RAINOLDI GIULIA R10924

A Journey in the Organocatalysed and Multicomponent Synthesis of 3,3-Disubstituted and Spiro-Oxindoles

CHIM/06 Organic Chemistry

Doctorate Course in Chemistry

XXX Cycle – A.Y. 2016/2017

Tutor:
Prof. Dr. Giordano Lesma
Co-Tutor:
Dr. Alessandra Silvani
Coordinator:
Prof. Dr. Emanuela Licandro

Università degli Studi di Milano
Dipartimento di Chimica

Acknowledgements

Il mio primo e doveroso ringraziamento va sicuramente ai miei genitori, Claudio e Miriam, per avermi permesso di studiare senza preoccuparmi di questioni finanziarie ma solo di inseguire i miei sogni. Al mio Papo vorrei anche dire GRAZIE per aver creduto in me e per avermi spronato a dare il massimo sempre. Un GRAZIE alla mia sorellona, Federica, e Roberto per avermi sempre ascoltato quando ne avevo bisogno e soprattutto per avermi regalato Nicolò. Ringrazio le mie nonne, Eli e Vittoria, per tutte le volte che mi hanno ascoltato parlare di chimica senza capire un tubo ma sempre con un sorriso in volto e tanto orgoglio negli occhi.
GRAZIE a Stefano, il mio fidanzato, perché anche quando tutto va storto, riesce sempre a strapparmi un sorriso.

Per quanto riguarda il contenuto di questa tesi, un grosso riconoscimento va a tutti coloro che hanno lavorato con me durante questi tre anni come il mio Capo, Cip&Ciop, Greta, Claudia, Francesco, Mariska e molti altri...a tutti voi GRAZIE.
Nulla di questo sarebbe stato però possibile senza l'aiuto e la disponibiltà del Prof. Giordano Lesma e della Dr.ssa Alessandra Silvani che mi hanno permesso di lavorare nel loro gruppo di ricerca e conseguire il titolo di dottorato, insegnandomi e seguendomi con passione, spronandomi a seguire ogni mia idea e facendomi crescere come chimico e come persona. GRAZIE PROF.
Ringrazio infine il SyBOrCh, in particolare il Dott. Eelco Ruijter e il Prof. Romano Orru per avermi ospitato nel loro gruppo ad Amsterdam per sei mesi e per avermi fatto sentire a casa dal primo momento. Ho avuto l'oppurtinità di imparare moltissimo, anche un pochino di olandese… DANK JE WEL.

In the last century, the strong demand for new compounds pushed organic chemists to develop new synthetic strategies for the easy and fast generation of compounds libraries. In particular, in the field of diversity oriented synthesis (DOS), convergent synthetic methods, such as the multicomponent reactions (MCRs), have been considered powerful strategies toward this aim. More recently, the pursuit of highly functionalized MCR products as biological probes, drug candidates and synthetic intermediates has resulted in an intensified effort to find catalysts for asymmetric MCR transformations. Because of various reasons, including that of air and moisture tolerance, chiral organocatalysts are emerging as efficient and environmentally friendly synthetic alternatives to chiral metal complexes.

In this context, my research was aimed to the synthesis of oxindole-based libraries, exploiting protocols at the cutting edge of synthetic chemistry, such as MCRs and organocatalysis.

2-Oxindoles, especially those 3,3-disubstituted or spiro-fused to other cyclic frameworks, continue to be recognized as valuable compounds for drug discovery since they are present in a lot of natural compounds and medicinal drugs.

The employment of auxiliary chiral components or, alternatively, organocatalysis, allowed me to address the hot issue of asymmetry, achieving the generation of various families of 3,3-disubstituted and spiro-oxindoles.

I. Introduction

Indoline-2,3-dione, commonly known as isatin, was first discovered by Erdmann[1] and Laurent[2] in the early 19th century as a product arising from the oxidation of indigo using a mixture of nitric and chromic acids (Figure 1). The compound was considered synthetic for almost 140 years until it was found to be present in plants from the *Isatis genus* and in fruits of the cannon ball tree, *Couropita guianancis aubl.*[3] More recently, it was found in the secretions of the *Bufo* frog,[4] and isolated as a metabolic derivative of adrenaline in humans.[5] Currently, isatin itself and many substituted isatins are commercially available at easily affordable prices.

Isatin, whose current structure was proposed by Kekulé,[6] has revealed 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 with different electrophiles, nucleophilic additions at the C-3 carbonyl group, chemoselective reductions, ring-expansions, spiro-annulations and many others.

The unique potential of indoline-2,3-diones to be used both as an electrophile and nucleophile and their easy availability have made them valuable building blocks in organic synthesis.

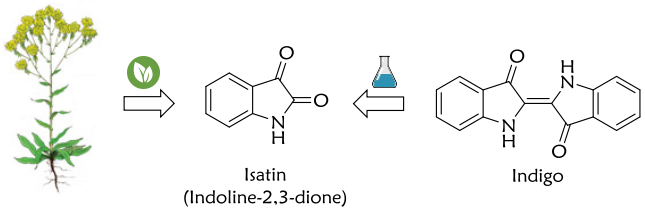


Figure 1. Isatin structure and its production from renewable source and synthetic production.

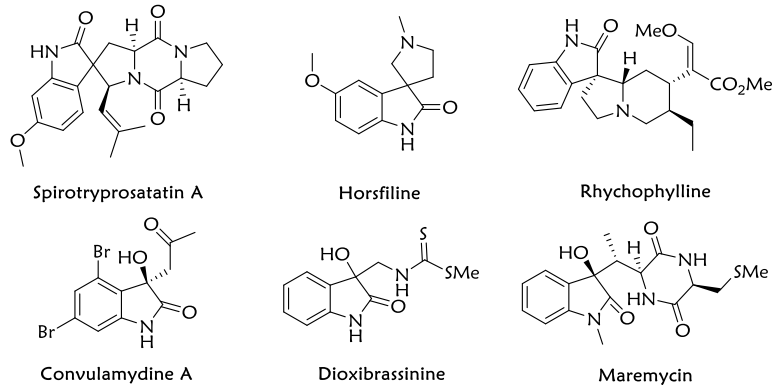
The most fascinating application of isatins in organic synthesis is undoubtedly due to the highly reactive C-3 carbonyl group that is a prostereogenic center as well. The reactions of the C-3 carbonyl group of isatins, mostly by nucleophilic additions or spiroannulation, transform it into 2-oxindole derivatives. These compounds, especially those which are spiro-fused to other cyclic frameworks, have drawn tremendous interest of researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide. In fact, they occur in many natural products such as spirotryprostatins, horsfiline, rhynchophylline, and elacomine, etc. and have been reported to have various types of bioactivity,[7] such as progesterone receptor modulation,[8] anti-HIV,[9] anticancer,[10] antitubercular,[11] antimalarial,[12] and MDM2 inhibition (Figure 2).[13]

The architecture of a spiro-cyclic framework has always been a challenging endeavour 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.

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.

Natural Products:



Bioactive Compounds:

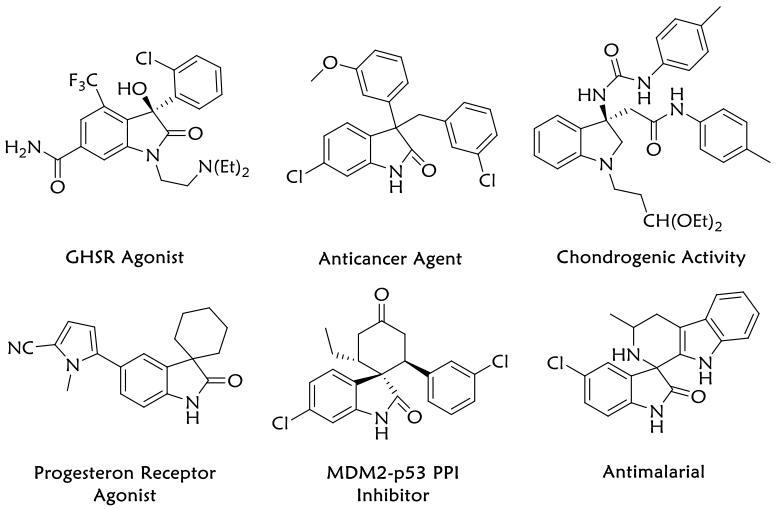


Figure 2. Selected example of natural products and bioactive compounds containing 3,3-disubstituted or spiro-fused oxindole moiety.

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.

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. The landmark achievements in the area of phytochemistry, combined with discovery of potential anticancer activity in some synthetic analogues of horsfiline, gave impetus to studies aimed toward the synthesis of spiro-cyclic oxindoles employing isatins as starting materials.

Most of these studies were, however, focused on development of appropriate methodologies for the synthesis of natural products and only in few cases non-natural spirocyclic compounds were faced. With further development in the area of medicinal chemistry and with the achievement that only a particular isomer was bioactive in many cases, researchers were encouraged to develop stereoselective methodologies. Furthermore, the biological evaluation of structure's analogues and synthetic precursors of such biological active compounds, sometimes found even more active, required an extensive investigation of new synthetic methodologies, also favoring the development of asymmetric versions.

With the strong demand for new compounds, it appeared obvious that a traditional *step-by-step* synthesis was not sufficient to provide a large number of compounds in a brief period. For this reason, in the early 1990s, with the advent of combinatorial chemistry and diversity oriented synthesis (DOS), new convergent synthetic strategies have been developed, as the multicomponent reactions (MCRs).[14]

MCRs use three or more reactants in one vessel under a set of fixed conditions, to provide products that contain a structure or substructure of all reactants. With respect to a traditional linear synthesis, these reactions offer different advantages as a higher overall yield and atom-economy, a reduction of synthetic and purification steps allowing to obtain the desired product in shorter times (Figure 3). This type of reactions is uniquely powerful in accessing products of high complexity and diversity from simple starting materials with easy operation. These important advantages made it an important tool in organic chemistry for the synthesis of functional molecular libraries[15] and natural products'[16] families. The use of MCRs for the preparation of diverse libraries carries the potential liability of having one core structure that is over-represented within a collection. The diversity of a library of MCR products is, on some level, limited by the

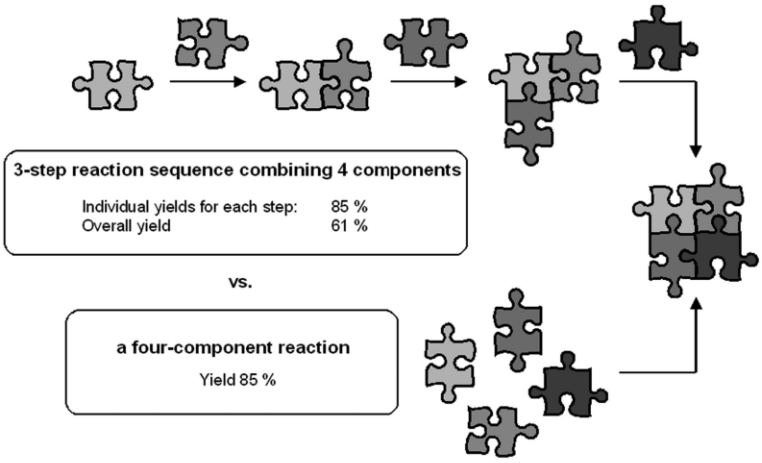


Figure 3. Comparison between a stepwise linear synthesis and multicomponent reaction (*Ref. 14a*).

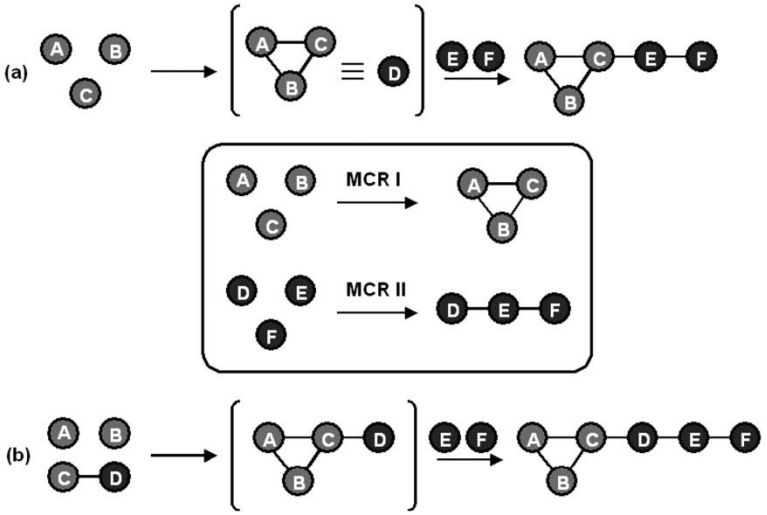


Figure 4. Unification of MCRs. Schematic representation of unifying two MCRs via (a) intermediate generation for a successive MCR, or (b) combination of MCRs with orthogonal functionalities (*Ref. 14a*).

structure of the appendages that emanate from the components. This liability is addressed by new variants of traditional MCRs that result in fundamentally different structures. Furthermore, the use of MCRs as a starting point for subsequent reactions that define the core connectivity of the components is a powerful approach to achieving further efficiency and diversity (Figure 4).

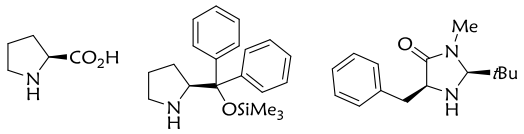
The pursuit of MCR products as biological probes, drug candidates and as synthetic intermediates has resulted in an intensified effort to find catalysts for MCRs. MCRs are striking in their ability to resist catalysis, as exemplified by the fact that more than a century elapsed between the discovery of the Hantzsch[17] and Biginelli[18] MCRs and their first catalysed versions.[19,20]

If the catalysed MCRs is an underdeveloped branch in catalysis field, asymmetric MCRs are even more rare,[21] and one of the reasons is the low compatibility of well-known metal-based catalysts with typical MCR experimental conditions. MCRs often proceed *via* imine intermediates, formed from condensation of carbonyls and amines. This results in the concomitant generation of water that deactivates some Lewis acid catalysts and ends the reaction prematurely. Thus, to catalyse a MCR, catalysts are mostly required to be water-moisture compatible.

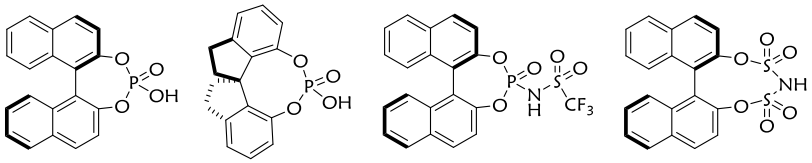
With the advent of organocatalysis in the last decade, an attractive tool was introduced in the organic chemistry's field.[22] The term 'organocatalysis' was coined in 2000 by MacMillan[23] and it is defined as the employment of organic molecules with low molecular weight as catalysts in organic reactions. In the case of asymmetric transformations, chiral organocatalysts usually activate the electrophile or the nucleophile (or both in the case of bifunctional catalysis) creating an asymmetric environment that drives the stereochemistry of the product (Figure 5).

This type of catalysis offers multiple advantages compared with metal-based and enzymatic catalysis: in general, organocatalysts are non-toxic and robust compounds, and a large number of them are commercially available and/or easily synthesized. Moreover, they are usually stable under aerobic conditions, and reactions do not require extremely dry conditions, and thus, inert-equipment such as vacuum lines or gloveboxes are not necessary. Frequently, the reactions are conducted under mild conditions and in high concentrations avoiding the use of large amounts of solvents and minimizing waste.

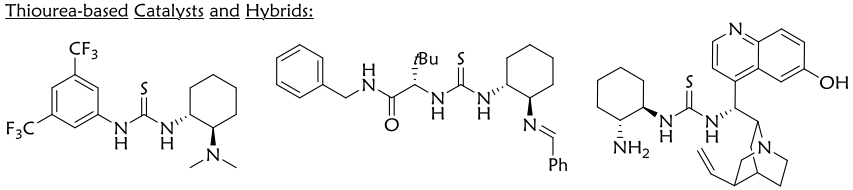
Proline-based Catalyst and McMillan catalyst:



BINOL-Phosphoric Acids and new Derivatives:



Thiourea-based Catalysts and Hybrids:



Cinchona-based Catalyst

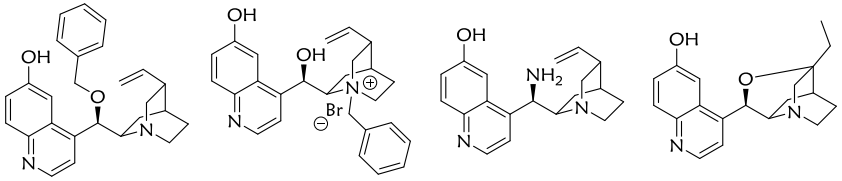


Figure 5. Selected examples of principal classes of organocatalysts.

Furthermore, organocatalysts are tolerant of numerous functional groups and avoid time-consuming and protecting-group manipulations.

Considering all these advantages, the organocatalysis field has grown exponentially from a handful of publications in 2001 to more than 2500 in 2015, and in parallel, the number of citations has also increased up.

In particular, during the ''golden-age''[24] and the ''gold-rush''[25] of organocatalysis, many researchers from academia and chemical industry were involved in this

field, with most of the efforts focused on the development of new reactivities and asymmetric methodologies.

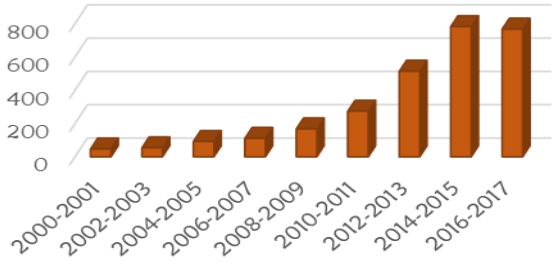
Currently, asymmetric organocatalysis is recognized as an independent synthetic toolbox besides asymmetric metal-based catalysis and bio-enzymatic catalysis for the synthesis of chiral organic molecules, and its application to MCRs has emerged quite recently as a robust synthetic tool. Major examples of these combined approaches were reported by Terada[26] and Akiyama[27] that established chiral Brønsted acid BINOL-based phosphoric acid as a privileged class of organocatalysts for asymmetric MCRs to access optically pure nitrogenous heterocycles in structural diversity.

Concluding with an overview on last years' literature, oxindoles have been increasingly investigated as privileged targets in medicinal chemistry (Graph 1a). Instead, MCRs can be considered a sort of 'evergreen' field since from the early 1990s. However, the number of publications on this topic are in continuous increment, demonstrating the great interest for this synthetic tool capable of creating great diversity in the chemical space (Graph 1b).

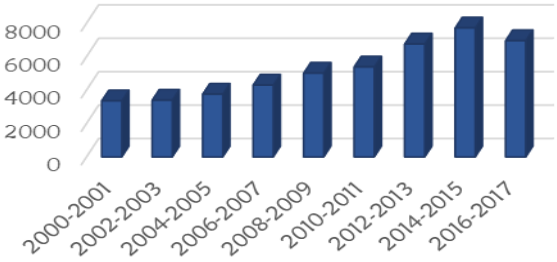
Since 2000, organocatalysis became an important emerging field (Graph 1c). Organocatalysts reported in the last decade fully demonstrate their suitability for the replacement of more classical metal-based catalysts in many different reactions.

As a natural consequence of above considerations, the idea of combining organocatalysis and MCRs appears as a valuable strategy for the efficient preparation of oxindole-based libraries, sharing isatin-derived ketimines as common starting materials.

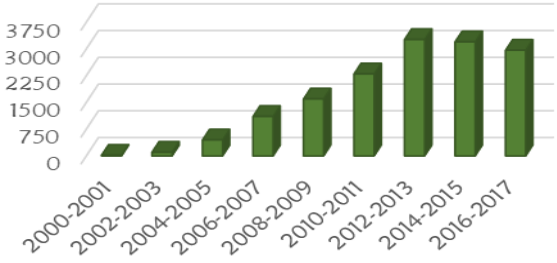
a) Oxindole



b) Multicomponent



c) Organocatalysis



Graph 1. Number of publications per year containing the term (a) 'oxindole' in orange, (b) 'multicomponent' in blue, (c) 'organocatalysis' in green searched on SciFinder®.[28]

References

1. Erdmann, O.L. J.; *Prakt. Chem.* **1840**, *19*, 321-362.

2. Laurent, A.; *Ann. Chim. Phys.* **1840**, *3*,393-434.

3. (a) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J. *Braz. Chem. Soc.* **2001**, *12*, 273. (b) Bergman, J.; Lindstrom, J, O.; Tilstam, U.; *Tetrahedron* **1988**, *41*, 2879.

4. Wei, L.; Wang, Q.; Liu, X.; *Yaowu Fenxi Zazhi*, **1982**, *2*, CA 98:95726b.

5. (a) Chiyanzu, I.; Hansell, E.; Gut, J.; Rosenthal, P. J.; McKerrowb, J. H.; Chibale, K.; *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3527. (b) Almeida, M. R.; Leitão, G. G.; Silva, B. V.; Barbosa, J. P.; Pinto, A. C.; *J. Braz. Chem. Soc.* **2010**, *21*, 764.

6. Kekule, A.; *Chem. Ber.* **1869**, *2*, 748.

7. Badillo, J. J.; Hanhan, N. V.; Franz, A. K.; *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758.

8. 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.; Slayeden, O. D.; Yudt, M.; Zhang, J.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E.; *J. Med. Chem.* **2008**, *51*, 1861.

9. Kumari, G.; Nutan; Modi, M.; Gupta, S. K.; Singh, R. K.; *Eur. J. Med. Chem.* **2011**, *46*, 1181.

10. (a) Lo, M. M.-C.; Newmann, C. S.; Nagayams, S.; Perlstein, E. O.; Schreiber, S. L.; *J. Am. Chem. Soc.* **2005**, *127*, 10130. (b) 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.

11. (a) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hubel, K.; Rauth, D.; Waldmann, H.; *Angew. Chem., Int. Ed.* **2010**, *49*, 5902. (b) 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.

12. (a) 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. (b) 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**. (c) Liu, J.-J.; Zhang, Z. (Hoffmann La Roche AG) *PCT Int. Appl.* WO 2008/055812, **2008**.

13. 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.

14. For an overview see: (a) Brauch, S.; van Berkela, S. S.; Westermann, B.; *Chem. Soc. Rev.* **2013**, *42*, 4948. (b) Zhu, J.; Bienayme´, H.; Multicomponent Reactions, *Wiley-VCH*, Weinheim, **2005**. (c) de Graaff, C.; Ruijter E.; Orru, R. V. A.; *Chem. Soc. Rev.* **2012**, *41*, 3969–4009. Biggs-Houck, J.; Younai, A.; Shaw, J.T.; *Curr. Opin. Chem. Biol.* **2010**, *14,* 371–382.

15. Domling, A.; *Chem. Rev.* **2006**, *106*, 17–89.

16. (a) Laurent, A.; Gerhardt, C.F.; *Ann. Chem. Phys.* **1838**, *66*, 281. (b) Liebigs *Ann. Chem.* **1838**, *28*, 265.

17. Hantzsch, A.; *Ber.* **1890**, *23*, 1474.

18. Biginelli, P.; *Ber. Dtsch. Chem. Ges.*, **1891**, *24*, 1317–1319.

19. (a) Wang L.M.; Sheng. J.; Zhang, L.; Han J.W.; Fan, Z.Y.; Tian, H.; Qian, C.T.; *Tetrahedron* **2005**, *61*, 1539-1543. (b) Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B.; *Synlett* **2008**, 509-512. (c) Kumar, A.; Maurya, R.A.; *Tetrahedron* **2007**, *63*, 1946-1952. Evans, C.G.; Gestwicki, J.E.; *Org. Lett.* **2009**, *11*, 2957-2959.

20. (a) Ma, Y.; Qian, C.; Wang, L.; Yang, M.; *J. Org. Chem.* **2000**, *65*, 3864-3868. (b) Huang. Y.; Yang, F.; Zhu, C.; *J. Am. Chem. Soc.* **2005**, *127*, 16386-16387. (c) Li, N.; Chen, X.H.; Song, J.; Luo, S.W.; Fan, W.; Gong, L.Z.; *J. Am. Chem. Soc.* **2009**, *131*, 15301-15310. (d) Chen, X.H.; Xu, X.Y.; Liu, H.; Cun, L.F.; Gong, L.Z.; *J. Am. Chem. Soc.* **2006**, *128*, 14802-14803. (e) Xin, J.; Chang, L.; Hou, Z.; Shang, D.; Liu, X.; Feng, X.; *Chem. Eur. J.* **2008**, *14*, 3177-3181.

21. For an overview see: Yu, J.; Shi, F.; Gong, L.Z.; *Acc. Chem. Res.*, **2011**, *44*, 1156–1171.

22. For an overview see: (a) MacMillan, D.W.C; *Nature*, **2008**, 455. (b) Alema, J.; Cabrera, S.; *Chem. Soc. Rev.* **2013**, *42*, 774.

23. (a) Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C; *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. (b) Bertelsen, S.; Jørgensen, K.A.; *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

24. Dalko, P.I.; Moisan, L.; *Angew. Chem., Int. Ed.*, **2004**, *43*, 5138–5175.

25. Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G.; *Angew. Chem., Int. Ed.*, **2008**, *47*, 6138–6171.

26. Terada, M.; *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

27. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K.; *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568.

28. These data were found searching on SciFinder® entering respectively 'oxindole', 'multicomponent' and 'organocatalysis' as research field and refining the results for each year.

