and  $In(III)$ , Bronsted acid such as phosphoric acids, some novel phosphines and thioureas bearing binaphthyl moiety, and cinchona alkaloids have emerged as powerful catalysts for diastereo- and enantioselective synthesis of spiro-cyclic frameworks on 2-oxindoles. *N*-Heterocyclic carbenes have been employed recently as a catalyst in a [2+2]-cycloaddition of isatins with ketenes for enantioselective synthesis of spiro- $\beta$ -lactone-oxindoles. *N*-Heterocyclic carbene-catalyzed reactions of isatins with enals are known to afford  $\gamma$ -lactones in diastereo- and enantioselective manner. The enantioselective syntheses of cyclohexanes are reported recently by asymmetric organocatalysis using a chiral bifunctional thiourea and a chiral pyrrolidine as the catalysts. Only in some cases, the mechanistic studies have been carried out and transition states proposed, but more details are yet to come. In MCRs, the stereocontrol is a challenging endeavor; only a few asymmetric syntheses are reported employing the MCRs.

Many of the spiro-cyclic compounds obtained from isatins and its C-3-functionalized derivatives have been subjected to simple functional group transformations leading to the formation of differently functionalized spiro-cyclic frameworks. The selective opening of the  $\gamma$ -lactone and  $\beta$ -lactam rings spiro-fused to 2-oxindoles are reported recently to furnish maremycine A and spiro-oxazolidinone, respectively. The chemistry of spiro-cyclic 2-oxindoles, thus, opens up further avenues for development of the novel spiro-heterocyclic frameworks which might be of potential biological value.

The large number of recent publications in high-impact journals on the synthesis of diverse types of spiro-cyclic frameworks containing 2-oxindoles utilizing isatins is an indicator of significant interest in the area and a lot more interesting chemistry is anticipated.

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### Notes

The authors declare no competing financial interest.

### Biographies



**Girija S. Singh** was born in Sasaram (Bihar), India. He received his B.Sc. and M.Sc. degrees from the U. P. College (then Gorakhpur University), Varanasi, India, in 1977 and 1979, respectively, under the mentorship of Dr. V.P. Singh. He received his Ph.D. degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines, and hydrazones under the supervision of Prof. K.N. Mehrotra in October, 1984. During his research for the Ph.D. degree, he was a recipient of the junior and senior research fellowships of the CSIR, New Delhi. Since then he has occupied teaching and research positions in various universities such as Banaras Hindu University, India (PDF with Prof. S.N. Pandeya, Research Associate, Pool-Officer, Reader), Osaka University, Japan (PDF with late Prof. Toshikazu Ibata), University of Zambia (Lecturer), and University of Botswana (Lecturer, Senior Lecturer, Associate Professor). He is currently working as a Professor of Chemistry at University of Botswana. He has authored 78 publications in books and in peer-reviewed journals. He is member of many professional societies including the American Chemical Society and Chemical Research Society of India. He is also on the editorial board of some chemistry journals. His research interests include the study of synthesis and reactivity of biologically important heterocycles, reactions of carbenoids and ketenes, metal-catalyzed oxidations, and organic chemistry education.



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## REFERENCES

- (1) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273 and references therein.
- (2) Bergman, J.; Lindstrom, J. O.; Tilstam, U. *Tetrahedron* **1988**, *41*, 2879.
- (3) Chiyanzu, I.; Hansell, E.; Gut, J.; Rosenthal, P. J.; McKerrow, J. H.; Chibale, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3527.
- (4) Almeida, M. R.; Leitão, G. G.; Silva, B. V.; Barbosa, J. P.; Pinto, A. C. *J. Braz. Chem. Soc.* **2010**, *21*, 764.
- (5) Kekule, A. *Chem. Ber.* **1869**, *2*, 748.
- (6) Sumpter, W. C. *Chem. Rev.* **1944**, *34*, 393.
- (7) Popp, F. D. *Adv. Heterocycl. Chem.* **1975**, *18*, 1.
- (8) Verma, M.; Pandeya, S. N.; Singh, K. N.; Stables, J. P. *Acta Pharm.* **2004**, *54*, 49.
- (9) Raj, A.; Raghunathan, R.; Sridevikumaria, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407. Patel, A.; Bari, S.; Talele, G.; Patel, J.; Sarangapani, M. *Iran. J. Pharm. Res.* **2006**, *4*, 249.
- (10) Tripathy, R.; Reiboldt, A.; Messina, P. A.; Iqbal, M.; Singh, J.; Bacon, E. R.; Angeles, T. S.; Yang, S. X.; Albom, M. S.; Robinson, C.; Chang, H.; Ruggeri, B. A.; Mallamo, J. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2158.
- (11) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntlad, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109.
- (12) Ratan, B. T.; Anand, B.; Yogeeshwari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4451. Sriram, D.; Yogeeshwari, P.; Meena, K. *Die Pharmazie* **2006**, *61*, 274.
- (13) Aboul-Fadl, T.; Bin-Jubair, F. A. S. *Int. J. Res. Pharm. Sci.* **2010**, *1*, 113.
- (14) For review on bioactivity: Pandeya, S. N.; Smitha, S.; Jyoti, M.; Sridhar, S. K. *Acta Pharm. (Zagreb, Croatia)* **2005**, *55*, 27.
