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MINI-REVIEW ARTICLE

Step Economy in the Stereoselective Synthesis of Functionalized Oxindoles *via* Organocatalytic Domino/One-pot Reactions

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Abstract: Oxindoles are an important class of heterocyclic scaffolds widely present in natural products and bioactive compounds. For this reason, a plethora of methodologies for the stereoselective synthesis of enantioenriched oxindoles has been studied over the years. Among all the reported synthetic strategies, organocatalysis has proven to be a powerful tool for the asymmetric synthesis of this class of compounds being a step- and atom-economical, environmentally friendly, and non-toxic approach. This review will outline the application of asymmetric organocatalysis in the synthesis of chiral oxindole-based structures, relying on domino/one-pot reaction sequences in a step-economical fashion.

Fabrizio Vetica

Keywords: Oxindoles, organocatalysis, domino reactions, one-pot reactions, cascade reactions, asymmetric synthesis, chiral building blocks, bioactive compounds.

1. INTRODUCTION

The stereoselective synthesis of chiral heterocyclic building blocks and optically pure complex molecular structures has been one of the major challenges for synthetic organic chemists [1]. In fact, heterocyclic compounds have appeared as privileged structures as part of natural and synthetic products with applications in the pharmaceutical and agrochemical industry [2]. The presence of one or more heteroatoms in the cyclic core is indeed a feature of molecules that play a key role in our daily life [3].

Within this context, oxindoles are molecular scaffolds widely present in bioactive compounds, active ingredients, as well as natural products [4]. Due to their potential applications, chemists have addressed their efforts all over the years to the development of new and efficient methodologies for the synthesis of such heterocycles starting from simple and readily available substrates, focusing mainly on enantioselective catalytic processes (Fig. **1**).

In this framework, asymmetric organocatalysis has emerged as a reliable and efficient approach to this aim [5].

Asymmetric organocatalysis is defined as the use of small optically pure organic compounds, either synthetic or chiral pool-derived, able to promote organic transformations in a stereoselective fashion. Even though the use of naturally-derived chiral organic compounds as catalysts was firstly reported in 1913 [6], it was only at the beginning of the 21st century that this approach addressed the attention of the scientific community with a renewed interest [5h-7]. This has paved the way to a tremendous development of this synthetic approach, extending the horizons of organic synthesis towards efficient, practical and more sustainable methodologies [8].

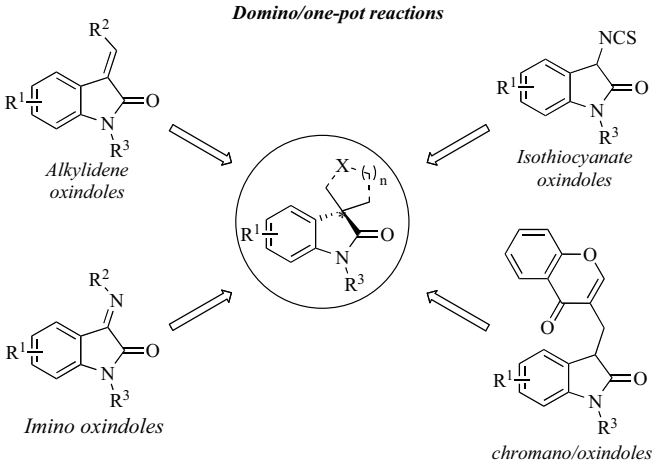

Fig. (1). Synthetic approaches towards enantioenriched oxindoles *via* step-economical methods.

In facts, several advantages can be addressed to the use of these organic catalysts:

- the stability of these catalysts in the presence of air and moisture compared to metal-complexes allows low-demanding reaction conditions;
- lower environmental impact and waste due to the absence of heavy metals;
- organocatalysts are usually cheaper than enzymes or metal-based catalysts and readily available;
- different activation modes, often simultaneous, are possible with respect of substrates, reagents, and reactions. (Fig. **2A**)

Due to these features, organocatalytic procedures ideally follow the principles of green chemistry. Additionally, among the extensive realm of organocatalytic methodologies, multicomponent reactions [8e, 9], sequential catalysis [10], domino/cascade [8a-11], and

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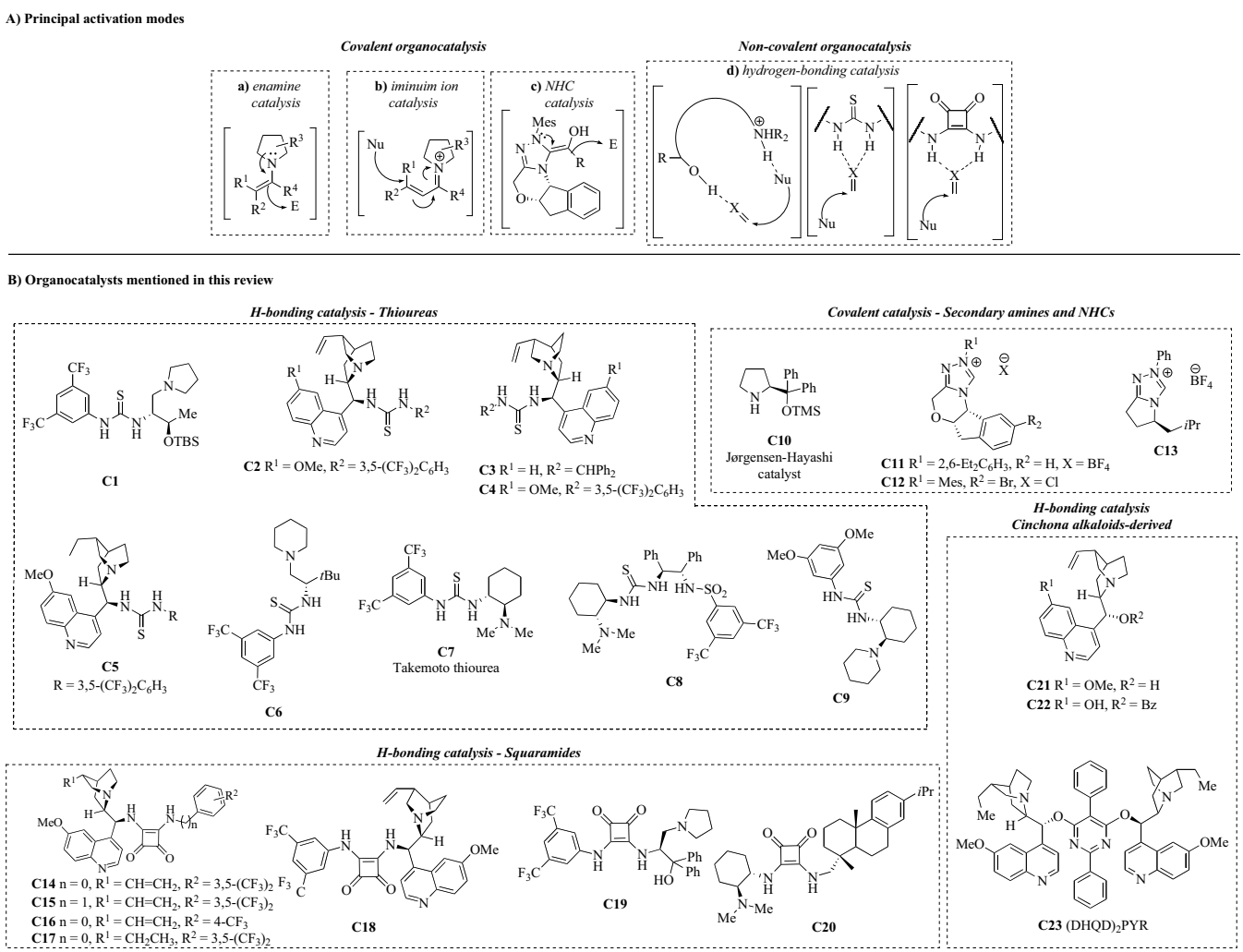


Fig. (2). Overview of organocatalysts covered in this review (**B**) and principal activation modes (**A**).

one-pot [12] reactions represent undoubtedly a breakthrough in the total synthesis of enantioenriched molecules. Key features are certainly the increased atom- and step-economy of these practical and efficient procedures, which dramatically decrease the cost and environmental impact of the syntheses, reducing the purification and isolation steps of the various intermediates.

Two main classes of organocatalysts can be distinguished on the basis of the type of activation (Fig. **2A**): *i)* the covalent organocatalysts (**C10-13**), typically secondary amines [13] and *N*-heterocyclic carbenes (NHCs), [14] which form a covalent bond with the substrates; *ii)* non-covalent organocatalysts, which rely on activations *via* H-bonds networks [8b, 8e, 15]. Within this context, the combination of multiple activation modes performed by the organocatalysts with the above-mentioned step-economical cascade reaction sequences has been successfully applied to the synthesis of oxygen [16] and nitrogen [17] containing heterocycles, and chiral oxindoles are no exceptions.

Over the years, various catalytic asymmetric strategies have been reported for the stereoselective synthesis [18] and heterofunctionalization [19] of oxindole derivatives [20] and spirooxindoles. [15]. This review will outline the most recent methodologies for the stereoselective synthesis of chiral oxindoles, which rely on step-economical domino/one-pot organocatalysed reactions, reported in the time frame 2015-2021. The discussion is divided on the basis of the class of substrates employed in the reactions, and a particular focus is given to the reaction sequences mechanistic features.

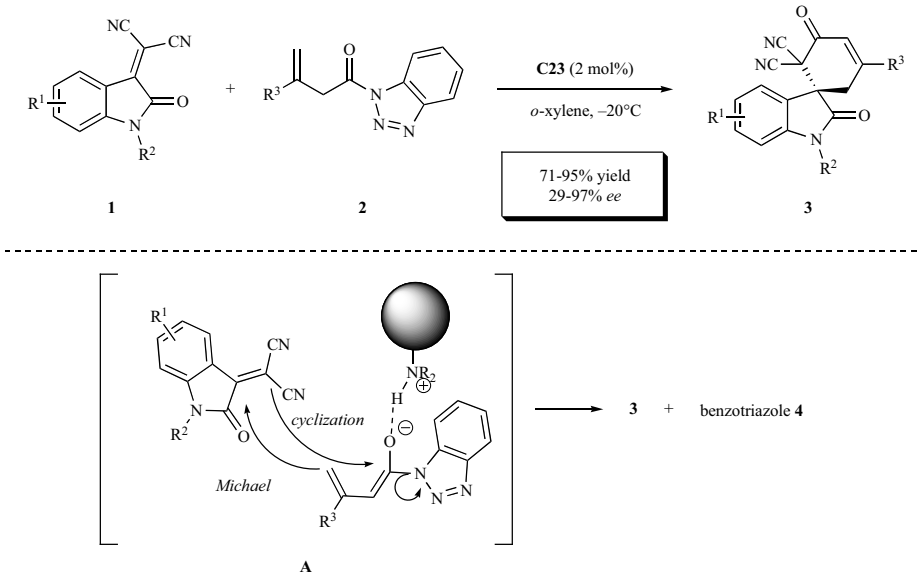
2. CASCADE APPROACHES FROM 3-ALKYLIDENE OXINDOLES

Among the various substrates commonly used for the cascade functionalization of oxindoles, 3-alkylidene-oxindoles are undoubtedly the most studied. Indeed, these peculiar compounds are characterized by a versatile reactivity on the α- and β-position adjacent to the lactam moiety. Often, the presence of electron-withdrawing groups on the alkylidene moiety favors a double electrophilic tendency to react with nucleophiles *via* conjugated addition on either the α or the β carbon with respect to the lactam functionality.

Consequently, the most frequently used synthetic approaches employed in the transformation of this class of substrates involve a Michael-type conjugate addition followed by a cyclization reaction in a one-pot/cascade fashion.

In 2015, Wu, Sha *et al.* developed a Michael/cyclization methodology towards substituted spirooxindoles **3**, relying on the catalytic activity of a cinchona alkaloid-derived dimer, $(DHQD)_2PYR$ **C23** (Scheme **1**) [21].

The substrates chosen were di-cyano-substituted *N*-protected oxindoles **1** and β,γ-unsaturated benzotriazole amides **2**. The tertiary amine of the quinuclidine moiety of catalyst **C23** promoted a



Scheme 1. Vinylogous Michael/cyclization strategy by Wu, Sha *et al*. [21].

vinylogous Michael addition onto the β-carbon of the isatylidene malononitrile **1**, activating the extended enolate of **2** in **A**. Subsequently, the α-carbon of the malononitrile moiety could perform a cyclization reaction on the amide function, with a simultaneous displacement of benzotriazole **4** and formation of product **3**. Spirooxindoles **3** were obtained in good to excellent yields with high stereocontrol of the newly formed quaternary stereocenter (up to 97% *ee*).

To achieve this level of enantioselectivity, two key points were studied by the authors once identified the best catalyst: *i)* the steric hindrance of the *N*-substituent on the starting material **1** proved crucial, since the *ee* value increased gradually going from methyl to $–CHPh_2$ group (29 and 90% *ee*, respectively); *ii*) the temperature screening showed the best results were obtained by decreasing it down to –20°C. Even though this approach proved efficient in the control of domino reaction sequence, the overall atom-economy of the process is not optimal, since benzotriazole **4** is formed as side product in order to achieve the desired compounds.

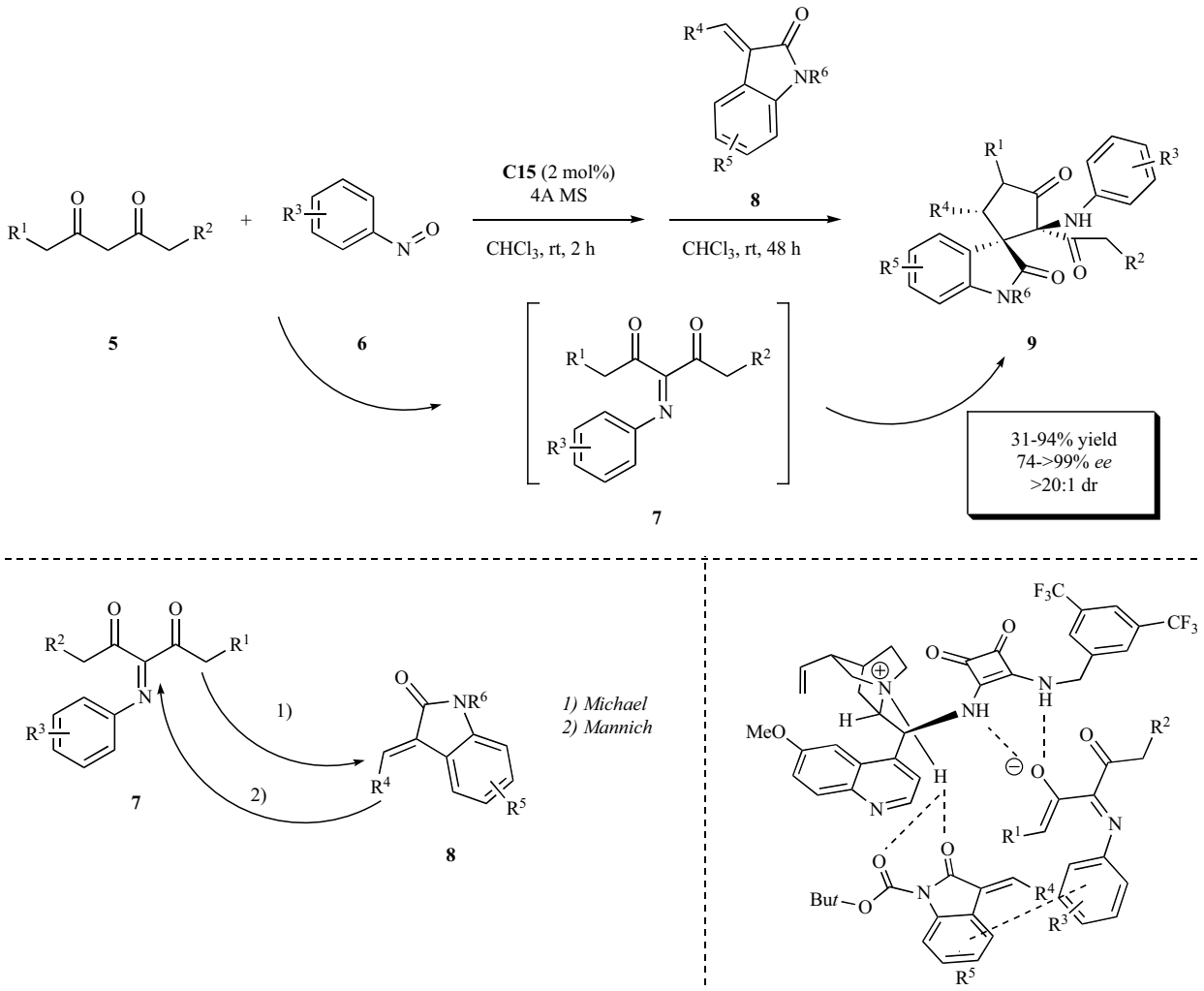
In the same year, the group of Sun reported a different one-pot strategy to form spirooxindoles **9**, relying on a squaramide-promoted Michael/Mannich domino reaction (Scheme **2**) [22]. The authors employed the *in situ* formation of ketimines starting from 1,3-diketones **5** and substituted nitroso-benzenes **6**, in the presence of catalyst **C15**. With the subsequent addition of the alkylidene oxindoles **8**, the bifunctional organocatalyst was able to activate the enolate of the formed imine intermediate by the two NH groups of the squaramide core, while coordinating the oxindole substrate with the quaternary ammonium group. Thus, a Michael addition could occur, followed by a Mannich reaction on the imine functionality, affording the desired products **9**. Noteworthy to mention is that in this reaction the conjugated addition occurred on the β-position of the lactam moiety and not on the C3-position (β-position considering the electron-withdrawing group (EWG)), opposite outcome compared to the previously mentioned method. This reactivity could be addressed to the presence in the substrate **1** of two EWGs, resulting in a more electrophilic C3-position, compared to this report.

The five-membered spirocyclic oxindoles **9** were achieved with moderate to excellent yields and excellent enantio- and diastereoselectivities (up to 99% *ee* and >20:1 dr).