II. 3-Aminooxindole Butenolides: Vinylogous Mannich-type Reactions

A family of chiral quaternary 3-aminooxindole butenolides have been synthesized, by BINOL-derived phosphoric acid-catalyzed addition of trimethylsiloxyfuran to isatin-derived ketimines. Such vinylogous Mannich-type reaction was found to produce the diastereoisomeric butenolides in good yields and in most cases high enantiomeric excesses. The configurational assignment of the obtained products was safely performed by chemical correlation. A computational study of the transition state allowed to rationalize the obtained stereochemical outcome, highlighting the possible binding modes of the catalyst-imine-nucleophile transition complex.

Published in *Org. Biomol. Chem.* **2016**, *14*, 7768-7776.

II.1 Introduction

Optically active δ-amino-α,β-unsaturated carbonyl compounds, particularly those bearing the γ-butenolide skeleton, are receiving considerable attention due to their broad application in the synthesis of biologically active compounds. The butenolide ring is in fact one of the most ubiquitous structures found in natural products and its incorporation into more complex heterocyclic architectures has continuously attracted the attention from a pharmaceutical point of view (Figure 1).[1]

The vinylogous Mannich-type reaction of imines with a dienolate equivalent, such as trimethylsiloxyfuran (TMSOF), is a useful mean to prepare γ–butenolide derivatives bearing an amine functionality.[2] Metal complexes and organocatalysts efficiently promote asymmetric vinylogous Mannich (AVM) reactions of aldimines, affording optically active δ-amino-α,β-unsaturated carbonyl compounds in high yields and enantiomeric excesses. With regard to catalytic methods, a milestone was placed in 2006 by Hoveyda,[3,4] who reported the first highly diastereo- and enantioselective protocol for such reaction. The AVM was catalyzed by a silver salt and an easily accessible chiral phosphine, and only

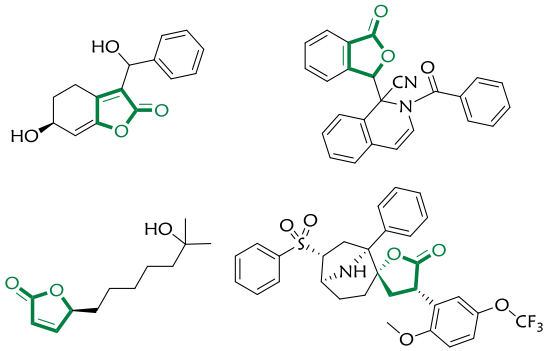
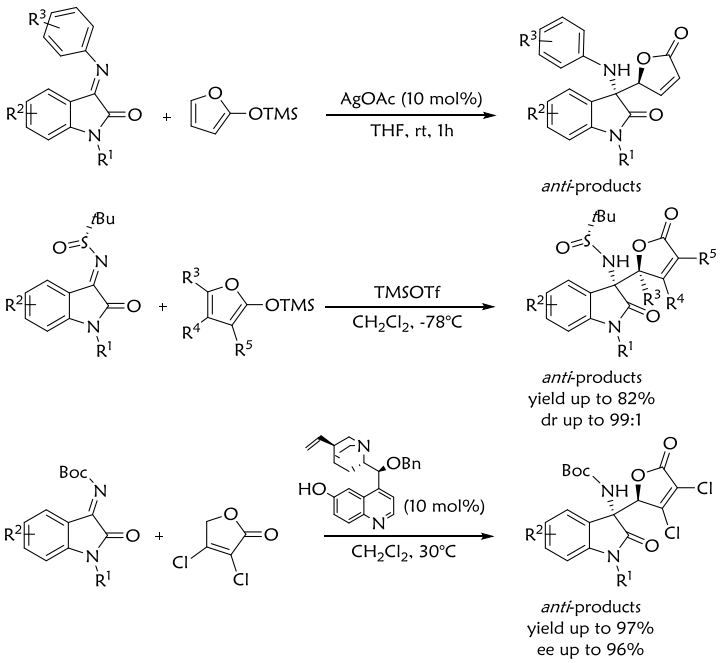


Figure 1. Examples of products containing the butenolide moiety.

aromatic aldimines were employed. More recently, a new Ag(I)-monophosphine complex was developed by Xu, displaying wide aldimine versatility, excellent yield and diastereoselectivity, and moderate enantioselectivity.[5] Among organocatalytic, metal-free methods, an iodine-substituted chiral phosphoric acid was demonstrated by Akiyama to efficiently catalysed the AVM of aliphatic as well as aromatic aldimines.[6]

Application of the vinylogous Mannich-type reaction to ketimines is more challenging, due to the lower reactivity of ketimines compared with aldimines and to the steric challenge inherent in the stereocontrolled formation of a quaternary stereocenter consecutive with a bulky tertiary one. To date, there are only few reports on the AVM of TMSOF with ketimines, to give chiral δ-amino-α,β-unsaturated carbonyl compounds having a quaternary carbon center. Besides the successful Ag-catalyzed process, applied by Hoveyda[7] also to α-ketimine esters, relevant is the contribution from Nakamura,[8] who reported a Cinchona alkaloid amide/copper (II) catalyzed diastereo- and enantioselective Mannich reaction of ketimines. Quite recently, the closely related Cinchona alkaloid amide/zinc (II) system was also developed by the same author,[9] and applied to the similar Mannich reaction employing γ-butenolide instead of TMSOF as nucleophile. Given the relevance of chiral δ-amino-α,β-unsaturated carbonyl compounds having a quaternary carbon center, the development of novel stereoselective methods for the construction of this attractive framework in an asymmetric manner is highly desirable.

As part of our interest in the asymmetric synthesis of 3,3-disubstituted oxindole derivatives and related spiro-compounds,[10] we recently turned our attention to BINOL-derived phosphoric acids that recently emerged as a new class of



Scheme 1. Previous works of AVM on isatin-derived imines.

environmentally benign chiral catalysts for different enantioselective reactions.[11] Herein, our ongoing interest was extended to the asymmetric preparation of quaternary 3-aminooxindole butenolides, which can be considered an intriguing combination of pharmacologically interesting γ-butenolide and oxindole motifs. A racemic preparation of such compounds in excellent yields and diastereoselectivities was realized by Deng,[12] employing AgOAc as the catalyst. A highly practical, sulfinyl amine chiral auxiliary-based approach was also recently developed,[13] based on a simple Lewis acid mediated diastereoselective vinylogous Mannich process (Scheme 1).

At the best of our knowledge, no organocatalytic methods employing TMSOF have been reported for the preparation of such scaffolds. Only a related AVM

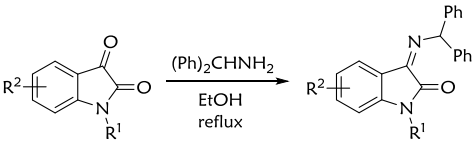
was recently realized, based on a bifunctional quinidine-derived catalyst and 3,4-dichlorofuran-2(5*H*)-one as the nucleophile.[14]

Herein, we report the BINOL-derived phosphoric acid-catalyzed asymmetric synthesis of quaternary 3-aminooxindole butenolides *via* a vinylogous Mannich-type reaction, consisting in the enantioselective addition of TMSOF to isatin-derived ketimines.

II.2 Results and Discussion

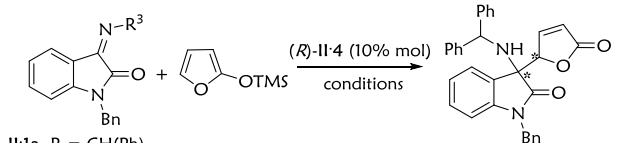
We began our investigation using *N*-diphenylmethyl ketimine **II·1a**, obtained as the only product in the reaction between *C*,*C*-diphenyl-methanamine and *N*-benzyl-isatin (Scheme 2), and two well-known isatin-derived ketimines, **II·2** and **II·3**.

Reaction of **II·1a**, **II·2** and **II·3** with TMSOF, initially carried out at room temperature, using THF as the solvent and 10 mol % of catalyst **II·4a**, proved to be completely ineffective. Reasoning that the addition of a protic co-solvent to the reaction mixture could be essential for the onset of the catalytic cycle, we repeated the reaction by adding MeOH (1% vol). In such conditions, all three ketimines proved to be reactive, affording the corresponding 3-aminooxindole butenolides with variable yields, up to 84% (Table 1, entries 1-3).



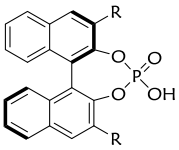
Scheme 2. Synthesis of isatin-based *N*-benzydryl ketimines **II·1**.

Table 1. Optimization of the asymmetric AVM reaction.[a]

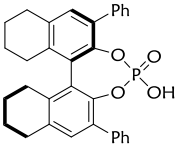


II·1a R = $CH(Ph)_2$
II·2 R = *p*-MeO-C_6H_4
II·3 R = Boc

II·5a,b (from II·1a)



(*R*)-II·4a: R = Ph;
(*R*)-II·4b: R = 4-Ph-C_6H_4;
(*R*)-II·4c: R = 9-Anthracenyl;
(*R*)-II·4d: R = 2,5,6-(*i*Pr)$_3$-C_6H_2;
(*R*)-II·4e: R = $SiPh_3$.



(*R*)-II·4f

Entry	Catalyst	T [°C], time	Yield (%)[b]	*dr*[c]	*ee* (%)[d]	
					II·5a	II·5b
1	II·4a	rt, 10min	84	75:25	0	25
2[e]	II·4a	rt, 20min	60	61:39	2	10
3[f]	II·4a	rt, 8h	15	51:49	5	7
4	II·4a	0 °C, 40min	87	69:31	1	31
5	II·4a	-20 °C, 1h	85	57:43	47	69
6	**II·4a**	**-40 °C, 7h**	**80**	**52:48**	**90**	**92**
7	II·4a	-78 °C, 48h	68	51:49	90	92
8[g]	II·4a	-40 °C, 48h	35	53:47	89	93
9[h]	II·4a	-40 °C, 48h	27	55:45	90	93
10	II·4b	-40 °C 48h	50	57:43	57	66
11	II·4c	-40 °C, 48h	nr	-	-	-
12	II·4d	-40 °C, 48h	nr	-	-	-
13	II·4e	-40 °C, 48h	nr	-	-	-
14	II·4f	-40 °C, 48h	41	50:50	67	78

[a] Reaction conditions: ketimine **II·1a-3** (0.12 mmol), TMSOF (0.14 mmol) in solvent (1.2 mL); MeOH was used as additive (1% vol). [b] Isolated yield. [c] **II·5a**:**II·5b** determined by ^{1}H NMR from integration of olefinic protons. [d] Determined by chiral HPLC analysis. [e] Ketimine **II·2** was used. [f] Ketimine **II·3** was used. [g] Toluene was used as solvent. [h] Dichloromethane was used as solvent. nr = no reaction.

We assumed that probably the protic co-solvent suppresses the undesired retroaddition reaction by rapidly converting the silylated butenolide ring into the final product, while also enabling the isolation of the adduct formed under conditions of kinetic control.[15] In addition, we can also suppose that, in absence of a protic source, the catalytic BINOL-derived phosphoric acid might be converted to the corresponding *O*-silylated BINOL-phosphate, evidently not able to promote the AVM reaction as the phosphoric acid form.[16]

Ketimine **II·1a**, performing best, was then chosen for subsequent conditions and catalyst screening, also in the light of

the potential greater versatility of the obtained products, due to the easy removal of the benzhydryl protective group. The temperature proved to be a key parameter for the asymmetric induction of this reaction. At room temperature (entry 1), the reaction proceeds to give **II·5** as a 75:25 mixture of the **II·5a** and **II·5b** diastereoisomers, each of which with a negligible enantiomeric excess. Upon lowering the reaction temperature (entries 4-7), we noticed a substantial maintenance of the obtained yields, with a collapse of diastereoselectivity (Figure 2) and an overall improvement of the enantioselectivity for both **II·5a** and **II·5b** diastereoisomers. In particular, carrying out the reaction at -40 °C, both diastereoisomers could be recovered in almost equal quantities (80% overall yield, **II·5a**: **II·5b** 52:48), showing excellent enantioselectivities (ee **II·5a** 90%, ee **II·5b** 92%).

Changing the solvent to toluene (entry 8) or dichloromethane (entry 9) entailed a significant negative effect on the chemical conversion, demonstrating that the originally chosen THF was the optimal solvent for this reaction. Screening of more hindered catalysts **II·4b-e**, aimed to evaluate the impact of the 3,3'-

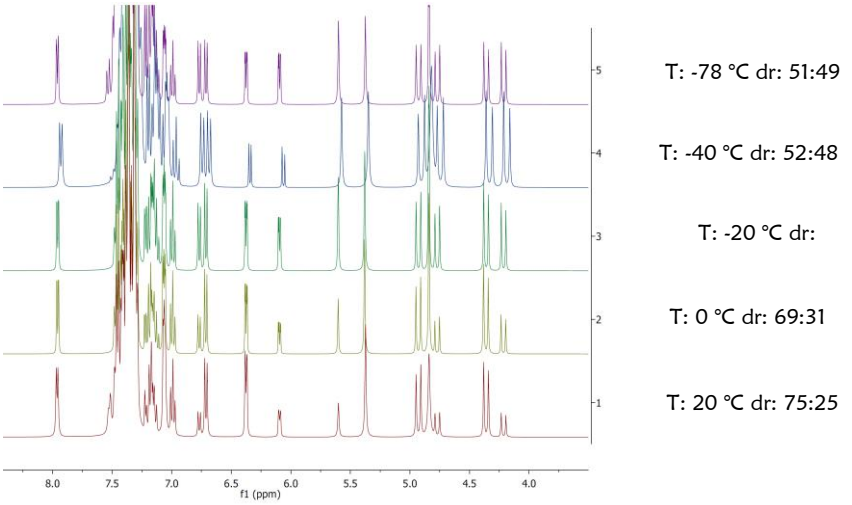


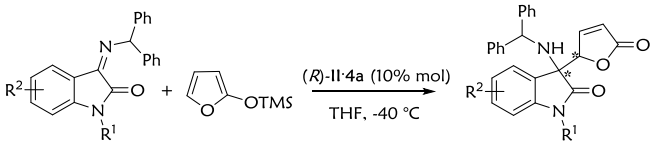
Figure 2. ^{1}H NMR spectra (400MHz, $CDCl_3$) of compound **II·5a,b** performing the reaction at different temperature.

substitution, and of octahydro-BINOL-based **II·4f** was performed (entries 10-14). Increasing the size of the 3,3'-substitents on the phosphoric acid proved detrimental for the chemical conversion, with only catalysts **II·4b** and **II·4f** able to produce product **II·5**, with maintenance of the same level of diastereo- and lower enantioselectivity with respect to catalyst **II·4a**, and in definitely decreased yields.

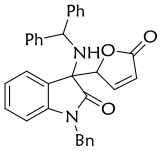
After having established **II·4a** as the catalyst of choice and to work in THF at -40 °C as the optimal conditions, the substrate scope of the AVM reaction was surveyed, by evaluating differently *N*-substituted isatins and the presence of substituents at 5- or 6-position of the isatin nucleus (Scheme 3).

In general, all isatins readily undergo this reaction, to afford the desired products **II·5-13** in moderate to high yields, with a good degree of enantioselectivity (entries 1-5). The presence of a halogen substituent on the oxindole (entries 6-9) results in a lower yield and enantiomeric excess, with a slight increase of

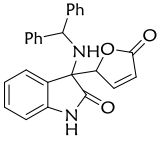
Scheme 3. Substrate scope of the asymmetric AVM reaction catalysed by **II·4a**.[a]



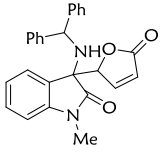
II·1a-i — II·5-13a,b



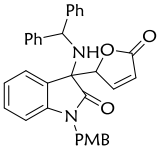
II·5a,b (80%)
dr a:b, 52:48
ee_a 90%
ee_b 92%



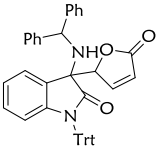
II·6a,b (78%)
dr a:b, 63:37
ee_a 80%
ee_b 88%



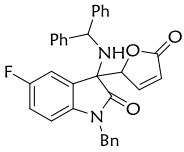
II·7a,b (81%)
dr a:b, 55:45
ee_a 91%
ee_b 68%



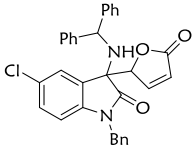
II·8a,b (79%)
dr a:b, 55:45
ee_a 84%
ee_b 89%



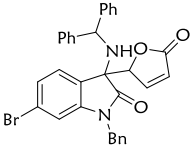
II·9a,b (81%)
dr a:b, 47:53
ee_a 4%
ee_b 96%



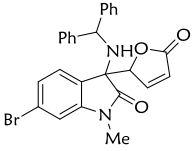
II·10a,b (45%)
dr a:b, 72:28
ee_a 1%
ee_b 15%



II·11a,b (42%)
dr a:b, 70:30
ee_a 26%
ee_b 74%



II·12a,b (65%)
dr a:b, 70:30
ee_a 31%
ee_b 42%



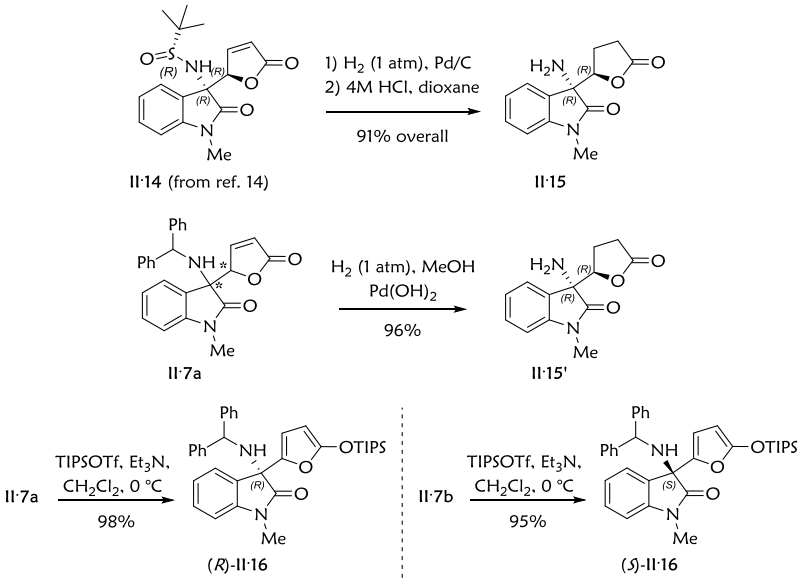
II·13a,b (68%)
dr a:b, 62:38
ee_a 32%
ee_b 31%

[a] Reaction conditions: ketimine **II·1a-i** (0.12 mmol), TMSOF (0.14 mmol), catalyst (*R*)-**II·4a** (0.012 mmol) in THF (1.2 mL) at -40 °C using MeOH as additive (1% vol). Isolated yields are reported. *dr* determined by ^{1}H NMR from integration of olefinic protons; for both relative and absolute configurational assignment of diastereoisomeric products, see below. *ee* was determined by chiral HPLC analysis. PMB = *p*-Methoxy benzyl. Trt = trityl.

diastereoselectivity. Since diastereoisomers **II·7a** and **II·7b** (entry 3) proved to be readily separable by flash chromatography, we selected them for the determination of absolute and relative stereochemistry. However, neither of them proved to be suitable for X-ray analysis. Thus, starting from the major **II·7a**, we performed a chemical correlation based on the literature compound **II·14**, as depicted in Scheme 4. From NMR and $[\alpha]_D$ comparison of compound **II·15**, derived from **II·14**, and compound **II·15'**, derived from **II·7a**, the (*R*,*R*) *anti* configuration could be safely assigned to **II·7a**.

For the configurational assignment of minor diastereoisomer **II·7b**, still we relied on a chemical correlation, performing on both **II·7a** and **II·7b** the same reaction to give the silyl enol ether derivative **II·16**. Since **II·16** was obtained as opposite

Scheme 4. Chemical correlations for the configurational assignment of **II·7a** and **II·7b**.



enantiomer starting from **II·7a** and **II·7b**, we could assign the (*S*,*R*) *syn* configuration to **II·7b**.

In order to propose a possible explanation of the stereochemical outcome, a preliminary investigation of the transition state organization was performed by means of computational tools. The theoretical study of this reaction is complicated by a number of factors, namely, the size of the system, the possible approach *endo* or *exo* of the nucleophile, with respect to both the *re* and *si* face of the imine and the several competing H-bonding possibilities in the assembly of the transition state. We were aware that also the *E*/*Z* geometry of the imine might play an important role in the enantioselection. However, since NMR analysis of starting imine **II·1c** showed the presence of a major isomer (9:1) and theoretical DFT calculations indicated the *Z*-**II·1c** imine more stable than the corresponding *E* isomer by 4.38 kcal/mol, we decided to consider only the *Z* geometry in our further studies.

In accordance with the enantioselectivity of the reaction, in the proposed model[17] the major enantiomer (3*R*,2'*R*)-**II·7a** is achieved through **TS-A**, whereas **TS-C** would lead to the diastereoisomeric (3*S*,2'*R*)-**II·7b**. To support this hypothesis, we calculated the energy for **TS-C** and **TS-D** at the B3LYP/6-31G(d) level.[18] **TS-C** resulted to be lower in energy for 0.6 kcal/mol at -40 °C, with respect to **TS-D**, in agreement with the measured 68% ee. In such favored **TS-C**, the 2-hydroxyfuran is coordinated to the catalyst **II·4a** through the OH hydrogen and it prefers to assume the *endo* orientation with respect to the imine as the third component (the opposite *exo* orientation is present in **TS-D**). The same considerations apply to **TS-A** (favored) and **TS-B** (Figure 3).

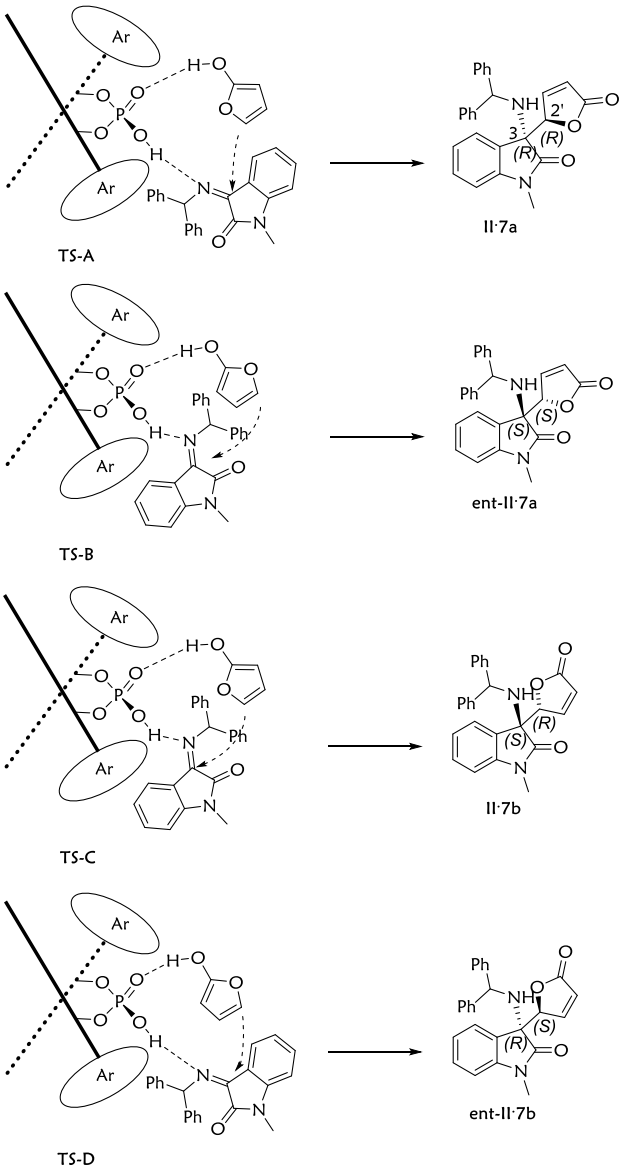


Figure 3. Possible binding modes of the catalyst **II·4a** - 2-hydroxyfuran - imine **II·1c** transition complex.

The orientation of the imine is less significant, probably due to the great steric hindrance around both faces of the imine double bond.

II.3 Conclusions

In summary, an organocatalytic approach for the asymmetric synthesis of quaternary 3-aminooxindole butenolides has been developed. The method exploits the vinylogous Mannich reaction of TMSOF with various isatin-derived benzhydryl-ketimines, affording diastereoisomeric products in good yields and in most cases high enantiomeric excesses.

The obtained products, containing a quaternary stereocenter consecutive with a bulky tertiary one, are suitable for further transformations, as demonstrated in the performed chemical correlation study. The stereochemical outcome was also rationalized by means of a computational study, which allowed to propose the most favoured binding modes of reaction components in the transition state.

II.4 Experimental section

All commercial materials (Aldrich, Fluka) were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with ninhydrin solution in ethanol. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source. Chiral HPLC analysis was performed on Jasco PU-2080 (UV Detector and binary HPLC pump) at 254 nm. Chiralcel ODH and AD columns were purchased from Daicel Chemical Industries®. Optical rotator power $[\alpha]^{T}_{D}$ was measured with a Jasco P-1030 polarimeter, endowed with a cell of 1 dm pathlength and 1 mL capacity. The light used has a wavelength of 589 nm (Sodium D line). All the *N*-substituted isatins[20] and BINOL-derived phosphoric acids[21] were synthetized according to reported literature.

General procedure A (GP-A) for the synthesis of isatins-derived benzhydryl imines II·1a-i. To a suspension of appropriate substituted isatin (1.5 mmol) in absolute EtOH (5 mL), under a nitrogen atmosphere, benzhydryl amine (1.5 mmol) was

added in one portion and the mixture was refluxed for 24 hours. The reaction was cooled to room temperature and stirred for 2 hours.