- (15) See for overview: Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758.
- (16) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Karen, J. C.; Hudak, M. A.; Marella, A. G.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, J.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861.
- (17) Kumari, G.; Nutan; Modi, M.; Gupta, S. K.; Singh, R. K. *Eur. J. Med. Chem.* **2011**, *46*, 1181.
- (18) Lo, M. M.-C.; Newmann, C. S.; Nagayams, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 10130. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qui, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.* **2004**, *126*, 16077.
- (19) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hubel, K.; Rauth, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902.
- (20) Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F.; Brun, R.; Dartois, V.; Diagana, T. T.; Keller, T. H. *J. Med. Chem.* **2010**, *53*, 5155.
- (21) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zhou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Paez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175. Ang, S. H.; Crastel, P.; Leong, S. Y.; Tan, L. J.; Wong, W. L. J.; Yeung, B. K. S.; Zou, B. (Novartis AG) US Patent 2009/0275560 A1, 2009. Liu, J.-J.; Zhang, Z. (Hoffmann La Roche AG) spiroindolinone derivatives: PCT Int. Appl. WO 2008/055812, 2008.
- (22) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stukey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432.
- (23) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.
- (24) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821.
- (25) Dou, X. W.; Lu, Y. X. *Chem.-Eur. J.* **2012**, *18*, 8315.
- (26) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060.
- (27) Piccirilli, R. M.; Popp, F. D. *J. Heterocycl. Chem.* **1973**, *10*, 671. Khan, K. M.; Mughal, U. R.; Samreen; Perveen, S.; Choudhary, M. I. *Lett. Drug Des. Discovery* **2008**, *5*, 243.
- (28) Sridhar, S. K.; Pandeya, S. N.; Stables, J. P.; Ramesh, A. *Eur. J. Pharm. Sci.* **2002**, *16*, 129.
- (29) Pandeya, S. N.; Raja, A. S. *J. Pharm. Pharm. Sci.* **2002**, *5*, 266.
- (30) Pervez, H.; Iqbal, M. S.; Choudhary, M. Y.; Khan, K. M. *Nat. Prod. Res.* **2007**, *21*, 1178.
- (31) Pinto, A. C.; Lapis, A. A. M.; da Silva, B. V.; Bastos, R. S.; Dupont, J.; Neto, B. A. D. *Tetrahedron Lett.* **2008**, *49*, 5639.
- (32) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091. Cava, M. P.; Little, R. L.; Naipier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257. Muthusamy, S.; Gunanathan, C. *Synlett* **2002**, 1783. Muthusamy, S.; Gunanathan, C.; Babu, S. A.; Suresh, E.; Dastidar, P. *J. Chem. Soc., Chem. Commun.* **2002**, 824. Muthusamy, S.; Srinivasan, P. *Tetrahedron Lett.* **2009**, *50*, 3794.
- (33) Muthusamy, S.; Gunanathan, C. *Synlett* **2002**, 1783. Muthusamy, S.; Gunanathan, C.; Babu, S. A.; Suresh, E.; Dastidar, P. *J. Chem. Soc., Chem. Commun.* **2002**, 824. Muthusamy, S.; Srinivasan, P. *Tetrahedron Lett.* **2009**, *50*, 3794.
- (34) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L. F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472.
- (35) Kato, S.; Yoshino, T.; Shibasaki, M.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7007.
- (36) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Eur. J. Org. Chem.* **2010**, 2845.
- (37) Maybe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324.
- (38) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537.
- (39) Yan, W. J.; Wang, D.; Feng, J. C.; Li, P.; Wang, R. *J. Org. Chem.* **2012**, *77*, 3311.
- (40) Guo, Q.-X.; Liu, Y.-W.; Li, X.-C.; Zhong, L.-Z.; Peng, Y.-G. *J. Org. Chem.* **2012**, *77*, 3589.
- (41) Shi, Y.-H.; Wang, Z.; Shi, Y.; Deng, W.-P. *Tetrahedron* **2012**, *68*, 3649.
- (42) Yan, W.; Wang, D.; Feng, G.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512.
- (43) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003.
- (44) Porcs-Makkay, M.; Volk, B.; Kapiller-Dezsöfi, R.; Mezei, T.; Simig, G. *Monatsh. Chem.* **2004**, *135*, 697.
- (45) Trost, B. M.; Zhang, Y. *Chem.-Eur. J.* **2011**, *17*, 2916.

- (46) Volk, B.; Simig, G. *Eur. J. Org. Chem.* **2003**, 3991.
- (47) Villemin, D.; Martin, B. *Synth. Commun.* **1998**, 28, 3201.
- (48) Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Galatulas, I.; Nineil, M. *Eur. J. Med. Chem.* **1990**, 25, 187.
- (49) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. F.; Haffron, T. P. *J. Am. Chem. Soc.* **1999**, 121, 6326. Raunak; Kumar, V.; Mukherjee, S.; Poonam; Prasad, A. K.; Olsen, C. E.; Schaffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W.; Parmar, V. S. *Tetrahedron* **2005**, 61, S687.
- (50) Junek, H.; Dworczak, R.; Sterk, H.; Fabian, W. *Leibigs Ann. Chem.* **1989**, 1065. Walter, W. *Chem. Ber.* **1902**, 35, 1320.