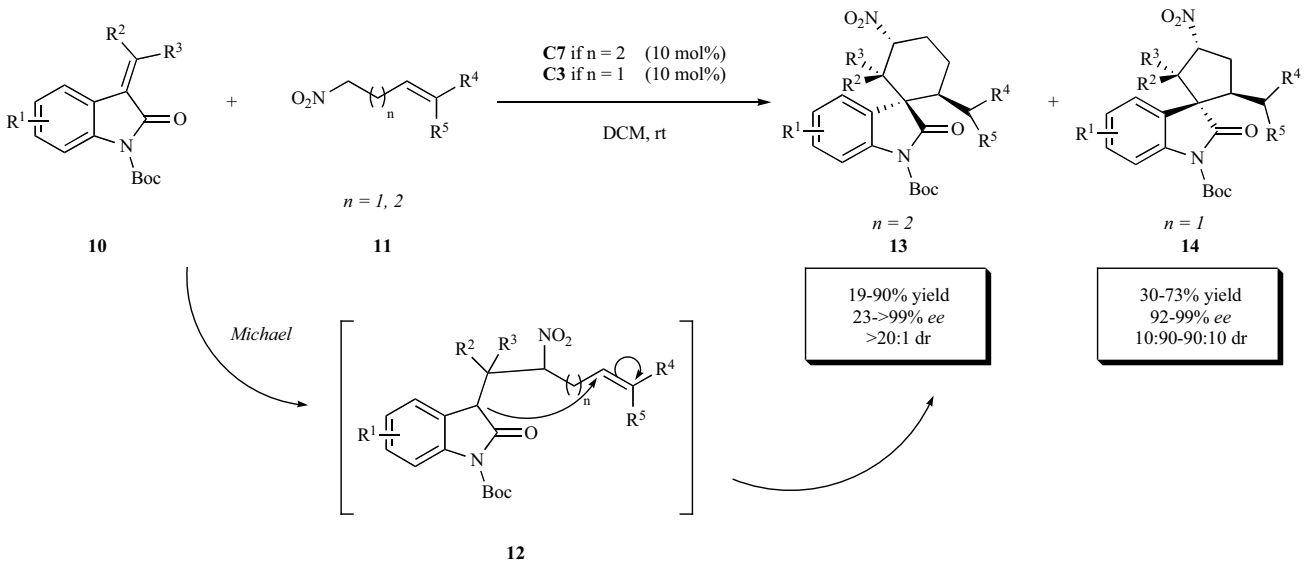
Later on, Quintavalla and co-workers reported a divergent synthesis of five- and six-membered spirocyclic oxindoles by employing terminally-NO_2-substituted alkenes in a similar reaction sequence (Scheme **3**) [23]. In particular, by varying the chain length of substrate **11** and switching the catalysts used, the authors were able to obtain two different sets of products *via* either a formal [3+2] or formal [4+2] annulation. Both strategies relied on non-covalent organocatalysts to promote a Henry-type conjugated addition, followed by an intramolecular Michael addition to the electron-poor alkene moiety. The reaction sequence was promoted by Takemoto thiourea (**C7**) to obtain the six-membered spiroproducts **13**, and a quinidine-derived thiourea (**C3**), in the case of products **14**. The procedure tolerated well various substituents on the Boc-protected oxindoles **10** as well as on the R^4 and R^5 positions of alkenes **11**, leading to the formation of the products with four contiguous stereogenic centres in good to excellent yields and stereoselectivities. Interestingly, by changing the configuration of the alkene substrate **10** from *E* to *Z*, the authors discovered the possibility to obtain the C3-epimer of both **13** and **14**. This developed methodology proved to be efficient and at the same time practical, performed under mild reaction conditions while maximizing the outcomes on both sets of products.

In 2018, Nakano and co-workers explored as well the use of H-bonding organocatalysts for the construction of 2-aminopyran-fused oxindoles **17** (Scheme **4**) [24]. The authors designed a new hybrid squaramide-based organocatalyst (**C19**) bearing a chiral amino alcohol moiety and they tested its reactivity in a Michael/cyclization cascade between oxindoles **15** and 1,3-diketones **16**. The catalyst proved efficient in the reaction in the study in terms of obtained yields, despite the enantioselection was strongly affected by the different substitutions on the aromatic ring of the oxindoles **15** and especially on the 1,3-diketones **16**, affording racemic products when open-chained ketones were used.

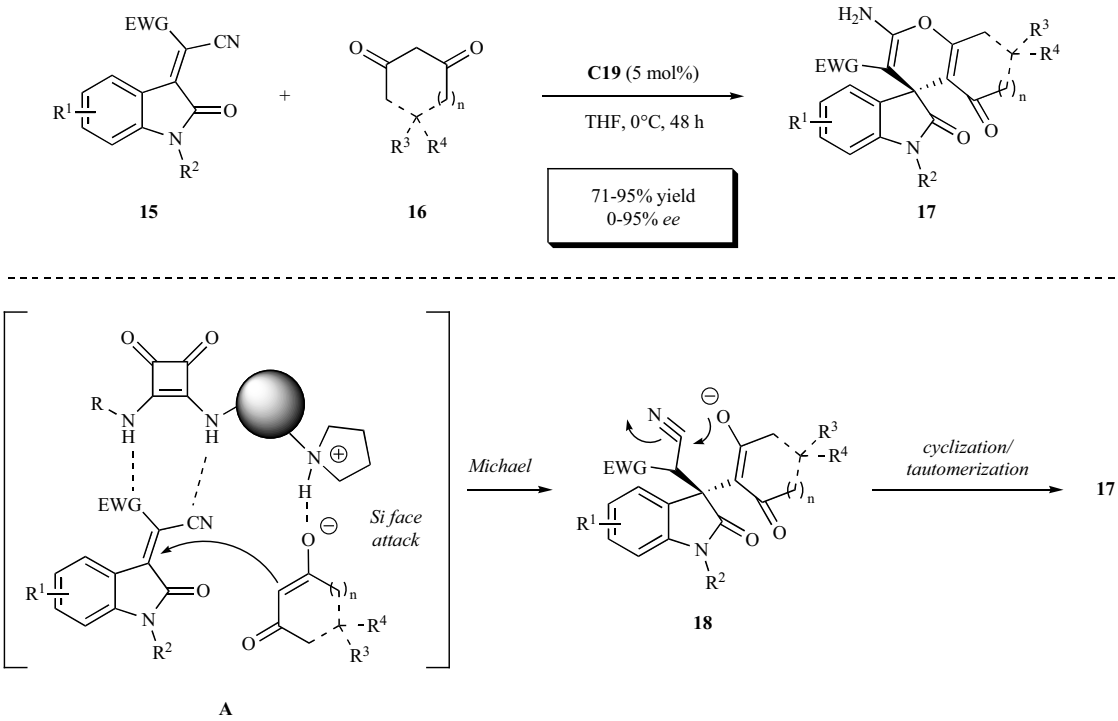
Subsequently, in 2019, the group of Xiang and Yang employed as well a squaramide-based catalyst to achieve complex polycyclic



Scheme 2. One-pot *in situ* formations of ketimines and Michael/Mannich sequence towards spirooxindoles **9**.



Scheme 3. Divergent spiroannulation of alkylidene oxindoles **10** and alkenes **11** by non-covalent organocatalysis.



Scheme 4. Organocatalytic access to 2-aminopyran-fused oxindoles **17**.

spirooxindoles **21** (Scheme **5**). [25]. By probing 3-hydroxyoxindoles **20** and ylideneoxindoles **19** in the presence of the catalyst, the initial Michael adduct could be formed from the nucleophilic attack of the C3 position of **20**. Then, a consecutive ring-opening/ring-closure occurred by the one-pot addition of *p*-toluenesulfonic acid and water, heating the reaction mixture at 80°C. At first, a trans-lactonization could occur with consequent opening of the lactam ring. Afterwards, the acid-catalysed lactamization on the CO_2Et substituent afforded the desired quinolinone scaffold of the final product **21**. This practical and step-economical protocol allowed the synthesis of a complex molecular architecture with excellent yields up to 97% and high levels of both enantio- and diastereoselectivities (up to >99% *ee* and >95:5 dr).

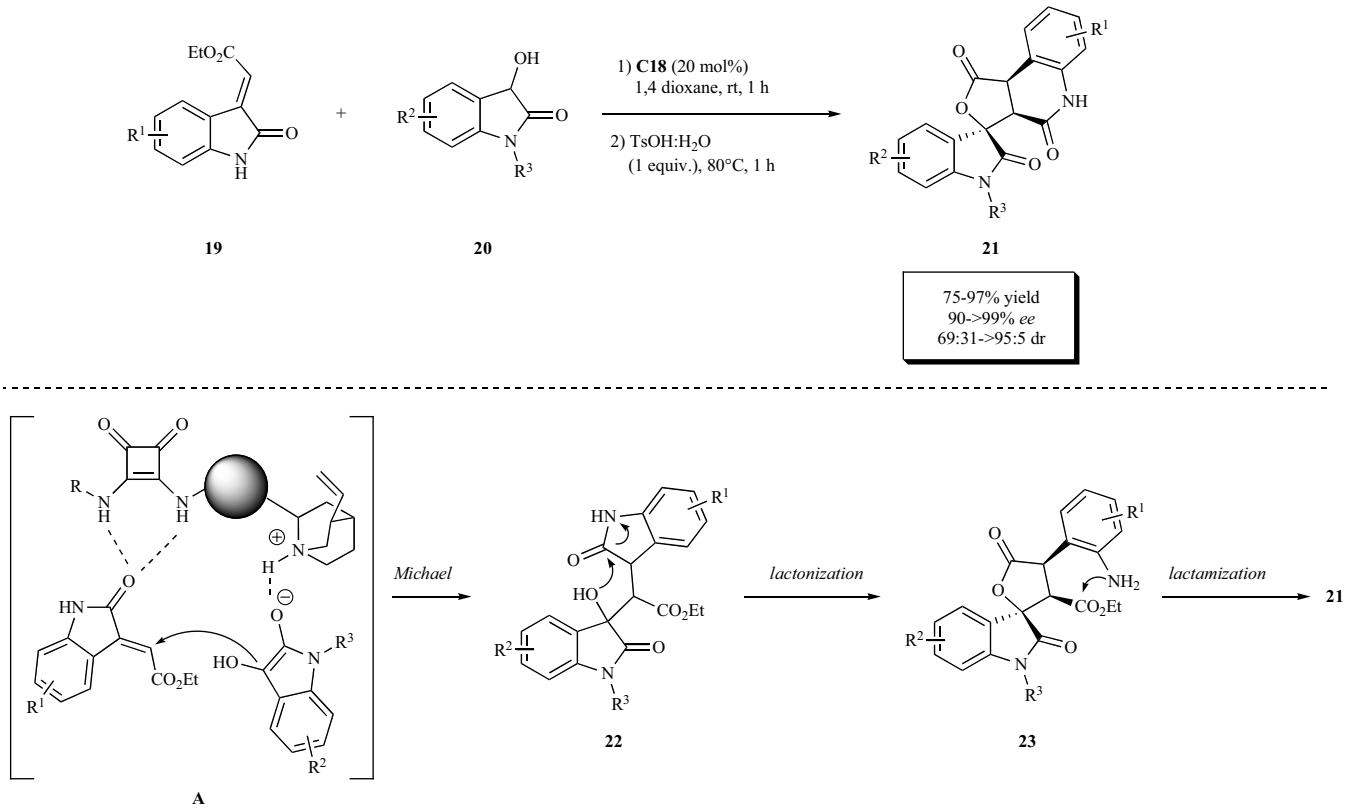
A different approach towards six-membered spirocyclic oxindoles was developed by Sun *et al.* (Scheme **6**) [26]. The authors employed a one-pot combination of a chiral H-bonding squaramide catalyst (**C15**) and an achiral secondary amine covalent organocatalyst (**27**). In particular, the squaramide **C15** could promote the initial Michael reaction between the 1,3-diketones **25** and the alkylidene oxindoles **24**, in 24 hours at 0°C. The Michael adduct **26** was not isolated, and to the reaction mixture piperidine (**X**) and α,β-unsaturated aldehydes **28** were added to catalyse the following domino Michael/aldol sequence *via* stepwise iminium ion/enamine activation (see Fig. **2** for details) and obtain the cyclized products **29**. The developed methodology resulted applicable to variously substituted starting materials, with consistent outcomes in terms of yields and excellent control over the six new stereocentres (up to 98% *ee*, >20:1 dr).

Other applications of covalent-bonding organocatalysis have been explored as well for the functionalization of alkylidene oxindoles. In 2017, Enders' group reported a switchable synthesis of complex spirocyclic oxindoles employing N-heterocyclic carbenes (NHCs) (Scheme **7**) [27]. The use of NHCs as organocatalysts has emerged as a privileged approach to promote Umpolung activations of carbonyl groups. In particular, the *in situ* generated carbenes (**NHCa** and **NHCb**) performed nucleophilic addition on the isatin-derived enals **30**, generating the so-called Breslow intermediate **34**. This kind of intermediate is characterized by a polarity reversal (Umpolung) of the former carbonyl carbon as well as of its β-position, considering the azolium homoenolate resonance form **34'**. Specifically, this newly generated nucleophile could perform a Michael addition on *N*-tosyl-azadienes **31** and the outcomes could be controlled by varying the reaction conditions. Switching the used base, solvent, and catalyst, the authors were able to promote either a Michael/aza-Dieckmann-type cyclization sequence (pathway B, Scheme **7**) or a domino Michael/Mannich/lactamization reaction (pathway A, Scheme **7**). The former pathway afforded enaminone-containing spirocyclic oxindoles **33**, potential building blocks for further modifications, while the latter pathway generated biologically relevant β-lactam fused spriocyclopentane oxindoles **32**, with 5 adjacent stereogenic centres. Both sets of products were isolated with remarkable yields and excellent levels of stereocontrol.

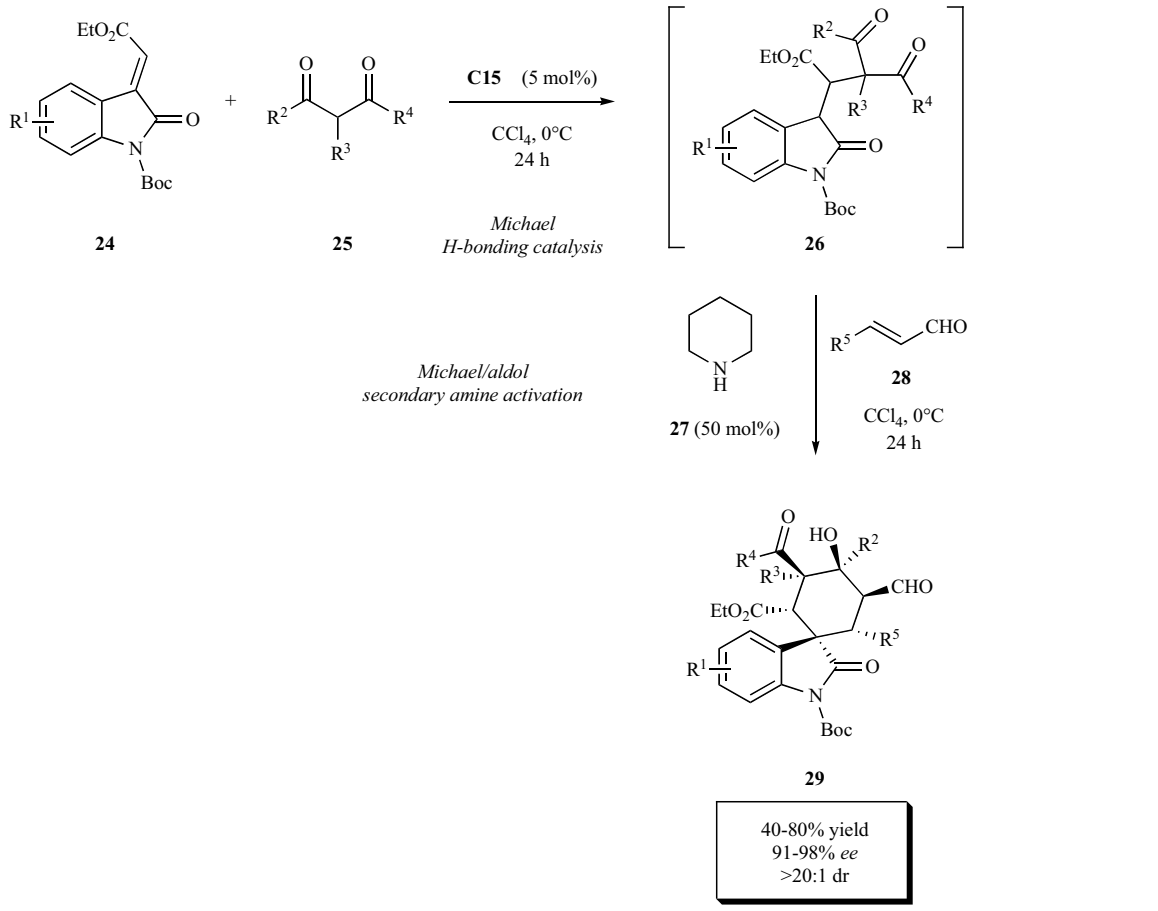
As mentioned above, the protocols reported so far in this chapter relied on the electrophilic reactivity of alkylidene oxindoles, which react smoothly with nucleophiles in initial Michael reactions, followed by tandem transformations in a domino/one-pot fashion. Nevertheless, this class of substrates could be used as nucleophiles as well.

Han *et al.* reported the synthesis of lactone-based spirooxindoles **41** starting from isopropylidene oxindoles **39** and isatins **40** (Scheme **8**) [28].