3-(Benzhydrylimino)-1-benzylindolin-2-one (II·1a). Prepared according to GP-A using 1-benzyl isatin. The desired product was collected by filtration; yield: 494 mg, 82%; yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$, 9:1 mixture of imine isomers) δ 7.87 (s, 0.9H), 7.77 (d, *J* = 7.5 Hz, 0.9H), 7.61-7.46 (m, 4H), 7.45-7.14 (m, 12.1H), 7.05 (t, *J* = 7.5 Hz, 0.9H), 6.98 (t, *J* = 7.5 Hz, 0.1H), 6.75 (d, *J* = 7.8 Hz, 0.1H), 6.66 (d, *J* = 7.8 Hz, 0.9H), 6.56 (s, 0.1H), 4.97 (s, 0.2H), 4.89 (s, 1.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 151.8, 144.6 and 143.0 (1C), 144.2 (2C), 135.3, 133.3 and 132.7 (1C), 128.9-127.1 (15C), 123.2, 122.9 and 122.5 (1C), 122.0, 110.3 and 109.3 (1C), 69.9 and 65.5 (1C), 43.9 and 43.5 (1C); HRMS (ESI) calcd for $C_{28}H_{22}N_2NaO^+$ [MNa]$^+$ 425.1624, found 425.1632.

3-(Benzhydrylimino)indolin-2-one (II·1b). Prepared according to GP-A using isatin. The desired product was collected by filtration; yield: 407 mg, 87%; yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$, 4:1 mixture of imine isomers) δ 8.83 (m, br, 0.2H), 7.98 (m, br, 0.8H), 7.83-7.69 (m, 2H), 7.52 (d, br, *J* = 7.8 Hz, 3.2H), 7.46 (d, br, *J* = 7.7 Hz, 0.8H), 7.38-7.13 (m, 7H), 7.06 (t, *J* = 7.5 Hz, 0.8H), 7.00 (t, *J* = 7.5 Hz, 0.2H), 6.92 (d, *J* = 7.6 Hz, 0.2H), 6.78 (d, *J* = 7.6 Hz, 0.8H), 6.53 (s, br, 0.2H); ^{13}C NMR (75 MHz, CD_2Cl_2+1%DMSO-*d*$_6$) δ 160.9, 153.6, 144.8 (2C), 143.8, 133.8 and 133.2 (1C), 128.9-127.2 (10C), 122.8, 122.7, 122.5, 111.8 and 110.8 (1C), 69.9 and 65.1 (1C); HRMS (ESI) calcd for $C_{21}H_{16}N_2NaO^+$ [MNa]$^+$ 335.1155, found 335.1144.

3-(Benzhydrylimino)-1-methylindolin-2-one (II·1c). Prepared according to GP-A using 1-methyl isatin. The desired product was collected by filtration; yield: 367 mg, 75%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 9:1 mixture of imine

isomers) δ 7.83 (*s*, 0.9H), 7.78 (d, br, *J* = 7.5 Hz, 0.9H), 7.76 (d, br, *J* = 7.5 Hz, 0.1H), 7.57 (d, br, *J* = 7.7 Hz, 3.6H), 7.52 (d, br, *J* = 7.8 Hz, 0.4H), 7.47 (dt, *J* = 7.8 and 1.5 Hz, 0.9H), 7.46 (dt, *J* = 7.7 and 1.5 Hz, 0.1H), 7.41-7.24 (m, 6H), 7.16 (dt, *J* = 7.6, 1.0 Hz, 0.9H), 7.06 (dt, *J* = 7.8, 1.0 Hz, 0.1H), 6.92 (d, br, *J* = 7.8 Hz, 0.1H), 6.86 (d, br, *J* = 7.8 Hz, 0.9H), 6.57 (*s*, 0.1H), 3.27 (*s*, 0.3H), 3.22 (*s*, 2.7H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.9, 152.3, 145.7 and 143.3 (1C), 144.4 (2C), 133.5 and 132.9 (1C), 128.6-127.3 (10C), 122.9, 122.5, 121.7, 109.2 and 108.4 (1C), 69.7 and 65.4 (1C), 26.0 and 25.5 (1C); HRMS (ESI) calcd for $C_{22}H_{18}N_2NaO^+$ $[MNa]^+$ 349.1311, found 349.1322.

3-(Benzhydrylimino)-1-(4-methoxybenzyl)indolin-2-one (II·1d). Prepared according to GP-A using 1-4-methoxybenzyl isatin. The desired product was collected by filtration; yield: 486 mg, 75%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 9:1 mixture of imine isomers) δ 7.88 (*s*, br, 0.9H), 7.79 (d, br, *J* = 7.6 Hz, 0.9H), 7.76 (d, br, *J* = 7.7 Hz, 0.1H), 7.59 (d, br, *J* = 7.4 Hz, 3.6H), 7.54 (d, br, *J* = 7.4 Hz, 0.4H), 7.44-7.23 (m, 9H), 7.12 (t, *J* = 7.6, 0.9H), 7.03 (t, *J* = 7.7, 0.1H), 6.88 (d, br, *J* = 8.0, 2H), 6.84 (d, br, *J* = 7.8, 0.1H), 6.78 (d, br, *J* = 7.8, 0.9H), 6.57 (*s*, br, 0.1H), 4.93 (*s*, 0.2H), 4.87 (*s*, 1.8H), 3.80 (*s*, 3H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.9, 159.4, 152.9, 145.5, 145.0 (2C), 144.0, 134.0 and 133.4 (1C), 129.4-127.6 (12C), 123.7 and 123.3 (1C), 122.6, 122.7, 114.8 (2C), 110.9 and 110.0 (1C), 70.5 and 66.1 (1C), 55.9, 43.9 and 43.5 (1C); HRMS (ESI) calcd for $C_{29}H_{24}N_2NaO_2^+$ $[MNa]^+$ 455.1730, found 455.1742.

3-(Benzhydrylimino)-1-tritylindolin-2-one (II·1e). Prepared according to GP-A using 1-trityl isatin. The desired product was collected by filtration; yield: 498 mg, 60%; pale yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$, 9:1 mixture of imine isomers) δ 7.82-7.69 (m, 1.9H), 7.61-7.37 (m, 10H), 7.35-7.17 (m, 15H), 7.04-

6.83 (m, 2H), 6.50 (s, br, 0.1H), 6.38 (d, *J* = 7.8 Hz, 0.1H), 6.16 (d, *J* = 7.8 Hz, 0.9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 151.8, 145.3, 144.5 (2C), 141.9 (3C), 131.6 and 131.2 (1C), 129.6-126.9 (25C), 123.4, 122.6, 122.2 and 122.8 (1C), 117.2 and 115.7 (1C), 74.7, 69.7 and 64.4 (1C); HRMS (ESI) calcd for $C_{40}H_{30}N_2NaO^+$ $[MNa]^+$ 577.2250, found 577.2239.

3-(Benzhydrylimino)-1-benzyl-5-fluoroindolin-2-one (II·1f). Prepared according to GP-A using 5-fluoro-1-benzyl isatin. The desired product was collected by filtration; yield: 428 mg, 68%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 9:1 mixture of imine isomers) δ 7.88 (s, 0.9H), 7.63-7.50 (m, 4H), 7.47-7.26 (m, 11H), 7.07 (dt, *J* = 8.0, 2.8 Hz, 1H), 6.75 (dd, *J* = 8.0, 4.2 Hz, 0.1H), 6.68 (dd, *J* = 8.0, 3.9 Hz, 0.9H), 6.50 (s, 0.1H), 4.99 (s, 0.2H), 4.93 (s, 1.9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 160.1 (d, *J* = 241.6Hz, 1C), 159.4, 152.4, 144.8 (2C), 143.7 and 141.5 (1C), 135.9, 131.0-127.8 (15C), 123.8 (d, *J* = 8.5Hz, 1C), 120.3 (d, *J* = 24.0Hz) and 119.6 (d, *J* = 24.0Hz) (1C), 116.0 (d, *J* = 24.0Hz) and 110.3 (d, *J* = 24.0Hz) (1C), 111.6 (d, *J* = 7.1Hz) and 111.0 (d, *J* = 7.1Hz) (1C), 70.6 and 66.4 (1C), 44.5 and 44.2 (1C); HRMS (ESI) calcd for $C_{28}H_{21}FN_2NaO^+$ $[MNa]^+$ 443.1530, found 443.1515.

3-(Benzhydrylimino)-1-benzyl-5-chloroindolin-2-one (II·1g). Prepared according to GP-A using 5-chloro-1-benzyl isatin. The desired product was collected by filtration; yield: 458 mg, 70%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 19:1 mixture of imine isomers) δ 7.86 (s, br, 0.95H), 7.81 (d, br, *J* = 1.6 Hz, 0.95H), 7.78 (d, br, *J* = 1.6 Hz, 0.05H), 7.60 (d, br, *J* = 7.5 Hz, 3.8H), 7.55 (d, br, *J* = 7.5 Hz, 0.2H), 7.46-7.26 (m, 12H), 6.76 (d, *J* = 8.5 Hz, 0.05H), 6.69 (d, *J* = 8.5 Hz, 0.95H), 6.53 (s, br, 0.05H), 5.00 (s, 0.1H), 4.93 (s, 1.9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.4, 151.2, 144.1 (2C), 143.3, 135.1, 132.9 and 132.3 (1C),

130.4-127.1 (16C), 123.3, 122.4, 111.3 and 110.6 (1C), 70.0 and 65.9 (1C), 43.9 and 43.6 (1C); HRMS (ESI) calcd for $C_{28}H_{21}ClN_2NaO^+$ $[MNa]^+$ 459.1234, found 459.1245.

3-(Benzhydrylimino)-1-benzyl-6-bromoindolin-2-one (II·1h). Prepared according to GP-A using 6-bromo-1-benzyl isatin. The desired product was collected by filtration; yield: 562 mg, 78%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 85:15 mixture of imine isomers) δ 7.83 (s, 0.85H), 7.68 (d, *J* = 7.7 Hz, 0.85H), 7.66-7.50 (m, 4.15H), 7.47-7.25 (m, 11.85H), 7.19 (dd, *J* = 7.8 and 1.2 Hz, 0.15H), 6.99 (d, *J* = 1.2 Hz, 0.15H), 6.93 (s, br, 0.85H), 6.51 (s, br, 0.15H), 4.98 (s, 0.3H), 4.91 (s, 1.7H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.6, 151.2, 145.9, 144.1 (2C), 135.0, 128.9-125.7 (17C), 123.4, 120.9, 113.5 and 112.7 (1C), 70.1 and 65.8 (1C), 43.9 and 43.6 (1C); HRMS (ESI) calcd for $C_{28}H_{21}BrN_2NaO^+$ $[MNa]^+$ 503.0729, found 503.0713.

3-(Benzhydrylimino)-6-bromo-1-methylindolin-2-one (II·1i). Prepared according to GP-A using 6-bromo-1-methyl isatin. The desired product was collected by filtration; yield: 424 mg, 70%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 85:15 mixture of imine isomers) δ 7.78 (s, br, 0.85H), 7.66 (d, *J* = 7.8 Hz, 0.85H), 7.61-7.46 (m, 4.15H), 7.44-7.19 (m, 7H), 7.10 (s, br, 0.15H), 7.03 (s, br, 0.85H), 6.48 (s, br, 0.15H), 3.25 (s, 0.45H), 3.20 (s, 2.55H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.2, 152.1, 147.3, 144.8 (2C), 131.1-123.9 (13C), 121.3, 113.5 and 112.7 (1C), 70.6 and 66.3 (1C), 26.9 and 26.4 (1C); HRMS (ESI) calcd for $C_{22}H_{17}BrN_2NaO^+$ $[MNa]^+$ 427.0416, found 427.0411.

General procedure B (GP-B) for the asymmetric organocatalyzed synthesis of compounds II·5-13. To a solution of isatin-derived imine **II·1a-i** (0.12 mmol, 1 eq)

and trimethylsilyloxyfuran (TMSOF) (0.14 mmol, 1.16 eq) in tetrahydrofuran (1 mL) cooled to -40 °C, a solution of catalyst (*R*)-**II·4a** (10% mol) in MeOH (25 μL) and tetrahydrofuran (200 μL) was slowly added. The resulting mixture was stirred at the same temperature for 7 hours. The reaction was quenched by adding $NaHCO_3$ saturated aq. (1 mL) and the product was extracted with EtOAc (2 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by FC, as indicated below.

3-(Benzhydrylamino)-1-benzyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·5a,b). Prepared according to GP-B using 3-(benzhydrylimino)-1-benzylindolin-2-one (**II·1a**); FC: *n*-Hexane:EtOAc, 7:3; yield: 47 mg, 80%; pale orange solid; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diasteroisomers *syn*:*anti*, 48:52) δ 7.83 (dd, *J* = 5.8 and 1.7 Hz, 0.52H), 7.43-7.13 (m, 15H), 7.10 (dd, *J* = 5.9 and 1.5 Hz, 0.48H), 7.08-6.91 (m, 2.48H), 6.87 (td, *J* = 7.6 and 1.0 Hz, 0.52H), 6.65 (d, *J* = 7.8 Hz, 0.48H), 6.59 (d, *J* = 7.8 Hz, 0.52H), 6.25 (dd, *J* = 5.8, 1.9 Hz, 0.52H), 5.97 (dd, *J* = 5.9, 2.2 Hz, 0.48H), 5.48 (t, br, *J* = 1.8 Hz, 0.48H), 5.26 (t, br, *J* = 1.7 Hz, 0.52H), 4.81 (d, *J* = 15.9 Hz, 0.52H), 4.73 (s, br, 0.48H), 4.72 (s, br, 0.52H), 4.65 (d, *J* = 15.4 Hz, 0.48H), 4.25 (d, *J* = 15.9 Hz, 0.52H), 4.10 (d, *J* = 15.4 Hz, 0.48H), 3.03-2.41 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 48:52) δ 176.0 and 174.3 (1C), 165.0 and 163.2 (1C), 152.4 and 151.1 (1C), 143.6 and 143.3 (2C), 142.2 and 141.8 (1C), 135.5 and 135.3 (1C), 130.1 and 129.9 (1C), 128.8-1258(17C), 124.2 and 123.9 (1C), 122.9 and 122.1 (1C), 109.6 and 109.5 (1C), 86.1 and 85.2 (1C), 68.1 and 67.3 (1C), 63.0 and 62.3 (1C), 43.9; HRMS (ESI) calcd for $C_{32}H_{26}N_2NaO_3^+$ $[MNa]^+$ 509.1836, found 509.1828; enantiomeric excess: *syn* 92%, *anti* 90%,

determined by HPLC (Chiracel-AD, *n*-Hexane:*i*PrOH = 1:1, flow rate 0.6 mL/min): t_R = 10.33 min (*anti*, minor), t_R = 11.75 min (*syn*, major); t_R = 14.27 min (*syn*, minor), t_R = 66.85 min (*anti*, major).

3-(Benzhydrylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·6a,b). Prepared according to GP-B using 3-(benzhydrylimino)indolin-2-one (**II·1b**); FC: CH_2Cl_2:MeOH, 99:1; yield: 37 mg, 78%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$+1% CD_3OD, mixture of diasteroisomers *syn:anti*, 37:63) δ 7.73 (d, br, *J* = 5.8 Hz, 0.63H), 7.32-6.82 (m, 15H), 6.81-6.62 (m, 1.37H), 6.16 (dd, *J* = 5.9 and 1.9 Hz, 0.63H), 5.92 (dd, *J* = 5.8 and 1.9 Hz, 0.37H), 5.34 (t, br, *J* = 1.8 Hz, 0.37H), 5.16 (t, br, *J* = 1.8 Hz, 0.63H), 4.64 (s, 0.37H), 4.62 (s, 0.63H); ^{13}C NMR (75 MHz, $CDCl_3$+1% CD_3OD, mixture of diasteroisomers *syn:anti*, 37:63) δ 178.1, 172.6 and 172.3 (1C), 153.1 and 151.7 (1C), 143.6 and 143.4 (2C), 142.6 and 142.0 (1C), 129.9-121.6 (15C), 110.3, 86.0 and 85.2 (1C), 66.0 and 64.8 (1C), 62.9 and 62.2 (1C); HRMS (ESI) calcd for $C_{25}H_{20}N_2NaO_3^+$ $[MNa]^+$ 419.1366, found 419.1354; enantiomeric excess: *syn* 88%, *anti* 80%, determined by HPLC (Chiracel-AD, *n*-Hexane:*i*PrOH = 4:1, flow rate 0.7 mL/min): t_R = 10.58 min (*syn*, minor), t_R = 11.38 min (*syn*, major), t_R = 13.61 min (*anti*, minor), t_R = 63.13 min (*anti*, major).

3-(Benzhydrylamino)-1-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·7a) and (II·7b). Prepared according to GP-B using 3-(benzhydrylimino)-1-methylindolin-2-one (**II·1c**); FC: *n*-Hexane:EtOAc, 7:3.

(**II·7a**) yield: 22 mg, 45%; orange foam; $[\alpha]^{20}_D$ –24.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, *anti* diasteroisomer) δ 7.88 (dd, *J* = 5.6 and 1.5 Hz, 1H), 7.43-7.13 (m, 10H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.87- 6.80 (m, 2H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.27 (dd, *J* = 5.6 and 1.5 Hz, 1H), 5.16 (t, *J* = 1.5 Hz, 1H), 4.68 (s,

br, 1H), 2.81 (*s*, 3H), 2.71-2.45 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 171.8, 152.6, 144.5, 143.3, 141.9, 130.2, 128.5-126.8 (11C), 124.0, 123.1, 122.1, 108.5, 85.1, 67.0, 62.2, 26.1; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO_3^+$ $[MNa]^+$ 433.1523, found 433.1529; enantiomeric excess: 91%, determined by HPLC (Chiracel-ODH, *n*-Hexane:*i*PrOH = 4:1, flow rate 0.7 mL/min): t_R = 5.51 min (minor), t_R = 15.34 min (major).

(**II·7b**) yield: 19 mg, 36%; orange foam; $[\alpha]^{20}_D$ + 115.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, *syn* diasteroisomer) δ 7.42-7.07 (m, 11H), 7.03 (t, br, *J* = 7.8 Hz, 1H), 6.94-6.86 (m, 2H), 6.64 (d, br, *J* = 7.8 Hz, 1H), 5.93 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.41 (*s*, 1H), 4.64 (*s*, 1H), 3.21-2.74 (m, br, 1H), 2.68 (*s*, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 172.1, 151.2, 143.6, 143.5, 141.4, 130.0, 128.4-127.1 (10C), 125.7, 123.9, 123.7, 122.9, 108.6, 86.0, 67.9, 63.1, 25.9; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO_3^+$ $[MNa]^+$ 433.1523, found 433.1531; enantiomeric excess: 68%, determined by HPLC (Chiracel-AD, *n*-Hexane:*i*PrOH = 4:1, flow rate 0.7 mL/min): t_R = 11.28 min (major), t_R = 13.51 min (minor).

3-(Benzhydrylamino)-1-(4-methoxybenzyl)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·8a,b). Prepared according to GP-B using 3-(benzhydrylimino)-1-(4-methoxybenzyl)indolin-2-one (**II·1d**); FC: *n*-Hexane:EtOAc, 7:3; yield: 51 mg, 79%; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 45:55) δ 7.73 (d, *J* = 4.9 Hz, 0.55H), 7.32-6.74 (m, 17.45H), 6.63 (d, br, *J* = 7.8 Hz, 0.45H), 6.58 (d, br, *J* = 7.8 Hz, 0.55H), 6.20 (d, br, *J* = 5.8 Hz, 0.55H), 5.93 (d, br, *J* = 5.9 Hz, 0.45H), 5.45 (s, br, 0.45H), 5.31 (s, br, 0.55H), 4.80-4.64 (m, 1.55H), 4.56 (d, *J* = 14.7 Hz, 0.45H), 4.15 (d, *J* = 15.8 Hz, 0.55H), 3.99 (d, *J* = 14.7 Hz, 0.45H), 3.75 (*s*, 3H), 3.34-2.47 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 45:55) δ 175.2 and

174.0 (1C), 172.0 and 171.6 (1C), 159.2, 152.2 and 151.1 (1C) , 143.5 and 143.4 (1C), 142.9, 141.6, 130.2 and 129.9 (1C), 128.8-127.2 (14C), 125.7 and 124.2 (1C), 122.8 and 122.2 (1C), 122.4, 114.2, 111.3, 109.6 and 109.5 (1C), 86.0 and 84.8 (1C), 68.0 and 67.3 (1C), 63.0 and 62.6 (1C), 55.3, 43.4 and 43.3 (1C); HRMS (ESI) calcd for $C_{33}H_{28}N_2NaO_4^+$ $[MNa]^+$ 539.1941, found 539.1950; enantiomeric excess: *syn* 89%, *anti* 84%, determined by HPLC (Chiracel-AD, *n*-Hexane:*i*PrOH = 9:1, flow rate 1.0 mL/min): t_R = 30.00 min (*anti* minor), t_R = 40.25 min (*syn* major), t_R = 42.46 min (*syn* minor), t_R = 112.89 min (*anti* major).

3-(Benzhydrylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)-1-tritylindolin-2-one (II·9a,b). Prepared according to GP-B using 3-(benzhydrylimino)-1-tritylindolin-2-one (**II·1e**); FC: *n*-Hexane:EtOAc, 4:1; yield: 64mg, 81%; pale orange solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 53:47) δ 7.81 (dd, *J* = 5.9 and 1.5 Hz, 0.47H), 7.67-6.99 (m, 23H), 6.95 (d, br, *J* = 7.7 Hz, 0.47H), 6.88 (t, br, *J* = 7.7 Hz, 0.47H), 6.81-6.86 (m, 3.06H), 6.55 (dd, *J* = 5.9 and 1.5 Hz, 0.53H), 6.41-6.27 (m, 2H), 6.22 (dd, *J* = 5.8 and 1.9 Hz, 0.47H), 5.83 (dd, *J* = 5.9 and 2.2 Hz, 0.53H), 5.35 (t, br, *J* = 1.7 Hz, 0.53H), 5.24 (t, br, *J* = 1.7 Hz, 0.47H), 4.60 (s, br, 0.53H), 4.17 (s, br, 0.47H), 3.47-2.32 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 53:47) δ 178.6 and 175.6 (1C), 172.0 and 171.4 (1C), 153.0 and 151.7 (1C), 144.1 and 144.0 (1C), 143.5 and 143.4 (1C), 143.3 and 143.2 (1C), 142.2 and 141.9 (3C), 129.2, 129.3-126.9 (26C), 126.5 and 125.4 (1C), 125.2, 123.9 and 123.2 (1C), 122.4 and 121.0 (1C), 116.0 and 115.8 (1C), 86.5 and 85.2 (1C), 75.4 and 75.2 (1C), 68.8 and 68.4 (1C), 62.9 and 62.6 (1C); HRMS (ESI) calcd for $C_{44}H_{34}N_2NaO_3^+$ $[MNa]^+$ 661.2462, found 661.2455; enantiomeric excess: *syn* 96%, *anti* 4%, determined by HPLC (Chiracel-AD, *n*-Hexane:*i*PrOH = 17:1, flow rate 0.7 mL/min): t_R =

15.85 min (*anti* minor), t_R = 24.13 min (*syn* minor), t_R = 27.90 min (*anti* major), t_R = 33.83 min (*syn* major).

3-(Benzhydrylamino)-1-benzyl-5-fluoro-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·10a,b). Prepared according to GP-B using 3-(benzhydrylimino)-1-benzyl-5-fluoroindolin-2-one (**II·1f**); FC: *n*-Hexane:EtOAc, 7:3; 29 mg, yield: 45%; pale orange solid; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 28:72) δ 7.81 (d, br, *J* = 4.9 Hz, 0.72H), 7.52-6.76 (m, 16.56H), 6.69 (d, br, *J* = 7.8 Hz, 0.72H), 6.57-6.42 (m, 1H), 6.25 (d, br, *J* = 5.8 Hz, 0.72H), 5.99 (d, br, *J* = 5.8 Hz, 0.28H), 5.42 (s, br, 0.28H), 5.21 (s, br, 0.72H), 4.81 (d, *J* = 15.7 Hz, 0.72H), 4.72-4.60 (m, 1.28H), 4.30 (d, *J* = 15.7 Hz, 0.72H), 4.11 (d, *J* = 15.7 Hz, 0.28H), 3.01-2.66 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 28:72) δ 175.8 and 174.1 (1C), 158.9 (d, *J* = 239.9Hz) and 158.1 (d, *J* = 244.0Hz) (1C), 152.1 and 150.8 (1C), 143.3 and 142.9 (1C), 142.1 and 141.8 (1C), 139.3 and 138.7 (1C), 135.1 and 134.9 (1C), 128.9- 127.1 (16C), 125.3 and 124.6 (1C), 124.4 and 124.0 (1C), 116.6-116.1 (m, 1C), 114.9 (d, *J* = 26.2Hz) and 113.8 (d, *J* = 22.8Hz) (1C), 110.0 (d, *J* = 8.7Hz) (1C), 85.8 and 84.8 (1C), 68.3 and 67.7 (1C), 63.1 and 62.5 (1C), 44.0; HRMS (ESI) calcd for $C_{32}H_{25}FN_2NaO_3^+$ $[MNa]^+$ 527.1741, found 527.1752; enantiomeric excess: *syn* 15%, *anti* 1%, determined by HPLC (Chiracel-ODH, *n*-Hexane:*i*PrOH = 4:1, flow rate 0.7 mL/min): t_R = 25.91 min (*syn* major), t_R = 32.60 min (*syn* minor), t_R = 35.53 min (*anti* major), t_R = 57.56 min (*anti* minor).