- (51) Aikawa, K.; Mimura, S.; Numata, Y.; Mikami, K. *Eur. J. Org. Chem.* **2011**, 62.
- (52) Liu, L.; Zhang, S.; Xue, F.; Lou, G.; Zhang, H.; Ma, S.; Duan, W.; Wang, W. *Chem.-Eur. J.* **2011**, 17, 7791.
- (53) Elinson, M. N.; Merkulova, V. M.; Illovaisky, A. I.; Chizhov, A. O.; Belyakov, P. A.; Barba, F.; Batanero, B. *Electrochim. Acta* **2010**, 55, 2129.
- (54) Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2010**, 66, 1441.
- (55) Allu, S.; Molletti, N.; Panem, R.; Singh, V. K. *Tetrahedron Lett.* **2011**, 52, 4080.
- (56) Peng, L.; Wang, L.-L.; Bai, J.-F.; Jia, L.-N.; Yang, Q.-C.; Huang, Q.-C.; Xu; Wang, L.-X. *Tetrahedron Lett.* **2011**, 52, 1157.
- (57) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, 63, 10437.
- (58) Chen, G.; Tang, Y.; Zhang, Q.-Z.; Wu, Y.; Mu, S.-Z. *J. Chem. Crystallogr.* **2010**, 40, 369.
- (59) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, 103, 811.
- (60) Garden, S. J.; Skakle, J. M. S. *Tetrahedron Lett.* **2002**, 43, 1969.
- (61) Chung, Y. M.; Im, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, 23, 1651.
- (62) Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, 44, 4365.
- (63) Guan, X.-Y.; Wei, Y.; Shi, M. *Chem.-Eur. J.* **2010**, 16, 13617.
- (64) Liu, Y.-L.; Wang, B. L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, 132, 15176.
- (65) Zhong, F.; Chen, G.-Y.; Lu, Y. *Org. Lett.* **2011**, 13, 82.
- (66) Wang, C. C.; Yu, X.-Y. *Tetrahedron* **2011**, 67, 2974.
- (67) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2005**, 70, 3198.
- (68) Qiao, X.-C.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2009**, 20, 1254.
- (69) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, 48, 6313.
- (70) Arndt, F.; Eistert, B.; Ender, W. *Chem. Ber.* **1929**, 62B, 44. Arndt, F.; Amende, J.; Ender, W. *Monatsch* **1932**, 59, 202.
- (71) Jacini, C. *Gazz. Chim. Ital.* **1943**, 73, 306; *ibid.* **1947**, 77, 295.
- (72) DeMayo, P.; Ryan, J. J. *J. Chem. Soc., Chem. Commun.* **1967**, 88.
- (73) Field, G. F. *J. Chem. Soc., Chem. Commun.* **1969**, 886.
- (74) Cornforth, J. W. *J. Chem. Soc., Perkin Trans. I* **1976**, 2004.
- (75) Wenkert, E.; Bringi, N. V. *J. Am. Chem. Soc.* **1958**, 80, 5575.
- (76) De Vivar, A. R.; Romo, J. J. *Org. Chem.* **1959**, 24, 1490.
- (77) Schonberg, A.; Junghaus, K. *Chem. Ber.* **1963**, 96, 3328.
- (78) Amiet, R. G.; Eastwood, F. W.; Rae, I. D. *Aust. J. Chem.* **1972**, 25, 1473.
- (79) James, M. N. G.; Williams, G. J. B. *Can. J. Chem.* **1972**, 50, 2407.
- (80) Jossang, A.; Jossang, P.; Hamid, A. H.; Sevenet, T.; Bodo, B. J. *Org. Chem.* **1991**, 56, 6527.
- (81) Cui, C.-B.; Kakeya, H.; Osada, H. *J. J. Antibiot.* **1996**, 49, 832. Cui, C.-B.; Kakeya, H.; Osada, H. *J. Tetrahedron* **1996**, 52, 12651.
- (82) Anderton, N.; Cockrum, P. A.; Cologate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I. *Phytochemistry* **1998**, 48, 437.
- (83) Shi, J.-S.; Yu, J.-X.; Chen, X.-P.; Xu, R.-X. *Acta Pharm. Sin.* **2003**, 24, 97.
- (84) Zhou, J.; Zhou, S. *J. Ethnopharmacol.* **2010**, 132, 15. Chou, C.-H.; Gong, C.-L.; Chao, C. C.; Lin, C.-H.; Kwan, C.-Y.; Hsieh, C.-L.; Leung, Y. M. *J. Nat. Prod.* **2009**, 72, 830. Kang, T. H.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H.; Matsumoto, K. *Life Sci.* **2004**, 76, 331.
- (85) Polonsky, J. M.; Merrien, M. A.; Prange, T.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1980**, 601.
- (86) Asakawa, M.; Miyazawa, K. *Jpn. J. Toxicol.* **1998**, 11, 361.
- (87) Potawel, S. E.; Mehta, U. K.; Waseem, S.; Dhalawat, H. J.; Lunya, K. P.; Mantri, R. A.; Vetol, Y. D. *Pharmacol.* **2008**, 2, 197. Litvinov, Y. M.; Mortikov, V. Y.; Shestopalov, A. M. *J. Comb. Chem.* **2008**, 10, 741.
- (88) Bergman, J.; Stalhandske, C.; Vallberg, H. *Acta Chem. Scand.* **1997**, 51, 753.