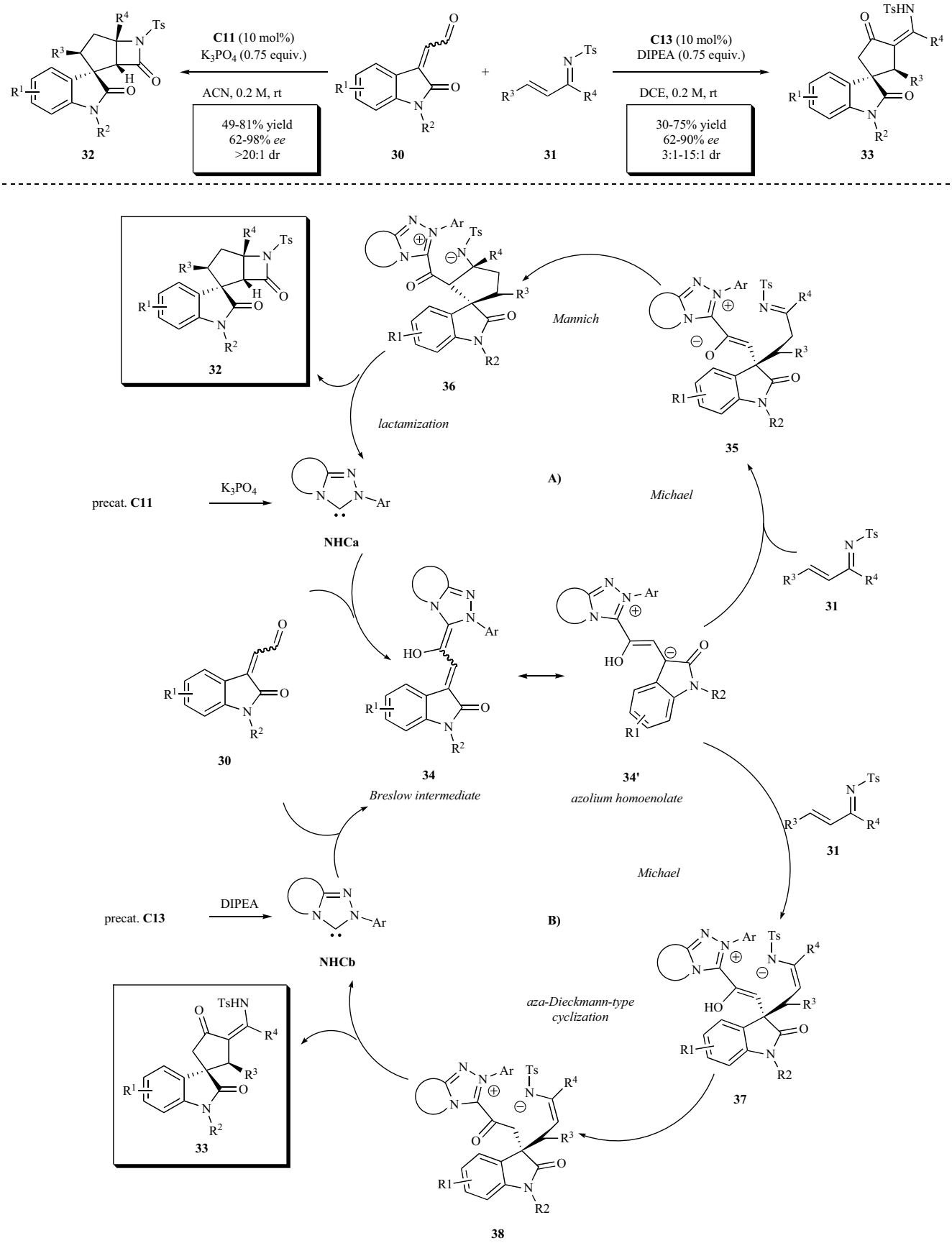
In the presence of cinchona alkaloid-derived squaramide **C14**, the γ-position of substrate **39** could be activated *via* extended enolate formation and, upon coordination of both substrate in **A**, a domino vinylogous aldol/transesterification reaction sequence could take place, yielding the final spiroproducts with very high enantiomeric excesses (up to 95% *ee*).



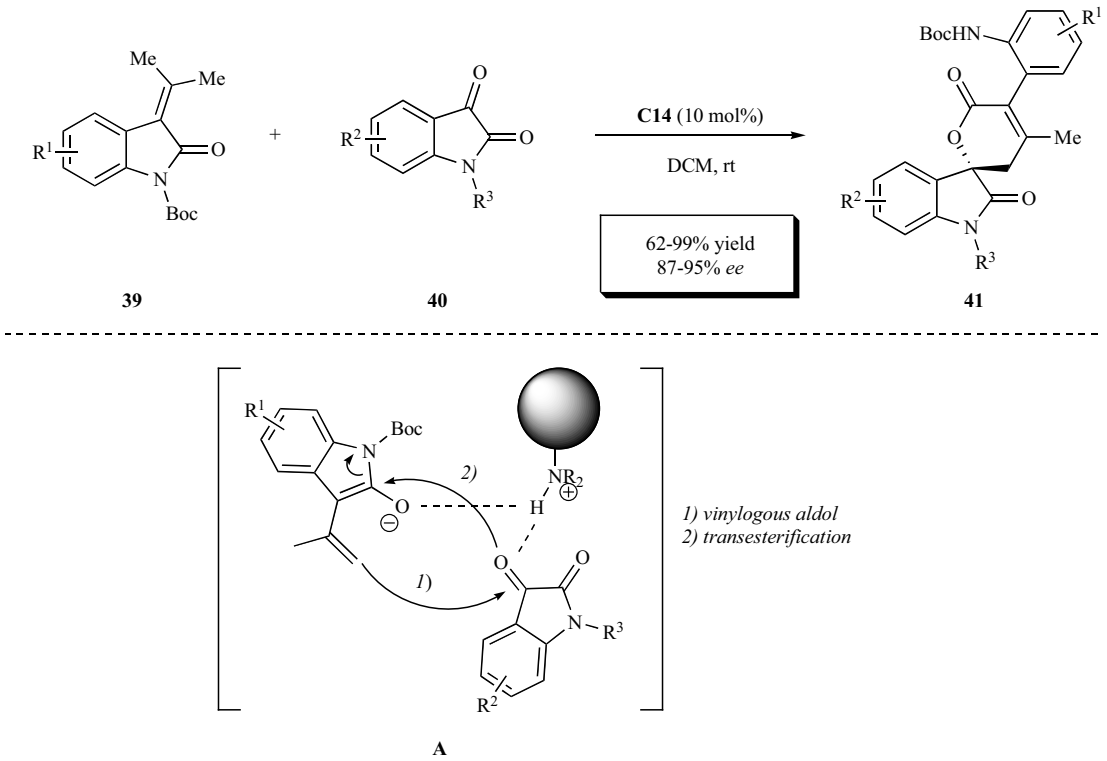
Scheme 5. Squaramide catalysed one-pot Michael/ring-opening/ring-closure sequence developed by Xiang and Yang [25].



Scheme 6. Covalent and non-covalent organocatalysts one-pot combination reported by Sun *et al.*



Scheme 7. Switchable NHC-catalysed domino reaction to achieve spirocyclopentane oxindoles **32** and **33**.



Scheme 8. Vinylogous aldol/transesterification domino reaction developed by Han *et al.* [28].

3. FORMAL CYCLOADDITION REACTIONS WITH 3-ISOTHIOCYANATE OXINDOLES

The reactivity of isothiocyanates has been widely studied over the years and has demonstrated to be an excellent tool in the synthesis of heterocycles [29]. This reactivity has been employed to obtain enantioenriched cyclic thiourea- and thioamide-based spirooxindoles.

In 2016, Shi's group studied the reactivity of different azadienes in the reaction with 3-Isothiocyanate oxindoles **42**, catalysed by chiral bifunctional thioureas (Scheme **9**) [30]. The α,β-unsaturated imines **43**, **45**, and **47** were used as electrophiles to initiate the cascade sequence, followed by a thiolactam ring closure, which depended on the starting imine.

In particular, when the reaction was performed on α,β-unsaturated aldehyde-derived imines **43** in ACN at -20° C, the initial nucleophilic attack was a Mannich reaction and then a subsequent aza-cyclization occurred to afford the cyclic thioureas **44** (Scheme **9a**). Conversely, starting from ketimines **45** in DCM at -40° C, the nucleophilic attack occurred 1,4 (Michael reaction) instead of 1,2 (Mannich), generating an intermediate enamine, which could then undergo cyclization from its α-carbon (Scheme **9b**). In both examples, the formal [3+2] cycloaddition worked smoothly, yielding to the two sets of products with excellent outcomes and stereoselectivities.

Additionally, the use of dienone-derived imines **47** allowed to achieve polycyclic spirooxindoles **48** *via* domino Michael/cyclization/sulfa-Michael reaction (Scheme **9c**). In this last case, the optimal catalyst was found to be the dihydroquinine-based thiourea **C5**, which effectively catalysed the reaction with complete diastereoselectivity and good to excellent *ee* values.

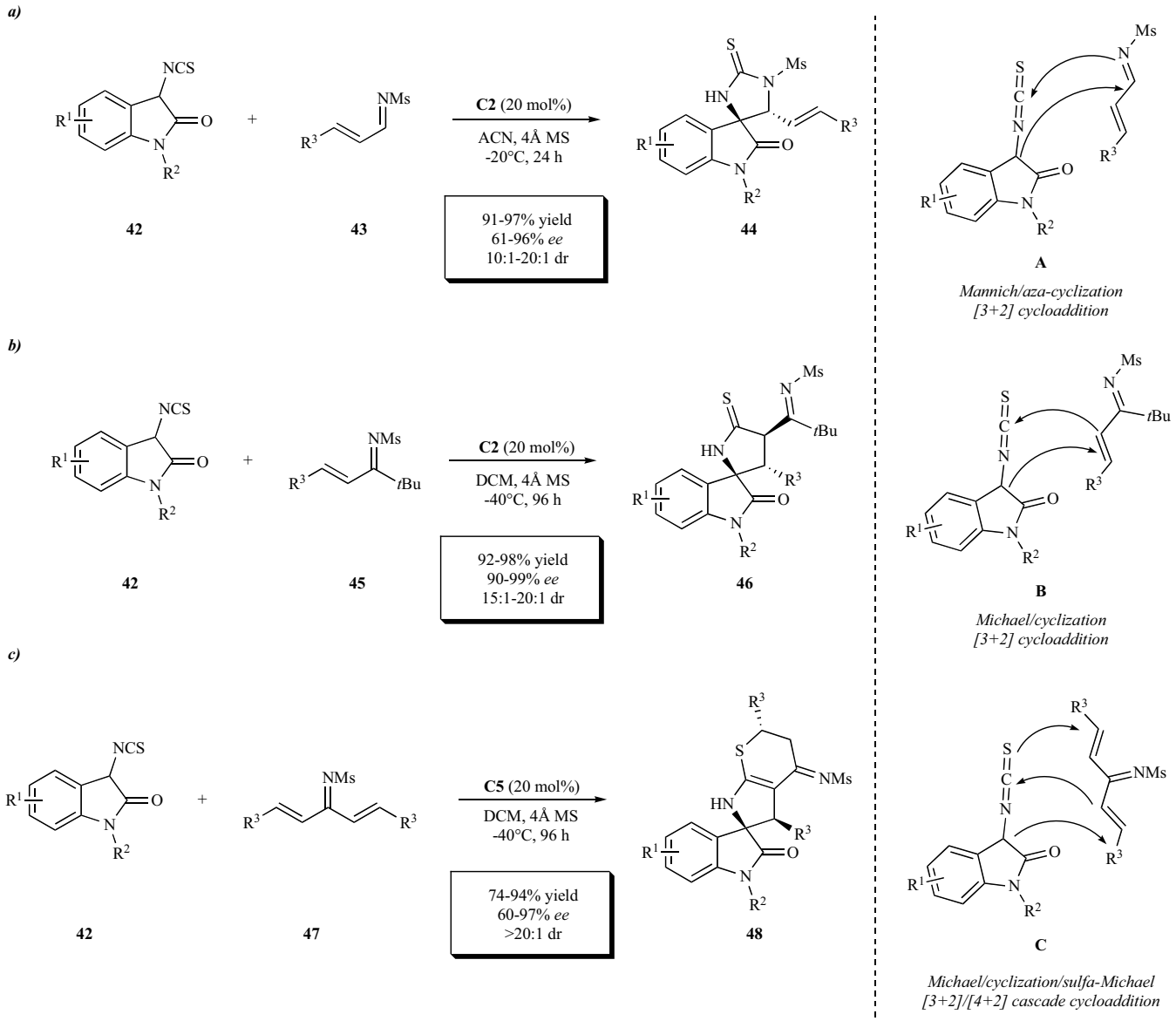
The same 3-Isothiocyanate-oxindole substrates **42** have been used by several research groups in the following years, paired with various electron-deficient exo-cyclic alkenes (Scheme **10**). In all these cases, the reactivity involved was a Michael addition followed by the cyclization of the thiolactam ring. However, the nature of the alkene substrates allowed to afford structurally diverse and potentially biologically relevant polycyclic scaffolds.

Lu, Lin, and Weng group worked in 2018 on this transformation and tested the reactivity of *E*-benzylidenechromanones **49** in the presence of **42** and a rosin-based squaramide catalyst **C20** (Scheme **10a**) [31]. The chroman structure is widely present in biologically active compounds and natural products and thus, the synthesis of chroman-based enantioenriched products has been extensively studied (for the synthesis of other chromano-oxindoles see Section **5**) [32]. The polycyclic bis-spirocompounds **50** were isolated with excellent outcomes in terms of yields and selectivity, well tolerating both electron-withdrawing and electron-donating groups on the chromanone substrates. Moreover, a gram-scale reaction was successfully attempted, with no influence on the reaction results.

The same group developed an analogous protocol employing CF_3-containing alkylidene-oxindoles **51** (Scheme **10b**) [33]. This methodology allowed for the generation of bis-oxindole spirocyclic frameworks bearing a CF_3 group under mild reaction conditions, with excellent yields and enantioselectivities.

In the same year, Du's group worked on a similar reaction, introducing a different heterocyclic alkene substrate **53** bearing a thiazolidinone moiety (Scheme **10c**) [34].

Thioazolidinones are also important fragments featured in many pharmaceutically active ingredients. In this report, the best catalyst proved to be a dihydroquinine-based squaramide, which supposedly coordinates the Isothiocyanate-oxindole **42** by the two NH groups, while coordinating the thiazolidinone substrate *via* H-bonding with the quaternary ammonium of the quinuclidine moiety.



Scheme 9. Reaction of various α,β-unsaturated imines with isothiocyanate oxindoles.

More recently, Grošelj *et al.* employed arylidene-pyrrolin-4-ones **56** in a similar fashion (Scheme **10d**) [35]. Interestingly, the authors evidenced that by using (*E*)-*N*-protected pyrrolidones **56** in the optimized reaction conditions, good to excellent levels of stereoselectivities were observed (up to 98% *ee* and up to 99:1 dr). Moreover, the authors investigated the reaction using alkenes with opposite configuration (from *E* to *Z*), with R^3 = H. The absolute configuration of the new products was not confirmed, but it was tentatively assigned as the opposite enantiomer of **57**. However, by probing (*Z*)-*N*-unsubstituted **56**, the reactivity and the enantioselectivity observed were drastically decreased (two examples of *Z* alkenes; 7% and 19%, –21% and –57% *ee*).

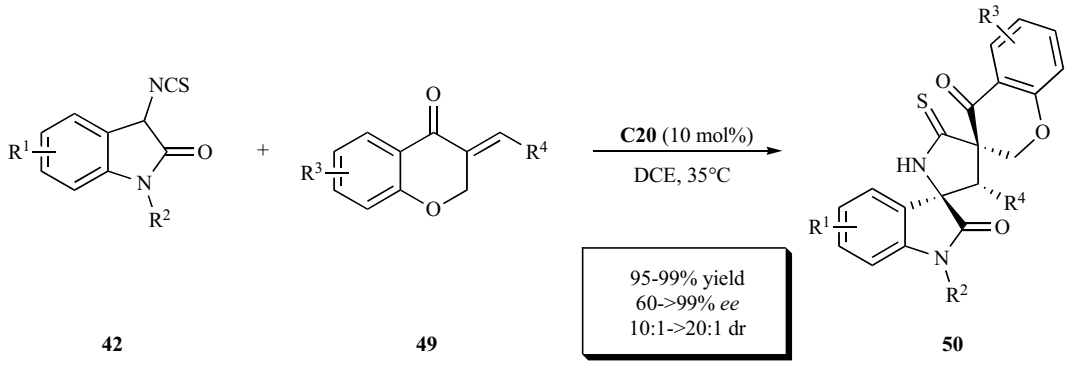
A different approach towards the synthesis of various polycyclic spiro compounds from Isothiocyanate-oxindoles **42** was reported by Yuan and co-workers in 2020 (Scheme **11**) [36]. In this report, structurally different ketimines were employed in a domino Mannich-aza-cyclization reaction with **42**, affording three sets of polycyclic thioureas. Mild reaction conditions were used in the presence of the chiral catalysts. When quinazolinones **58** and saccharin-derived ketimines **60** were tested, the reaction proceeded smoothly in short time, affording the desired enantioenriched products with high levels of stereocontrol. Additionally, also benzoxazinone-based ketimines **62** produced the spirocyclic products **63**, despite lower yields and *ee* values.

4. FUNCTIONALIZATION OF 3-IMINO OXINDOLES

Within the framework of different oxindoles functionalization, another class of substrates studied is 3-imino-oxindoles.

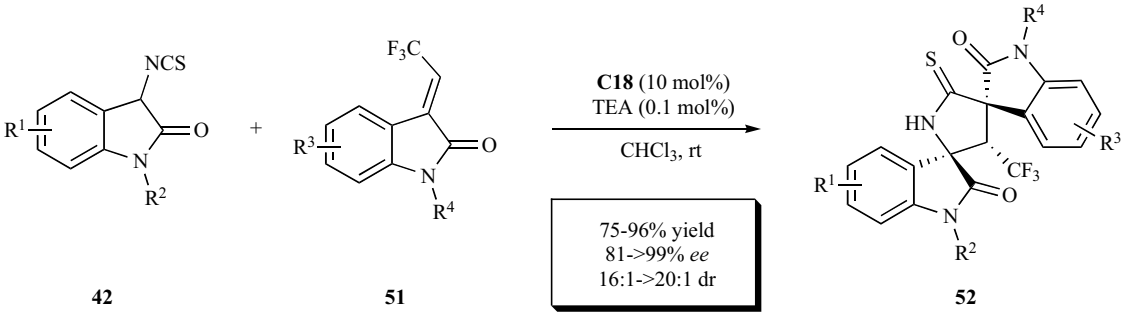
The groups of Enders [37] and Du [38] independently reported the use of isatin-derived ketimines **64** in a Michael/Mannich domino sequence to produce 3-pyrrolidinyl-spirooxindoles **66** and **68** (Scheme **12a** & **b**, respectively). Specifically, trifluoroethyl ketimines **64** possess an acidic CH_2 site, which could be easily deprotonated and could undergo nucleophilic addition on appropriate Michael acceptors (Scheme **12**, **A**). Afterwards, a Mannich reaction on the electrophilic imine site could produce the formal [3+2] cyclization product.