3-(Benzhydrylamino)-1-benzyl-5-chloro-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·11a,b). Prepared according to GP-B using 3-(benzhydrylimino)-1-benzyl-5-chloroindolin-2-one (**II·1g**); FC: *n*-Hexane:EtOAc, 7:3; yield: 27 mg, 42%; pale orange solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*,

3:7) δ 7.83 (dd, *J* = 5.8, 1.2 Hz, 0.7H), 7.46-6.98 (m, 16.6H), 6.92 (d, , *J* = 2.0 Hz, 0.7H) 6.54 (d, *J* = 8.4 Hz, 0.3H), 6.50 (d, *J* = 8.4 Hz, 0.7H), 6.29 (dd, *J* = 5.8, 1.7 Hz, 0.7H), 6.06 (dd, *J* = 5.8, 1.9 Hz, 0.3H), 5.44 (t, *J* = 1.5 Hz, 0.3H), 5.24 (t, *J* = 1.5 Hz, 0.7H), 4.84 (d, *J* = 15.8 Hz, 0.7H), 4.76-4.62 (m, 1.3H), 4.34 (d, *J* = 15.8 Hz, 0.7H), 4.14 (d, *J* = 15.8 Hz, 0.3H), 3.11-2.68 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 3:7) δ 176.4 and 174.7 (1C), 172.2 and 172.0 (1C), 152.7 and 151.5 (1C), 143.8-142.1 (3C), 135.7 and 135.6 (1C), 130.7 and 130.5 (1C), 129.6 to 126.8 (17C), 126.6 and 125.2 (1C), 125.1 and 124.8 (1C), 111.1, 86.5 and 85.4 (1C), 68.9 and 68.3 (1C), 63.8 and 63.3 (1C), 44.8 and 44.7 (1C); HRMS (ESI) calcd for $C_{32}H_{25}ClN_2NaO_3^+$ [MNa]$^+$ 543.1446, found 543.1454; enantiomeric excess: *syn* 74%, *anti* 26%, determined by HPLC (Chiracel-AD, *n*-Hexane:*i*PrOH = 9:1 to 3:7, flow rate 1.0 mL/min): t_R = 18.02 min (*syn* major), t_R = 19.84 min (*anti* major), t_R = 37.38 min (*syn* minor), t_R = 57.02 min (*anti* minor).

3-(Benzhydrylamino)-1-benzyl-6-bromo-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·12a,b). Prepared according to GP-B using 3-(benzhydrylimino)-1-benzyl-6-bromoindolin-2-one (**II·1h**); FC: *n*-Hexane:EtOAc, 7:3; yield: 44 mg, 65%; orange solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diasteroisomers 3:7) δ 7.83 (d, br, *J* = 5.6 Hz, 0.7H), 7.46-7.02 (m, 14.6H), 7.01-6.94 (m, 2H), 6.86 (d, br, *J* = 7.9 Hz, 0.7H), 6.79 (*s*, br 0.3H), 6.74 (*s*, br, 0.7H), 6.26 (dd, *J* = 5.6, 1.5 Hz, 0.7H), 6.00 (dd, *J* = 5.8, 1.9 Hz, 0.3H), 5.44 (*s*, br, 0.3H), 5.22 (*s*, br, 0.7H), 4.79 (d, *J* = 15.8 Hz, 0.7H), 4.72- 4.58 (m, 1.3H), 4.25 (d, *J* = 15.8 Hz, 0.7H), 4.08 (d, *J* = 15.8 Hz, 0.3H), 3.10-2.69 (m, br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 3:7) δ 176.6 and 174.9 (1C), 172.3 and 172.0 (1C), 152.8 and 151.4 (1C), 145.5-142.2 (4C), 135.6 and 135.4 (1C),

129.7 to 127.6 (15C), 126.5 and 125.7 (1C), 125.0 and 124.9 (1C), 124.6 and 124.4 (1C), 123.6 and 123.5 (1C), 113.5, 86.4 and 85.4 (1C), 68.5 and 67.9 (1C), 63.8 and 63.1 (1C), 44.7; HRMS (ESI) calcd for $C_{32}H_{25}BrN_2NaO_3^+$ $[MNa]^+$ 587.0941 found 587.0944. enantiomeric excess: *syn* 42%, *anti* 31%, determined by HPLC (C-AD, *n*-Hexane:*i*PrOH = 9:1, flow rate 1.0 mL/min): t_R = 16.04 min (*anti* minor), t_R = 17.91 min (*syn* major), t_R = 24.31 min (*syn* minor), t_R = 63.35 min (*anti* major).

3-(Benzhydrylamino)-6-bromo-1-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (II·13a) and (II·13b). Prepared according to GP-B using 3-(benzhydrylimino)-6-bromo-1-methylindolin-2-one (**II·1i**); FC: *n*-Hexane:EtOAc, 7:3. (**II·13a**) yield: 25 mg, 42%; orange foam; $[\alpha]^{20}_D$ – 18.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, *anti* diasteroisomer) δ 7.84 (dd, *J* = 5.8, 1.9 Hz, 1H), 7.24-7.10 (m, 8H), 7.06 (d, br, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.88-6.80 (m, 3H), 6.25 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.12 (s, br, 1H), 4.61 (s, 1H), 2.78 (s, 3H), 2.72-2.06 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 171.6, 152.3, 145.7, 142.8, 141.6, 128.3-127.1 (11C), 125.0, 124.3, 124.1, 121.9, 112.1, 84.6, 66.9, 62.3, 26.2; HRMS (ESI) calcd for $C_{26}H_{21}BrN_2NaO_3^+$ $[MNa]^+$ 511.0628, found 511.0637; enantiomeric excess: *anti* 32%, determined by HPLC (Chiracel-ODH, *n*-Hexane:*i*PrOH = 4:1, flow rate 0.7 mL/min): t_R = 23.33 min (major), t_R = 75.68 min (minor).

(**II·13b**) yield: 15 mg, 26%; orange foam; $[\alpha]^{20}_D$ – 2.82 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, *syn* diasteroisomer) δ 7.44-7.03 (m, 11H), 7.01-6.90 (m, 2H), 6.80 (d, *J* = 1.4 Hz, 1H), 5.97 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.39 (s, br, 1H), 4.62 (s, 1H), 2.68 (s, 3H), 2.16-1.77 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 171.7, 150.9, 144.9, 142.8, 140.9, 128.3-126.9 (11C), 125.8, 124.2, 123.9, 122.5,

112.2, 85.5, 67.8, 63.4, 26.1; HRMS (ESI) calcd for $C_{26}H_{21}BrN_2NaO_3^+$ $[MNa]^+$ 511.0628, found 511.0633; enantiomeric excess: *syn* 31%, determined by HPLC (Chiracel-ODH, *n*-Hexane:*i*PrOH = 4:1, flow rate 0.7 mL/min): t_R = 14.81 min (major), t_R = 23.13 min (minor).

Post-transformation reactions

3-Amino-1-methyl-3-(5-oxotetrahydrofuran-2-yl)indolin-2-one (II·15). To a solution of Mannich adduct **II·14** (100 mg, 0.29 mmol) in EtOAc (3 mL), 10% Pd/C (10% w/w) was added. The reaction mixture was degassed *in vacuo*, placed under an atmosphere of H_2 (g), stirred at rt and the conversion was monitored by TLC. The mixture was filtered through a pad of Celite eluting with EtOAc (10 mL) and the solvent was concentrated *in vacuo*. The crude residue was dissolved in dry MeOH (1 mL) followed by the dropwise addition of HCl solution (0.5 mL, 4M HCl in dioxane) and the resulting mixture was stirred at room temperature for 4h. After quenching with saturated aq $NaHCO_3$ (2 mL), and dilution with CH_2Cl_2 (2 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$, dried over anhydrous Na_2SO_4 and the solvent was removed under reduce pressure. The crude was subjected to FC (CH_2Cl_2:MeOH, 95:5) giving the desired product **II·15**, as a white foam (65 mg, 91% overall yield).

$[\alpha]^{20}_D$ – 83.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, br, *J* = 7.8 Hz, 1H), 7.36 (t, br, *J* = 7.6 Hz, 1H), 7.09 (t, br, *J* = 7.7 Hz, 1H), 6.86 (d, br, *J* = 7.8 Hz, 1H), 4.62 (dd, br, *J* = 7.8 and 5.9 Hz, 1H), 3.21 (s, 3H), 2.58-2.33 (m, 4H), 1.88 (m, br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 176.6, 143.7, 130.1,

128.2, 124.8, 123.2, 108.7, 82.4, 62.1, 28.0, 26.5, 21.7; HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_3^+$ $[MNa]^+$ 269.0897, found 269.0908.

3-Amino-1-methyl-3-(5-oxotetrahydrofuran-2-yl)indolin-2-one (II·15')

Palladium hydroxide (20 wt.% on carbon, 12 mg) was added to a solution of vinylogous Mannich-adduct **II·7a** (82 mg, 0.20 mmol) in MeOH (1 mL). The reaction mixture was degassed *in vacuo*, placed under an atmosphere of H_2 (g), stirred at rt and the conversion was monitored by TLC. The mixture was filtered through a pad of Celite eluting with MeOH (10 mL), and the solvent was concentrated *in vacuo*. The crude was subjected to FC (CH_2Cl_2:MeOH, 95:5) to give **II·15'** as a white foam (47 mg, 96%). $[\alpha]^{20}_D$ – 90.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) were identical to those of compound **II·15**. HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_3^+$ $[MNa]^+$ 269.0897, found 269.0879.

3-(Benzhydrylamino)-1-methyl-3-(5-((triisopropylsilyl)oxy)furan-2-yl)indolin-2-one (II·16). To a solution of 3-(benzhydrylamino)-1-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (**II·7a** or **II·7b**) (60 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (1.5 mL) cooled to 0 °C, anhydrous trimethylamine (0.15 mmol, 1eq) and TIPSOTf (0.17 mmol, 1.1 eq) were added. The solution was stirred at the same temperature for 1 hour (monitored by TLC). The reaction was quenched by adding water (1.5 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to give **II·16** as a viscous oil.

Compound ***(R)*- II·16** from **II·7a**: Yield: 72 mg, 98%; $[\alpha]^{20}_D$ – 33.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.10 (m, 12H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.13 (d, br, *J* = 2.9 Hz, 1H), 5.04 (d, br, *J* = 2.9 Hz, 1H), 4.79 (*s*, 1H), 3.07-2.95 (m, br, 1H), 2.72 (*s*, 3H), 1.22 (hept, *J* = 7.8 Hz, 3H),

1.04 (d, J = 7.8 Hz,18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 157.1, 144.2, 143.4, 142.5, 141.1, 128.1-126.9 (12C), 123.1, 122.2, 109.7, 109.0, 84.3, 71.7, 62.6, 25.2, 17.5 (6C), 12.2 (3C); HRMS (ESI) calcd for $C_{35}H_{42}N_2NaO_3Si^+$ $[MNa]^+$ 589.2857, found 589.2866.

Compound **(*S*)- II·16** from **II·7b**: Yield: 69 mg, 95%; $[\alpha]^{20}_D$ + 31.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) were identical to those of compound **(*R*)-16**; HRMS (ESI) calcd for $C_{35}H_{42}N_2NaO_3Si^+$ $[MNa]^+$ 589.2857, found 589.2869.

II.5 References

1. (a) Ruan S.-T.; Luo J.-M.; Du Y.; Huang P.-Q.; *Org. Lett.* **2011**, *13*, 4938-4941. (b) González-Gálvez D.; García-García E.; Alibés R.; Bayón P.; de March P.; Figueredo M.; Font J.; *J. Org. Chem.* **2009**, *74*, 6199-6211. (c) Cantó M.; Alibés R.; Bayón P.; Busqué F.; de March P.; Figueredo M.; Font J.; *J. Org. Chem.* **2008**, *73*, 7657-7662.

2. (a) Oudeyer S.; Dudot B.; Rorer J.; *Heterocycles* **2005**, *65*, 823. (b) Spanedda M. V.; Ourévitch M.; Benoit B.; Bégué J.-P.; Bonnet-Delpon D.; *Tetrahedron Lett.* **2004**, *45*, 5023-5025. (c) Martin S. F.; *Acc. Chem. Res.* **2002**, *35*, 895-904.

3. Carswell E. L.; Snapper M. L.; Hoveyda A. H.; *Angew. Chem. Int. Ed.* **2006**, *45*, 7230-7233.

4. Silverio D. L.; Fu P.; Carswell E. L.; Snapper M. L.; Hoveyda A. H.; *Tetrahedron Letters* **2015**, *56*, 3489-3493.

5. Zheng L.-S.; Li L.; Yang K.-F.; Zheng Z.-J.; Xiao X.-Q.; *Tetrahedron* **2013**, *69*, 8777-8784.

6. Akiyama T.; Honma Y.; Itoh J.; Fuchibe K.; *Adv. Synth. Catal.* **2008**, *350*, 399-402.

7. Wieland L. C.; Vieira E. M.; Snapper M. L.; Hoveyda A. H.; *J. Am. Chem. Soc.* **2009**, *131*, 570-576.

8. Hayashi M.; Sano M.; Funahashi Y.; Nakamura S.; *Angew. Chem. Int. Ed.* **2013**, *52*, 5557-5560.

9. Nakamura S.; Yamaji R.; Hayashi M.; *Chem. Eur. J.* **2015**, *21*, 9615-9618.

10. (a) Lesma G.; Meneghetti F.; Sacchetti A.; Stucchi M.; Silvani A.; *Belstein J. Org. Chem.* **2014**, *10*, 1383-1389. (b) Sacchetti A.; Silvani A.; Gatti F. G.; Lesma G.; Pilati T.; Trucchi B.; *Org. Biomol. Chem.* **2011**, *9*, 5515-5522. (c) Lesma G.;

Landoni N.; Sacchetti A.; Silvani A.; *Tetrahedron* **2010**, *66*, 4474-4478. (d) Lesma G.; Landoni N.; Pilati T.; Sacchetti A.; Silvani A.; *J. Org. Chem.* **2009**, *74*, 4537-4541. Stucchi M.; Lesma G.; Meneghetti F.; Rainoldi G.; Sacchetti A.; Silvani A.; *J. Org. Chem.* **2016**, *81*, 1877-1884.

11. (a) Terada M.; *Synthesis* **2010**, *12*, 1929-1982. (b) Sickert M.; Schneider C.; *Angew. Chem. Int. Ed.* **2008**, *47*, 3631-3634.

12. Shi Y.-H.; Wang Z.; Shi Y.; Deng W.-P.; *Tetrahedron* **2012**, *68*, 3649-3653.

13. Rao V. U. B.; Jadhav A. P.; Garad D.; Singh R. P.; *Org. Lett.* **2014**, *16*, 648-651.

14. Guo Y.; Zhang Y.; Qi L.; Tiana F.; Wang L.; *RSC Adv.* **2014**, *4*, 27286-27289.

15. Denmark S. E.; Heemstra J. R.; Beutner G. L.; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682-4698.

16. Zamfir A.; Tsogoeva S. B.; *Org. Lett.* **2010**, *12*, 188-191.

17. Reid J. P.; Simón L.; Goodman J. M.; *Acc. Chem. Res.* **2016**, *49*, 1029-1041.

18. Spartan'08, Wavefunction Inc, Irvine, C.A.; Shao Y.; Molnar L. F.; Jung Y.; Kussmann J.; Ochsenfeld C.; Brown S. T.; Gilbert A. T. B.; Slipchenko L. V.; Levchenko S. V.; O'Neill D. P.; DiStasio R. A. Jr.; Lochan R. C.; Wang T.; Beran G. J. O.; Besley N. A.; Herbert J. M.; Lin C. Y.; Van Voorhis T.; Chien S. H.; Sodt A.; Steele R. P.; Rassolov V. A.; Maslen P. E.; Korambath P. P.; Adamson R. D.; Austin B.; Baker J.; Byrd E. F. C.; Dachsel H.; Doerksen R. J.; Dreuw A.; Dunietz B. D.; Dutoi A. D.; Furlani T. R.; Gwaltney S. R.; Heyden A.; Hirata S.; Hsu C.-P.; Kedziora G.; Khalliulin R. Z.; Klunzinger P.; Lee A. M.; Lee M. S.; Liang W. Z.; Lotan I.; Nair N.; Peters B.; Proynov E. I.; Pieniazek P. A.; Rhee Y. M.; Ritchie J.; Rosta E.; Sherrill C. D.; Simmonett A. C.; Subotnik J. E.; Woodcock H. L. III; Zhang W.; Bell A. T.; Chakraborty A. K.; Chipman D. M.; Keil F. J.; Warshel A.;

Hehre W. J.; Schaefer H. F.; Kong J.; Krylov A. I.; Gill P. M. W.; Head-Gordon M.; *Phys. Chem. Chem. Phys.*, **2006**, *8*, 3172–3191.

19. Lu S.; BeiPoh S.; Siau W.-Y.; Zhao Y.; *Angew. Chem. Int. Ed.* **2013**, *52*, 1731-1734.

20. Simonsen K. B.; Gothelf K. V.; Jørgensen K. A.; *J. Org. Chem.* **1998**, *63*, 7536-7538.

III. Spiro[Indoline-Pyrimidine]-Diones Derivatives: Biginelli Reaction

The first asymmetric, Brønsted acid-catalyzed Biginelli-like reaction of a ketone has been developed, employing N-substituted isatins as carbonyl substrates, and urea and alkyl acetoacetates as further components. BINOL-derived phosphoric acid catalysts have been used to achieve the synthesis of a small library of chiral, enantioenriched spiro(indoline-pyrimidine)-diones derivatives. The absolute configuration of the new spiro stereocenter was assessed on diastereoisomeric derivatives through computer-assisted NMR spectroscopy. X-Ray diffractometry allowed to disclose the overall molecular conformation in the solid state and to characterize the crystal packing of a Br-substituted Biginelli-like derivative, while computational studies on the reaction transition state allowed to rationalize the stereochemical outcome.

Published in *J. Org. Chem.*, **2016**, *81*, 1877-1884

III.1 Introduction

Simple heterocyclic compounds, such as pyrimidin-2(1*H*)-ones, are well known because of their important natural representatives, namely, the uracil, thymine, and cytosine nucleobases, which are essential components of DNA and RNA molecules.[1] Moreover, such heterocyclic scaffolds have found increasing applications in medicinal chemistry, because of their important pharmacological and biological properties (Figure 1).[2]

As part of our interest in the asymmetric synthesis of 3,3-disubstituted oxindole derivatives and related spiro-compounds,[3] we focused on the Biginelli reaction (Scheme 1), one of the well-established MCRs, mainly employed for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs).

Only few examples are reported on enantioselective organocatalytic Biginelli reactions, all involving aromatic aldehydes as carbonyl components.[4] The milestone was placed by Gong,[7] who disclosed the first highly enantioselective

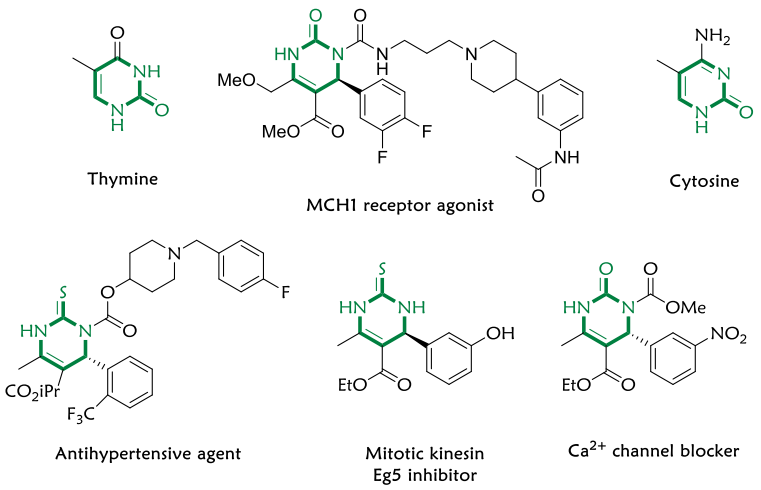
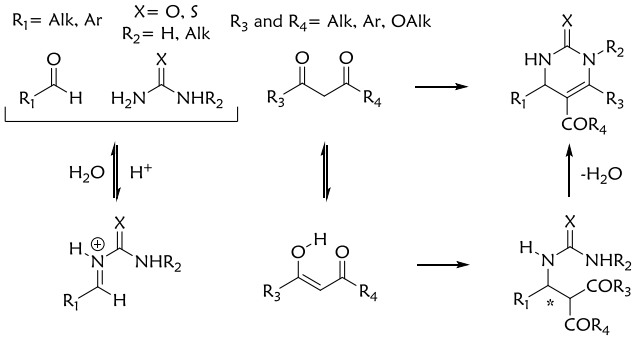


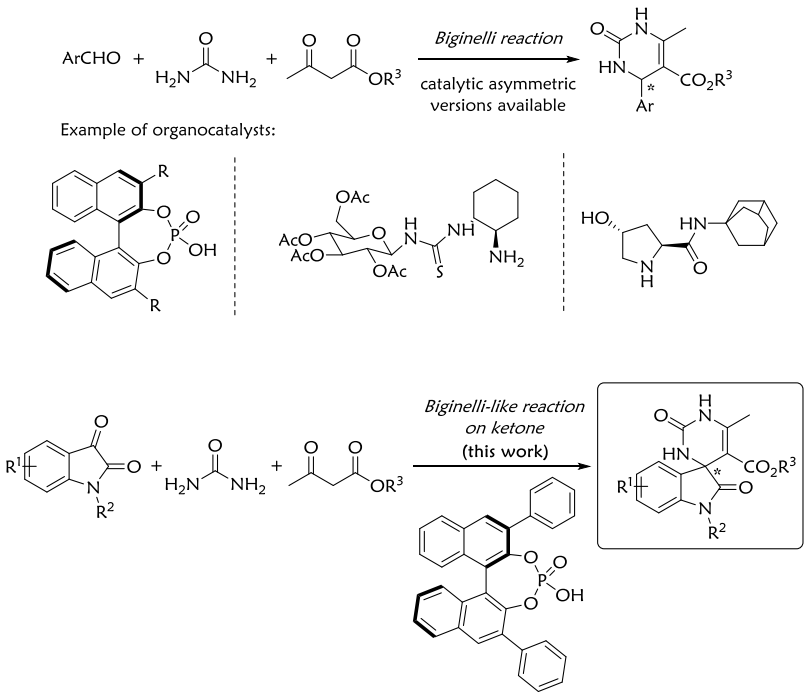
Figure 1. Example of biologically important pyrimidin-2(1*H*)-one-based compounds.



Scheme 1. Most accepted Biginelli reaction mechanism.

protocol, based on BINOL-derived chiral phosphoric acids as organocatalysts. Also dual-activation routes have been developed,by using combined catalysts consisting of a Brønsted acid and a chiral secondary amine[8,9] or, alternatively, a chiral bifunctional primary amine-thiourea.[10]

At the best of our knowledge, only two examples of the multicomponent preparation of racemic DHPMs derivatives starting from isatin are reported.[11,12] In general, application of organocatalysis to the Biginelli-like reaction, employing a ketone as the carbonyl component, is even now quite unexplored. Herein, we report the Brønsted acid-catalyzed asymmetric synthesis of spiro(indoline-pyrimidine)-diones derivatives via a Biginelli-like reaction, consisting of a three component cyclocondensation of alkyl acetoacetates, urea and isatin derivatives instead of aldehydes (Scheme 2).



Scheme 2. Strategy used for the asymmetric construction of the spiro(indoline-pyrimidine)-dione scaffold.

III.2 Results and Discussion

Our initial studies were performed taking into account the Brønsted acid-catalytic enantioselective protocol reported by Gong for the true, aldehyde-involving, Biginelli reaction. Isatin **III·1a**, urea **III·2a**, ethyl acetoacetate **III·3a** and (*R*)-BINOL-derived phosphoric acid **III·4a** were chosen for preliminary experiments (Table 1).

At room temperature, the reaction proceeds with difficulty both in CH_2Cl_2 and in toluene (entries 1 and 2) and, after 96 hours, only trace amounts of the desired compound **III·5a** could be detected by ^1H NMR of the crude reaction mixture. The lower reactivity of C-3 carbonyl group of isatin compared to aldehydes,

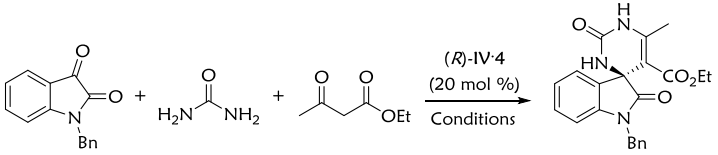
along with its higher steric demand, appears to be the key factor hindering the reaction from successfully proceeding at room temperature.

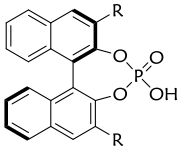
To our delight, increasing the temperature to 50 °C (entries 3 and 4) entailed a significant effect on the chemical conversion. Toluene proved to be the solvent of choice, affording product **III·5a** in acceptable yield and with a good level of enantioselectivity. Screening of more hindered catalysts **III·4b-f**, aimed to evaluate the impact of the 3,3'-substitution, and of octahydro-BINOL-based **III·4g** was performed (entries 5-10). Increasing the size of the 3,3'-substitents on the phosphoric acid proved detrimental for the chemical conversion, with only catalysts **III·4c** and **III·4d** able to afford product **III·5a**, with maintenance of the same level of enantioselectivity as **III·4a**, but in definitely decreased yields.