- (89) Bergman, J.; Engqvist, R.; Stalhandske, C.; Wallberg, H. *Tetrahedron* **2003**, 59, 1033.
- (90) Neume, K.; Kurusawa, S.; Toda, F.; Hasegawa, M.; Iwakura, Y. *Bull. Chem. Soc. Jpn.* **1982**, 55, 2293.
- (91) Joshi, K. C.; Chand, P.; Dandia, A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, 23B, 743. Joshi, B. S.; Lakhati, M. A.; Visheanathan, N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, 23B, 114.
- (92) Gurevich, P. G.; Sattarova, L. F.; Petrovskiy, A. S.; Frolova, N. A.; Strunin, B. P.; Musin, R. Z. *Chem. Heterocycl. Compd. (New York, NY, U. S.)* **2010**, 46, 1527.
- (93) Hu, Y.; Wang, M.-M.; Chen, H.; Shi, D.-Q. *Tetrahedron* **2011**, 67, 9342.
- (94) Mohammadi, A. A.; Dabiri, M.; Qaraat, H. *Tetrahedron* **2009**, 65, 3804.
- (95) Joshi, K. C.; Jain, R.; Chand, P.; Sharma, V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, 23B, 386.
- (96) Perez, A. L.; Cicco, J. F. *Ing. Cience. Quim.* **1991**, 13, 20.
- (97) Ribeiro, N. M.; Pinto, A. C.; Violante, F. A.; Dias, M. O. *Catal. Commun.* **2007**, 8, 2130.
- (98) Dos Santos, E. L.; Gomes, W. A., Jr.; Ribeiro, N. M.; Andrade, H. M. C. *J. Mol. Catal. A: Chem.* **2008**, 295, 18.
- (99) Sakai, S.; Aimi, N.; Kubo, A.; Kitagawa, M.; Hanasawa, M.; Katano, K.; Yamaguchi, K.; Higinawa, J. *Chem. Pharm. Bull.* **1975**, 23, 2805.
- (100) Rekhter, M. A.; Radul, O. M.; Bukhanyuk, S. M. *Chem. Heterocycl. Compd. (New York, NY, U. S.)* **1999**, 35, 792.
- (101) Joshi, K. C.; Dandia, A.; Khanna, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1990**, 29B, 824.
- (102) Dandia, A.; Khanna, S.; Joshi, K. C. *J. Ind. Chem. Soc.* **1990**, 67, 824.
- (103) Jackson, A. H.; Johnston, D. N.; Shannon, P. V. R. *J. Chem. Soc., Chem. Commun.* **1975**, 911.
- (104) Bazgir, A.; Tisseh, Z. N.; Mirzaei, P. *Tetrahedron Lett.* **2008**, 49, S165.
- (105) Jadidi, K.; Ghahremanzadeh, R.; Bazgir, Y. *Tetrahedron* **2009**, 65, 2005.
- (106) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, 44, 2030. Whaley, W. M.; Govindachari, T. M. *Org. React.* **1951**, 6, 151.
- (107) Baiocchi, L.; Giannangeli, M. *J. Heterocycl. Chem.* **1988**, 25, 1905.
- (108) Shmidt, M. S.; Perillo, I. A.; Gonzalez, M.; Blanco, M. M. *Tetrahedron Lett.* **2012**, 53, 2514.
- (109) Schulz, V.; Davoust, M.; Lemarie, M.; Lohier, J. F.; Santos, J. S. D.; Metzner, P.; Briere, J. F. *Org. Lett.* **2007**, 9, 1745.
- (110) Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Saez, J. A.; Domingo, L. R.; Mongin, F. *Org. Biomol. Chem.* **2008**, 6, 3144.
- (111) Nair, V.; Sethumadhavan, D.; Nair, S. M.; Viji, S.; Rath, N. P. *Tetrahedron* **2002**, 58, 3003.
- (112) Nair, V.; Mathai, S.; Augustine, A.; Viji, S.; Radhakrishnan, K. *Synthesis* **2004**, 2617.
- (113) Nair, V.; Rajesh, C.; Dhaniya, R.; Rath, N. P. *Tetrahedron Lett.* **2002**, 43, 5349.
- (114) Nair, V.; Sheela, K. C.; Sethumadhawan, D.; Bindu, S.; Rath, N. P.; Eigendorf, G. K. *Synlett* **2001**, 272.
- (115) Liu, X.-G.; Feng, Y.-Q.; Tan, C.-J.; Chen, H.-L. *Synth. Commun.* **2006**, 36, 2655.

- (116) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.  
 (117) Wasielewsky, M. R. *Chem. Rev.* **1992**, *92*, 435.  
 (118) Ali, H.; Lier, J. E. *Chem. Rev.* **1999**, *99*, 2379.  
 (119) Gein, V. L.; Levandovskaya, E. B.; Vichegjanina, V. N. *Chem. Heterocycl. Compd. (New York, NY, U. S.)* **2010**, *46*, 931.  
 (120) Gurevich, P. A.; Akhmetova, G. Z.; Gubaidullin, A. T.; Moskva, V. V.; Litvinov, I. A. *Russ. J. Gen. Chem.* **1998**, *68*, 1501. Sharma, D.; Bansal, R. K. *J. Indian Chem. Soc.* **1990**, *67*, 29.  