a) Lu, Lin, Weng, et al., 2018



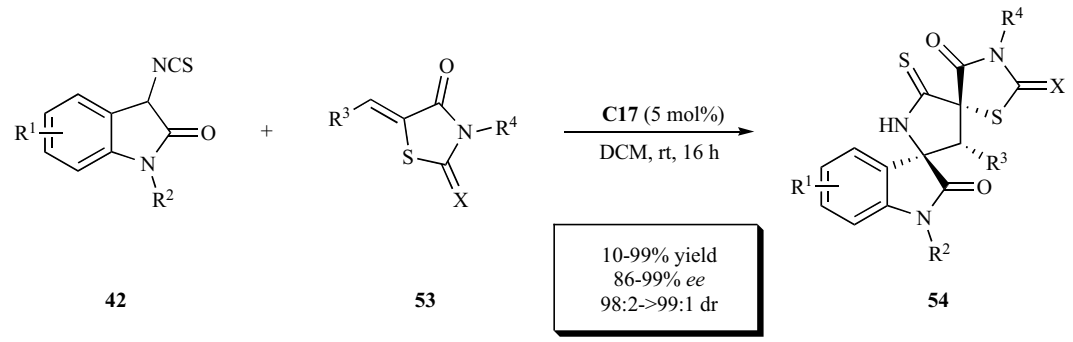
42 **49** **50**

b) Lu, Lin, et al., 2018



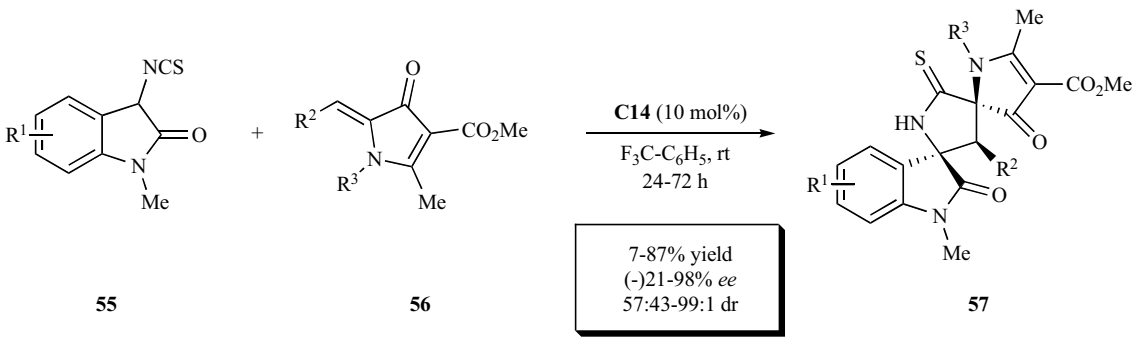
42 **51** **52**

c) Du et al., 2018



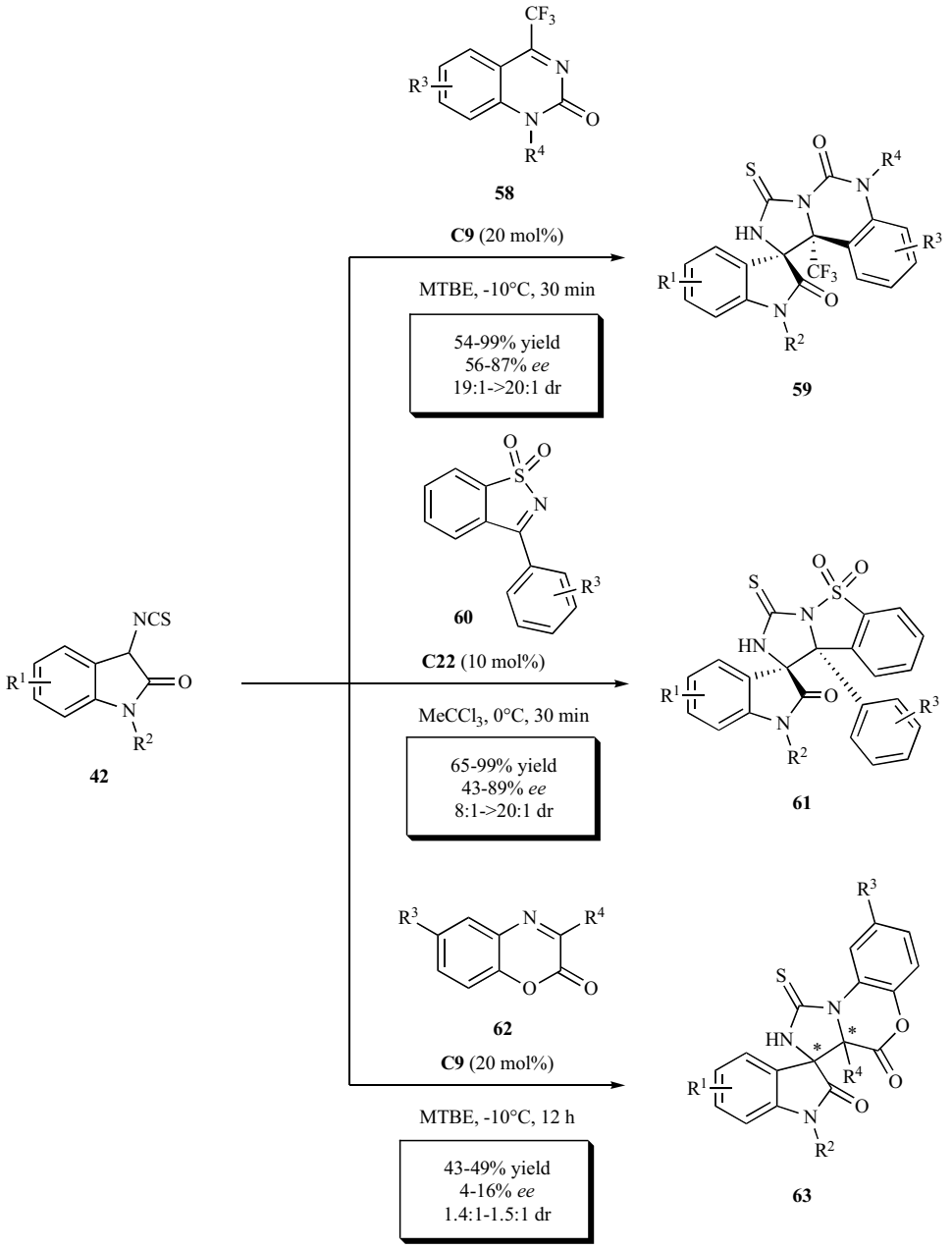
42 **53** **54**

d) Groselj et al., 2020



55 **56** **57**

Scheme 10. Domino Michael/cyclization reactions of different electron-poor alkenes with **42**/**55**.

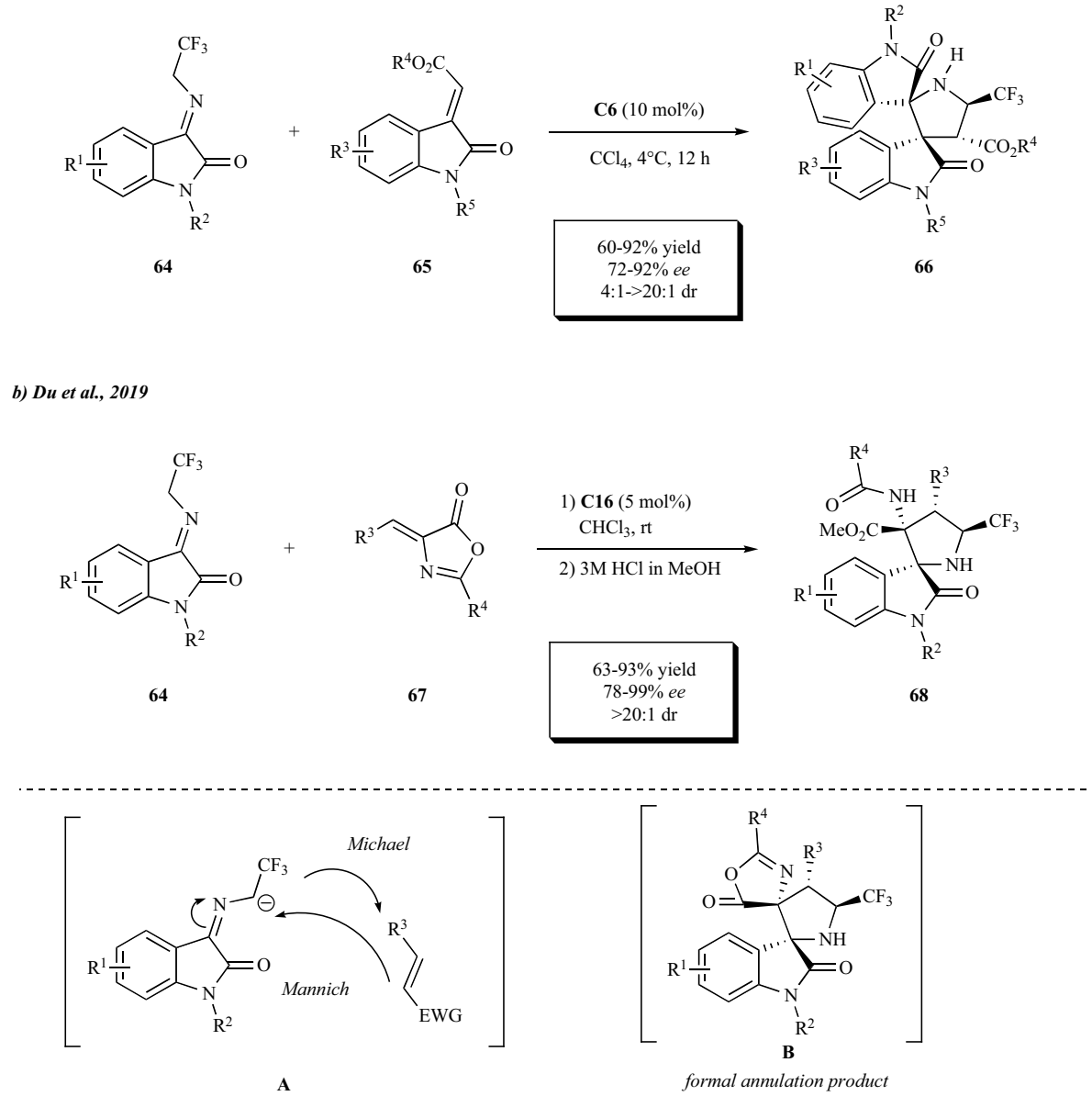


Scheme 11. Structurally diverse polycyclic spirooxindoles obtained from various ketimines.

The Michael acceptors of choice for Enders *et al*. were alkylidene oxindoles **65** (Scheme **12a**). In the presence of an aminothiourea organocatalyst **C6** under mild reaction conditions, bis-spirooxindoles **66** were isolated with high yields and good control over the four generated contiguous stereocentres.

Similar excellent results were obtained by Du's group, who used instead of a squaramide-based catalyst **C16** and arylidene azalactones **67** (Scheme **12b**). Noteworthy to mention, the authors isolated at first the products of the formal [3+2] cycloaddition **B**, which showed to be unstable. Thus, they opted for a one-pot treatment with HCl/MeOH to produce the corresponding 3,2'-pyrrolidinyl spirooxindoles **68**, with good to excellent yields and stereoselectivities.

Another approach in the use of imino-oxindoles was reported by Han *et al*. in 2017 (Scheme **13**) [39]. The authors explored the application of covalent-bonding organocatalysis to generate enantioenriched nucleophilic intermediates **71** that, upon reaction with Boc-protected isatin-imines **72** in a one-pot fashion, would lead to the formation of piperidinyl-spirooxindoles **74**. By treatment of enolizable aldehydes **70** with the proline-derived catalyst **C10**, a catalytic amount of nucleophilic enamine could be formed, which could undergo Michael addition on various nitrostyrenes **69**. The generated Michael adducts have been involved directly in a subsequent domino aza-Henry 1,2-addition/hemiaminalization reaction with the addition of **72** and diazabicycloundecene (DBU) as base. In order to achieve more stable products, the authors successfully explored the possibility to perform a dihydroxylation of the hemiaminals **73**, yielding the final products with outstanding results. This 3-steps one-pot process allowed for the identification of one promising lead compound with potent antiproliferative effects on breast cancer cells.



Scheme 12. Michael/Mannich sequence starting from trifluoroethyl isatin-imines **64.**

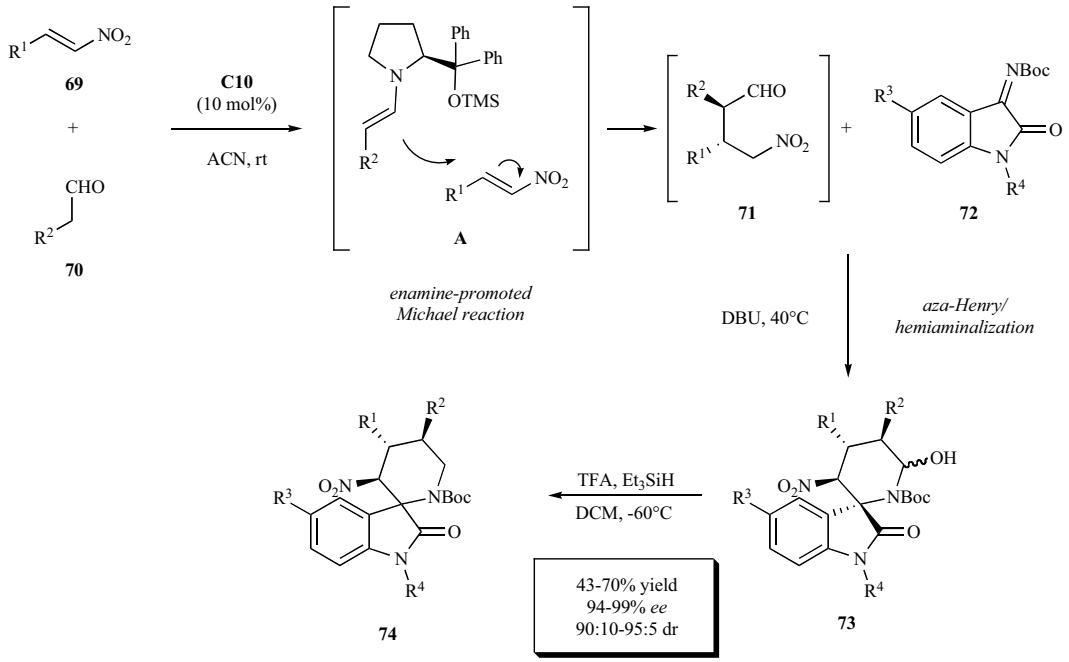
Lastly, in 2020 Šebesta and co-workers studied the combination of organocatalysis and mechanochemistry for a domino Mannich/fluorination sequence on Boc-protected imines **72** (Scheme **14**) [40]. Ball milling has recently emerged as an efficient and green approach towards more environmentally friendly synthetic methodologies [41]. The mechanical activation of pyrazolones **75** and Boc-isatin-imines **72** in the presence of a low amount of squaramide-based organocatalysts **C15** (1 mol%) efficiently promoted the initial Mannich reaction to afford intermediate **76**. Subsequently, the one-pot treatment with *N*-fluorobenzenesulfonimide (NFSI), in the presence of a base, yielded the final domino product in short reaction times and outstanding outcomes in terms of yields and stereoselectivites (up to 98% *ee*, >20:1 dr). Despite the necessity to use a small amount of DCM to perform a liquid-assisted grinding (LAG), this procedure highlights the potential application of mechanochemistry to organocatalysed domino/one-pot synthetic procedures.

5. SYNTHESIS OF CHROMAN-DERIVED OXINDOLES

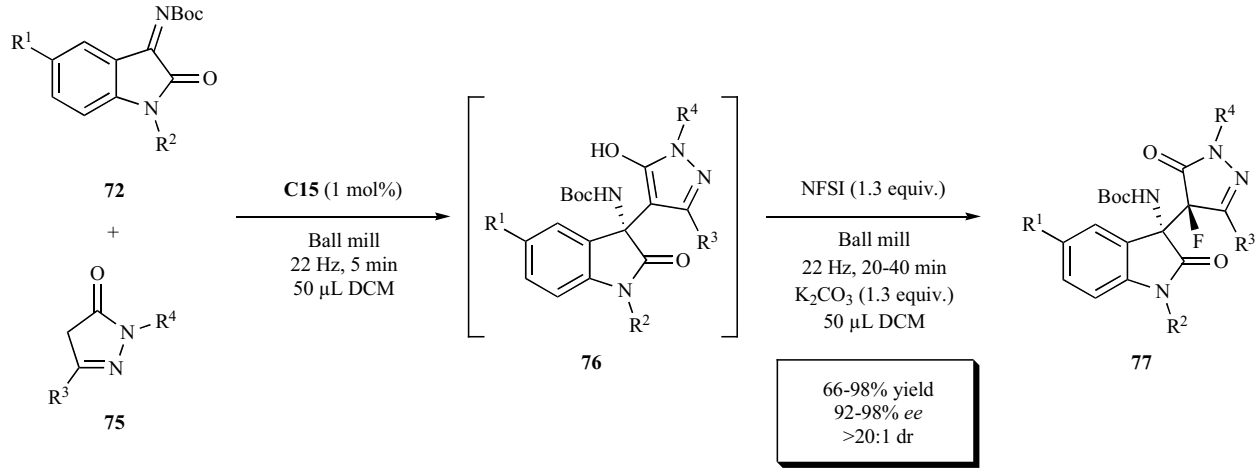
As above mentioned, the chroman scaffold is an important structure of many natural and bioactive compounds [32]. For this reason, over the years many research groups have worked on the synthesis of chroman-fused oxindoles, since the combination of these two potentially important heterocycles could lead to relevant products with pharmacological applications.

Substrates **78**, characterized by methylene-bridged fused oxindoles and chromanones, have been tested in the reaction with activated alkenes bearing EWGs in several reports (Scheme **15**). Spirooxindole-based hexahydroxanthones with 5 contiguous stereogenic centres were successfully isolated *via* double Michael domino sequence (Fig. **3**).

In 2019, Liu and Zhou group reported two different methodologies yielding the spiro-bis-heterocycles starting from substrates **78**



Scheme 13. Four-steps one-pot synthesis of piperidinyl-spirooxindoles **74** *via* covalent-bonding organocatalysis.



Scheme 14. Mechanochemical domino Mannich/fluorination reaction.