After that, we established **III·4a** as the catalyst of choice, and further screening of the reaction conditions were performed. Some yield improvement without sacrificing the stereoselectivity could be achieved by prolonging the reaction time until 96 hours (entry 11).

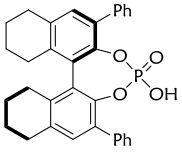
More prolonged times are not convenient for the balance of yield vs *ee* (entry 12). Increasing the reaction temperature deeply eroded the enantioselectivity, albeit with better yield (entry 13). The same happened when the reaction was conducted in more concentrated conditions (entry 14). Lowering the reactant concentration or the catalyst loading led to a significant decrease in yield.

Table 1. Optimization of the asymmetric Biginelli-like reaction.[a]





(*R*)-III·4a: R = Ph;
(*R*)-III·4b: R = 4-NO_2-C_6H_4;
(*R*)-III·4c: R = 4-Ph-C_6H_4;
(*R*)-III·4d: R = 9-Anthracenyl;
(*R*)-III·4e: R = 2,5,6-(*i*Pr)$_3$-C_6H_2;
(*R*)-III·4f: R = $SiPh_3$.



(*R*)-III·4g

Entry	Catalyst	Solvent	Conc. [mol/L]	T [°C], t [h]	Yield[b] [%]	*ee*[c] [%]
1	III·4a	CH_2Cl_2	0.2	rt, 96	trace	-
2	III·4a	Toluene	0.2	rt, 96	trace	-
3	III·4a	CH_2Cl_2	0.2	50, 48	32	75
4	III·4a	Toluene	0.2	50, 48	51	80
5	III·4b	Toluene	0.2	50, 48	trace	-
6	III·4c	Toluene	0.2	50, 48	30	79
7	III·4d	Toluene	0.2	50, 48	31	81
8	III·4e	Toluene	0.2	50, 48	trace	-
9	III·4f	Toluene	0.2	50, 48	trace	-
10	III·4g	Toluene	0.2	50, 48	26	79
11	**III·4a**	**Toluene**	**0.2**	**50, 96**	**60**	**80**
12	III·4a	Toluene	0.2	50, 240	66	77
13	III·4a	Toluene	0.2	70, 96	65	48
14	III·4a	Toluene	0.4	50, 96	62	66

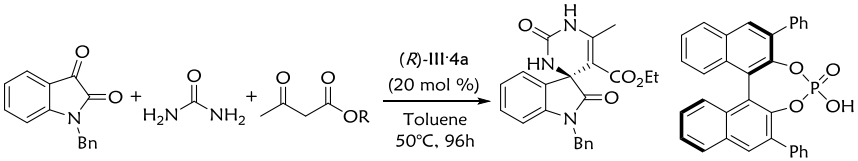
[a] Reaction conditions: isatin **III·1a** (0.16 mmol), urea **III·2a** (0.19 mmol), acetoacetate **III·3a** (0.48 mmol) and catalyst (*R*)-**III·4** (0.032 mmol) in different solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

After establishing the optimal conditions, the Biginelli-like reaction of a isatins series was examined, using (*R*)-**III·4a** as catalyst, in toluene at 50 °C for 96 h (Scheme 3). The substrate scope was surveyed, by evaluating differently *N*-substituted isatins and the presence of substituents at 5- or 6-position of the isatin nucleus. In general, all isatins readily undergo this reaction, to afford the desired products **III·5a-h** in moderate to high yields, with a good degree of enantioselectivity. Only the sterically demanding *N*-trityl isatin failed to participate in the reaction and the corresponding Biginelli-like adduct could not be detected. The *N*-Me isatin gave a better result than the corresponding *N*-Benzyl, *N*-p-Nitrobenzyl and *N*-p-Methoxybenzyl ones in terms of yield (93% in comparison to up to 63%), but suffering a drop in *ee* (50% in comparison to up to 80%).

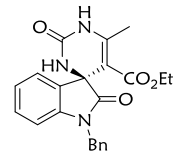
The presence of various halogen substituents at the aryl ring has almost no effect on both yield and *ee*. Variations at the ester moiety of the β-ketoester component were also evaluated. Methyl and benzyl acetoacetates participated at the reaction efficiently to provide adducts **III·5i-j** in good yields and moderate *ee*'s. In this kind of reaction, surprisingly, neither thiourea in place of urea, nor various linear or cyclic β-diketones in place of alkyl acetoacetates, showed to be suitable, together with *N*-benzyl- isatin.

With thiourea no reaction occurred, while with β-diketones a complex mixture of products could be detected.

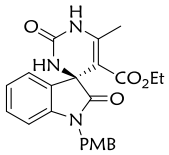
Scheme 3. Substrate scope of the Biginelli-like reaction catalyzed by (*R*)-**III·4a**.[a]



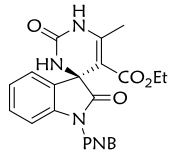
III·1a-h **III·2a** **III·3a-c** **III·5a-j** (*R*)-**III·4a**



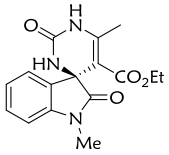
III·5a (60%)
ee: 80%



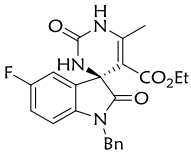
III·5b (63%)
ee: 75%



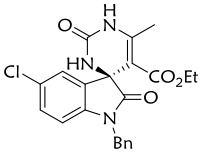
III·5c (49%)
ee: 70%



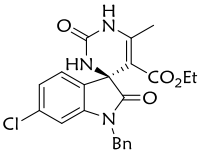
III·5d (93%)
ee: 50%



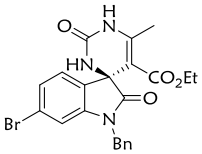
III·5e (51%)
ee: 75%



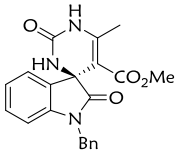
III·5f (66%)
ee: 74%



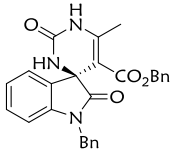
III·5g (62%)
ee: 77%



III·5h (63%)
ee: 75%



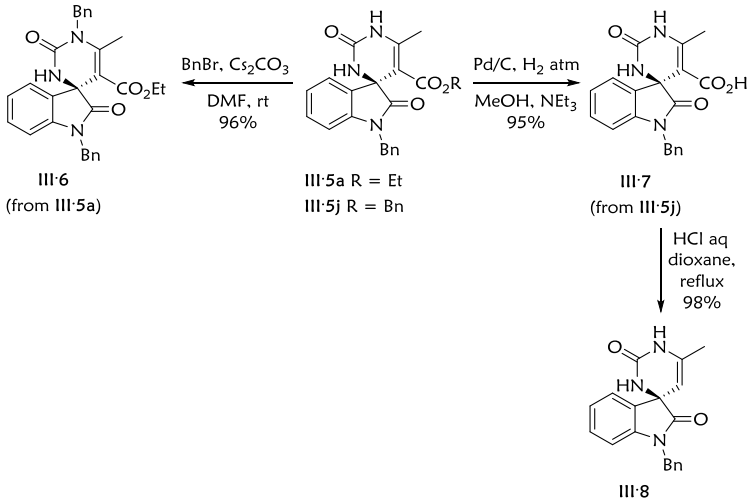
III·5i (65%)
ee: 61%



III·5j (55%)
ee: 74%

[a] Reaction conditions: isatin **III·1a-h** (0.16 mmol), urea **III·2a** (0.19 mmol), acetoacetate **III·3a-c** (0.48 mmol) and catalyst (*R*)-**III·4a** (0.032 mmol) in toluene (0.8 mL). Isolated yields are reported. *ee* were determined by chiral HPLC analysis.

Scheme 4. Synthetic transformations on compounds **III·5a** and **III·5j**.



Then, we examined some products transformations, first of all the facile regioselective mono-*N*-alkylation of the dihydropyrimidin-2-one ring. Starting from the Biginelli-like compound **III·5a**, the corresponding *N*-benzyl derivative **III·6** was achieved in high yield and regioselectivity, by reaction with benzyl bromide and cesium carbonate, in DMF at room temperature (Scheme 4).

Further, catalytic hydrogenolysis of the benzyl ester moiety of compound **III·5j** allowed to easily obtain the carboxylic acid derivative **III·7**, that can be regarded as a useful key intermediate toward the synthesis of peptidomimetic compounds. The carboxylic acid functional group of **III·7** can also be quantitatively removed to give **III·8**, by heating in acidic conditions.

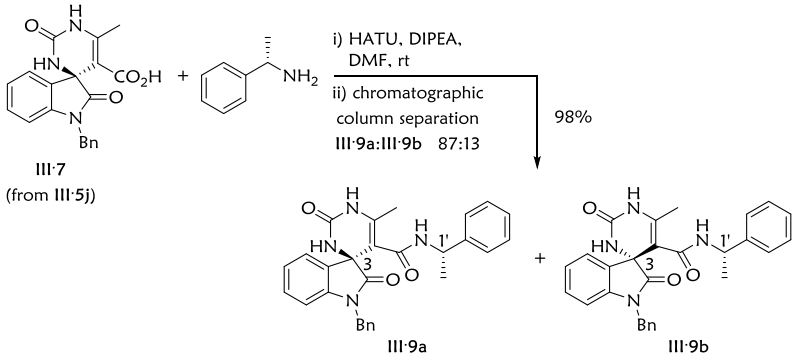
In order to demonstrate the reactivity of acid **III·7** and aiming at the same time to gain information on the absolute configuration of the major enantiomer **III·5j**

(*vide infra*), obtained in the (*R*)-**III·4a**-catalyzed Biginelli-like reaction, we pursued the transformation depicted in Scheme 5.

By reaction with (*S*)-1-phenylethanamine in the presence of the condensing agent HATU, acid **III·7** was cleanly converted into diastereoisomeric amides **III·9a** and **III·9b**, which could be efficiently separated by flash chromatography, establishing the possible application of **III·7** in peptidomimetic chemistry.

Confiding at first on X-ray diffractometry in order to determine the *C*3 absolute configuration of compounds **III·5**, we planned to perform the crystallographic analysis on **III·5h**. This molecule was selected as a suitable derivative, due to the presence of the bromine atom as anomalous dispersor. Initially, **III·5h** disclosed a recalcitrant crystallization behavior in yielding single crystals and, only after many attempts, well diffracting crystals were obtained. The X-ray data revealed that the 12:88 molar mixture of enantiomers crystallized in a centrosymmetric space group, showing the more favored crystallization of the racemate instead of the major enantiomer.

Scheme 5. Synthesis of diastereoisomeric compounds **III·9a** and **III·9b**, starting from acid **III·7**.



In the solid state, the overall molecular conformation is determined by the spiro(indoline-pyrimidine)-dione system, with the dihydropyrimidin-2-one ring, having an almost planar conformation, perpendicularly oriented with respect to oxindole (Figure 2a). The conformation of the benzyl group shows the phenyl ring pointing in the same direction of the dihydropyrimidin-2-one carbonyl moiety. The crystal packing is characterized by strong centrosymmetric N-H...O hydrogen bonds, leading to the formation of dimers, that are in turns stabilized by Cp-H...O contacts, as depicted in Figure 2b.

This interactions pattern can be employed for rationalizing the preferential crystallization of the racemate, which is indeed consistent with the close packing found in the crystal environment, dominated by unique characteristics of hydrogen bonds involved in dimers formation.

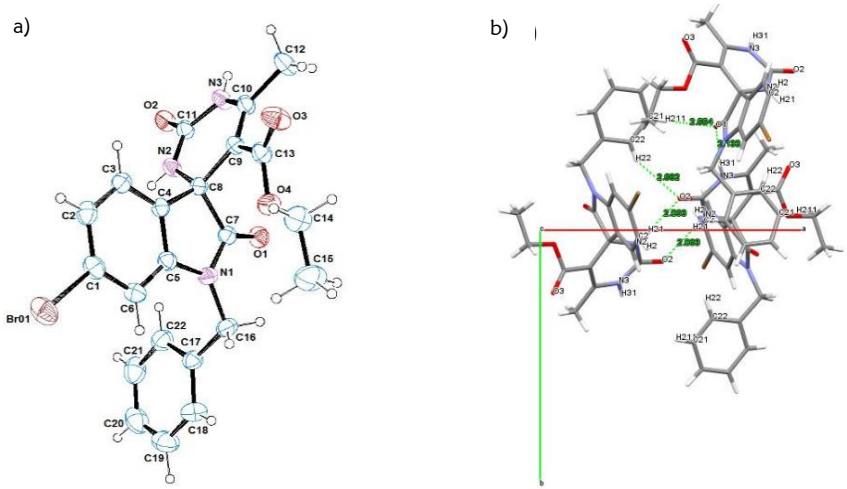


Figure 2. (a) ORTEP[13] drawing of **III·5h**, showing the arbitrary atomic numbering (displacement ellipsoids at 40% probability). (b) Intermolecular interactions viewed along *c* axis.

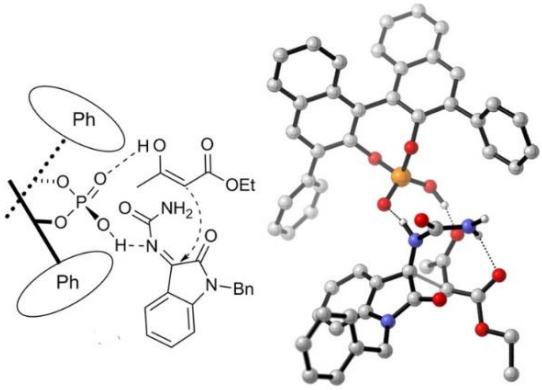
This easier racemate crystallization is in agreement with previous literature data,[14] showing the tendency for several racemic crystals to be more stable and denser than their chiral counterparts.Although it was not possible to obtain suitable crystals for X-ray-based determination of the prevailing enantiomer **III·5h**, we were able to determine the *C*3 stereochemistry through *ab initio* calculation of NMR shifts, a technique pioneered by Bifulco.[15] We considered the differences in both ^{1}H and ^{13}C NMR spectra for compounds **III·9a** and **III·9b** and then performed a theoretical conformational search on both (3*S*,1'*S*) and (3*R*,1'*S*) possible diastereoisomers, employing the Monte Carlo algorithm and molecular mechanics (MMFF force field). After DFT optimization, we calculated ^{1}H and ^{13}C NMR chemical shifts, by subjecting the shielding constants to Boltzmann averaging over the conformers, followed by linear regression, as reported by Pierens.[16] From comparison of experimental and calculated data, the (3*S*,1'*S*) absolute configuration could be confidently assigned to the major diastereoisomer **III·9a** and, consequently, the (3*R*,1'*S*) one to the minor **III·9b**. To make this assignment safe beyond any doubt, we also calculated the comparison parameter (CP3), especially designed[17] for the computer-assisted assignment of the stereochemistry of diastereoisomers pairs, in which only the configuration of one stereocenter is unknown. By this way, our stereochemical assignment could be made quite secure also from a quantitative point of view.

These results allowed us to disclose the *C*3-*S* favoring enantioselectivity of the described organocatalyzed reaction and prompted us to perform theoretical calculations on the stereogenic centre forming step. The mechanism of the Biginelli reaction has been previously investigated by means of computational tools,[18] also in the presence of tartaric acid as catalyst.[19] Results indicated the

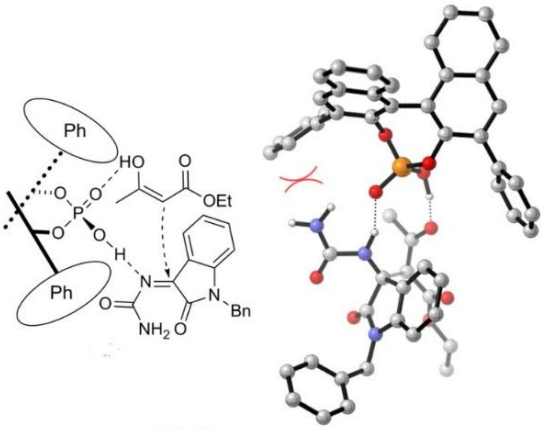
iminium path as the most favorable, in accordance with previously proposed mechanism.[20] Therefore, we decided to investigate the initial addition of the enol form of ethyl acetoacetate on the imine formed between isatin **III·1a** and urea **III·2a**, in the presence of (*R*)-**III·4a**, since in this step the final configuration of **III·5a** is determined. DFT study at the B3LYP/6-31G(d,p) level of theory were performed taking into account the two possible spatial arrangement of the more stable *Z*-imine in the reagents-catalyst complex,[21] leading to the diastereoisomeric transition state models **TS-A** and **TS-B** (Figure 3).

All the calculations were performed with the *Spartan '08* [22] suite. The energy profiles clearly indicate a strong preference for **TS-A**, with a $\Delta\Delta G^{\ddagger}$ = 1.47 Kcal/mol with respect to **TS-B**, at T = 323K, from which an expected 85% *ee* could be calculated.

These results are in satisfactory agreement with the experimentally observed *ee*'s, and once again support the previously predicted (*S*)-configuration for major diastereoisomer **III·9a**. Looking at the transition state 3D structures, the steric hindrance between one phenyl substituent of (*R*)-**III·4a** and the ureidic residue could explain the higher activation energy of **TS-B** and the resulting favored nucleophilic attack on the *si*-face of the imine (**TS-A**). Moreover, in **TS-A** a hydrogen bond between the ureidic NH of the imine and the carbonyl oxygen of the acetoacetate ester is established, thus further stabilizing this structure.



TS-A



TS-B

Figure 3. Proposed transition states **TS-A** and **TS-B** (and the corresponding 3D structures) of the BINOL-derived phosphoric acid catalyzed Biginelli-like reaction to give **III·5a**.
In 3D **TS-B** red lines highlight the steric hindrance between one phenyl substituent of (*R*)-**III·4a** and the ureidic residue.

III.3 Conclusion

In conclusion, we developed the first enantioselective organocatalyzed Biginelli-like reaction applied to a ketone, namely isatin, with good yields and enantioselectivity. By employing BINOL-based phosphoric acids as catalysts and different isatins and alkyl acetoacetates as substrates, together with urea, a small library of enantioenriched spiro[indoline-pyrimidine]-dione derivatives could be obtained. Post-condensation reactions have been performed, increasing the number of potentially useful compounds.

The solid state conformation of a Br-containing Biginelli-like compound was investigated, putting in evidence its crystallization behaviour leading to the more favored racemate, instead of the major enantiomer. The absolute configuration at the oxindole *C3* quaternary stereocenter was assessed to be *(S)* for the major enantiomer, by means of quantum mechanical methods and NMR spectroscopy on diastereoisomeric derivatives. Computational studies on the reaction transition state (TS) allowed us to explain the experimentally observed enantioselectivity and stereochemical outcome.

III.4 Experimental section

All commercial materials were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with a 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). ^1H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^1H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Q-ToF mass spectrometer, equipped with an ESI source. Chiral HPLC analysis was performed with UV Detector and binary HPLC pump at 254 nm. Chiralcel OD column was used. Specific optical rotation $[\alpha]^T_D$ was measured with a cell of 1 dm pathlength and 1 mL capacity. The light used has a wavelength of 589 nm (Sodium D line). *N*-substituted isatins[23] and BINOL-phosphoric acids[24] were synthetized according to reported literature.

General procedure for the asymmetric organocatalyzed synthesis of compounds III·5a-j. Substituted isatin **III·1a-h** (0.16 mmol, 1 eq), urea **III·2a** (0.19 mmol, 1.2 eq), alkyl acetoacetate **III·3a-c** (0.48 mmol, 3 eq) and (*R*)-**III·4a** catalyst (0.03 mmol, 0.2 eq) were dissolved in toluene (0.800 mL, 0.2 M). The reaction was stirrer at 50 °C for 96 hours. The resulting mixture was then

concentrated under reduced pressure, to give a residue which was purified by flash chromatography (FC) as indicated below.

(*S*)-ethyl 1-benzyl-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5a). Prepared according to general procedure starting from *N*-benzyl isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 60%; white solid; mp 223-224 °C; $[\alpha]^{20}_D$ – 45.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.24 (m, 4H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.69 (br s, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.80 (d, *J* = 15.5 Hz, 1H), 3.99 – 3.86 (m, 1H), 3.70 – 3.55 (m, 1H), 2.38 (s, 3H), 0.71 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 165.2, 151.9, 149.9, 143.2, 136.3, 132.9, 130.5, 129.5 (2C), 128.5 (3C), 124.6, 124.0, 109.9, 99.4, 64.2, 60.6, 45.0, 20.1, 14.1; HRMS (ESI) calcd for $C_{22}H_{21}N_3NaO_4^+$ $[MNa]^+$ 414.1434, found 414.1442; enantiomeric excess: 80%, determined by chiral HPLC (*n*-hexane:isopropanol = 80:20, flow rate 1.0 mL/min): t_R = 14.98 min (major), t_R = 33.78 min (minor).

(*S*)-ethyl 1-(4-methoxybenzyl)-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5b). Prepared according to general procedure starting from *N*-(4-methoxybenzyl) isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 63%; white solid; mp 193-194 °C; $[\alpha]^{20}_D$ + 4.5 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 6:1) δ 8.87 (br s, 0.15H), 8.74 (br s, 0.85H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.88 – 6.70 (m, 3H), 6.01 (br s, 0.86H), 5.81 (br s, 0.14H), 4.85 (d, *J* = 15.3 Hz, 1H), 4.71 (d, *J* = 15.3 Hz, 1H), 3.96 – 3.78 (m, 1H), 3.74 (s, 0.43H), 3.71 (s,

2.57H), 3.64 – 3.43 (m, 1H), 2.33 (s, 0.44H), 2.27 (s, 2.56H), 0.64 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of conformers 6:1) δ 175.9, 164.6, 159.1, 152.1, 149.5, 142.6, 132.5, 129.7, 129.2 (2C), 127.8, 123.9, 123.2, 114.1 (2C), 109.2, 98.5, 63.4, 59.8, 55.2, 43.7, 19.1, 13.5; HRMS (ESI) calcd for $C_{23}H_{23}N_3NaO_5^+$ $[MNa]^+$ 444.1530, found 444.1519; enantiomeric excess: 75%, determined by chiral HPLC (*n*-hexane:isopropanol = 65:35, flow rate 1.0 mL/min): t_R = 9.85 min (major), t_R = 27.96 min (minor).

(*S*)-ethyl 6'-methyl-1-(4-nitrobenzyl)-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5c). Prepared according to general procedure starting from *N*-(4-nitrobenzyl) isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 49%; white solid; mp 201-202 °C; $[\alpha]^{20}_D$ – 8.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 5:1) δ 8.48 (br s, 0.17H), 8.40 (br s, 0.83H), 8.21 – 8.08 (m, 2H), 7.65 – 7.54 (m, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.28 (br s, 0.84H), 6.12 (br s, 0.16H), 5.09 – 4.87 (m, 2H), 4.07 – 3.89 (m, 1H), 3.86 – 3.68 (m, 1H), 2.34 (s, 0.5H), 2.30 (s, 2.5H), 0.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of conformers 5:1) δ 176.0, 164.6, 151.8, 149.0, 147.5, 143.0, 141.9, 132.2, 130.0, 128.4 (2C), 124.1, 124.0 (2C), 123.8, 109.0, 98.9, 63.51, 60.3, 43.7, 19.5, 13.8; HRMS (ESI) calcd for $C_{22}H_{20}N_4NaO_6^+$ $[MNa]^+$ 459.1275, found 459.1268; enantiomeric excess: 70%, determined by chiral HPLC (*n*-hexane:isopropanol = 50:50, flow rate 1.0 mL/min): t_R = 10.05 min (major), t_R = 45.50 min (minor).

(*S*)-ethyl 1,6'-dimethyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5d). Prepared according to general procedure starting from *N*-methyl isatin and ethyl acetoacetate; FC:

dichlorometane:methanol, 95:5; yield: 93%; white solid; mp 228-229 °C; $[\alpha]^{20}_D$ – 1.6 (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 9.45 (br s, 1H), 7.75 (br s, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 3.68 (q, *J* = 7.1 Hz, 2H), 3.10 (s, 3H), 2.26 (s, 3H), 0.75 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.2, 164.8, 150.9 (2C), 144.0, 134.0, 129.6, 123.4, 122.8, 108.7, 97.1, 63.1, 59.5, 26.6, 18.7, 13.8; HRMS (ESI) calcd for $C_{16}H_{17}N_3NaO_4^+$ $[MNa]^+$ 338.1111, found 338.1123; enantiomeric excess: 50%, determined by chiral HPLC (*n*-hexane:isopropanol = 65:35, flow rate 1.0 mL/min): t_R = 7.25 min (major), t_R = 38.20 min (minor).

(*S*)-ethyl 1-benzyl-5-fluoro-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5e). Prepared according to general procedure starting from 5-fluoro-*N*-benzyl isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 51%; white solid; mp 135-136 °C; $[\alpha]^{20}_D$ + 3.8 (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, mixture of conformers 5:1) δ 8.76 – 8.49 (br, m, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.34 – 7.16 (m, 3H), 7.03 (dd, *J* = 7.3, 2.5 Hz, 1H), 6.88 (td, *J* = 8.8, 2.4 Hz, 1H), 6.67 (dd, *J* = 8.5, 3.8 Hz, 1H), 6.13 – 5.88 (br, m, 1H), 4.92 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 15.5 Hz, 1H), 4.04 – 3.83 (m, 1H), 3.74 – 3.52 (m, 1H), 2.35 (s, 0.5H), 2.30 (s, 2.5H), 0.83 – 0.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of conformers 5:1) δ 175.7, 164.4, 161.1, 157.9, 151.80, 149.75, 138.42, 135.34, 128.77 (2C), 127.81, 127.74 (2C), 116.17 and 115.86 (1C), 112.19 and 111.9 (1C), 110.0 and 109.9 (1C), 98.2, 63.6, 60.1, 44.4, 19.3, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}FN_3NaO_4^+$ $[MNa]^+$ 432.1330, found 432.1326; enantiomeric excess: 75%, determined by chiral HPLC (*n*-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 8.15 min (major), t_R = 16.35 min (minor).