 (121) Hosomi, A.; Hayashi, S.; Hoashi, K.; Kohra, S.; Tominaga, Y. J. *Chem. Soc., Chem. Commun.* **1987**, 1442.  
 (122) Lian, Z.; Shi, M. *Eur. J. Org. Chem.* **2012**, 581.  
 (123) Wang, X.-N.; Zhang, Y.-Y.; Ye, S. *Adv. Synth. Catal.* **2010**, *352*, 1892.  
 (124) Sun, L.-H.; Shen, L.-T.; Ye, S. *J. Chem. Soc., Chem. Commun.* **2011**, *47*, 10136.  
 (125) Basavaiah, D.; Rao, J. S.; Reddy, R. J.; Rao, A. J. *J. Chem. Soc., Chem. Commun.* **2005**, 2621.  
 (126) Badillo, J.; Arevalo, G. E.; Fettinger, J. C.; Franz, A. K. *Org. Lett.* **2011**, *13*, 418.  
 (127) Hanhan, N. V.; Ball-Jones, N. R.; Tran, N. T.; Franz, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 989.  
 (128) Duce, S.; Pesciaoli, F.; Graminga, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 860.  
 (129) Badillo, J. J.; Silva-Garcia, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. *Tetrahedron Lett.* **2011**, *52*, 5550.  
 (130) Shintani, R.; Hayashi, S.-Y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754.  
 (131) Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5820.  
 (132) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786.  
 (133) Jiang, X.; Cao, Y.; Wang, Y.; Liu, L.; Shen, F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328.  
 (134) Han, Y.-Y.; Chen, B.-W.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 490.  
 (135) For review on MCRs: Sunderhaus, J. D.; Martin, S. F. *Chem.-Eur. J.* **2009**, *15*, 1300. Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.  
 (136) Liu, H.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 633.  
 (137) Litvinov, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Shestopalov, A. M. *J. Comb. Chem.* **2009**, *11*, 914.  
 (138) See for overviews on spiro-pyrrolidine natural products: Marti, C.; Carreira, E. *Eur. J. Org. Chem.* **2003**, 2209. Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.  
 (139) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182.  
 (140) Coulter, T.; Grigg, R.; Malone, J. F.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417. Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602. Ardill, H.; Dorritt, M. J. R.; Grigg, R.; Leon-Ling, M. S.; Malone, J. F.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron* **1990**, *46*, 6433. Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180. Casaschi, A.; Desimoni, G.; Faita, G.; Invernizzi, A. G.; Grunanger, P. *Heterocycles* **1994**, *37*, 1673. Palmisano, G.; Annuziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1. Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2235.  
 (141) Rehn, S.; Bergman, J.; Stainsland, B. *Eur. J. Org. Chem.* **2004**, 413.  
 (142) Nair, V.; Sheela, K. C.; Rath, N. P. *Chem. Lett.* **2000**, 980.  
 (143) Ghandi, M.; Taheri, A.; Abbasi, A. *Tetrahedron* **2010**, *66*, 6744.  
 (144) Babu, A. R. S.; Raghunathan, R.; Gayatri, G.; Sastry, N. J. *Heterocycl. Chem.* **2006**, *43*, 1.  
 (145) Lakshmi, N. V.; Thirumurugan, P.; Perumal, P. T. *Tetrahedron Lett.* **2010**, 1064.  
 (146) Rao, J. N. S.; Raghunathan, R. *Tetrahedron Lett.* **2012**, *53*, 854.  
 (147) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4618.  
 (148) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4487.  
 (149) Jayashankaran, J.; Maniyan, R. D. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303.  
 (150) Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 305.  
 (151) Thangamani, A. *Eur. J. Med. Chem.* **2010**, *45*, 6120.  
 (152) Ganguly, A. K.; Seah, N.; Popov, V.; Wang, C. H.; Kuang, R.; Saksena, A. K.; Pramanik, B. N.; Chan, T. M.; McPhail, A. T. *Tetrahedron Lett.* **2002**, *43*, 8981.  
 (153) Kumar, R. S.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 7164.  
 (154) Kumar, R. S.; Rajesh, S. M.; Perumal, S.; Banerjee, D.; Yogeeshwari, P.; Sriram, D. *Eur. J. Med. Chem.* **2010**, *45*, 411.  
 (155) Velikorodov, A. V.; Podubnyi, O. Y.; Krivosheev, O. O.; Titova, O. L. *Russ. J. Org. Chem.* **2011**, *47*, 402.  
 (156) Liu, H.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 292.  
 (157) Patel, P. N.; Patel, H. S. *Pharm. Lett.* **2011**, *3*, 307.  
 (158) Hu, X.-F.; Feng, Y.-Q. *Synth. Commun.* **2005**, *37*, 1747.  
 (159) Prasanna, P.; Balamurugan, K.; Perumal, S.; Yogeeshwari, P.; Sriram, D. *Eur. J. Med. Chem.* **2010**, *45*, 5653.  
 (160) Zhang, X.-N.; Li, Y.-X.; Zhang, Z.-H. *Tetrahedron* **2011**, *67*, 7426.  
 (161) Li, J.; Liu, Y.; Li, C.; Jia, X. *Chem.-Eur. J.* **2011**, *17*, 7409.  
 (162) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507.  
 (163) Chen, H.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 571.  