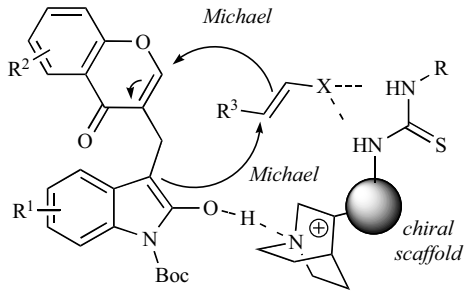


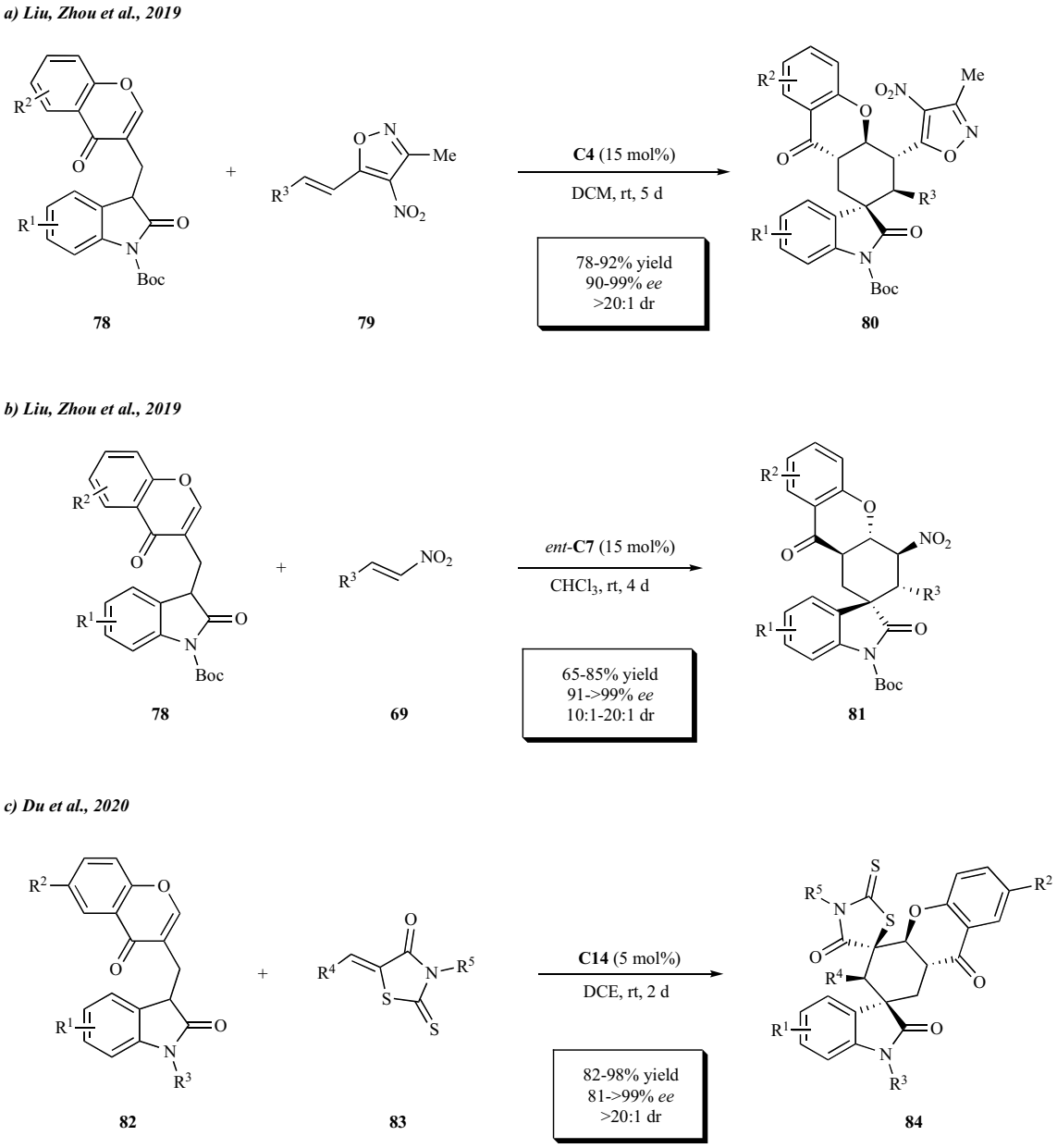
Fig. (3). Transition state for the sequential Michael/Michael sequences reported by Liu and Zhou (Scheme **15b**).

and alkenyl-isoxazoles **79** [42] or nitroalkenes **69** [43] (Scheme **15**, **a** & **b**, respectively).

Initially, double-bond-containing isoxazoles **79** were chosen as pairing substrates with **78** (Scheme **15a**). Thiourea **C4** was found to be the best catalyst to efficiently catalyse the reaction in study with excellent outcomes. Interestingly, while exploring the substrate scope, once established the optimal reaction conditions, the authors tested various electron-deficient alkenes such as: chalcones, α,β-unsaturated aldehydes, acrylates, and nitroalkenes **69**. Surprisingly, none of the probed substrates produced the desired corresponding products.

Nevertheless, later that year, the same researchers were able to perform and optimize the double Michael reaction between **78** and nitroalkenes **69**, before non-reactive, by replacing the organocatalyst with a quinine-based thiourea *ent*-**C7** (Scheme **15b**). Both methods produced the corresponding hexahydroxanthones with high to excellent yields and stereoselectivities, well tolerating various substitutions on both aromatic rings of **78**.

More recently, Du and co-workers applied substrates **82** in a similar reaction catalysed by a squaramide-based organocatalyst **C14** (Scheme **15c**) [44]. Even if the core structure of the catalyst was different, the reaction was proposed to be promoted similarly to



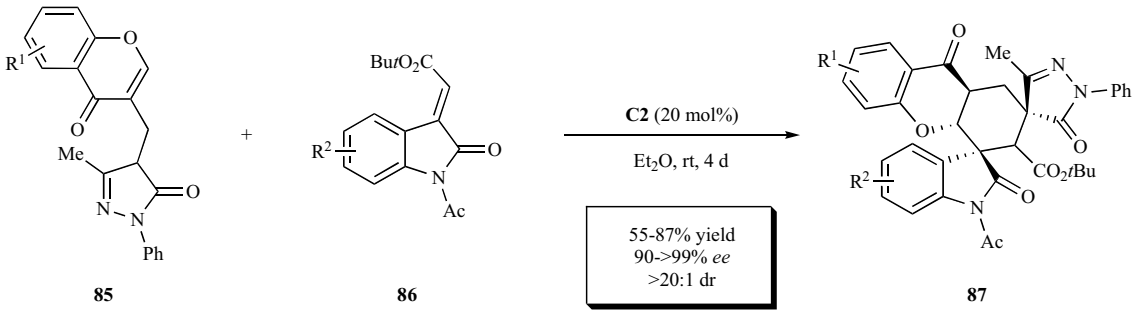
Scheme 15. Methylene-bridged chromanone-oxindoles **78**/**82** used in the synthesis of hexahydroxanthones.

the previous examples (Fig. **3**), where the coordination of the Michael acceptors thiazolidinones **83** could be performed by the squaramide NH groups instead. The spirothioazolidinone derivatives **84** were obtained with excellent outcomes and also examples of late-stage functionalization were proposed, demonstrating the potential application of these products in the synthesis of more complex pharmaceutically interesting compounds.

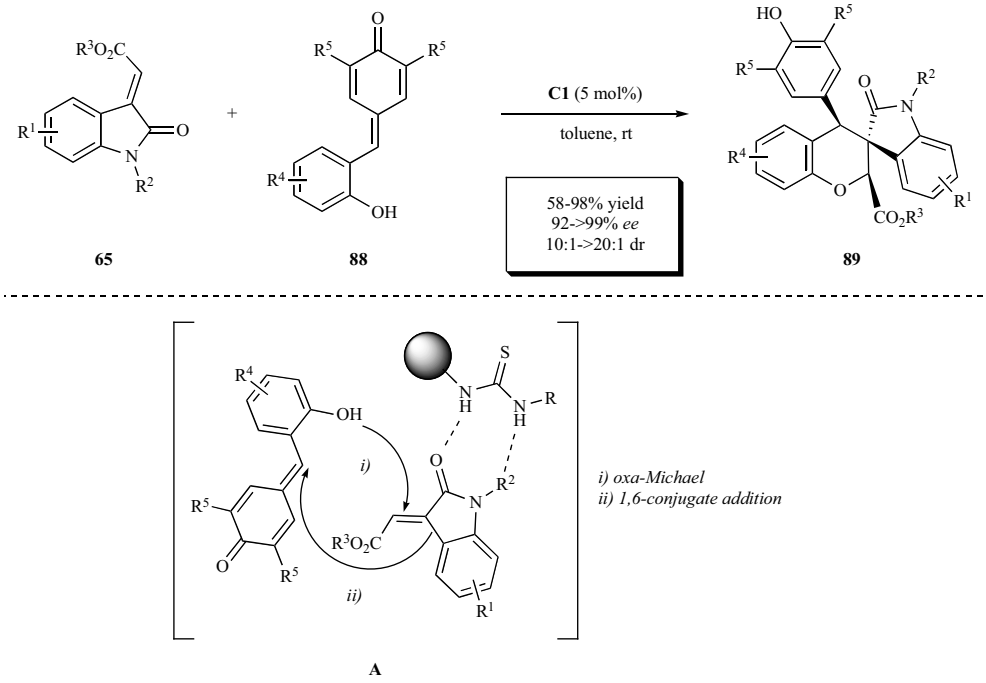
A reverse approach to this transformation was also explored by the group of Liu and Zhou (Scheme **16**) [45]. In particular, the authors introduced the chromanone functionality on a methylene-bridged pyrazolone-derived substrate **85**, while the oxindole moiety was included in the electron-poor alkene as alkylidene-oxindoles **86**. This method allowed for the combination of three important heterocycles, including also the pyrazolone one that has demonstrated tremendous applications in medicinal chemistry [46], yielding bis-spiro polycyclic frameworks with excellent levels of optical purity.

Enders' group also worked on the synthesis of oxindole-containing chromans obtained by H-bonding catalysis (Scheme **17**) [47]. In this report, the chroman cycle was not pre-formed and it was produced *via* domino oxa-Michael/1,6 addition sequence catalysed by chiral thiourea **C1** in very low catalyst loading (5 mol%). The authors designed a peculiar substrate characterized by a nucleophilic site installed on *para*-quinone methides (*p*-QMs) **88**. This class of substrates has been, in facts, widely employed in 1,6-conjugate additions, due to their high reactivity driven by the aromatization in the final products [48]. The introduction of a nucleophilic phenolic site on the substrates lead to new reactivity in a domino approach, pairing these substrates with alkylidene-oxindoles, as shown in Scheme **17A**.

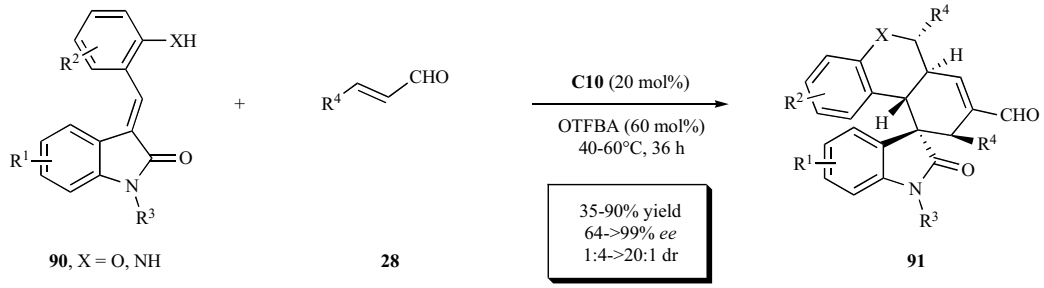
The desired chromans bearing spiro-connected oxindoles with three contiguous stereogenic centres were successfully synthesized with moderate to good yields and high to excellent diastereo- and enantioselectivities.



Scheme 16. Synthesis of pyrazolone-containing spirooxindole-hexahydroxanthanes.



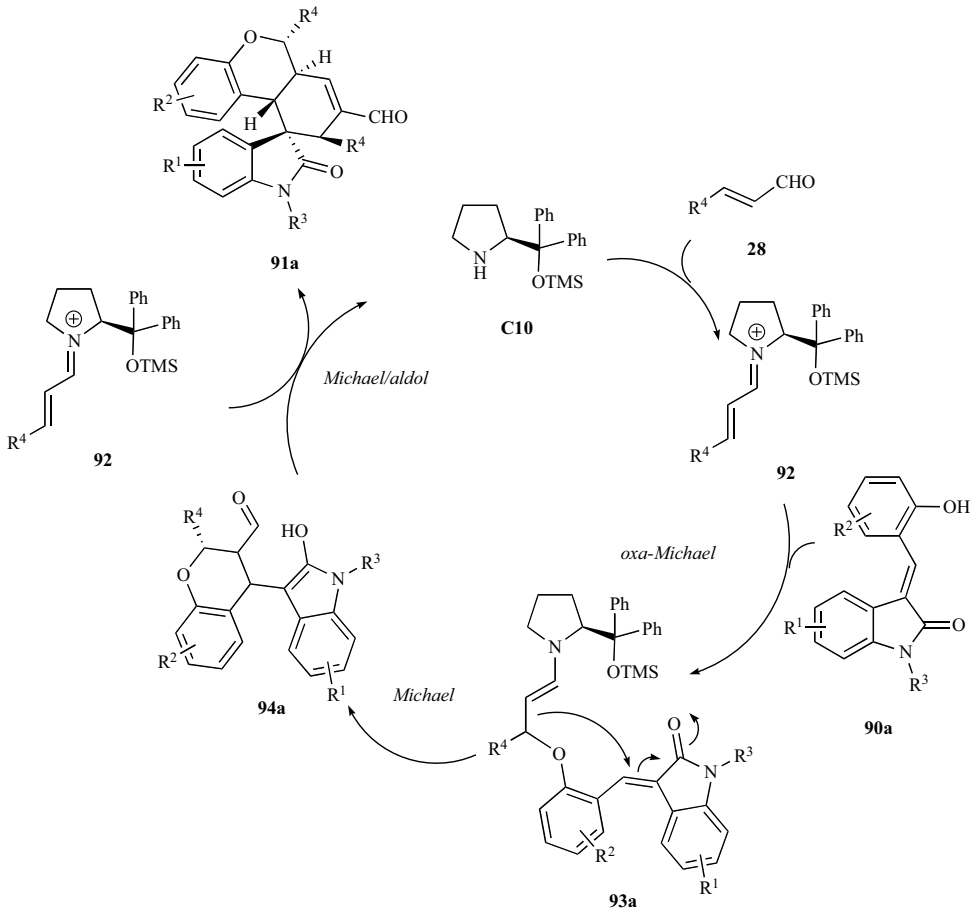
Scheme 17. oxa-Michael/1,6 addition sequence towards chroman-derived oxindoles **89**.



Scheme 18. Synthesis of bioactive polycyclic spiro-compounds containing chroman and oxindole moieties.

Subsequently, covalent-bonding organocatalysis was also applied in a domino reaction sequence to afford chroman- and oxindole-derived spiro-products **91** (Scheme **18**) [49]. The secondary amine proline-derived organocatalyst **C10** was employed to catalyse a quadruple oxa-Michael/Michael/Michael/aldol cascade reaction between oxindole-containing alkenyl-phenols and anilines **90** and α,β-unsaturated aldehydes **28**. The proposed mechanism of this transformation started with the iminium-ion activation of the aldehydes **28** by the catalyst (Scheme **19**).

Then, the initial oxa-Michael addition from the phenol group could occur on the electrophilic β-position of **92**, generating intermediate enamine **93a**. Subsequently, the enamine could undergo intramolecular conjugate addition on the ylidene β-carbon achieving intermediate **94a**. At this point, another activated iminium ion could react with enol **94a** *via* domino Michael reaction/aldol condensation yielding to the desired product **91a** and regenerating catalyst **C10**. This highly step-economical methodology achieved products with five adjacent stereocentres with excellent enantiocontrol (up to >99% *ee*) and moderate to good diastereomeric ratios. Moreover, the protocol was successfully applied replacing the phenol group with NH_2, leading to the corresponding spiro-tetrahydroquinolines. Additionally, the biological effects of the



Scheme 19. Postulated mechanism for the oxa-Michael/Michael/Michael/aldol domino sequence by Liu and Wang [49].

obtained compounds were investigated, identifying a potential lead compound possessing promising antiproliferative activity against human cancer cell lines.

6. MISCELLANEOUS

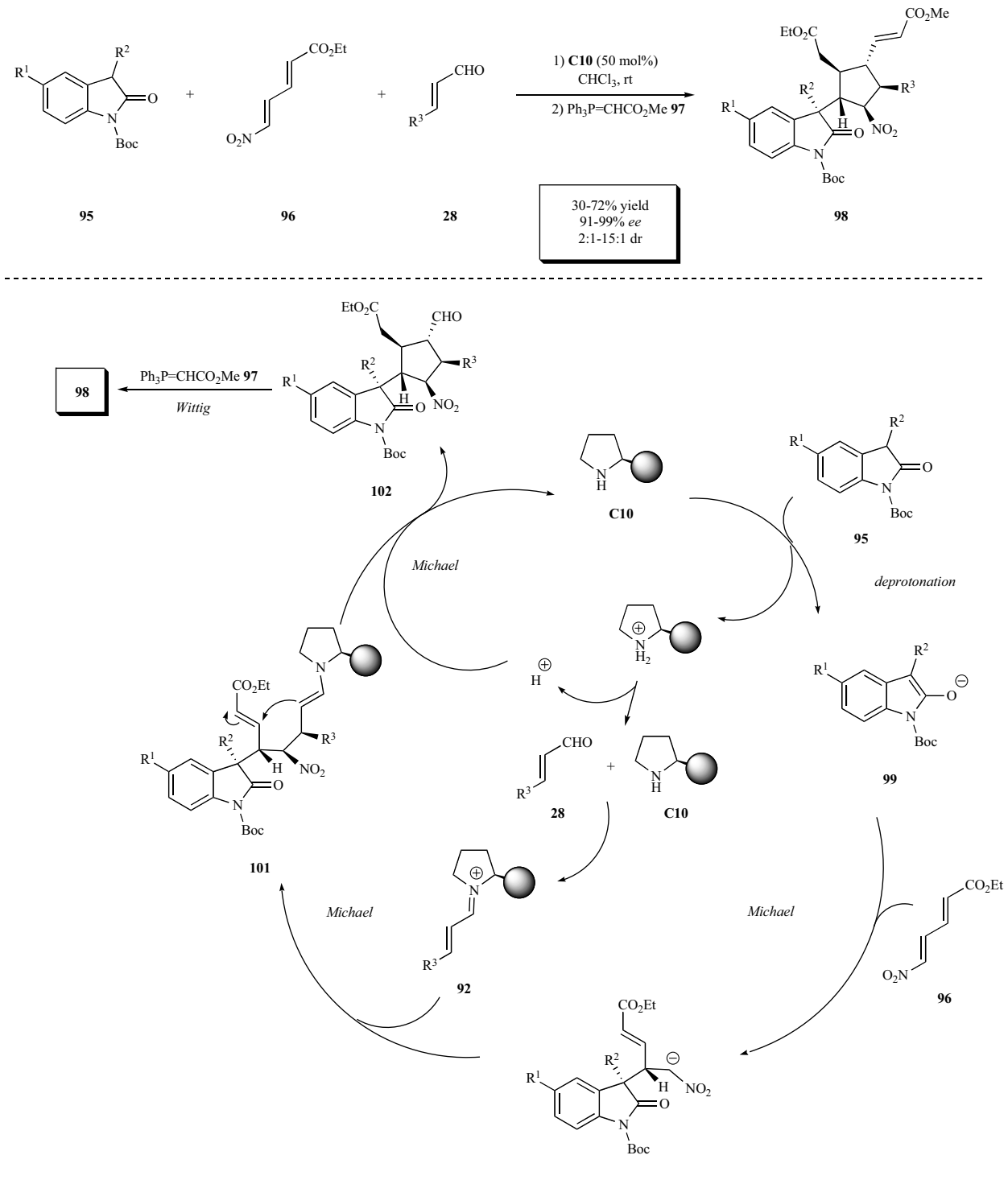
Apart from the more common classes of compounds employed in the stereoselective functionalization of oxindoles described so far, other types of substrates were investigated as well over the years.

In 2015, Enders *et al.* developed a three components method for the synthesis of cyclopentane-oxindoles starting from 3-susbtituted *N*-Boc-protected oxindoles **95**, nitro-diene **96** and α,β-unsaturated aldehydes **28** (Scheme **20**) [50]. The optimization of the reaction conditions identified *O*-TMS-diaryl-prolinol **C10** as a catalyst of choice to promote the triple Michael cascade reaction. **C10** was proposed to act as both Brønsted base as well as covalent-bonding organocatalyst, as depicted in (Scheme **20**).