(*S*)-ethyl 1-benzyl-5-chloro-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5f). Prepared according to general procedure starting from 5-chloro-*N*-benzyl isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 66%; white solid; mp 126-127 °C; $[\alpha]^{20}_D$ + 33.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers 5:1) δ 8.76 (br s, 0.16H), 8.69 (br s, 0.84H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.33 – 7.18 (m, 4H), 7.14 (d, *J* = 8.3, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.24 (br s, 0.83H), 6.18 (br s, 0.17H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 4.01 – 3.84 (m, 1H), 3.75 – 3.56 (m, 1H), 2.34 (s, 0.5H), 2.29 (s, 2.5H), 0.83 – 0.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 164.4, 151.9, 149.8, 141.1, 135.2, 134.0, 129.7, 128.8 (2C), 128.5, 127.8, 127.7 (2C), 124.3, 110.3, 98.1, 63.4, 60.1, 44.4, 19.3, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}ClN_3NaO_4^+$ $[MNa]^+$ 448.1035, found 448.1049; enantiomeric excess: 74%, determined by chiral HPLC (*n*-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 9.05 min (major), t_R = 16.45 min (minor).

(*S*)-ethyl 1-benzyl-6-chloro-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5g). Prepared according to general procedure starting from 6-chloro-*N*-benzyl isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 62%; white solid; mp 213-214 °C; $[\alpha]^{20}_D$ – 1.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.39 (d, *J* = 7.0 Hz, 2H), 7.35 – 7.22 (m, 3H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.79 (s, 1H), 6.14 (br s, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 2.29 (s, 3H), 0.74 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 164.4, 151.9, 149.4, 143.9, 135.6, 135.1, 130.7, 128.8 (2C), 127.9, 127.8 (2C), 124.8, 123.1, 109.9, 98.4, 63.0, 60.1, 44.4, 19.2,

13.6; HRMS (ESI) calcd for $C_{22}H_{20}ClN_3NaO_4^+$ $[MNa]^+$ 448.1035, found 448.1039; enantiomeric excess: 77%, determined by chiral HPLC (*n*-hexane:isopropanol = 65:35, flow rate 1.0 mL/min): t_R = 8.65 min (major), t_R = 15.35 min (minor).

(*S*)-ethyl 1-benzyl-6-bromo-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5h). Prepared according to general procedure starting from 6-bromo-*N*-benzyl isatin and ethyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 63%; white solid; mp 221-222 °C; $[\alpha]^{20}_D$ + 7.6 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.26 (m, 3H), 7.18 – 7.06 (m, 2H), 6.95 (s, 1H), 6.22 (br s, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.00 – 3.77 (m, 1H), 3.70 – 3.49 (m, 1H), 2.27 (s, 3H), 0.72 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 164.4, 152.0, 149.5, 144.0, 135.1, 131.3, 128.8 (2C), 127.9, 127.8 (2C), 126.1, 125.2, 123.4, 112.6, 98.3, 63.1, 60.1, 44.1, 19.2, 13.6; HRMS (ESI) calcd for $C_{22}H_{20}BrN_3NaO_4^+$ $[MNa]^+$ 492.0529, found 492.0518; enantiomeric excess: 75%, determined by chiral HPLC (*n*-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 9.35 min (major), t_R = 16.50 min (minor).

(*S*)-methyl 1-benzyl-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5i). Prepared according to general procedure starting from *N*-benzyl isatin and methyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 65%; white solid; mp 143-144 °C; $[\alpha]^{20}_D$ – 6.8 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.36 – 7.23 (m, 4H), 7.20 (td, *J* = 7.8, 1.2 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.29 (br s, 1H), 4.94 (d, *J* = 15.5 Hz, 1H), 4.83 (d, *J* = 15.4 Hz, 1H), 3.20 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 175.8, 165.0, 151.3, 149.2, 142.3, 135.6, 132.1, 129.9, 128.8 (2C), 127.9 (2C), 127.8, 123.8, 123.3, 109.2, 98.7, 63.5, 51.0, 44.3, 19.4; HRMS (ESI) calcd for $C_{21}H_{19}N_3NaO_4^+$ $[MNa]^+$ 400.1268, found 400.1257; enantiomeric excess: 61%, determined by chiral HPLC (*n*-hexane:isopropanol = 70:30, flow rate 1.0 mL/min): t_R = 9.15 min (major), t_R = 18.30 min (minor).

(*S*)-benzyl 1-benzyl-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·5j). Prepared according to general procedure starting from *N*-benzyl isatin and benzyl acetoacetate; FC: dichlorometane:methanol, 97.5:2.5; yield: 55%; white solid; mp 147-148 °C; $[\alpha]^{20}_D$ +17.2 (*c* 0.5, dioxane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.41 – 7.17 (m, 10H), 7.18 – 7.09 (m, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 6.5 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 5.39 (br s, 1H), 4.85 – 4.70 (m, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.81 (d, *J* = 15.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 164.4, 162.2, 150.2, 142.3, 135.8, 132.2, 129.9, 128.9 (4C), 128.6 (2C), 128.3, 127.8, 127.7 (2C), 124.0, 123.4, 109.8, 66.5, 43.8, 19.6 (3 quaternary carbons are missed); HRMS (ESI) calcd for $C_{27}H_{23}N_3NaO_4^+$ $[MNa]^+$ 476.1581, found 476.1589; enantiomeric excess: 74%, determined by chiral HPLC (*n*-hexane:isopropanol = 80:20, flow rate 1.0 mL/min): t_R = 13.50 min (major), t_R = 28.20 min (minor).

Post-transformations

Procedure for the synthesis of ethyl (*S*)-1,1'-dibenzyl-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylate (III·6). To a solution of compound **III·5a** (0.25 mmol, 1 eq) in anhydrous dimethylformamide (0.830 mL, 0.3 M), $CsCO_3$ (0.33 mmol, 1.3 eq) was added, then the mixture was stirred for 1

hour at room temperature. Benzyl bromide (0.38 mmol, 1.5 eq) was slowly added and the mixture was stirred overnight. After the completion of reaction (monitored by TLC), saturated aq. NaCl (1 mL) was added. The reaction mixture was extracted with ethyl acetate (3 x 2 mL). The combined organic layer was washed with water (2 x 6 mL), followed by brine (2 x 6 mL). the organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product, which was purified by FC (*n*-hexane:ethyl acetate, 7:3), affording the desired product **III·6** (115 mg, 96%) as a white solid; mp 91-92 °C; $[\alpha]^{20}_D$ – 32.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.24 (m, 11H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.16 (br s, 1H), 5.00-4.78 (m, 3H), 3.91 – 3.73 (m, 1H), 3.57 – 3.42 (m, 1H), 2.40 (s, 3H), 0.52 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 165.1, 152.2, 150.7, 142.9, 137.7, 135.6, 131.7, 129.8, 128.9 (2C), 128.7 (2C), 127.8 (3C), 127.1, 126.0 (2C), 123.9, 123.2, 109.1, 101.9, 62.3, 60.0, 46.0, 44.2, 16.8, 13.2; HRMS (ESI) calcd for $C_{29}H_{27}N_3NaO_4^+$ $[MNa]^+$ 504.1894, found 504.1898.

Procedure for the synthesis of (*S*)-1-benzyl-6'-methyl-2,2'-dioxo-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxylic acid (III·7). Palladium (10 wt.% on carbon, 0.025 mmol, 0.05 eq) was added to a solution of Biginelli-adduct **III·5j** (0.50 mmol, 1 eq) and Et_3N (0.50 mmol, 1 eq) in 7.5 mL of dioxane/methanol (2:1). The reaction mixture was degassed *in vacuo*, placed under an atmosphere of H_2 (g), and stirred in the dark at rt for 3h. The mixture was filtered through a pad of Celite eluting with methanol (10 mL), and the combined organic layers were concentrated *in vacuo* to give the crude carboxylic acid derivative **III·7** (173 mg, 95%) as a white solid, sufficiently pure to be directly used in the next step;

mp not misured (decomposition); $[\alpha]^{20}_D$ – 19.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.97 (br s, 1H), 9.39 (br s, 1H), 7.89 (br s, 1H), 7.47 (d, *J* = 6.7 Hz, 2H), 7.39 – 7.25 (m, 3H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 4.96 (d, *J* = 16.3 Hz, 1H), 4.70 (d, *J* = 16.3 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.1, 166.4, 150.7, 149.4, 142.7, 136.3, 133.9, 128.8, 128.3 (2C), 127.1 (2C), 127.0, 123.0, 122.3, 108.9, 97.8, 63.0, 43.4, 18.5; HRMS (ESI) calcd for $C_{20}H_{17}N_3NaO_4^+$ $[MNa]^+$ 386.1111, found 386.1121.

Procedure for the synthesis of (*R*)-1-benzyl-6'-methyl-1'H-spiro[indoline-3,4'-pyrimidine]-2,2'(3'H)-dione (III·8). To a solution of the carboxylic acid derivative **III·7** (0.1 mmol, 1 eq) in 1 mL of dioxane/methanol (1:1), hydrochloric acid in dioxane (4 M, 0.4 mmol, 4 eq) was added, and the reaction was stirred at 90 °C for 0.5h. The solvent was removed under reduced pressure to afford compound **III·8** (31 mg, 98%) in high purity as a white solid, with no need for further purifications; mp 95-96 °C; $[\alpha]^{20}_D$ – 25.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.37 – 7.23 (m, 5H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 5.72 (br s, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.24 (s, 1H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 154.4, 142.0, 136.4, 136.1, 132.6, 130.5, 129.5 (2C), 128.4, 128.0 (2C), 125.7, 124.2, 110.2, 95.4, 64.3, 44.7, 19.4; HRMS (ESI) calcd for $C_{19}H_{17}N_3NaO_2^+$ $[MNa]^+$ 342.1213, found 342.1206.

Procedure for the synthesis of diastereoisomers (*S*)-1-benzyl-6'-methyl-2,2'-dioxo-*N*-((*S*)-1-phenylethyl)-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxamide (III·9a) and (*R*)-1-benzyl-6'-methyl-2,2'-dioxo-*N*-((*S*)-1-phenylethyl)-2',3'-dihydro-1'H-spiro[indoline-3,4'-pyrimidine]-5'-carboxamide (III·9b). To a

solution of carboxylic acid derivative **III·8** (0.9 mmol, 1 eq) and DIPEA (1.8 mmol, 2 eq) in 9.4 mL of anhydrous dimethylformamide, HATU (1.4 mmol, 1.5 eq) was added. After 5 min, (*S*)-(−)-α-methylbenzylamine (0.9 mmol, 1 eq) and DIPEA (1.8 mmol, 2 eq) were added, and the reaction was stirred at room temperature for 24 hours. The resulting mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic phase was washed with brine (6 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude diastereoisomeric mixture **III·9**, which was purified by flash chromatography (ethyl acetate:*n*-hexane, 95:5), obtaining the two isolated stereoisomers **III·9a** (358 mg, 86%) and **III·9b** (54 mg, 12%).

III·9a: white solid; mp 149-150 °C; $[\alpha]^{20}_D$ +16.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (br s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.62 (br s, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.22 (m, 7H), 7.18 (q, *J* = 8.4, 7.8 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 4.78 (s, 2H), 4.71 – 4.59 (m, 1H), 1.91 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 165.6, 153.2, 145.3, 144.4, 138.0, 137.3, 132.4, 130.2, 129.4 (2C), 129.3 (2C), 128.3 (2C), 128.1, 127.6, 127.2 (2C), 125.3, 123.0, 109.9, 105.1, 64.3, 48.6, 44.2, 23.0, 18.3. HRMS (ESI) calcd for $C_{28}H_{26}N_4NaO_3^+$ $[MNa]^+$ 489.1897, found 489.1905.

III·9b: white solid; mp 138-139 °C; $[\alpha]^{20}_D$ – 89.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (br s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.62 (br s, 1H), 7.42 (d, *J* = 6.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.11 (m, 3H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 4.88 – 4.67 (m, 3H), 2.01 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.4, 165.6, 153.0, 144.9, 144.32, 138.3,

137.3, 132.7, 130.1, 129.4 (2C), 128.9 (2C), 128.2 (2C), 128.07, 127.1, 126.8 (2C), 125.3, 123.2, 110.0, 105.12, 64.4, 48.1, 44.2, 22.5, 18.4. HRMS (ESI) calcd for $C_{28}H_{26}N_4NaO_3^+$ $[MNa]^+$ 489.1897, found 489.1909.

III.5 References

1. Sukach V. A.; Tkachuk V. M.; Shoba V. M.; Pirozhenko V. V.; Rusanov E. B.; Chekotilo A. A.; Röschenthaler G. V.; Vovk V. M.; *Eur. J. Org. Chem.* **2014**, 1452–1460.

2. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043. (c)Tron, G. C.; Minassi, A.; Appendino, G. *Eur. J. Org. Chem.* **2011**, *2011*, 5541. (d) De Fatima, A.; Braga, T.C.; Da S. Neto, L.; Terra, B.S.; Oliveira, B.G.F.; Da Silva, D.L.; Modolo, L.V. J. *Adv. Res.* **2014**, http://dx.doi.org/ 10.1016/j.jare.2014.10.006.

3. (a) Lesma, G.; Meneghetti, F.; Sacchetti, A.; Stucchi, M.; Silvani, A. *Belstein J. Org. Chem.* **2014**, *10*, 1383-1389. (b) Sacchetti, A.; Silvani, A.; Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, *9*, 5515-5522. (c) Lesma, G.; Landoni, N.; Sacchetti, A.; Silvani, A. *Tetrahedron* **2010**, *66*, 4474-4478. (d) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537-4541.

4. Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463-472.

5. Goss, J. M.; Schaus, S. E. *J. Org. Chem.* **2008**, *73*, 7651–7656.

6. Heravi, M. M.; Asadi, S.; Lashkariani, B. M. *Mol Divers* **2013**, *17*, 389–407.

7. Li, N.; Chen, X.-H.; Song, J.; Luo, S.-W.; Fan, W.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 15301–15310.

8 Gong, L.-Z.; Chen, X.-H.; Xu, X.-Y. *Chem. Eur. J.* **2007**, *13*, 8920–8926.

9. Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802-14803.

10. Wang, Y.; Yang, H.; Yu, J.; Miao, Z.; Chena, R. *Adv. Synth. Catal.* **2009**, *351*, 3057–3062.

11. Lahsasni S.; Mohamed M. A. A.; El-Saghier A. M. M. *Res. J. Chem. Environ.* **2014**, *18*, 38–42.

12. Kefayati, H.; Rad-Moghadam, K.; Zamani, M.; Hosseyni, S. *Lett. Org. Chem.* **2010**, *7*, 277–282.

13. Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837-838.

14. (a) Wallach, O. *Liebigs Ann. Chem.* **1895**, *279*, 119−143. (b) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811−9820. (c) Dunitz, J. D.; Gavezzotti, A. *J. Phys. Chem. B* **2012**, *116*, 6740−6750. (d) Ernst, K.-H. *Phys. Status Solidi B* **2012**, *249*, 2057−2088. (e) Seibel, J.; Parschau, M.; Ernst, K.-H. *J. Am. Chem. Soc.* **2015**, *137*, 7970−7973. (f) Mughal, R. K.; Davey, R. J.; Black, S. N. *Cryst Growth Des* **2007**, *7*, 225-228.

15. (a) Barone, G.; Gomez-Paloma, L.; Duca, D.; Silvestri, A.; Riccio, R.; Bifulco, G. *Chem. Eur. J.* **2002**, *8*, 3233-3239. b) Barone, G.; Gomez-Paloma, L.; Duca, D.; Silvestri, A.; Riccio, R.; Bifulco, G. *Chem. Eur. J.* **2002**, *8*, 3240-3245.

16. Pierens, G. K. *J. Comp. Chem.* **2014**, *35*, 1388-1394.

17. Smith, S. G.; Goodman, J. M. *J. Org. Chem.* **2009**, *74*, 4597-4607.

18. (a) Ma, J. G.; Zhang, J. M.; Jiang, H. H.; Ma, W. Y.; Zhou, J. H. *Chin. Chem. Lett.* **2008**, *19*, 375–378. (b) De Souza, R. O. M. A.; da Penha, E. T.; Milagre, H. M. S.; Garden, S. J.; Esteves, P. M.; Eberlin, M. N.; Antunes, O. A. C. *Chem. Eur. J.* **2009**, *15*, 9799–9804.

19. Lu, N.; Chen, D.; Zhang, G.; Liu, Q. *Int. J. Quantum Chem.* **2011**, *111*, 2031–2038.

20. Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3784–3791.

21. Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775–1788.

22. Spartan'08, Wavefunction Inc, Irvine, C.A.; Shao, Y.; Molnar, L.F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S.T.; Gilbert, A.T.B.; Slipchenko, L.V.; Levchenko, S.V.; O'Neill, D.P.; DiStasio, R.A. Jr; Lochan, R.C.; Wang, T.; Beran, G.J.O.; Besley, N.A.; Herbert, J.M.; Lin, C.Y.; Van Voorhis, T.; Chien, S.H.; Sodt, A.; Steele, R.P.; Rassolov, V.A.; Maslen, P.E.; Korambath, P.P.; Adamson, R.D.; Austin, B.; Baker, J.; Byrd, E.F.C.; Dachsel, H.; Doerksen, R.J.; Dreuw, A.; Dunietz, B.D.; Dutoi, A.D.; Furlani, T.R.; Gwaltney, S.R.; Heyden, A.; Hirata, S.; Hsu, C.-P.; Kedziora, G.; Khalliulin, R.Z.; Klunzinger, P.; Lee, A.M.; Lee, M.S.; Liang, W.Z.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E.I.; Pieniazek, P.A.; Rhee, Y.M.; Ritchie, J.; Rosta, E.; Sherrill, C.D.; Simmonett, A.C.; Subotnik, J.E.; Woodcock, H.L. III; Zhang, W.; Bell, A.T.; Chakraborty, A.K.; Chipman, D.M.; Keil, F.J.; Warshel, A.; Hehre, W.J.; Schaefer, H.F.; Kong, J.; Krylov, A.I.; Gill, P.M.W.; Head-Gordon. *M. Phys. Chem. Chem. Phys.*, **2006**, *8*, 3172–3191.

23. Lu, S.; BeiPoh, S.; Siau, W.-Y.; Zhao, Y. *Angew. Chem. Int. Ed.*, **2013**, *52*, 1731-1734.

24. Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.*, **1998**, *63*, 7536–7538.

IV. Spirooxindole-fused 3-Thiazoline Compounds: Asinger-Type Reaction

A one-pot, three-component reaction has been developed and successfully employed for the synthesis of biologically relevant, highly functionalized spirooxindole-fused 3-thiazoline derivatives. Starting from ammonia, three different mercapto carbonyl components and a series of differently substituted isatins, products were obtained in good yields (24 examples), by means of a simple and rapid protocol. The obtained thiazolines proved to be optimal substrates for further transformations, including the three-component Ugi-Joullié reaction.

Published in *Synlett*, **2016**, *27*, 2831-2836.

IV.1 Introduction

Thiazoline heterocycles are privileged motifs found in an array of biologically active natural products. For instance, they represent a relevant structural fragment of various cyclopeptide alkaloids extracted from different marine organisms and endowed with a promising cytotoxic activity (Figure 1).[1] Compounds bearing thiazoline moieties have also been reported to exhibit a wide spectrum of different biological effects, including anti-tubercular,[2] anti-inflammatory[3,4] and antimicrobial[5] activity, boosting numerous synthetic and medicinal chemistry investigations.[6,7] Recently, many research groups have paid attention to the anticancer properties of thiazoline-based compounds, ranging from cytotoxicity against various cell lines[8] to histone deacetylase inhibitory activity[9] and MDM2-p53 protein-protein interaction modulation.[10] As part of our interest in the synthesis of spirooxindoles,[11] we looked into the biological significance of the thiazoline ring, aiming to introduce it as a spiro-fused heterocycle in our oxindole-based drug discovery programs.[12] It is well known as the conjugation of privileged heterocycles into spiro structures is of special interest, being able to provide compounds with great three-dimensionality, often

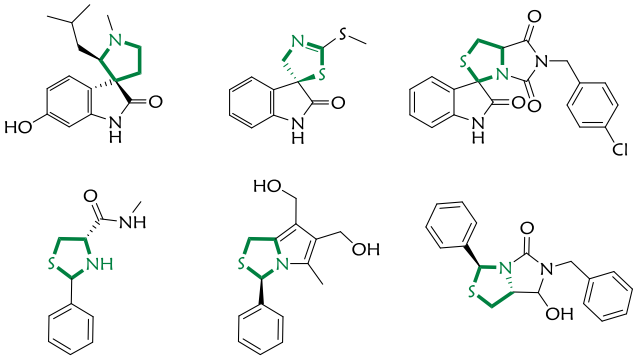
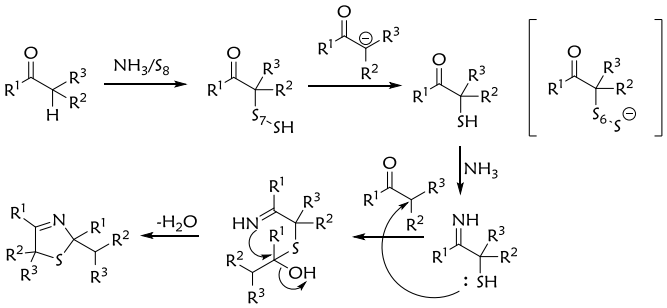


Figure 1. Examples of products containing thiazoline and 3,3'-disubstituted oxindole motifs.

improved properties in their interaction with biological systems and overall more likely to be successfully developed as drugs.[13] Spirocyclic oxindoles have recently emerged as attractive targets, since they seem to be promising candidates for their anticancer potentials.[14] Among the class, there are natural products like Spirotryprostatins A and B[15] and synthetic spirooxindoles such as MI-888, currently in preclinical research for the treatment of human cancers.[16] The common characteristic of such bioactive compounds is the presence of various heterocyclic motifs, jointed at the C-3 position of the oxindole core. This key structural element is the focus of a huge interest to develop rapid and efficient synthetic methods providing access to such spiro building blocks.

In the context of sulfur-containing compounds' synthesis, a number of methods have been carried out for the preparation of spirooxindole-based 4-thiazolidinones, by reacting amines with isatins and mercaptoacetic acid under different conditions.[17] At the best of our knowledge, no efforts have been made yet in synthesizing spiro oxindole-fused 3-thiazolines, which would represent more versatile intermediates, thanks to the presence of the reactive C-N double bond.

Relying on our previous experience in multicomponent reactions (MCRs) applied to the synthesis of heterocyclic compounds,[18] we turned our attention to the Asinger sulfur-involving MCR.[19] The method, which allows to synthesize the thiazoline scaffold by treating a ketone with sulfur and ammonia, exhibits high atom-economy (Scheme 1).

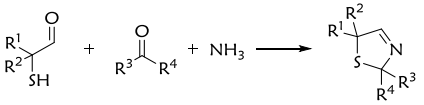


Scheme 1. Most widely accepted mechanism for the Asinger four components reaction (A-4CR).

However, considerable more flexibility with respect to the original protocol is seen in the "resynthesis", also discovered by Asinger, that is the reaction of preformed α-sulfanyl-ketones or aldehydes with ammonia and an oxo component, able to largely widen the scope of substituents on the thiazoline ring (Scheme 2).[20] Herein we report the first application of an Asinger-type reaction to isatin as the oxo component, allowing the synthesis of a large family of unprecedented 5'*H*-spiro[indoline-3,2'-thiazol]-2-one derivatives.

IV.2 Results and Discussion

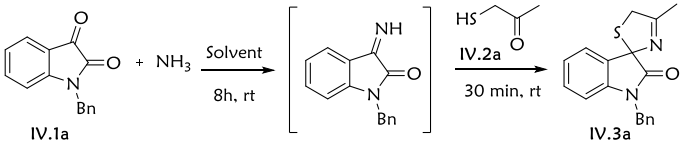
Initially, *N*-benzyl-isatin **IV·1a** and 1-mercaptopropan-2-one **IV·2a** were selected to optimize the reaction conditions (Table 1). Since the reaction conducted by



Scheme 2. "Resynthesis" variant of the Asinger reaction.

simultaneous addition of all components proved to be sluggish, probably due to the high instability of the isatin-derived *NH*-imine,[21] we introduced a waiting time of 8 h before adding the mercapto component, in order to maximize the imine formation. Using aqueous ammonia solution in MeOH as solvent, after addition of **IV·2a** the desired thiazoline **IV·3a** could be detected only in traces (entry 1). We obtained better results employing 2N ammonia solution in methanol and changing the solvent to toluene. The addition of a dehydrating agent proved to be beneficial, with $MgSO_4$ working better than molecular sieves (entry 2-3). Finally, lowering the substrate concentration elongated the reaction time reducing the conversion, while increasing the concentration gave a clean reaction, with a high isolated yield for **IV·3a** (entries 4-5). Finally, also CH_2Cl_2 proved to be a good solvent for the reaction, although thiazoline **IV·3a** could be isolated in a bit lower yield (entry 6).