 (164) Quiroga, J.; Portillo, S.; Pérez, A.; Gálvez, J.; Abonia, R.; Insuasty, B. *Tetrahedron Lett.* **2011**, *52*, 2664.  
 (165) Ghahremanzadeh, R.; Ahadi, S.; Shakibaei, G. I.; Bazgir, A. *Tetrahedron Lett.* **2010**, *51*, 499.  
 (166) Rad-Moghadam, K.; Youseftabar-Miri, L. *J. Fluorine Chem.* **2012**, *135*, 213.  
 (167) Zhu, S.-L.; Ji, S.-J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365.  
 (168) Shemchuk, L. A.; Chernykh, V. P.; Red'kin, R. G. *Russ. J. Org. Chem.* **2008**, *44*, 1789.  
 (169) Redkin, G. R.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkin, S. V. *Tetrahedron* **2007**, *63*, 11444.  
 (170) Elinson, M. N.; Dorofeev, A. S.; Miloserdov, F. M.; Nikishin, G. I. *Mol. Diversity* **2009**, *13*, 47.  
 (171) Shanthi, G.; Perumal, P. *J. Chem. Sci. (Bangalore, India)* **2010**, *122*, 415.  
 (172) Hari, G. S.; Lee, Y. R. *Synthesis* **2010**, 453.  
 (173) Zhao, L.; Zhou, B.; Li, Y. *Heteroat. Chem.* **2011**, *22*, 673.  
 (174) Chai, S.-J.; Lai, Y.-F.; Xu, J.-C.; Zheng, H.; Zhu, Q.; Zhang, P.-F. *Adv. Synth. Catal.* **2011**, *353*, 371.  
 (175) Zou, Y.; Hu, Y.; Liu, H.; Shi, D. *ACS Comb. Sci.* **2012**, *14*, 38.  
 (176) Elinson, M. N.; Illovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron* **2007**, *63*, 10543.  
 (177) Elinson, M. N.; Merkulova, V. M.; Illovaisky, A. I.; Demchuk, D. V.; Belyakov, P. A.; Nikishin, G. I. *Mol. Diversity* **2010**, *14*, 833.  
 (178) Li, Y.; Chen, H.; Shi, C.; Shi, D.; Ji, S. *J. Comb. Chem.* **2010**, *12*, 231.  
 (179) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132.  
 (180) Macaev, F.; Sucman, N.; Shepeli, F.; Zveaghintseva, M.; Pogrebnoi, V. *Symmetry* **2011**, *3*, 165.  
 (181) Liang, B.; Kalidindi, S.; Porco, J. A., Jr.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 572.  
 (182) Alizadeh, A.; Mokhtari, J. *Tetrahedron* **2011**, *67*, 3519.  
 (183) Sun, J.; Sun, Y.; Gao, H.; Yan, C.-G. *Eur. J. Org. Chem.* **2012**, 1976.  
 (184) Balamurugan, K.; Perumal, S.; Menendez, J. C. *Tetrahedron* **2011**, *67*, 3201.  
 (185) Chen, H.; Shi, D. *Tetrahedron* **2011**, *67*, 5686.  
 (186) Loreto, M. A.; Migliorini, A.; Tardella, P. A.; Gambacorta, A. *Eur. J. Org. Chem.* **2007**, 2365.

- (187) Ammetto, I.; Gasperi, T.; Loreto, M. A.; Migliorini, A.; Palmarelli, F.; Tardella, P. A. *Eur. J. Org. Chem.* **2009**, 6189.
- (188) Gasperi, T.; Loreto, M. A.; Migliorini, A.; Ventura, C. *Eur. J. Org. Chem.* **2011**, 385.
- (189) Rossiter, S. *Tetrahedron Lett.* **2002**, 43, 4671.
- (190) Shimazawa, R.; Kurijama, M.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2008**, 18, 3350.
- (191) Singh, G. S.; Dhooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, 107, 2080.
- (192) Singh, G. S.; Dhooghe, M.; De Kimpe, N. *Tetrahedron* **2011**, 67, 1989.
- (193) Singh, G. S. *Tetrahedron* **2003**, 59, 7631. Singh, G. S.; Dhooghe, M.; De Kimpe, N. In *Comprehensive Heterocyclic Chemistry-III*; Katritzky, A. R., Ramsden, C., Scriven, E., Taylor, R., Eds.; Elsevier: UK, 2008; Vol. 2, p 1.
- (194) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.
- (195) Singh, G. S.; Mehrotra, K. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1985**, 24B, 129.
- (196) Singh, G. S.; Singh, T.; Lakhan, R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, 36B, 951.
- (197) Singh, G. S.; Mmolotsi, B. *J. J. Heterocycl. Chem.* **2006**, 43, 1665.
- (198) Singh, G. S.; Luntha, P. *Eur. J. Med. Chem.* **2009**, 44, 2265.
- (199) Singh, G. S. *J. Heterocycl. Chem.* **2000**, 37, 1355.
- (200) Singh, G. S.; Luntha, P. M. *J. Heterocycl. Chem.* **2011**, 48, 1312.
- (201) Jarrahpour, A.; Khalili, D. *Tetrahedron Lett.* **2007**, 48, 7140.
- (202) Azizian, J.; Sarrafi, Y.; Mehrdad, M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2000**, 39B, 304.
- (203) Mulwad, V. V.; Mir, A. A. *J. Korean Chem. Soc.* **2008**, 52, 649.