The initial deprotonation of the 3-position of oxindoles **95** forming enolates **99** could activate the first Michael addition on electrophilic nitro-diene **96**. Afterward, a Henry-type Michael addition could occur from the deprotonated α-position to the NO_2 group of intermediate **100** on a molecule of α,β-unsaturated aldehyde **28** activated *via* iminium ion formation. Then, the final Michael addition from the formed enamine **101** closes the catalytic cycle affording cyclopentane carbaldehydes **102**. At this point, the authors opted for a one-pot Wittig olefination in order to achieve molecular complexity and guaranteeing the stability of the products. The method proved to be highly atom-economical since all substrates were used in equimolar amounts, and the procedure could be easily scaled up to gram scale with excellent stereocontrol, albeit the catalyst loading required was quite high (50 mol%).

Later on, Tanaka's group reported diastereoselective formal (4+1) cycloaddition reaction followed by a quinine catalysed domino Michael/Henry cascade sequence to achieve complex spiropolycyclic oxindoles **106** (Scheme **21**) [51]. Starting from enone-derived 3-hydroxyoxindoles **103** in the presence of triflic acid **104**, the thermally induced elimination of water lead to the dienone **107**, which could undergo double Michael reaction with cyclic 1,3-diketones **16** towards spirodecanes **105** with moderate to good diastereoselectivites. Subsequently, compounds **105** were successfully converted to the more complex polycyclic structures **106** in the presence of quinine (**C21**) and nitrostyrenes **69**, *via* organocatalytic Michael/Henry tandem reaction. Moreover, the authors realized that during the cascade formation of **106**, a kinetic resolution of **105** occurred, affording highly enantioenriched unreacted starting material (92-98 *ee*). The isolated enantiopure **105** was subsequently probed under the optimized reaction conditions, yielding to the opposite enantiomer of **106** with high yield and enantioselectivity.

3-Heterofunctionalysed oxindoles were later explored in combination with electron-poor alkenes. Wang *et al.* studied the secondary amine-activated Michael/cyclization/oxidation sequence between 3-aminooxindoles **108** and α,β-unsaturated aldehydes **28** (Scheme **22**) [52]. The reaction sequence was promoted by catalyst **C10** and proceeded as well *via* iminium ion activation of the aldehyde. Once the intermediate Michael adduct **110** was formed, an

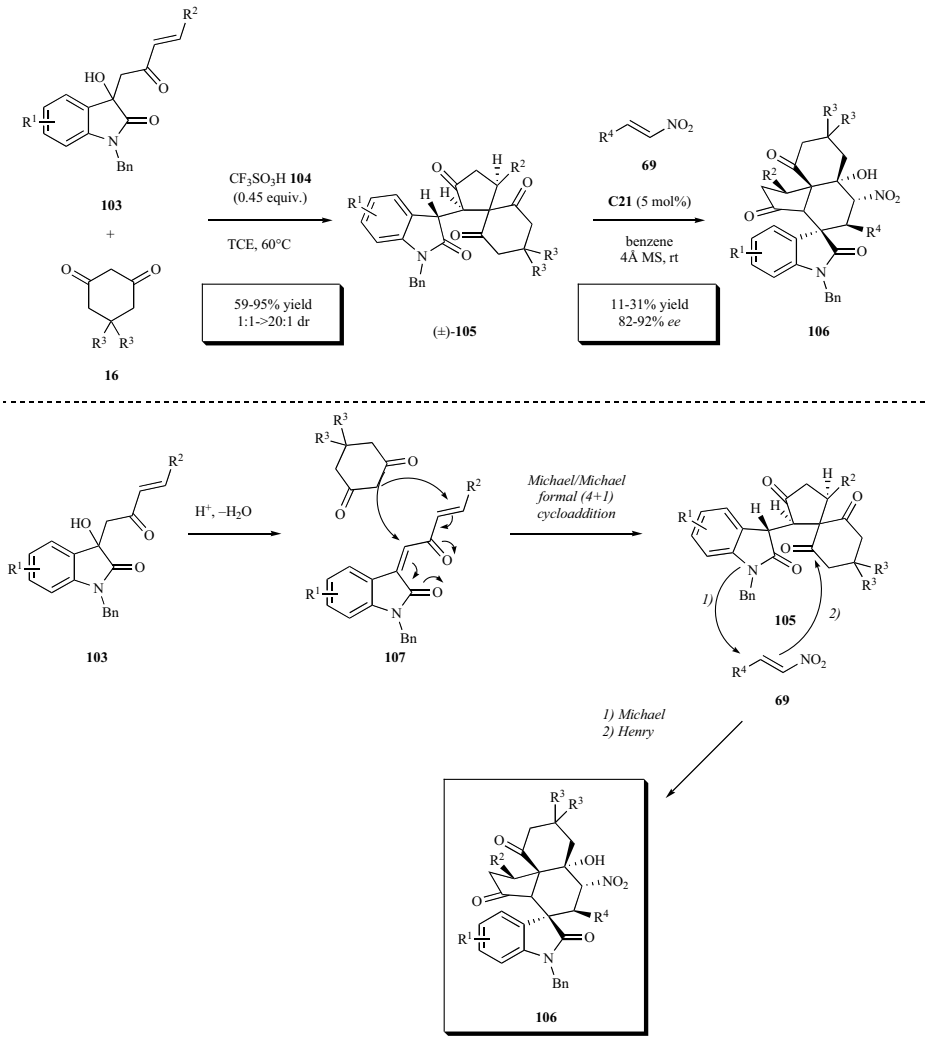


Scheme 20. Triple Michael cascade/one-pot Wittig olefination sequence reported by Enders *et al*. [50].

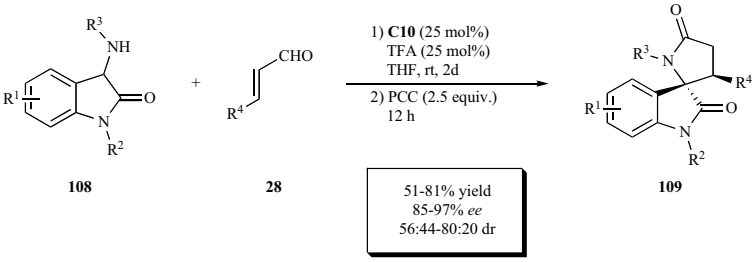
intramolecular hemiaminalization could close the five-membered ring, which upon treatment with pyridinium chlorochromate (PCC) could be effectively oxidised to the corresponding γ-lactam **109** in a one-pot fashion.

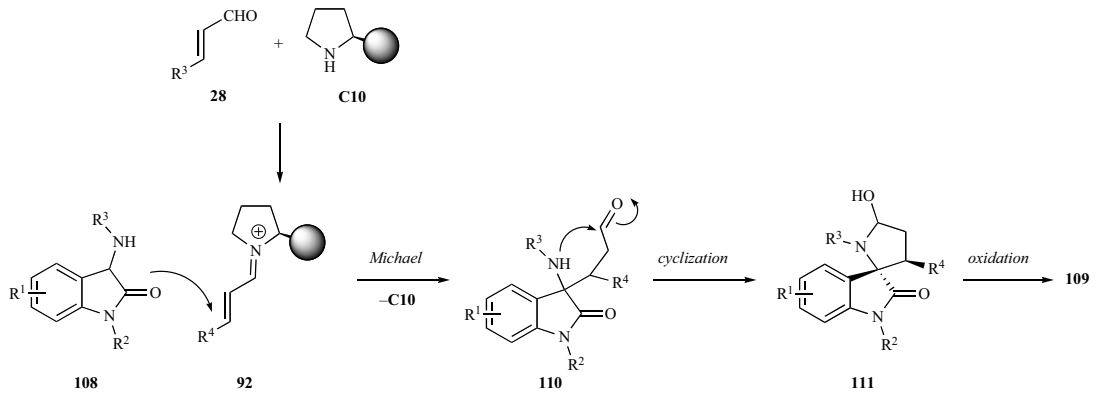
In 2018, Wang and Sheng tested instead 3-sulfur containing oxindoles **112** in an H-bonding catalysed domino Michael/Henry reaction followed by one-pot sulfonium-mediated rearrangement (Scheme **23**) [53].

Initially, tetrahydrothiopyrans were efficiently prepared by reaction of **112** with nitrostyrenes **69** in the presence of a chiral non symmetrical bis-diamine thiourea **C8**, which could simultaneously coordinates both substrates *via* H-bonds network (**A**). The products **113** were isolated and characterized, observing moderate to good yields and high stereoselectivities. Subsequently, the authors envisaged the following rearrangement reaction promoted by thionyl chloride. The mechanism for this rearrangement was proposed to proceed *via* thionyl chloride-promoted elimination and formation of

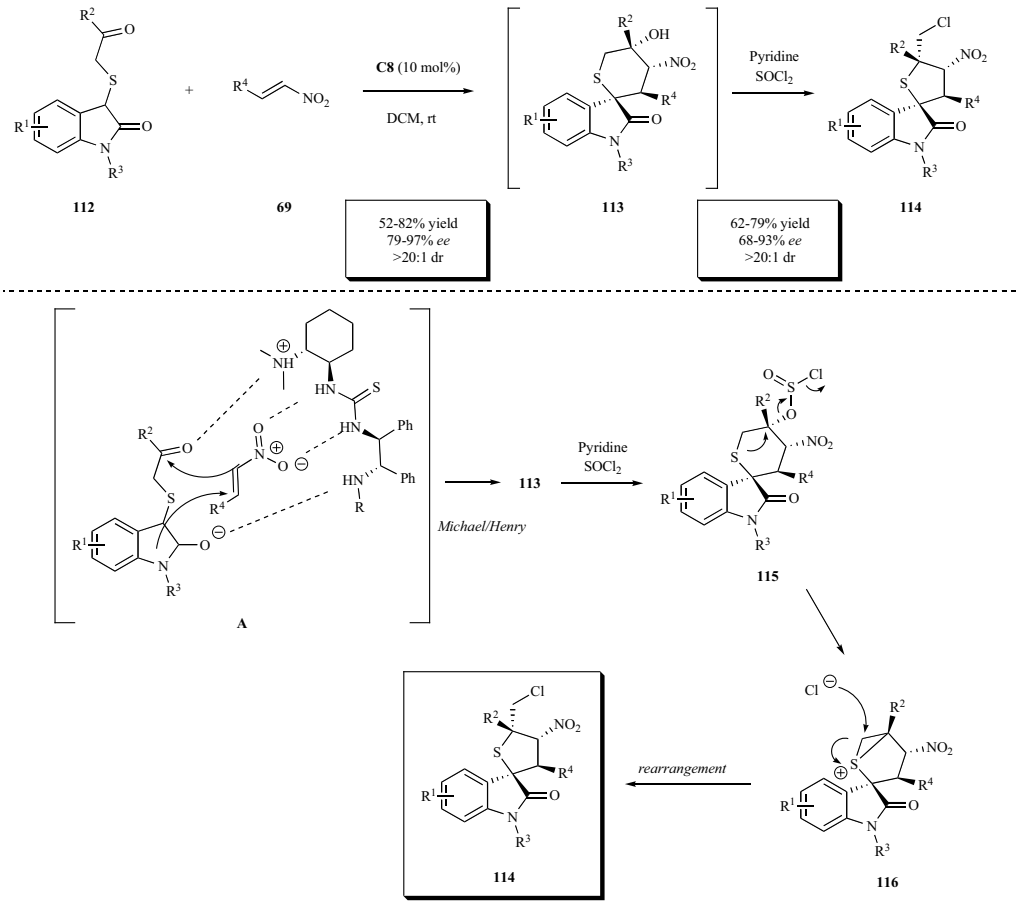


Scheme 21. Diastereoselective (4+1) cycloaddition/domino Michael/Henry reaction reported by Tanaka [51].

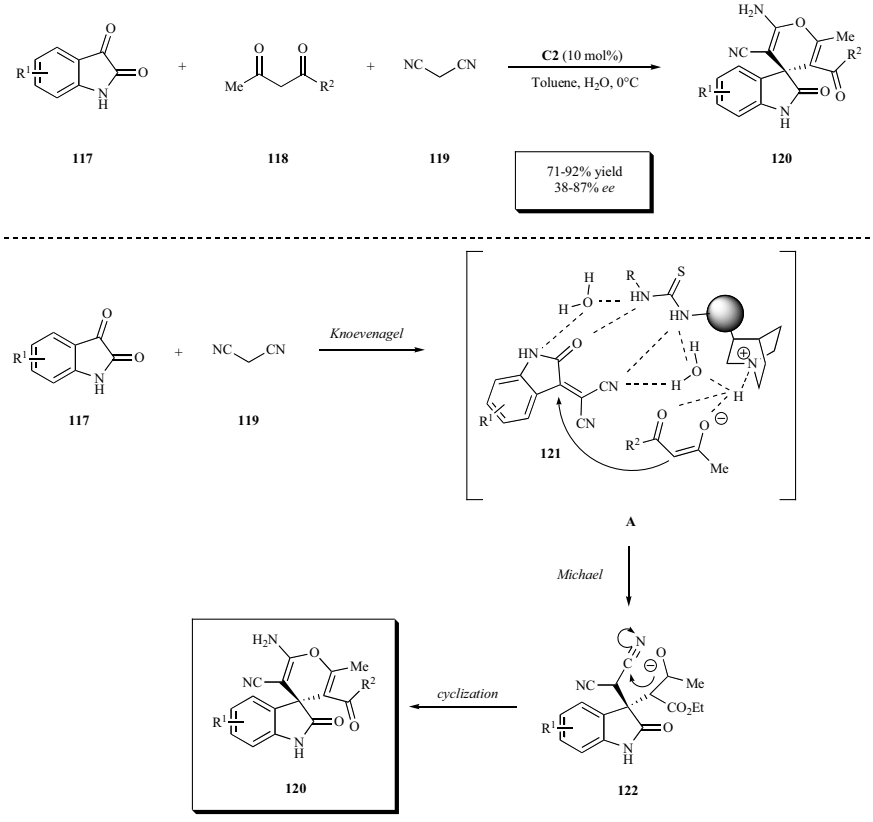




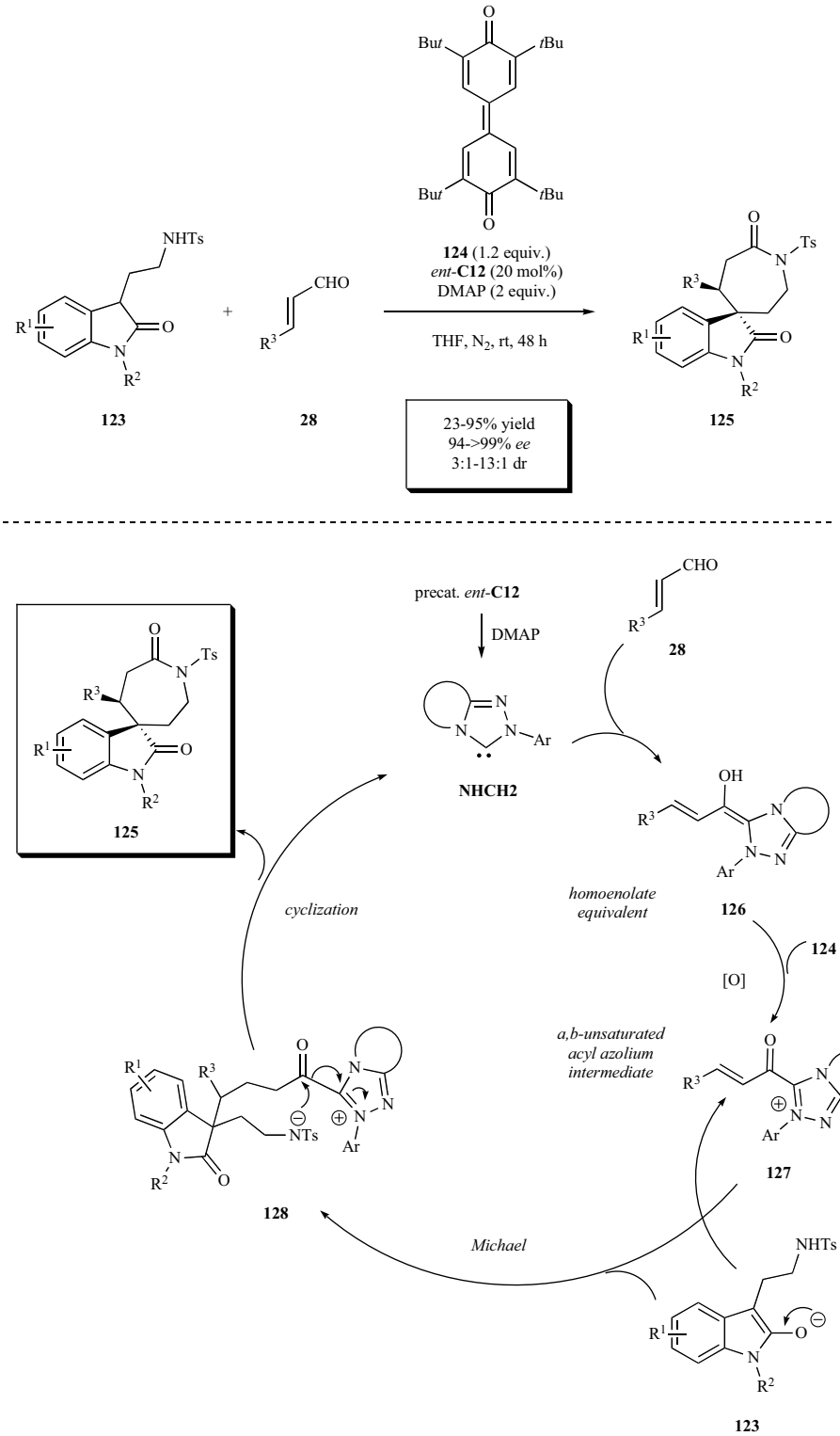
Scheme 22. Michael/hemiaminalization-one-pot oxidation protocol for the synthesis of γ-lactam spirooxindoles **109**.



Scheme 23. Domino Michael/Henry-one-pot rearrangement yielding oxindole-containing tetrahydrothiophenes **114**.



Scheme 24. Multicomponent domino Knoevenagel/Michael/cyclization sequence described by Zhao and co-workers [54].



Scheme 25. NHC-catalysed synthesis of seven-membered spirolactam oxindoles **125** *via* Michael/cyclization cascade reaction.

the three membered-sulfonium intermediate, followed by nucleophilic ring-opening by chloride attack. The authors were able to optimize the reaction conditions to perform this rearrangement in a one-pot way, without the isolation of compounds **113**, obtaining variously substituted tetrahydrothiophenes **114** bearing four consecutive stereocentres with excellent outcomes in term of yields and stereoselection.