Table 1. Optimization of the one-pot reaction conditions.[a]



Entry	Solvent	Conc. [M]	Dehydr. agent	Ammonia source	Yield (%)[b]
1	MeOH	0.5	none	aq. NH_3	trace
2	Toluene	0.5	3Å ms	NH_3 2N in MeOH	60
3	Toluene	0.5	$MgSO_4$	NH_3 2N in MeOH	66
4	Toluene	0.3	$MgSO_4$	NH_3 2N in MeOH	61
5	**Toluene**	**1.0**	**$MgSO_4$**	**NH_3 2N in MeOH**	**88**
6	CH_2Cl_2	1.0	$MgSO_4$	NH_3 2N in MeOH	84

[a] Reaction conditions: *N*-benzyl-isatin **IV·1a** (0.25 mmol), NH_3 (0.5 mmol); then 1-mercaptopropan-2-one **IV·2a** (0.3 mmol). [b] Isolated yields. ms = molecular sieves.

Therefore, the optimized conditions for this one-pot reaction has been found by adding 2N ammonia solution in methanol (0.5 mmol) to a toluene solution of **IV·1a** (0.25 mmol), waiting for 8 h and then completing the reaction by addition of **IV·2a** (0.3 mmol). The whole process is carried out at room temperature and the imine conversion is complete after just 30 minutes from the addition of the mercapto component. The scale-up experiment, performed employing 1 mmol of isatin **IV·1a**, afforded the desired thiazoline **IV·3a** in the same time and yield quite similar to that obtained on the small scale.

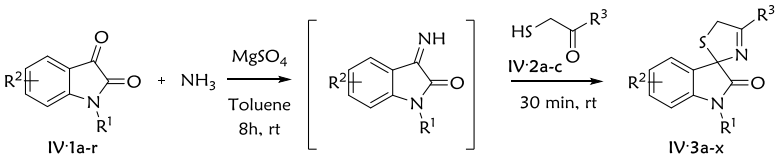
With the optimized reaction conditions in hand, a variety of diversely substituted isatins **IV·1a-r** were next explored to investigate the substrate scope of this Asinger-type reaction. The generality was also evaluated with respect to the mercapto component **IV·2a-c** (Scheme 3).

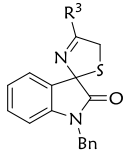
Working with 1-mercaptopropan-2-one **IV·2a**, the protecting group on oxindole nitrogen atom was found to have a moderate effect on the reaction, with all compounds **IV·3a-g** obtained in definitely satisfactory yields starting from corresponding isatins **IV·1a-g**. Notably, unprotected *NH*-isatin **IV·1d** also afforded the corresponding thiazoline derivative **IV·3d** in very high yield, as a quite stable compound. Next, *N*-benzyl isatins (**IV·1h-m**) with various substituents on the aromatic ring were explored. Good yields of the corresponding thiazolines were obtained in the presence of a variety of substituents, including an electron-donating group (compound **IV·3h**), halogen substituents (compounds **IV·3i-k,m**) and a strong electron-withdrawing group (compound **IV·3l**) at the 5- or 6-position on the oxindole aromatic ring. Finally, we investigated the Asinger-type reaction with two different mercaptocarbonyl compounds, namely 2-mercaptoacetaldehyde **IV·2b** and ethyl 3-mercapto-2-oxopropanoate **IV·2c**. We

were delighted to see that, also with these components, the desired thiazolines could be easily obtained, with yields up to 81% for the most reactive *N*-Me isatin **V·1b** in reaction with 2-mercaptoacetaldehyde **IV·2b** obtaining **IV·3o**.

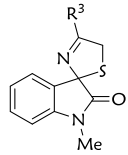
Having established the scope of the method, we examined some further transformations.

Scheme 3. Synthesis of various spirooxindole-fused 3-thiazoline derivatives.[a]

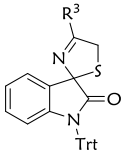




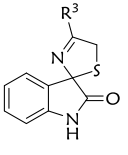
IV·3a (88%),
R^3=Me.
IV·3n (71%),
R^3=H.



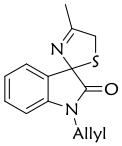
IV·3b (90%),
R^3=Me.
IV·3o (81%),
R^3=H.



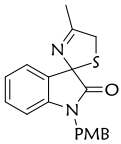
IV·3c (87%),
R^3=Me.
IV·3p (62%),
R^3=H.



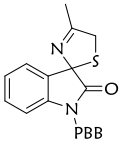
IV·3d (89%),
R^3=Me.
IV·3q (68%),
R^3=H.



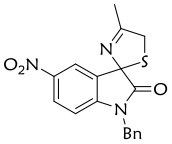
IV·3e (70%)



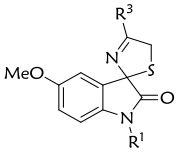
IV·3f (62%)



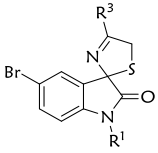
IV·3g (69%)



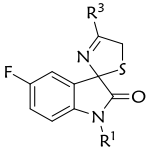
IV·3l (64%)



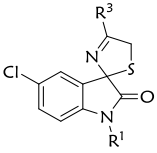
IV·3h (70%),
R^1=Bn, R^3=Me.
IV·3r (68%),
R^1=Me, R^3=H.



IV·3i (75%),
R^1=Bn, R^3=Me.
IV·3s (66%),
R^1=Me, R^3=H.

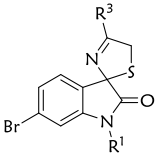


IV·3j (78%),
R^1=Bn, R^3=Me.
IV·3t (71%),
R^1=Me, R^3=H.

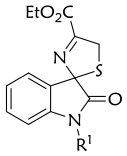


IV·3k (80%),
R^1=Bn, R^3=Me.
IV·3u (70%),
R^1=Me, R^3=H.

continued



IV·3m (65%),
R^1=Bn, R^3=Me.
IV·3v (66%),
R^1=Me, R^3=H.

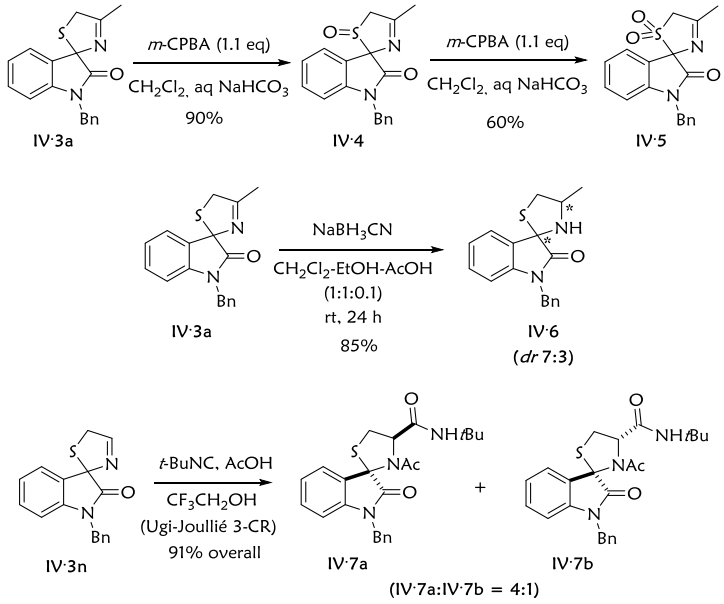


IV·3w (65%),
R^1=Bn.
IV·3x (61%),
R^1=Me.

[a] Reaction conditions: isatin **IV·1** (1 mmol), NH_3 (2 mmol); then compound **IV·2** (1.1 mmol). Isolated yields are reported. Trt = trityl. PMB = *p*-Methoxy benzyl. PBB = *p*-Bromo benzyl.

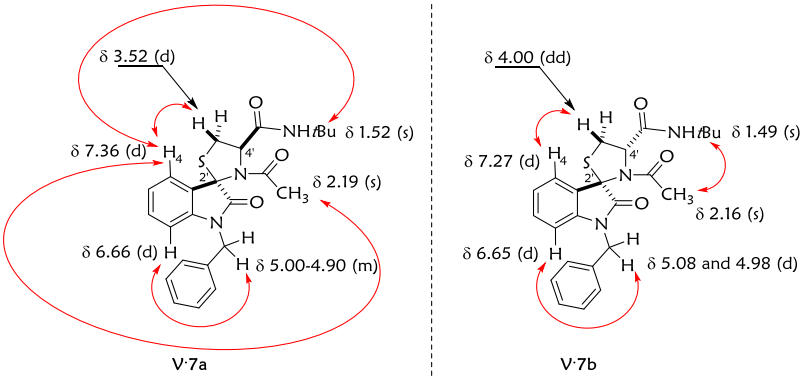
The reaction of thiazoline **IV·3a** with *m*-chloroperbenzoic acid under the standard conditions gave the sulfoxide **IV·4** in quantitative yield, as a single diastereoisomer (as demonstrated by ^{1}H and ^{13}C NMR spectra) whose relative stereochemistry was not further investigated. The latter compound could be then successfully further oxidized to sulfone **IV·5**. When the reduction of **IV·3a** was performed under standard conditions, the expected thiazolidine **IV·6** could be easily obtained, as an inseparable 7:3 diastereoisomeric mixture. Even more interesting, thiazoline **IV·3n** proved to be an optimal substrate for a subsequent multicomponent reaction (MCR), namely the Ugi-Joullié 3-CR, involving an isocyanide and a carboxylic acid as components, beside the cyclic imine. Reacting **IV·3n** with *t*-butyl isocyanide and acetic acid, compound **IV·7** was readily achieved in high yield, as a 4:1 mixture of **IV·7a** and **IV·7b** diastereoisomers, that could be easily separated by means of flash chromatography (Scheme 4).

Scheme 4. Further transformations of spirooxindole-fused 3-thiazolines.



Diastereoisomers **IV·7a** and **IV·7b** were fully characterized by means of mono- and bi-dimensional NMR. In particular, the NOESY experiment allowed to disclose the 2'-4'-trans-configuration for the major diastereoisomer **IV·7a** and the 2'-4'-cis one for the minor **IV·7b**. Diagnostic NOE contacts between H4 of the oxindole nucleus and thiazolidine's protons (safely assigned on the basis of the observed signals' multiplicity and dihedral angles considerations) could be indeed easily highlighted for both diastereoisomers. They are reported in Figure 2, together with most relevant chemical shift values.

Figure 2. Diagnostic NOE contacts for compounds **IV·7a** and **IV·7b**.



IV.3 Conclusion

In conclusion, we have successfully developed the application of an Asinger-type reaction to isatin as the oxo component, allowing the synthesis of a large family of spirooxindole-fused 3-thiazoline derivatives. The reaction's conditions have been optimized and applied to a wide variety of substituted isatins and different mercapto components underlining the robustness of the method. In addition, some post-transformations have been performed to increase the number of useful compounds. In particular, the discovery of the high reactivity of the C-N double bond in the thiazoline ring was the starting point for a related project aimed to explore diversity oriented synthesis (DOS) of spirooxindole-3-fused thiazolidine derivatives as possible leads compounds for drug discovery programs.

IV.4 Experimental Section

All commercial materials (Aldrich, Fluka) were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with ninhydrin solution in ethanol. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Q-ToF micro TM mass spectrometer, equipped with an ESI source. All diversely substituted isatins (**IV·1a-r**) were synthesized following literature procedures and the analytical data were consistent with those reported.[21]

General procedure A (GP-A) for the synthesis of spirooxindole-fused 3-thiazoline derivatives IV·3a-x. To a solution of isatin derivative **IV·1a-r** (1 mmol) in anhydrous toluene (1 mL, 1.0 M), $MgSO_4$ (3 mmol) and NH_3 solution 2M in methanol (2 mmol) were added. The reaction was stirred 8 hours at room temperature and then the mercapto-derivative **IV·2a-c** was added (1.1 mmol). The resulting mixture was stirred for further 30 minutes at the same temperature. The reaction was diluted with CH_2Cl_2 (5 mL) and then the solvent was removed

under reduced pressure. The crude was purified by flash chromatography (FC) as indicated below.

1-Benzyl-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3a). Prepared according to GP-A using isatin **IV·1a** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 271 mg, 88%; pale orange foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (m, 6H), 7.19 (t, br, *J* = 7.7 Hz, 1H), 7.04 (t, br, *J* = 7.7 Hz, 1H), 6.69 (d, br, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 15.7 Hz, 1H), 4.84 (d, *J* = 15.7 Hz, 1H), 4.43 (d, *J* = 15.8 Hz, 1H), 4.27 (d, *J* = 15.8 Hz, 1H), 2.32 (*s*, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 174.9, 142.4, 135.4, 130.2, 129.6, 128.9 (2C), 127.7, 127.3 (2C), 125.5, 123.5, 109.5, 88.2, 48.7, 44.2, 19.9; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaOS^+$ $[MNa]^+$ 331.0876, found 331.0884.

1,4'-Dimethyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3b). Prepared according to GP-A using isatin **IV·1b** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 9:1; yield: 209 mg, 90%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.21 (m, 2H), 7.08 (t, br, *J* = 7.7 Hz, 1H), 6.81 (d, br, *J* = 7.7 Hz, 1H), 4.39 (d, *J* = 15.8 Hz, 1H), 4.24 (d, *J* = 15.8 Hz, 1H), 3.19 (*s*, 3H), 2.28 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 174.6, 143.2, 130.3, 130.0, 125.4, 123.3, 108.4, 88.1, 48.6, 26.6, 19.8; HRMS (ESI) calcd for $C_{12}H_{12}N_2NaOS^+$ $[MNa]^+$ 255.0563, found 255.0557.

4'-Methyl-1-trityl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3c). Prepared according to GP-A using isatin **IV·1c** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 400 mg, 87%; brown foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, br, *J* = 7.6 Hz, 6H), 7.36-7.18 (m, 10 H), 6.98 (t, br, *J* = 7.6 Hz, 1H), 6.93 (td, *J* = 7.7 and 1.7 Hz, 1H), 6.27 (d, br, *J* = 7.8 Hz, 1H), 4.34 (d, *J* = 15.8 Hz, 1H), 4.21 (d, *J* = 15.8 Hz, 1H), 2.30 (*s*, 3H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 176.4, 176.0, 143.7, 142.5 (3C), 130.3, 130.2(6C), 129.3, 128.6, 128.4 (6C), 127.6 (3C), 125.5, 123.5, 116.7, 88.8, 48.9, 20.6; HRMS (ESI) calcd for $C_{30}H_{24}N_2NaOS^+$ $[MNa]^+$ 483.1502, found 483.1511.

4'-Methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3d). Prepared according to GP-A using isatin **IV·1d** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 7:3; yield: 194 mg, 89%; pale orange foam; ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (*s*, br, 1H), 7.30-7.16 (m, 2H), 7.03 (d, br, *J* = 7.7 Hz, 1H), 6.85 (d, br, *J* = 7.7 Hz, 1H), 4.39 (d, *J* = 15.9 Hz, 1H), 4.26 (d, *J* = 15.9 Hz, 1H), 2.30 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 175.5, 140.5, 130.3, 130.1, 125.7, 123.4, 110.5, 88.7, 48.6, 19.9; HRMS (ESI) calcd for $C_{11}H_{10}N_2NaOS^+$ $[MNa]^+$ 241.0406, found 241.0413.

1-Allyl-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3e). Prepared according to GP-A using isatin **IV·1e** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 180 mg, 70%; brown foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.23 (m, 2H), 7.08 (t, br, *J* = 7.6 Hz, 1H), 6.82 (d, br, *J* = 7.7 Hz, 1H), 5.84 (ddt, *J* = 15.6, 10.8 and 4.9 Hz, 1H), 5.35-5.14 (m, 2H), 4.40 (d, *J* = 16.6 Hz, 1H), 4.32 (m, br, 2H), 4.25 (d, *J* = 16.6 Hz, 1H), 2.30 (*s*, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 175.1, 143.2, 131.6, 130.8, 130.2, 126.2, 124.0, 118.6, 110.0, 88.7, 49.3, 43.5, 20.8; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaOS^+$ $[MNa]^+$ 281.0719, found 281.0711.

1-(4-Methoxybenzyl)-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3f). Prepared according to GP-A using isatin **IV·1f** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 209 mg, 62%; brown foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 -7.16 (m, 4H), 7.04 (t, br, *J* = 7.6 Hz, 1H), 6.83 (d, br, *J* = 8.6 Hz, 2H), 6.71 (d, br, *J* = 7.7 Hz, 1H), 4.88 (d, *J* = 15.5 Hz, 1H), 4.78 (d, *J* =

15.5 Hz, 1H), 4.43 (d, *J* = 15.8 Hz, 1H), 4.26 (d, *J* = 15.8 Hz, 1H), 3.76 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 174.8, 159.2, 142.4, 130.2, 129.6, 128.7 (2C), 127.3, 125.5, 123.4, 114.2 (2C), 109.6, 88.2, 55.3, 48.6, 43.7, 19.9; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_2S^+$ $[MNa]^+$ 361.0981, found 361.0987.

1-(4-Bromobenzyl)-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3g). Prepared according to GP-A using isatin **IV·1g** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 267 mg, 69%; orange foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, br, *J* = 8.3 Hz, 2H), 7.31 (d, br, *J* = 7.6 Hz, 1H), 7.25-7.15 (m, 3H), 7.06 (t, br, *J* = 7.5 Hz, 1H), 6.64 (d, br, *J* = 7.7 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.43 (d, *J* = 15.8 Hz, 1H), 4.27 (d, *J* = 15.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 170.1, 143.1, 142.1, 132.0, 130.2 (2C), 129.6, 129.1 (2C), 129.0, 125.7, 123.7, 109.3, 88.1, 48.7, 43.6, 19.9; HRMS (ESI) calcd for $C_{18}H_{15}N_2BrNaOS^+$ $[MNa]^+$ 408.9981, found 408.9988.

1-Benzyl-5-methoxy-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3h). Prepared according to GP-A using isatin **IV·1h** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 237 mg, 70%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 6.92 (d, br, *J* = 2.6 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.57 (d, br, *J* = 8.5 Hz, 1H), 4.92 (d, *J* = 15.7 Hz, 1H), 4.82 (d, J = 15.7 Hz, 1H), 4.44 (d, *J* = 15.8 Hz, 1H), 4.27 (d, *J* = 15.8 Hz, 1H), 3.74 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 174.8, 156.6, 135.7, 135.4, 128.9 (2C), 127.7 (2C), 127.2, 115.4, 112.0, 111.4, 110.2, 88.5, 55.8, 48.7, 44.3, 19.9; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_2S^+$ $[MNa]^+$ 361.0981, found 361.0974.

1-Benzyl-5-bromo-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3i). Prepared according to GP-A using isatin **IV·1i** and mercaptoacetone **IV·2a**. FC:

CH_2Cl_2:EtOAc, 19:1; yield: 290 mg, 75%; brown foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, br, *J* = 1.9 Hz, 1H), 7.35-7.22 (m, 6H), 6.54 (d, br, J = 8.3 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.81 (d, *J* = 15.7 Hz, 1H), 4.42 (d, *J* = 15.8 Hz, 1H), 4.27 (d, *J* = 15.8 Hz, 1H), 2.32 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 174.4, 141.4, 134.8, 133.0, 131.7, 129.0 (2C), 128.8, 128.0, 127.2 (2C), 116.1, 111.1, 87.9, 48.9, 44.3, 19.9; HRMS (ESI) calcd for $C_{18}H_{15}BrN_2NaOS^+$ $[MNa]^+$ 408.9981, found 408.9990.

1-Benzyl-5-fluoro-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3j).

Prepared according to GP-A using isatin **IV·1j** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 254 mg, 78%; pale orange foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 7.05 (dd, *J* = 7.8, 2.9 Hz, 4 1H), 6.89 (td, *J* = 8.8, 2.9 Hz, 1H), 6.59 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.93 (d, *J* = 15.8 Hz, 1H), 4.83 (d, *J* = 15.8 Hz, 1H), 4.44 (d, *J* = 15.8 Hz, 1H), 4.28 (d, *J* = 15.8 Hz, 1H), 2.33 (*s*, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 174.8, 159.6 (d, J = 241.8 Hz), 138.3, 135.0, 131.2 (d, J = 7.4 Hz), 128.9 (2C), 127.9, 127.2 (2C), 116.6 (d, J = 23.6 Hz), 113.6 (d, J = 25.1 Hz), 110.2 (d, J = 8.8 Hz), 88.1, 48.8, 44.4, 19.9; HRMS (ESI) calcd for $C_{18}H_{15}FN_2NaOS^+$ $[MNa]^+$ 349.0781, found 349.0786.

1-Benzyl-5-chloro-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3k).

Prepared according to GP-A using isatin **IV·1k** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 274 mg, 80%; brown foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.23 (m, 6H), 7.16 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.59 (d, br, *J* = 8.3 Hz, 1H), 4.93 (d, *J* = 15.8 Hz, 1H), 4.83 (d, *J* = 15.8 Hz, 1H), 4.44 (d, *J* = 15.8 Hz, 1H), 4.28 (d, *J* = 15.8 Hz, 1H), 2.33 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 174.6, 140.9, 134.9, 131.2, 130.1, 130.0, 129.0 (2C), 127.9, 127.2 (2C),

126.1, 110.5, 90.4, 48.8, 44.3, 19.9; HRMS (ESI) calcd for $C_{18}H_{15}ClN_2NaOS^+$ $[MNa]^+$ 365.0486, found 365.0492.

1-Benzyl-4'-methyl-5-nitro-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3l). Prepared according to GP-A using isatin **IV·1l** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 226 mg, 64%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23-8.13 (m, 2H), 7.40-7.23 (m, 5H), 6.77 (d, br, *J* = 7.8 Hz, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 4.91 (d, *J* = 15.6 Hz, 1H), 4.48 (d, *J* = 15.9 Hz, 1H), 4.36 (d, *J* = 15.9 Hz, 1H), 2.36 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 175.0, 147.9, 144.0, 134.2, 130.8, 129.2, 128.3 (2C), 127.2 (2C), 127.0, 121.7, 109.3, 87.4, 49.1, 44.6, 19.9; HRMS (ESI) calcd for $C_{18}H_{15}N_3NaO_3S^+$ $[MNa]^+$ 376.0726, found 376.0721.

1-Benzyl-6-bromo-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3m). Prepared according to GP-A using isatin **IV·1m** and mercaptoacetone **IV·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 252 mg, 65%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40- 7.14 (m, 7H), 6.84 (s, br, 1H), 4.92 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.8 Hz, 1H), 4.43 (d, *J* = 15.8 Hz, 1H), 4.26 (d, *J* = 15.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 174.8, 143.7, 134.7, 129.0 (2C), 128.5, 128.0, 127.2 (2C), 126.8, 126.4, 123.9, 112.9, 88.9, 48.7, 44.4,19.9; HRMS (ESI) calcd for $C_{18}H_{15}BrN_2NaOS^+$ $[MNa]^+$ 408.9981, found 408.9987.

1-Benzyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3n). Prepared according to GP-A using isatin **IV·1a** and mercaptoacetaldehyde **IV·2b**. FC: *n*-Hexane:EtOAc, 19:1; yield: 209 mg, 71%; brown foam; ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (s, br, 1H), 7.44-7.18 (m, 7H), 7.09 (t, br, *J* = 7.8 Hz, 1H), 6.87 (d, br, *J* = 7.8 Hz, 1H), 4.94 (m, 2H), 4.52 (d, br *J* = 16.8 Hz, 1H), 4.40 (d, br, *J* = 16.8 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.8, 169.0, 143.8, 137.1, 131.9, 131.2, 130.2

(2C), 129.2, 128.5 (2C), 127.0, 125.2, 111.4, 90.6, 48.2, 45.1; HRMS (ESI) calcd for $C_{17}H_{14}N_2NaO_2S^+$ $[MNa]^+$ 317.0719, found 317.0711.

1-Methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3o). Prepared according to GP-A using isatin **V·1b** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 9:1; yield: 176 mg, 81%; orange foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (*s*, br, 1H), 7.35 (t, br, *J* = 7.8 Hz, 1H), 7.27 (d, br, *J* = 7.8 Hz, 1H), 7.10 (t, br, *J* = 7.8 Hz, 1H), 6.85 (d, br, *J* = 7.8 Hz, 1H), 4.50-4.30 (m, 2H), 3.23 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 165.2, 143.4, 130.5, 129.4, 125.5, 123.5, 108.6, 89.1, 47.1, 26.8; HRMS (ESI) calcd for $C_{11}H_{10}N_2NaOS^+$ $[MNa]^+$ 241.0406, found 241.0414.

1-Trityl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3p). Prepared according to GP-A using isatin **IV·1c** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 277 mg, 62%; yellow foam; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (*s*, br, 1H), 7.44 (d, br, *J* = 7.8 Hz, 6H), 7.33-7.15 (m, 10H), 7.00-6.86 (m, 2H), 6.25 (d, br, *J* = 7.8 Hz, 1H), 4.32 (*s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 165.5, 143.2, 141.7 (3C), 141.5, 129.4 (6C), 127.9, 127.7 (6C), 127.0 (3C), 125.0, 122.9, 116.1, 89.3, 74.6, 46.8; HRMS (ESI) calcd for $C_{29}H_{22}N_2NaOS^+$ $[MNa]^+$ 469.1453, found 469.1446.