- (204) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, 33, 440.
- (205) Moura, S.; Chen, Z.; Mitsunuma, H.; Furutachi, H.; Matsunaga, H.; Shibusaki, S. *J. Am. Chem. Soc.* **2010**, 132, 1255.
- (206) Azmi, A. S.; Philip, P. A.; Beck, F. W. J.; Wang, Z.; Banerjee, S.; Wans, S.; Yang, D.; Sarkar, F. H.; Mohammad, R. M. *Oncogene* **2011**, 30, 117.
- (207) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, 38, 3186.
- (208) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, 124, 14826.
- (209) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, 83, 1175.
- (210) Carreira, E. M.; Meyers, C. *Angew. Chem., Int. Ed.* **2003**, 42, 694.
- (211) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, 122, 5666.
- (212) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, 58, 6311.
- (213) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, 5, 3135. Sebahar, P. R.; Williams, R. M. *Heterocycles* **2002**, 58, 563.
- (214) Ding, K.; Wang, G.; Deschamps, R.; Parrish, D. A.; Wang, S. *Tetrahedron Lett.* **2005**, 46, 5949.
- (215) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, 131, 13819.
- (216) Liu, T.-L.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Org. Biomol. Chem.* **2011**, 9, 1980.
- (217) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schurmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, 2, 735.
- (218) Antonchick, A. P.; Schuster, H.; Bruss, H.; Schurmann, M.; Preut, H.; Rauth, D.; Waldmann, H. *Tetrahedron* **2011**, 67, 10195.
- (219) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, 50, 9124.
- (220) Tan, B.; Zeng, X.; Leong, W. W. Y.; Shi, Z.; Barbas, C. F., III; Zhong, G. *Chem.-Eur. J.* **2012**, 18, 63.
- (221) Kumar, U. K. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, 3, 4193.
- (222) Sacchetti, A.; Silvani, A.; Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, 9, 5515.
- (223) Brittain, D. R.; Wood, R. Eur. Pat. Appl. EP 28906, 1981; *Chem. Abstr.* **1981**, 95, 150660.
- (224) Nair, V.; Treesa, P. M.; Rath, N. P.; Kunwar, A. C.; Kumar, K. S. K.; Sankar, A. R.; Vairamani, M.; Prabhakar, S. *Tetrahedron* **2002**, 58, 7221.
- (225) Shanmugam, P.; Vaithyanathan, V. *Tetrahedron* **2008**, 64, 3322.
- (226) Bergonzini, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, 51, 971.
- (227) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, 71, 2346.
- (228) Viswambharan, B.; Selvakumar, K.; Madhavan, S.; Shanmugam, P. *Org. Lett.* **2010**, 12, 2108.
- (229) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, 46, 5237.
- (230) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 18, 3003.
- (231) Selvakumar, K.; Vaithyanathan, V.; Shanmugam, P. *J. Chem. Soc., Chem. Commun.* **2010**, 46, 2826.
- (232) Ibrahim, M. N.; EL-Messmary, M. F.; Elarfi, M. G. A. *E. J. Chem.* **2010**, 7, 55.
- (233) Azizian, J.; Shaabanzadeh, M.; Hatamjafari, F.; Mohammadzadeh, M. R. *ARKIVOC (Gainesville, FL, U. S.)* **2006**, XI, 47.
- (234) Ribeiro, C. J. A.; Kumar, S. P.; Moreira, R.; Santos, M. M. M. *Tetrahedron Lett.* **2012**, 53, 281.
- (235) Pedras, M. S. C.; Okanga, F. I.; Zaharia, I. I.; Khan, A. O. *Phytochemistry* **2000**, 53, 161.
- (236) Pedras, M. S. C.; Hosain, M. *Org. Biomol. Chem.* **2006**, 4, 2581.
- (237) Mehta, R. G.; Liu, J.; Constantinou, A.; Hawthorne, M.; Pezzuto, J. M.; Moon, R. C.; Moriarty, R. M. *Anticancer Res.* **1994**, 14, 1209.
- (238) Joshi, K.; Dandia, A.; Bhagat, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1990**, 29B, 766.
- (239) Mashelkar, U. C.; Rane, D. M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2005**, 44B, 1937.
- (240) Dandia, A.; Sharma, G.; Singh, R.; Laxkar, A. *ARKIVOC (Gainesville, FL, U. S.)* **2009**, XIV, 100.
- (241) Thadhaney, B.; Sain, D.; Pemawat, G.; Talesara, G. L. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2010**, 49B, 368.
- (242) Kaminsky, D.; Khyluk, D.; Vasylenko, O.; Zaprutko, L.; Lesyk, R. *Sci. Pharm.* **2011**, 79, 763.
- (243) Choudhari, B. P.; Mulwad, V. V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2005**, 44B, 1074.
- (244) Vintonyak, V. V.; Warburg, K.; Over, B.; Hubel, K.; Rauh, D.; Waldmann, H. *Tetrahedron* **2011**, 67, 6713.
- (245) Islam, M. R.; Mohsin, M. *Bangladesh J. Pharmacol.* **2007**, 2, 7.
- (246) Somogyi, L. *Bull. Chem. Soc. Jpn.* **2001**, 74, 873.
- (247) Kouznetsov, V. V.; Forero, J. S. B.; Torres, D. F. A. *Tetrahedron Lett.* **2008**, 49, 5855.