As above mentioned, isatins have already been used for the stereoselective construction of oxindole-based molecular architectures. Zhao and co-workers described in 2019 a multicomponent strategy to achieve spiropyran-oxindoles **120** by reaction of isatins **117**, β-keto-esters/ketones **118** and malononitrile (**119**) (Scheme **24**) [54]. Catalyst **C2** was employed to perform the initial Knoevenagel condensation between isatins **117** and **119** affording com-

pound **121**, which is subsequently coordinated in a network of H-bonds with the β-keto-ester/ketone **118** to undergo Michael addition. Lastly, a cyclization reaction on one of the nitrile groups yielded the final product. The authors investigated the influence of water as an additive in the reaction in the study, highlighting that water positively influences the reaction outcomes for both yield and *ee*. The results could be rationalized by the involvement of water molecules in the H-bonds network, resulting in a more compact transition state and thus favouring the enantioselective Michael reaction.

In the same year, an interesting NHC-catalysed reaction sequence applied to the formation of seven-membered sprirolactam oxindoles was reported by Fu and Huang group (Scheme **25**) [55]. Oxotryptamines **123** were employed as four-atom synthons in a formal [4+3] cycloaddition domino Michael/cyclization sequence, paired with NHC-activated α,β-unsaturated aldehydes **28**. The reaction pathway started from the *in situ* generation of the NHC by deprotonation of pre-catalyst *ent*-**C12**. The NHC could generate the homoenolate equivalent **126** by reaction with the α,β-unsaturated aldehyde **28**. This intermediate was efficiently oxidised to the α,β-unsaturated acyl azolium **127** in the presence of oxidant **124**. Afterward, the Michael addition between intermediate **127** and substrate **123** could occur, generating the Michael adduct **128**, which upon intramolecular displacement of the NHC could close the seven-membered ring and yield the final product **125**.

CONCLUSION

In summary, in this review we described how asymmetric organocatalysis paved the way for the stereoselective synthesis of complex oxindole-based molecular structures bearing multiple stereogenic centres with an excellent level of stereocontrol. Most importantly, the advent of organocatalysed domino/one-pot sequential reaction sequences has increased the potential applications of asymmetric catalysis to industrial synthetic chemistry, since constant efforts are addressed to the search of innovative procedures to obviate unnecessary time-, energy-, atom- and cost-consuming processes. A plethora of strategies involving the organocatalytic stereoselective approaches to structurally diverse oxindoles has been described, providing step-economical and practical tools for the construction of potentially biologically relevant compounds. The methods described in this review have several salient features, such as simple operational procedures, mild reaction conditions, and often high atom economy. However, there is space for further improvements, for instance, the decrease of the catalyst loading, often used in 20 mol% or higher, and the avoidance of chlorinated solvents to reduce the environmental impact of the protocols.

We hope that this review could serve as an updated compendium of the recent methodologies to inspire the synthetic chemistry community towards novel and exciting new applications of stereoselective organocatalytic cascade reactions aimed at more sustainable and industrially attractive production of enantioenriched oxindole-based products.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] (a) Dondoni, A.; Massi, A. Design and synthesis of new classes of heterocyclic C-glycoconjugates and carbon-linked sugar and heterocyclic amino acids by asymmetric multicomponent reactions (AMCRs). *Acc. Chem. Res.,* **2006**, *39*(7), 451- 463.
http://dx.doi.org/10.1021/ar068023r PMID: 16846209
(b) Lu, L-Q.; Chen, J-R.; Xiao, W-J. Development of cascade reactions for the concise construction of diverse heterocyclic architectures. *Acc. Chem. Res.,* **2012**, *45*(8), 1278-1293.
http://dx.doi.org/10.1021/ar200338s PMID: 22577988

[2] (a) Peng, X-M.; Damu, G.L.V.; Zhou, C. Current developments of coumarin compounds in medicinal chemistry. *Curr. Pharm. Des.,* **2013**, *19*(21), 3884-3930.
http://dx.doi.org/10.2174/1381612811319210013 PMID: 23438968
(b) Kumar, V.; Kaur, K.; Gupta, G.K.; Sharma, A.K. Pyrazole containing natural products: Synthetic preview and biological significance. *Eur. J. Med. Chem.,* **2013**, *69*, 735-753.
http://dx.doi.org/10.1016/j.ejmech.2013.08.053 PMID: 24099993
(c) Zhang, L.; Peng, X-M.; Damu, G.L.V.; Geng, R-X.; Zhou, C-H. Comprehensive review in current developments of imidazole-based medicinal chemistry. *Med. Res. Rev.,* **2014**, *34*(2), 340-437.
http://dx.doi.org/10.1002/med.21290 PMID: 23740514

[3] (a) Cheng, Y.; Huang, Z-T.; Wang, M-X. Heterocyclic enamines. The versatile intermediates in the synthesis of heterocyclic compounds and natural products. *Curr. Org. Chem.,* **2004**, *8*, 325-351.
http://dx.doi.org/10.2174/1385272043485936
(b) Jin, Z. Muscarine, imidazole, oxazole and thiazole alkaloids. *Nat. Prod. Rep.,* **2009**, *26*(3), 382-445.
http://dx.doi.org/10.1039/b718045b PMID: 19240947
(c) Narasimhan, B.; Sharma, D.; Kumar, P. Benzimidazole: A medicinally important heterocyclic moiety. *Med. Chem. Res.,* **2012**, *21*, 269-283.
http://dx.doi.org/10.1007/s00044-010-9533-9
(d) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications. *Eur. J. Med. Chem.,* **2014**, *76*, 193-244.
http://dx.doi.org/10.1016/j.ejmech.2014.02.005 PMID: 24583357

[4] Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. Oxindole: A chemical prism carrying plethora of therapeutic benefits. *Eur. J. Med. Chem.,* **2016**, *123*, 858-894.
http://dx.doi.org/10.1016/j.ejmech.2016.08.011 PMID: 27543880

[5] (a) Dalko, P.I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem. Int. Ed. Engl.,* **2001**, *40*(20), 3726-3748.
http://dx.doi.org/10.1002/1521-3773(20011015)40:20<3726::AID-ANIE3726>3.0.CO;2-D PMID: 11668532
(b) Benaglia, M.; Puglisi, A.; Cozzi, F. Polymer-supported organic catalysts. *Chem. Rev.,* **2003**, *103*(9), 3401-3429.
http://dx.doi.org/10.1021/cr010440o PMID: 12964876
(c) Houk, K.N.; List, B. Asymmetric organocatalysis. *Acc. Chem. Res.,* **2004**, *37*, 487-487.
http://dx.doi.org/10.1021/ar040216w
(d) Berkessel, A.; Groerger, H. *Asymmetric Organocatalysis*; Wiley-VCH Verlag GmbH, **2005**.
http://dx.doi.org/10.1002/3527604677
(e) Pellissier, H. Asymmetric organocatalysis. *Tetrahedron,* **2007**, *63*, 9267-9331.
http://dx.doi.org/10.1016/j.tet.2007.06.024
(f) MacMillan, D.W.C. The advent and development of organocatalysis. *Nature,* **2008**, *455*(7211), 304-308.
http://dx.doi.org/10.1038/nature07367 PMID: 18800128
(g) Dondoni, A.; Massi, A. Asymmetric organocatalysis: From infancy to adolescence. *Angew. Chem. Int. Ed. Engl.,* **2008**, *47*(25), 4638-4660.
http://dx.doi.org/10.1002/anie.200704684 PMID: 18421733
(h) Vetica, F.; de Figueiredo, R.M.; Orsini, M.; Tofani, D.; Gasperi, T. Recent advances in organocatalytic cascade reactions toward the formation of quaternary stereocenters. *Synthesis,* **2015**, *47*, 2139-2184.
http://dx.doi.org/10.1055/s-0034-1378742

[6] Bredig, G.; Fiske, P.S. Asymmetric synthesis caused by catalyts, *Biochem. Z,* **1913**, Vol. *46,* pp.7-23.

[7] (a) Yu, X.; Wang, W. Hydrogen-bond-mediated asymmetric catalysis. *Chem. Asian J.,* **2008**, *3*(3), 516-532.
http://dx.doi.org/10.1002/asia.200700415 PMID: 18286564
(b) Moyano, A.; Rios, R. Asymmetric organocatalytic cyclization and cycloaddition reactions. *Chem. Rev.,* **2011**, *111*(8), 4703-4832.
http://dx.doi.org/10.1021/cr100348t PMID: 21615119
(c) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K.A. Squaramides: Bridging from molecular recognition to bifunctional organocatalysis. *Chemistry,* **2011**, *17*(25), 6890-6899.
http://dx.doi.org/10.1002/chem.201003694 PMID: 21590822

(d) Pellissier, H. Recent developments in asymmetric organocatalytic domino reactions. *Adv. Synth. Catal.,* **2012**, *354*, 237-294.
http://dx.doi.org/10.1002/adsc.201100714
(e) Volla, C.M.R.; Atodiresei, I.; Rueping, M. Catalytic C-C bond-forming multi-component cascade or domino reactions: Pushing the boundaries of complexity in asymmetric organocatalysis. *Chem. Rev.,* **2014**, *114*(4), 2390-2431.
http://dx.doi.org/10.1021/cr400215u PMID: 24304297
(f) Vetica, F.; Chauhan, P.; Dochain, S.; Enders, D. Asymmetric organocatalytic methods for the synthesis of tetrahydropyrans and their application in total synthesis. *Chem. Soc. Rev.,* **2017**, *46*(6), 1661-1674.
http://dx.doi.org/10.1039/C6CS00757K PMID: 28262863

[8] (a) Grondal, C.; Jeanty, M.; Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.,* **2010**, *2*(3), 167-178.
http://dx.doi.org/10.1038/nchem.539 PMID: 21124474
(b) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional amine-squaramides: Powerful hydrogen-bonding organocatalysts for asymmetric domino/cascade reactions. *Adv. Synth. Catal.,* **2015**, *357*, 253-281.
http://dx.doi.org/10.1002/adsc.201401003
(c) Nayak, S.; Panda, P.; Bhakta, S.; Mishra, S.K.; Mohapatra, S. Current advances of organocatalytic Michael-Michael cascade reaction in the synthesis of highly functionalized cyclic molecules. *RSC Advances,* **2016**, *6*, 96154-96175.
http://dx.doi.org/10.1039/C6RA21191G
(d) Chauhan, P.; Mahajan, S.; Enders, D. Achieving molecular complexity *via* stereoselective multiple domino reactions promoted by a secondary amine organocatalyst. *Acc. Chem. Res.,* **2017**, *50*(11), 2809-2821.
http://dx.doi.org/10.1021/acs.accounts.7b00406 PMID: 29125741
(e) Parvin, T.; Yadav, R.; Choudhury, L.H. Recent applications of thiourea-based organocatalysts in asymmetric multicomponent reactions (AMCRs). *Org. Biomol. Chem.,* **2020**, *18*(29), 5513-5532.
http://dx.doi.org/10.1039/D0OB00595A PMID: 32644077

[9] Gasperi, T.; Orsini, M.; Vetica, F.; de Figueiredo, R.M. *Organocatalytic Asymmetric Multicomponent Reactions in Multicomponent Reactions*; John Wiley & Sons, Inc, **2015**, pp. 16-71.

[10] (a) Shao, Z.; Zhang, H. Combining transition metal catalysis and organocatalysis: A broad new concept for catalysis. *Chem. Soc. Rev.,* **2009**, *38*(9), 2745-2755.
http://dx.doi.org/10.1039/b901258n PMID: 19690751
(b) Zhong, C.; Shi, X. When organocatalysis meets transition-metal catalysis. *Eur. J. Org. Chem.,* **2010**, 2999-3025.
http://dx.doi.org/10.1002/ejoc.201000004
(c) Du, Z.; Shao, Z. Combining transition metal catalysis and organocatalysis-an update. *Chem. Soc. Rev.,* **2013**, *42*(3), 1337-1378.
http://dx.doi.org/10.1039/C2CS35258C PMID: 23154522
(d) Hack, D.; Chauhan, P.; Deckers, K.; Mizutani, Y.; Raabe, G.; Enders, D. Combining silver- and organocatalysis: An enantioselective sequential catalytic approach towards pyrano-annulated pyrazoles. *Chem. Commun. (Camb.),* **2015**, *51*(12), 2266-2269.
http://dx.doi.org/10.1039/C4CC09495F PMID: 25564304
(e) Dochain, S.; Vetica, F.; Puttreddy, R.; Rissanen, K.; Enders, D. Combining organocatalysis and lanthanide catalysis: A sequential one-pot quadruple reaction sequence/hetero-diels-alder asymmetric synthesis of functionalized tricycles. *Angew. Chem. Int. Ed. Engl.,* **2016**, *55*(52), 16153-16155.
http://dx.doi.org/10.1002/anie.201610196 PMID: 27879031
(f) Meazza, M.; Tur, F.; Hammer, N.; Jørgensen, K.A. Synergistic diastereo- and enantioselective functionalization of unactivated alkyl quinolines with α,β-unsaturated aldehydes. *Angew. Chem. Int. Ed. Engl.,* **2017**, *56*(6), 1634-1638.
http://dx.doi.org/10.1002/anie.201611306 PMID: 28067446
(g) Wu, D.; Bu, Q.; Guo, C.; Dai, B.; Liu, N. *Cooperative catalysis of molybdenum with organocatalysts for distribution of products between amines and imines*; Molecular Catalysis, **2021**, p. 503.

[11] (a) Tietze, L.F. Domino reactions in organic synthesis. *Chem. Rev.,* **1996**, *96*(1), 115-136.
http://dx.doi.org/10.1021/cr950027e PMID: 11848746
(b) Enders, D.; Grondal, C.; Hüttl, M.R. Asymmetric organocatalytic domino reactions. *Angew. Chem. Int. Ed. Engl.,* **2007**, *46*(10), 1570-1581.
http://dx.doi.org/10.1002/anie.200603129 PMID: 17225236
(c) Vetica, F.; Pelosi, A.; Gambacorta, A.; Loreto, M.A.; Miceli, M.; Gasperi, T. Catalytic friedel-crafts/lactonization domino reaction: Facile access to 3-hydroxybenzofuran-2-one scaffold. *Eur. J. Org. Chem.,* **2014**, *2014*, 1899-1906.
http://dx.doi.org/10.1002/ejoc.201301686
(d) Vetica, F.; Bailey, S.J.; Kumar, M.; Mahajan, S.; von Essen, C.; Rissanen, K.; Enders, D. Palladium-catalyzed [3+2] cycloaddition of vinylaziridine and indane-1,3-diones: Diastereo- and enantioselective access to spiro-pyrrolidines. *Synthesis,* **2020**, 2038-2044.
http://dx.doi.org/10.1055/s-0040-1707472

[12] (a) Tietze, L.F.; Beifuss, U. Sequential transformations in organic chemistry: A synthetic strategy with a future. *Angew. Chem. Int. Ed. Engl.,* **1993**, *32*, 131-163.
http://dx.doi.org/10.1002/anie.199301313
(b) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci. (Camb.),* **2016**, *7*(2), 866-880.
http://dx.doi.org/10.1039/C5SC02913A PMID: 28791118

[13] Lelais, G.; MacMillan, D.W.C. Modern strategies in organic catalysis: The advent and development of iminium activation. *Aldrichim Acta,* **2006**, *39*, 79-87.

[14] (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-heterocyclic carbenes. *Chem. Rev.,* **2007**, *107*(12), 5606-5655.
http://dx.doi.org/10.1021/cr068372z PMID: 17956132
(b) Grossmann, A.; Enders, D. N-heterocyclic carbene catalyzed domino reactions. *Angew. Chem. Int. Ed. Engl.,* **2012**, *51*(2), 314-325.
http://dx.doi.org/10.1002/anie.201105415 PMID: 22121084
(c) Feroci, M.; Chiarotto, I.; Inesi, A. Electrolysis of ionic liquids. A possible keystone for the achievement of green solvent-catalyst systems. *Curr. Org. Chem.,* **2013**, *17*, 204-219.
http://dx.doi.org/10.2174/1385272811317030003
(d) Chen, X. Y.; Li, S.; Vetica, F.; Kumar, M.; Enders, D. N-heterocyclic-carbene-catalyzed domino reactions *via* two or more activation modes. *iScience,* **2018**, *2*, 1-26.
(e) Liu, Q.; Chen, X-Y.; Li, S.; Vetica, F.; Raabe, G.; Enders, D. Two-step synthesis of α,β-unsaturated γ-amino acid esters *via* n-heterocyclic carbene catalyzed [4+2] cycloaddition of enals and nitroso compounds. *Synthesis,* **2018**, *50*, 127-133.
(f) Vetica, F.; Bortolami, M.; Petrucci, R.; Rocco, D.; Feroci, M. Electrogenerated NHCs in organic synthesis: Ionic liquids *vs.* organic solvents effects. *Chem. Rec.,* **2021**, *21*.
http://dx.doi.org/10.1002/tcr.202000178 PMID: 33507627

[15] Gasperi, T.; Miceli, M.; Campagne, J.-M.; Marcia de Figueiredo, R. Non-covalent organocatalyzed domino reactions involving oxindoles: Recent advances. *Molecules,* **2017**, *22*, 1636/1631-1636/1630.

[16] (a) Vetica, F.; de Figueiredo, R.M.; Cupioli, E.; Gambacorta, A.; Loreto, M.A.; Miceli, M.; Gasperi, T. First asymmetric organocatalyzed domino Friedel–Crafts/lactonization reaction in the enantioselective synthesis of the GABAB receptor modulator (S)-BHFF. *Tetrahedron Lett.,* **2016**, *57*, 750-753.
http://dx.doi.org/10.1016/j.tetlet.2016.01.015
(b) Vetica, F.; Fronert, J.; Puttreddy, R.; Rissanen, K.; Enders, D. Asymmetric organocatalytic synthesis of 4-amino-isochromanones *via* a direct one-pot intramolecular Mannich reaction. *Synthesis,* **2016**, *48*, 4451.
http://dx.doi.org/10.1055/s-0035-1562522

[17] (a) Vetica, F.; Bailey, S.; Chauhan, P.; Turberg, M.; Ghaur, A.; Raabe, G.; Enders, D. Desymmetrization of Cyclopentenediones *via* Organocatalytic Cross-Dehydrogenative Coupling. *Adv. Synth. Catal.,* **2017**, *359*(21), 3729-3724.
http://dx.doi.org/10.1002/adsc.201700917
(b) Vetica, F.; Chauhan, P.; Mahajan, S.; Raabe, G.; Enders, D. Asymmetric organocatalytic Friedel–Crafts hydroxyalkylation of indoles using electrophilic pyrazole-4,5-diones. *Synthesis,* **2018**, *50*, 1039-1046.

[18] (a) Cao, Z-Y.; Zhou, J. Catalytic asymmetric synthesis of polysubstituted spirocyclopropyl oxindoles: Organocatalysis versus transition metal catalysis. *Org. Chem. Front.,* **2015**, *2*, 849-858.
http://dx.doi.org/10.1039/C5QO00092K
(b) Dalpozzo, R.; Mancuso, R. Enantioselective vinylogous reactions of 3-alkylidene oxindoles. *Synthesis-Stuttgart,* **2018**, *50*, 2463-2472.
http://dx.doi.org/10.1055/s-0037-1609731

[19] Freckleton, M.; Baeza, A.; Benavent, L.; Chinchilla, R. Asymmetric organocatalytic electrophilic heterofunctionalization of oxindoles. *Asian J. Org. Chem.,* **2018**, *7*, 1006-1014.
http://dx.doi.org/10.1002/ajoc.201800146

[20] Pellissier, H. Synthesis of chiral 3-substituted 3-amino-2-oxindoles through enantioselective catalytic domino and tandem reactions. *Synthesis,* **2019**, *51*, 1311-1318.
http://dx.doi.org/10.1055/s-0037-1610350

[21] Li, T.Z.; Xie, J.; Jiang, Y.; Sha, F.; Wu, X.Y. Enantioselective vinylogous michael/cyclization cascade reaction of acyclic β,γ-unsaturated amides with isatylidene malononitriles: Asymmetric construction of spirocyclic oxindoles. *Adv. Synth. Catal.,* **2015**, *357*, 3507-3511.
http://dx.doi.org/10.1002/adsc.201500469

[22] Sun, Q-S.; Zhu, H.; Chen, Y-J.; Yang, X-D.; Sun, X-W.; Lin, G-Q. Squaramide-Catalyzed Synthesis of Enantioenriched Spirocyclic Oxindoles *via* Ketimine Intermediates with Multiple Active Sites. *Angew. Chem. Int. Ed. Engl.,* **2015**, *54*(45), 13253-13257.
http://dx.doi.org/10.1002/anie.201506206 PMID: 26337819

[23] Monari, M.; Montroni, E.; Nitti, A.; Lombardo, M.; Trombini, C.; Quintavalla, A. Highly stereoselective [4+2] and [3+2] spiroannulations of 2-(2-oxoindolin-3-ylidene)acetic esters catalyzed by bifunctional thioureas. *Chemistry,* **2015**, *21*(31), 11038-11049.
http://dx.doi.org/10.1002/chem.201500676 PMID: 26032428

[24] Chennapuram, M.; Owolabi, I.A.; Seki, C.; Okuyama, Y.; Kwon, E.; Uwai, K.; Tokiwa, M.; Takeshita, M.; Nakano, H. New Hybrid-type Squaramide-Fused Amino Alcohol Organocatalyst for Enantioselective Domino Michael Addition/Cyclization Reaction of Oxoindolines with Cyclic 1,3-Diketones. *ACS Omega,* **2018**, *3*(9), 11718-11726.
http://dx.doi.org/10.1021/acsomega.8b01271 PMID: 31459268

[25] Ren, J-W.; Zheng, L.; Ye, Z-P.; Deng, Z-X.; Xie, Z-Z.; Xiao, J.A.; Zhu, F.W.; Xiang, H.Y.; Chen, X.Q.; Yang, H. Organocatalytic, enantioselective,

polarity-matched ring-reorganization domino sequence based on the 3-oxindole scaffold. *Org. Lett.,* **2019**, *21*(7), 2166-2170. http://dx.doi.org/10.1021/acs.orglett.9b00477 PMID: 30908056

[26] Sun, Q-S.; Lin, H.; Sun, X.; Sun, X-W. Highly efficient synthesis of enantio-enriched fully-substituted spirocyclohexane oxindoles *via* a Michael-Michael-aldol cascade reaction. *Tetrahedron Lett.,* **2016**, *57*, 5673-5676. http://dx.doi.org/10.1016/j.tetlet.2016.11.019

[27] Wang, L.; Li, S.; Blümel, M.; Puttreddy, R.; Peuronen, A.; Rissanen, K.; Enders, D. Switchable access to different spirocyclopentane oxindoles by N-heterocyclic carbene catalyzed reactions of isatin-derived enals and N-sulfonyl ketimines. *Angew. Chem. Int. Ed. Engl.,* **2017**, *56*(29), 8516-8521. http://dx.doi.org/10.1002/anie.201704210 PMID: 28568965

[28] Han, J-L.; Chang, C-H. An asymmetric assembly of spirooxindole dihydropyranones through a direct enantioselective organocatalytic vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles with isatins. *Chem. Commun. (Camb.),* **2016**, *52*(11), 2322-2325. http://dx.doi.org/10.1039/C5CC08883F PMID: 26728396

[29] (a) Mukerjee, A.K.; Ashare, R. Isothiocyanates in the chemistry of heterocycles. *Chem. Rev.,* **1991**, *91*, 1-24. http://dx.doi.org/10.1021/cr00001a001
(b) Brandsma, L.; Nedolya, N.A.; Tarasova, O.A.; Trofimov, B.A. *Synthesis of heterocyclic compounds from metallated unsaturated compounds and isothiocyanates*; Khimiya Geterotsiklicheskikh Soedinenii, **2000**, pp. 1443-1463.

[30] Du, D.; Xu, Q.; Li, X-G.; Shi, M. Construction of spirocyclic oxindoles through regio- and stereoselective [3+2] or [3+2]/[4+2] cascade reaction of α,β-unsaturated imines with 3-isothiocyanato oxindole. *Chemistry,* **2016**, *22*(14), 4733-4737. http://dx.doi.org/10.1002/chem.201600497 PMID: 26853427

[31] Lin, N.; Long, X-w.; Chen, Q.; Zhu, W-r.; Wang, B-c.; Chen, K-b.; Jiang, C-w.; Weng, J.; Lu, G. Highly efficient construction of chiral dispirocyclic oxindole/thiobutyrolactam/chromanone complexes through Michael/cyclization cascade reactions with a rosin-based squaramide catalyst. *Tetrahedron,* **2018**, *74*, 3734-3741. http://dx.doi.org/10.1016/j.tet.2018.05.052

[32] Emami, S.; Ghanbarimasir, Z. Recent advances of chroman-4-one derivatives: synthetic approaches and bioactivities. *Eur. J. Med. Chem.,* **2015**, *93*, 539-563. http://dx.doi.org/10.1016/j.ejmech.2015.02.048 PMID: 25743215

[33] Zhu, W-R.; Chen, Q.; Lin, N.; Chen, K-B.; Zhang, Z-W.; Fang, G.; Weng, J.; Lu, G. Organocatalytic Michael/cyclization cascade reactions of 3-Isothiocyanate oxindoles with 3-trifluoroethylidene oxindoles: an approach for the synthesis of 3′-trifluoromethyl substituted 3,2′-pyrrolidinyl-bispirooxindoles. *Org. Chem. Front.,* **2018**, *5*, 1375-1380. http://dx.doi.org/10.1039/C8QO00044A

[34] Song, Y-X.; Du, D-M. Squaramide-catalyzed asymmetric michael/cyclization cascade reaction of unsaturated thiazolidinones and 3-isothiocyanate oxindoles: synthesis of new bispirocyclic heterocycles. *Synthesis,* **2018**, *50*, 1535-1545. http://dx.doi.org/10.1055/s-0036-1591527

[35] Ricko, S.; Testen, Z.; Ciber, L. PoZgan, F.; Stefane, B.; Brodnik, H.; Svete, J.; Groselj, U. Double spirocyclization of arylidene-Δ2-pyrrolin-4-ones with 3-Isothiocyanate oxindoles. *Catalysts,* **2020**, *10*, 1211. http://dx.doi.org/10.3390/catal10101211

[36] Zhang, C-B.; Dou, P-H.; Zhao, J-Q.; Yuan, W-C. Organocatalyzed asymmetric cascade Mannich/cyclization of 3-isothiocyanate oxindoles with cyclic ketimines for the synthesis of polycyclic spiro-thioimidazolidine-oxindoles. *Tetrahedron,* **2020**, *76*, 131116. http://dx.doi.org/10.1016/j.tet.2020.131116

[37] Zhi, Y.; Zhao, K.; Von Essen, C.; Rissanen, K.; Enders, D. Thiourea-catalyzed domino Michael-Mannich [3+2] cycloadditions: A strategy for the asymmetric synthesis of 3,3′-pyrrolidinyl-dispirooxindoles. *Synlett,* **2017**, *28*, 2876-2880. http://dx.doi.org/10.1055/s-0036-1589070

[38] Lin, Y.; Song, Y-X.; Du, D-M. Enantioselective synthesis of CF3-containing 3,2′-pyrrolidinyl spirooxindoles and dispirooxindoles *via* thiourea-catalyzed domino Michael/Mannich [3+2] cycloaddition reactions. *Adv. Synth. Catal.,* **2019**, *361*, 1064-1070. http://dx.doi.org/10.1002/adsc.201801608

[39] Yang, M-C.; Peng, C.; Huang, H.; Yang, L.; He, X-H.; Huang, W.; Cui, H-L.; He, G.; Han, B. Organocatalytic asymmetric synthesis of spiro-oxindole piperidine derivatives that reduce cancer cell proliferation by inhibiting MDM2-p53 Interaction. *Org. Lett.,* **2017**, *19*(24), 6752-6755. http://dx.doi.org/10.1021/acs.orglett.7b03516 PMID: 29210587

[40] Kristofikova, D.; Meciarova, M.; Rakovsky, E.; Sebesta, R. Mechanochemically activated asymmetric organocatalytic domino mannich reaction-fluorination. *ACS Sustain. Chem.& Eng.,* **2020**, *8*, 14417-14424. http://dx.doi.org/10.1021/acssuschemeng.0c04260

[41] (a) James, S.L.; Adams, C.J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K.D.M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A.G.; Parkin, I.P.; Shearouse, W.C.; Steed, J.W.; Waddell, D.C. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.,* **2012**, *41*(1), 413-447. http://dx.doi.org/10.1039/C1CS15171A PMID: 21892512
(b) Hernández, J.G.; Bolm, C. Altering product selectivity by mechanochemistry. *J. Org. Chem.,* **2017**, *82*(8), 4007-4019. http://dx.doi.org/10.1021/acs.joc.6b02887 PMID: 28080050
(c) Bolm, C.; Hernández, J.G. Mechanochemistry of gaseous reactants. *Angew. Chem. Int. Ed. Engl.,* **2019**, *58*(11), 3285-3299. http://dx.doi.org/10.1002/anie.201810902 PMID: 30417972

[42] Liu, X-L.; Wei, Q-D.; Zuo, X.; Xu, S-W.; Yao, Z.; Wang, J-X.; Zhou, Y. Organocatalytic Michael/Michael cycloaddition enabled asymmetric construction of hexahydroxanthones with skeletal diversity. *Adv. Synth. Catal.,* **2019**, *361*, 2836-2843. http://dx.doi.org/10.1002/adsc.201900119

[43] Zuo, X.; Liu, X-L.; Wang, J.X.; Yao, Y.M.; Zhou, Y.Y.; Wei, Q.D.; Gong, Y.; Zhou, Y.; Wei, Q-D.; Gong, Y. Organocatalytic reaction of chromone-oxindole synthon: Access to chromanone-based spirocyclohexaneoxindoles with five adjacent stereocenters. *J. Org. Chem.,* **2019**, *84*(11), 6679-6688. http://dx.doi.org/10.1021/acs.joc.9b00326 PMID: 31083948

[44] Song, Y-X.; Lin, Y.; Yan, L.; Du, D-M. An organocatalytic domino Michael addition strategy: construction of bispiro[oxindole-thiazolidinone-hexahydroxanthone]s with five contiguous stereocenters. *Org. Biomol. Chem.,* **2020**, *18*(37), 7373-7378. http://dx.doi.org/10.1039/D0OB01613F PMID: 32926035

[45] Liu, X-L.; Zuo, X.; Wang, J-X.; Chang, S-q.; Wei, Q-D.; Zhou, Y. A bifunctional pyrazolone-chromone synthon directed organocatalytic double Michael cascade reaction: forging five stereocenters in structurally diverse hexahydroxanthones. *Org. Chem. Front.,* **2019**, *6*, 1485-1490. http://dx.doi.org/10.1039/C9QO00265K

[46] (a) Clark, M.P.; Laughlin, S.K.; Laufersweiler, M.J.; Bookland, R.G.; Brugel, T.A.; Golebiowski, A.; Sabat, M.P.; Townes, J.A.; VanRens, J.C.; Djung, J.F.; Natchus, M.G.; De, B.; Hsieh, L.C.; Xu, S.C.; Walter, R.L.; Mekel, M.J.; Heitmeyer, S.A.; Brown, K.K.; Juergens, K.; Taiwo, Y.O.; Janusz, M.J. Development of orally bioavailable bicyclic pyrazolones as inhibitors of tumor necrosis factor-alpha production. *J. Med. Chem.,* **2004**, *47*(11), 2724-2727. http://dx.doi.org/10.1021/jm049968m PMID: 15139749
(b) Chande, M.S.; Barve, P.A.; Suryanarayan, V. Synthesis and antimicrobial activity of novel spirocompounds with pyrazolone and pyrazolthione moiety. *J. Heterocycl. Chem.,* **2007**, *44*, 49-53. http://dx.doi.org/10.1002/jhet.5570440108
(c) Fujimori, Y.; Katsuno, K.; Nakashima, I.; Ishikawa-Takemura, Y.; Fujikura, H.; Isaji, M. Remogliflozin etabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. *J. Pharmacol. Exp. Ther.,* **2008**, *327*(1), 268-276. http://dx.doi.org/10.1124/jpet.108.140210 PMID: 18583547
(d) Hadi, V.; Koh, Y-H.; Sanchez, T.W.; Barrios, D.; Neamati, N.; Jung, K.W. Development of the next generation of HIV-1 integrase inhibitors: pyrazolone as a novel inhibitor scaffold. *Bioorg. Med. Chem. Lett.,* **2010**, *20*(22), 6854-6857. http://dx.doi.org/10.1016/j.bmcl.2010.08.057 PMID: 20864343
(e) Cox, S.R.; Lesman, S.P.; Boucher, J.F.; Krautmann, M.J.; Hummel, B.D.; Savides, M.; Marsh, S.; Fielder, A.; Stegemann, M.R. The pharmacokinetics of mavacoxib, a long-acting COX-2 inhibitor, in young adult laboratory dogs. *J. Vet. Pharmacol. Ther.,* **2010**, *33*(5), 461-470. http://dx.doi.org/10.1111/j.1365-2885.2010.01165.x PMID: 20840390

[47] Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, K.; Enders, D. Organocatalytic domino Oxa-Michael/1,6-addition reactions: Asymmetric synthesis of chromans bearing oxindole scaffolds. *Angew. Chem. Int. Ed. Engl.,* **2016**, *55*(39), 12104-12108. http://dx.doi.org/10.1002/anie.201606947 PMID: 27600477

[48] (a) Li, W.; Xu, X.; Zhang, P.; Li, P. Recent advances in the catalytic enantioselective reactions of para-quinone methides. *Chem. Asian J.,* **2018**, *13*(17), 2350-2359. http://dx.doi.org/10.1002/asia.201800415 PMID: 29676855
(b) Wang, J-Y.; Hao, W-J.; Tu, S-J.; Jiang, B. Recent developments in 1,6-addition reactions of para-quinone methides (p-QMs). *Org. Chem. Front.,* **2020**, *7*, 1743-1778. http://dx.doi.org/10.1039/D0QO00387E
(c) Lima, C.G.S.; Pauli, F.P.; Costa, D.C.S.; de Souza, A.S.; Forezi, L.S.M.; Ferreira, V.F.; de Carvalho da Silva, F. Para-quinone methides as acceptors in 1,6-nucleophilic conjugate addition reactions for the synthesis of structurally diverse molecules. *Eur. J. Org. Chem.,* **2020**, *2020*, 2650-2692. http://dx.doi.org/10.1002/ejoc.201901796

[49] Ren, W.; Wang, X-Y.; Li, J-J.; Tian, M.; Liu, J.; Ouyang, L.; Wang, J-H. Efficient construction of biologically important functionalized polycyclic spiro-fused carbocyclicoxindoles *via* an asymmetric organocatalytic quadruple-cascade reaction. *RSC Advances,* **2017**, *7*, 1863-1868. http://dx.doi.org/10.1039/C6RA24910H

[50] Zou, L-H.; Philipps, A.R.; Raabe, G.; Enders, D. Asymmetric synthesis of fully substituted cyclopentane-oxindoles through an organocatalytic triple Michael domino reaction. *Chemistry,* **2015**, *21*(3), 1004-1008. http://dx.doi.org/10.1002/chem.201406047 PMID: 25470781

[51] Huang, J-R.; Sohail, M.; Taniguchi, T.; Monde, K.; Tanaka, F. Formal (4+1) cycloaddition and enantioselective Michael-Henry cascade reactions to synthesize spiro[4,5]decanes and spirooxindole polycycles. *Angew. Chem. Int. Ed. Engl.,* **2017**, *56*(21), 5853-5857.

http://dx.doi.org/10.1002/anie.201701049 PMID: 28397989

[52] Yang, P.; Wang, X.; Chen, F.; Zhang, Z-B.; Chen, C.; Peng, L.; Wang, L-X. Organocatalytic enantioselective Michael/Cyclization domino reaction between 3-amideoxindoles and α,β-unsaturated aldehydes: One-pot preparation of chiral spirocyclic oxindole-γ-lactams. *J. Org. Chem.,* **2017**, *82*(7), 3908-3916.
http://dx.doi.org/10.1021/acs.joc.6b03090 PMID: 28287726

[53] Wang, S.; Guo, Z.; Chen, S.; Jiang, Y.; Zhang, F.; Liu, X.; Chen, W.; Sheng, C. Organocatalytic asymmetric synthesis of spiro-tetrahydrothiophene oxindoles bearing four contiguous stereocenters by one-pot Michael-Henry-cascade-rearrangement reactions. *Chemistry,* **2018**, *24*(1), 62-66.
http://dx.doi.org/10.1002/chem.201703837 PMID: 28940858

[54] Konda, S.; Jakkampudi, S.; Arman, H.D.; Zhao, J.C.G. Enantioselective synthesis of spiro[*4H*-pyran-3,3′-oxindole] derivatives catalyzed by cinchona alkaloid thioureas: Significant water effects on the enantioselectivity. *Synth. Commun.,* **2019**, *49*(21), 2971-2982.
http://dx.doi.org/10.1080/00397911.2019.1651866 PMID: 33012850

[55] Liu, D.; Hu, Z.; Zhang, Y.; Gong, M.; Fu, Z.; Huang, W. Access to enantio-enriched spiro-ϵ-Lactam oxindoles by an N-heterocyclic carbene-catalyzed [4+3] annulation of flexible oxotryptamines with enals. *Chemistry,* **2019**, *25*(48), 11223-11227.
PMID: 31298766