- (248) Lesma, G.; Landoni, N.; Sacchetti, A.; Silvani, A. *Tetrahedron* **2010**, 66, 4474.
- (249) Jiang, K.; Jia, Z. J.; Chen, S.; Wu, L.; Chen, Y. C. *Chem.-Eur. J.* **2010**, 16, 2852.
- (250) Castaldi, M. P.; Troast, D. M.; Porco, J. A., Jr. *Org. Lett.* **2009**, 11, 3362.
- (251) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, 128, 13640.
- (252) Muschalek, B.; Weidner, I.; Butenschon, S. *J. Organomet. Chem.* **2007**, 692, 2415.
- (253) Wang, J.; Crane, E. A.; Scheidt, K. A. *Org. Lett.* **2011**, 13, 3086.
- (254) Kusunuru, R. A.; Ghate, M.; Kulkarni, M. V. *J. Chem. Sci. (Bangalore, India)* **2004**, 116, 265.
- (255) Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, 11, 3366.
- (256) Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M., Y.; Kobayashi, J. *Org. Lett.* **2004**, 6, 3087. Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, 70, 9430.
- (257) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, 47, 3573.
- (258) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, 30, 824.
- (259) Cordonqq, M. E.; Karp, G. M.; Birk, J. H. European Patent 459,133; *Chem. Abstr.* **1992**, 117, 48332.

- (260) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, C. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.
- (261) Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turnerc, P. *Tetrahedron* **2005**, *61*, 8120. Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 1191.
- (262) Crestini, C.; Saladno, R. *Synth. Commun.* **1994**, *24*, 2835.
- (263) Muthusamy, S.; Azhagan, D.; Gnanaprakasam, B.; Suresh, E. *Tetrahedron Lett.* **2010**, *51*, 5662.
- (264) Kumari, G.; Nutan; Modi, M.; Gupta, S. K.; Singh, R. K. *Eur. J. Med. Chem.* **2011**, *46*, 1181.
- (265) Reddy, B. V. S.; Rajasekaran, T.; Karthik, G.; Rao, T. P. *Tetrahedron Lett.* **2012**, *53*, 3416.
- (266) Eberle, M. K.; Kahle, G. G.; Shapiro, M. *J. J. Org. Chem.* **1982**, *47*, 2210.
- (267) Bennet, G. B.; Mason, R. B.; Shapiro, M. *J. J. Org. Chem.* **1978**, *43*, 4383.
- (268) Kayukova, O. V.; Kayukov, Y. S.; Lapteva, E. S.; Bardasov, I. N.; Ershov, O. V.; Nasakin, O. E. *Russ. J. Org. Chem.* **2006**, *42*, 1414.
- (269) Shanmugam, P.; Vaithyanathan, V.; Viswambharan, B. *Tetrahedron* **2006**, *62*, 4342.
- (270) Yu, H.; Liu, Y.; Zhang, H.; Chen, J.; Deng, H.; Shao, M.; Ren, Z.; Cao, W. *Tetrahedron* **2010**, *66*, 2598.
- (271) Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57.
- (272) Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2008**, *49*, 7139.
- (273) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.-Eur. J.* **2010**, *16*, 12541.
- (274) Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348.
- (275) Zhang, X.-C.; Kao, S.-H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 1142.
- (276) Zhang, X.-C.; Kao, S.-H.; Wei, Y.; Shi, M. *J. Chem. Soc., Chem. Commun.* **2011**, *47*, 1548.
- (277) Tan, B.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, *133*, 4672.
- (278) Trost, B. M.; Cramer, N. A.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396.
- (279) Tan, B.; Candeias, N. R.; Barbas, C. F., III *Nat. Chem.* **2011**, *3*, 473.
- (280) Li, X.; Li, Y.-M.; Peng, F.-Z.; Wu, S.-T.; Li, Z.-Q.; Sun, Z.-W.; Zhang, H.-B.; Shao, Z.-H. *Org. Lett.* **2011**, *13*, 6160.
- (281) Li, Y.-M.; Li, X.; Peng, F.-Z.; Li, Z.-Q.; Wu, S.-T.; Sun, Z.-W.; Zhang, H.-B.; Shao, Z.-H. *Org. Lett.* **2011**, *13*, 6200.
- (282) Babu, T. H.; Joseph, A. A.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 994.
- (283) Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaoli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.
- (284) Wei, Q.; Gong, L. Z. *Org. Lett.* **2010**, *12*, 1008.
- (285) Hoffman, F.; La Roche L. T. D. 2008, WO-2008055812.
- (286) Wang, L.-L.; Peng, L.; Bai, J.-F.; Jia, L.-N.; Luo, X.-Y.; Huang, Q.-C.; Xu, X.-U.; Wang, L.-X. *J. Chem. Soc., Chem. Commun.* **2011**, *47*, 5593.
- (287) Jiang, K.; Jia, Z. J.; Yin, X.; Wu, L.; Chen, Y. C. *Org. Lett.* **2010**, *12*, 2766.
- (288) Lan, Y.-B.; Zhao, H.; Liu, Z.-M.; Liu, G.-G.; Tao, J.-C.; Wang, X.-W. *Org. Lett.* **2011**, *13*, 4866.
- (289) Tan, B.; Hernandez-Torres, G.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, *133*, 12354.