5'H-Spiro[indoline-3,2'-thiazol]-2-one (IV·3q). Prepared according to GP-A using isatin **IV·1d** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 7:3; yield: 154 mg, 68%; grey foam; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (m, br, 1H), 7.87 (*s*, br, 1H), 7.36-7.19 (m, 2H), 7.07 (t, br, *J* = 7.8 Hz, 1H), 6.89 (d, br, *J* = 7.8 Hz, 1H), 4.41 (*s*, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.4, 166.6, 142.0, 130.7, 126.2, 125.9, 122.9, 110.6, 89.6, 47.3. HRMS (ESI) calcd for $C_{10}H_8N_2NaOS^+$ $[MNa]^+$ 227.0250, found 227.0259.

5-Methoxy-1-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3r). Prepared according to GP-A using isatin **IV·1n** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 9:1; yield: 169 mg, 68%; grey foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, br, 1H), 6.92-6.85 (m, 2H), 6.75 (d, br, *J* = 7.8 Hz, 1H), 4.43 (d, *J* = 16.6 Hz, 1H), 4.37 (dd, *J* = 16.6 and 1.9 Hz, 1H), 3.77 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 165.4, 156.7, 136.7, 130.5, 115.5, 112.1 109.2, 89.4, 55.9, 47.1, 26.8 ; HRMS (ESI) calcd for $C_{12}H_{12}N_2NaO_2S^+$ $[MNa]^+$ 271.0512, found 271.0519.

5-Bromo-1-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3s). Prepared according to GP-A using isatin **IV·1o** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 9:1; yield: 196 mg, 66%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, br, 1H), 7.47 (dd, *J* = 7.8 and 2.0 Hz, 1H), 7.37 (d, br, *J* = 1.9 Hz, 1H), 6.73 (d, br, *J* = 7.8 Hz, 1H), 4.50-4.320 (m, 2H), 3.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 165.6, 142.5, 133.3, 131.3, 128.8, 116.0, 110.1, 88.8, 47.3, 26.9; HRMS (ESI) calcd for $C_{11}H_9BrN_2NaOS^+$ $[MNa]^+$ 318.9511, found 318.9504.

5-Fluoro-1-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3t). Prepared according to GP-A using isatin **IV·1p** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 9:1; yield: 167 mg, 71%; grey foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.06 (td, *J* = 8.8, 2.4 Hz, 1H), 7.02 (dd, *J* = 7.5, 2.4 Hz, 1H), 6.79 (dd, *J* = 8.5, 4.1 Hz, 1H), 4.43 (dd, *J* = 16.7 and 1.0 Hz, 1H), 4.39 (dd, *J* = 16.7 and 1.4 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 165.6, 159.7 (d, J = 241.8 Hz), 139.3, 130.9 (d, J = 8.8 Hz), 116.8 (d, J = 23.6 Hz), 113.6 (d, J = 25.0 Hz), 109.2 (d, J = 7.4 Hz), 89.1, 47.2, 26.9; HRMS (ESI) calcd for $C_{11}H_9FN_2NaOS^+$ $[MNa]^+$ 259.0312, found 259.0320.

5-Chloro-1-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3u). Prepared according to GP-A using isatin **IV·1q** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 9:1; yield: 177 mg, 70%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, br, 1H), 7.32 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.25 (m, 1H), 6.78 (d, br, *J* = 8.3 Hz, 1H), 4.41 (m, 2H), 3.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 165.6, 141.9, 130.4, 130.3, 128.8, 126.1, 109.6, 88.8, 47.2, 26.8; HRMS (ESI) calcd for $C_{11}H_9ClN_2NaOS^+$ $[MNa]^+$ 275.0016, found 275.0022.

6-Bromo-1-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one (IV·3v). Prepared according to GP-A using isatin **IV·1r** and mercaptoacetaldehyde **IV·2b**. FC: CH_2Cl_2:EtOAc, 90:10; yield: 196 mg, 66%; brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, br, 1H), 7.23 (dd, *J* = 7.8 and 1.9 Hz, 1H), 7.11 (d, br, *J* = 7.8 Hz, 1H), 7.00 (d, br, *J* = 1.9 Hz, 1H), 4.41 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 15.6 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 165.5, 144.7, 128.3, 126.8, 126.3, 124.2, 112.1, 88.6, 47.1, 26.9; HRMS (ESI) calcd for $C_{11}H_9BrN2NaOS^+$ $[MNa]^+$ 318.9511, found 318.9516.

Ethyl 1-benzyl-2-oxo-5'H-spiro[indoline-3,2'-thiazole]-4'-carboxylate (IV·3w). Prepared according to GP-A using isatin **IV·1a** and ethyl mercaptopiruvate **IV·2c**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 238 mg, 65%; brown foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.22 (m, 7H), 7.09 (t, br, *J* = 7.8 Hz, 1H), 6.74 (d, br, *J* = 7.8 Hz, 1H), 4.99 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 16.9 Hz, 1H), 4.64 (d, *J* = 16.9 Hz, 1H), 4.43 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 168.2, 161.8, 143.3, 135.6, 131.4, 129.6 (2C), 129.2, 128.5, 128.0 (2C), 126.8, 124.3, 110.3, 89.2, 63.7, 46.0, 45.1, 14.8; HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_3S^+$ $[MNa]^+$ 389.0930, found 389.0937.

Ethyl 1-methyl-2-oxo-5'H-spiro[indoline-3,2'-thiazole]-4'-carboxylate (IV·3x). Prepared according to GP-A using isatin **IV·1b** and ethyl mercaptopiruvate **IV·2c**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 177 mg, 61%; orange foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.31 (m, 2H), 7.10 (t, br, *J* = 7.7 Hz, 1H), 6.83 (d, br, *J* = 7.7 Hz, 1H), 4.65 (d, *J* = 16.6 Hz, 1H), 4.59 (d, *J* = 16.6 Hz, 1H), 4.38 (m, 2H), 3.21 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.1, 161.1, 143.5, 130.9, 128.5, 126.1, 123.6, 108.6, 88.6, 62.9, 45.3, 26.8, 14.1; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_3S^+$ $[MNa]^+$ 313.0617, found 313.0625.

Post-transformation reactions

1-benzyl-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one 1'-oxide (IV·4). To solution of **IV·3a** (308 mg, 1 mmol) in CH_2Cl_2 (0.5 mL) and aq. 5% $NaHCO_3$ (1.5 mL) cooled at 0°C, *m*-CPBA (1.1 mmol) was added in portions. The reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude was purified by flash column chromatography (*n*-Hexane:EtOAc, 1.5:1) on silica gel affording **IV·4** as single diastereoisomer (291 mg, 90% yield); brown foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, br, *J* = 7.5 Hz, 1H), 7.39-7.21 (m, 6H), 7.13 (t, br, *J* = 7.6 Hz, 1H), 6.81 (d, br, *J* = 7.7 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.84 (d, *J* = 15.6 Hz, 1H), 4.44 (d, *J* = 17.6 Hz, 1H), 3.98 (d, *J* = 17.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 168.9, 142.8, 134.7, 131.2, 129.0 (2C), 128.0, 127.6, 127.2 (2C), 123.9, 120.9, 109.8, 102.1, 66.9, 44.4, 21.0; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_2S^+$ $[MNa]^+$ 347.0825, found 347.0813.

1-benzyl-4'-methyl-5'H-spiro[indoline-3,2'-thiazol]-2-one 1',1'-dioxide (IV·5). To a solution of **IV·4** (33 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) and aq. 5% $NaHCO_3$ (1.5 mL) cooled at 0°C, *m*-CPBA (0.11 mmol) was added in one portion. The reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude was purified by flash column (CH_2Cl_2:EtOAc, 19:1) to give compound **IV·5** (20 mg, 60% yield); yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, br, *J* = 7.4 Hz, 1H), 7.39-7.23 (m, 6H), 7.13 (t, br, *J* = 7.6 Hz, 1H), 6.76 (d, br, *J* = 7.6 Hz, 1H), 5.10 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.42 (d, *J* = 16.6 Hz, 1H), 3.92 (d, *J* = 16.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 168.0, 144.2, 134.4, 131.8, 129.0 (2C), 128.0, 127.8, 127.1 (2C), 123.8, 118.7, 110.2, 90.7, 56.2, 44.6, 24.4; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_3S^+$ $[MNa]^+$ 363.0774, found 363.0782.

1-benzyl-4'-methylspiro[indoline-3,2'-thiazolidin]-2-one (IV·6). To a solution of **V·3a** (62 mg, 0.2 mmol) in CH_2Cl_2:EtOH:AcOH, 1:1:0.1 (2 mL), $NaBH_3CN$ (76 mg, 1.2 mmol) was added at room temperature. The reaction mixture was stirred for 24 h at the same temperature and then quenched with saturated aq. solution of $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude was purified by flash column chromatography (*n*-Hexane:EtOAc, 1.5:1) on silica gel affording **IV·6** as a 7:3 inseparable mixture of distereoisomers (53 mg, 85% yield); white oil; ^{1}H NMR (400 MHz, $CDCl_3$, 7:3 mixture of two diastereoisomers) δ 7.43 (dd, *J* = 7.5 and 1.0 Hz, 0.7H), 7.40 (dd, *J* = 7.5 and

1.0 Hz, 0.3H), 7.38-7.25 (m, 5H), 7.22 (td, *J* = 7.6 and 1.2 Hz, 0.3H), 7.17 (td, *J* = 7.6 and 1.2 Hz, 0.7H), 7.07 (t, br, *J* = 7.6 Hz, 1H), 6.72 (d, br, *J* = 7.7 Hz, 0.7H), 6.69 (d, br, *J* = 7.7 Hz, 0.3H), 5.00 (d, J = 15.6 Hz, 0.7H), 4.96 (d, *J* = 15.6 Hz, 0.3H), 4.92 (d, *J* = 15.6 Hz, 0.7H), 4.83 (d, *J* = 15.6 Hz, 0.3H), 4.38 (ddq, *J* = 9.5, 6.1 and 6.4 Hz, 0.3H), 3.86 (ddq, *J* = 10.3, 6.1 and 4.9 Hz, 07H), 3.58 (dd, *J* = 9.5 and 6.1 Hz, 0.3H), 3.49 (dd, *J* = 10.3 and 4.9 Hz, 0.7H), 2.96 (t, *J* = 9.5 Hz, 0.3H), 2.92 (t, *J* = 10.3 Hz, 0.7H), 2.25-1.80 (m, br, 1H), 1.54 (d, *J* = 6.1 Hz, 2.1H), 1.49 (d, *J* = 6.4 Hz, 0.9H); ^{13}C NMR (101 MHz, $CDCl_3$, 7:3 mixture of two diastereoisomers) δ 177.0 and 176.9(1C), 142.5 and 141.2 (1C), 135.6 and 135.2 (1C), 133.9 and 128.3 (1C), 130.0 and 129,1 (1C), 128.9 (2C), 127.8 and 127.7 (1C), 127.3 and 127.2 (2C), 124.6 and 123.7 (1C), 123.6 and 123.1 (1C), 109.7 and 109.4 (1C), 76.4 and 75.7 (1C), 63.5 and 60.4 (1C), 44.8 and 43.9 (1C), 44.4 and 43.8 (1C), 19.3 and 18.6 (1C); HRMS (ESI) calcd for $C_{18}H_{18}N_2NaOS^+$ $[MNa]^+$ 333.1032, found 333.1039.

3'-acetyl-1-benzyl-*N*-(tert-butyl)-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (IV·7). To a solution of **IV·3n** (88 mg, 0.2 mmol) in 2,2,2-trifluoroethanol (400 μL), acetic acid (23 μL, 0.4 mmol) and *tert*-buthylisocyanide (45 μL, 0.4 mmol) were added at room temperature. The reaction was stirred at the same temperature and the conversion was monitored by TLC. The solvent was removed under reduced pressure and the crude was purified by flash chromatography (FC: *n*-Hexane:EtOAc, 3:7) obtaining the two diasteroisomer in 91% overall yield.

IV·7a (major diasteroisomer, 2'-4'-trans): 64 mg; pale beige foam; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers 4:1) δ 7.44 (d, br, *J* = 7.5 Hz, 0.2H), 7.42-7.24 (m, 6H), 7.20 (t, br, *J* = 7.7 Hz, 0.8H), 7.13 (t, br, *J* = 7.6 Hz, 0.2H), 7.06

(t, br, *J* = 7.6 Hz, 0.2H), 6.94 (m, br, 0.2H), 6.84 (d, br, *J* = 7.6 Hz, 0.2H), 6.66 (d, br, *J* = 7.7 Hz, 0.8H), 6.58 (m, br, 0.8H), 5.41 (d, br, *J* = 5.9 Hz, 0.2H), 5.08 (d, *J* = 15.7 Hz, 0.2H), 5.00-4.90 (m, 2.8H), 4.82 (d, *J* = 15.7 Hz, 0.2H), 4.13 (dd, br, *J* = 11.4, 6.2 Hz, 0.8H), 3.79 (dd, br, *J* = 11.2, 5.9 Hz, 0.2H), 3.62 (d, *J* = 11.2 Hz, 0.2H), 3.52 (d, *J* = 11.4 Hz, 0.8H), 2.19 (*s*, 3H), 1.52 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers 4:1) δ 175.3, 169.5, 168.7, 142.6, 135.4 and 135.1 (1C), 130.8 and 130.1 (1C), 129.0 and 128.9 (2C), 128.8, 128.1 and 127.5 (1C), 127.0 (2C), 124.5 and 123.0 (1C), 124.2 and 122.8 (1C), 110.2 and 110.1 (1C), 72.3, 67.6 and 67.1 (1C), 52.2 and 51.4 (1C), 44.3 and 44.1 (1C), 33.9, 28.8 (3C), 23.7; HRMS (ESI) calcd for $C_{24}H_{27}N_3NaO_3S^+$ $[MNa]^+$ 460.1665, found 460.1677.

IV·7b (minor diasteroisomer, 2'-4'-*cis*): 16 mg; pale beige foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (m, br, 1H), 7.44- 7.23 (m, 6H), 7.17 (t, br, *J* = 7.7 Hz, 1H), 7.04 (t, br, *J* = 7.7 Hz, 1H), 6.65 (d, br, *J* = 7.7 Hz, 1H), 5.08 (d, *J* = 16.1 Hz, 1H), 4.98 (d, *J* = 16.1 Hz, 1H), 4.96 (d, br, *J* = 7.0 Hz, 1 H), 4.00 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.63 (d, *J* = 12.2 Hz, 1H), 2.16 (*s*, 3H), 1.49 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 169.4, 168.0, 141.0, 134.9, 131.1, 129.4, 128.9 (2C), 127.6, 126.9 (2C), 123.6, 120.7, 110.4, 73.4, 67.4, 52.3, 44.7, 36.1, 28.4 (3C), 23.3; HRMS (ESI) calcd for $C_{24}H_{27}N_3NaO_3S^+$ $[MNa]^+$ 460.1665, found 460.1674.

IV.5 References

1. (a) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *Bioorg. Med. Chem.* **2002**, *10*, 1973-1978. (b) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418-5423.

2. Reddy, D. S.; Hosamani, K. M.; Devarajegowdab, H. C.; Kurjogic, M. M. *RSC Adv.* **2015**, *5*, 64566-64581.

3. Lynch, D. E.; Hayer, R.; Beddows, S.; Howdle, J.; Thake, C. D. *J. Heterocyclic Chem.* **2006**, *43*, 191-197.

4. Pontiki, E.; Hadjipavlou-Litina, D.; Chaviara, A. T.; Bolos, C. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2234-2237.

5. Bonde, C. G.; Gaikwad, N. *J. Bioorg. Med. Chem.* **2004**, *12*, 2151-2161.

6. Gaumont, A.-C.; Gulea, M.; Levillain, J. *Chem. Rev.* **2009**, *109*, 1371-1401.

7. (a) Ino, A.; Murabayashi, A. Tewahedron **1999**, *55*, 10271-10282. (b) Ino, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron*
1999, *55*, 10283-10294.

8. Altıntop, M. D.; Kaplancıklı, Z. A.; Çiftçi, G. A.; Demirel, R. *Eu. J. Med. Chem.* **2014**, *74*, 264-277.

9. Marson, C. M.; Matthews, C. J.; Yiannaki, E.; Atkinson, S. J.; Soden, P. E.; Shukla, L.; Lamadema, N.; Thomas, N. S. B. *J. Med. Chem.* **2013**, *56*, 6156-6174.

10. Bertamino, A.; Soprano, M.; Musella, S.; Rusciano, M. R.; Sala, M.; Vernieri, E.; Di Sarno, V.; Limatola, A.; Carotenuto, A.; Cosconati, S.; Grieco, P.; Novellino, E.; Illario, M.; Campiglia, P.; Gomez-Monterrey, I. *J. Med. Chem.* **2013**, *56*, 5407-5421.

11. (a) Stucchi, M.; Lesma, G.; Meneghetti, F.; Rainoldi, G.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2016**, *81*, 1877-1884. (b) G. Lesma, N. Landoni, A. Sacchetti, A. Silvani, *Tetrahedron* **2010**, *66*, 4474-4478.

12. (a) Lesma, G.; Meneghetti, F.; Sacchetti, A.; Stucchi, M.; Silvani, A. *Belstein J. Org. Chem.* **2014**, *10*, 1383-1389. (b) Sacchetti, A.; Silvani, A.; Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, *9*, 5515-5522. (c) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537-4541.

13. (a) Yang, C.; Li, J.; Zhou, R.; Chen, X.; Gao, Y.; He, Z. *Org. Biomol. Chem.* **2015**, *13*, 4869-4878. (b) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Letters* **2014**, *24*, 3673-3682. (c) Tian, Y.; Nam, S.; Liu, L.; Yakushijin, F.; Yakushijin, K.; Buettner, R.; Liang, W.; Yang, F.; Ma, Y.; Horne, D.; Jove, R. *PLoS One* **2012**, *7*, e49306.

14. (a) Yu, B.; Yu, D.-Q.; Liu, H.-M. *Eu. J. Med. Chem.* **2015**, *97*, 673-698. (b) Santos, M. M. M. *Tetrahedron* **2014**, *70*, 9735-9757. (c) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104-6155.

Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651-12666.

15. Zhao, Y.; Yu, S.; Sun, W.; Liu, L.; Lu, J.; McEachern, D.; Shargary, S.; Bernard, D.; Li, X.; Zhao, T.; Zou, P.; Sun, D.; Wang, S. *J. Med. Chem.* **2013**, *56*, 5553-5561.

16. (a) Preetam, A.; Nath, M. *Tetrahedron Lett.* **2016**, *57*, 1502-1506. (b) Cheng, P.; Guo, W.; Chen, P.; Liu, Y.; Du, X.; Li, C. *Chem.Commun.* **2016**, *52*, 3418-3421. (c) Jain, R.; Sharma, K.; Kumar, D. *Helvetica Chim. Acta* **2013**, *96*, 414-418.

17. (a) Stucchi, M.; Cairati, S.; Cetin-Atalay, R.; Christodoulou, M. S.; Grazioso, G.; Pescitelli, G.; Silvani, A.; Yildirime, D. C.; Lesma, G. *Org. Biomol. Chem.*

2015, *13*, 4993-5005. (b) Stucchi, M.; Gmeiner, P.; Huebner, H.; Rainoldi, G.; Sacchetti, A.; Silvani, A.; Lesma, G. *ACS Med. Chem. Lett.* **2015**, *6*, 882-887. (c) Lesma, G.; Bassanini, I.; Bortolozzi, R.; Colletto, C.; Bai, R.; Hamel, E.; Meneghetti, F.; Rainoldi, G.; Stucchi, M.; Sacchetti, A.; Silvani, A.; Viola, G. *Org. Biomol. Chem.* **2015**, *13*, 11633-11644. (d) Silvani, A.; Lesma, G.; Crippa, S.; Vece, V. *Tetrahedron* **2014**, *70*, 3994-4001. (e) Lesma, G.; Cecchi, R.; Crippa, S.; Giovanelli, P.; Meneghetti, F.; Musolino, M.; Sacchetti, A.; Silvani, A. *Org. Biomol. Chem.* **2012**, *10*, 9004-9012.

18. (a) Liu, Z.-Q. *Curr. Org. Synth.* **2015**, *12*, 20-60. (b) Brockmeyer, F.; van Gerven, D.; Saak, W.; Martens, J. *Synthesis* **2014**, *46*, 1603-1612.

19. Keim, W.; Offermanns, H. *Angew. Chem. Int. Ed.* **2007**, 46, 6010-6013.

20. Žari, S.; Kudrjashova, M.; Pehk, T.; Lopp, M.; Kanger, T. *Org. Lett.* **2014**, *16*, 1740-1743.

21. (a) Ganga, M.; Kashyap, N.; Kumar, K.; Goyal, S.; Nair, V. A. Tetrahedron Lett. 2015, 56, 7074-7081. (b) Aikawa, K.; Mimura, S.; Numata, Y.; Mikami, K. *Eur. J. Org. Chem.* **2011**, *1*, 62-65. (c) Ogura, Y.; Agakura, M.; Sakakura, A.; Ishihara, K. *Angew. Chem. Int. Ed.* **2013**, *125*, 8457-8461. (d) Senadi, G. C.; Chandru, H. W.; Boominathan, S. S. K.; Wang, J. J. *Chem. Eur. J.* **2015**, *21*, 998-1003.

V. Spirooxindole-fused 3-Thiazolidine-Carboxamide and Tetrazol Derivatives: Sequential Asinger/Ugi-like Reactions

We developed two Ugi-type three-component reactions of spirooxindole-fused 3-thiazolines, isocyanides and either carboxylic acids or trimethylsilylazide to give highly functionalized spirooxindole-fused thiazolidines. Two small but diverse libraries were generated using practical and robust procedures affording the products in typically good yields. The obtained thiazolidines proved to be suitable substrates for further transformations. Notably, both the Ugi-Joullié and the azido-Ugi reactions were highly diastereoselective, affording predominantly the trans-configured products, as confirmed by X-ray crystallographic analysis.

Submitted to *ACS Combinatorial Science*

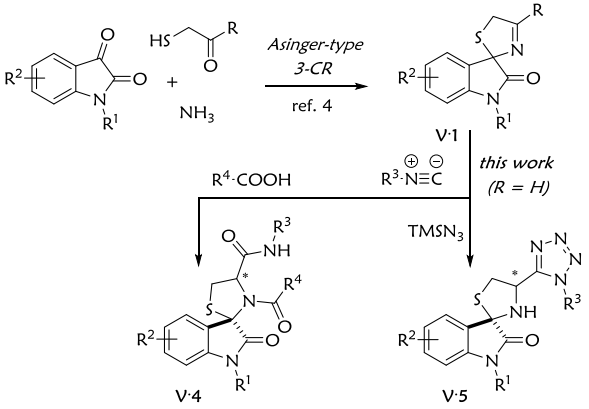
V.1 Introduction

In light of our interest in 3,3-disubstituted oxindoles and spiro-fused analogues,[1] we have recently reported the synthesis of a small library of spirooxindole-fused 3-thiazoline derivatives, by means of a one-pot Asinger-type three-component reaction (Scheme 1).[2]

Such compounds represent an underexploited scaffold in the context of sulfur-containing spirooxindoles. As demonstrated, they are in themselves endowed with R^1 and R^2 diversity, but can be also regarded as versatile intermediates towards further scaffold diversity, because of the presence of the reactive C–N double bond (see *Chapter IV*).

In continuation of our oxindole-based diversity oriented synthesis (DOS) program, we demonstrate here the suitability of spirooxindole-fused 3-thiazolines as useful substrates for two further multicomponent transformations, *i.e.* the Ugi–Joullié and the azido-Ugi reaction.

Scheme 1. Previously reported Asinger-type synthesis of spirooxindole-fused thiazolines.



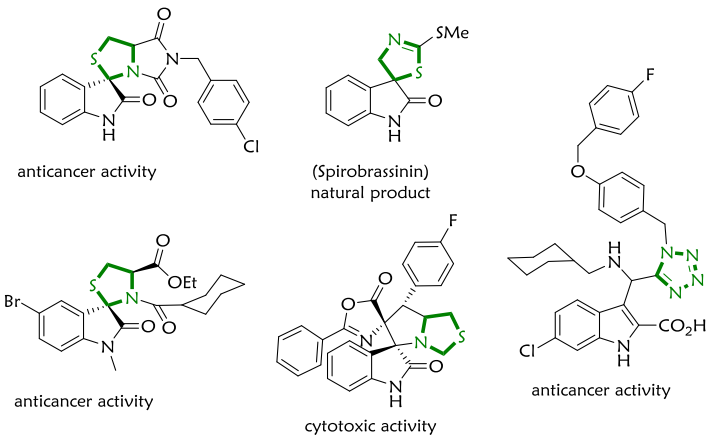


Figure 1. Examples of biologically relevant compounds containing spirooxindoles, thiazolidine and tetrazole moieties.[3]

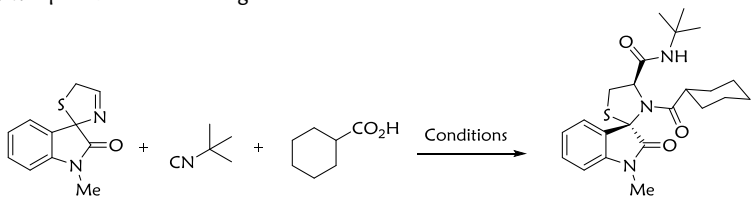
Since the important and diverse bioactivity of spirooxindole-based products, we aimed to functionalize the central spiro scaffold with a variety of lipophilic and polar groups, as well as with the pharmacologically relevant tetrazole ring (Figure 1).

V.2 Results and Discussion

Initially, isatin-derived thiazoline **V·1a**, *tert*-butyl isocyanide **V·2a** and cyclohexyl carboxylic acid **V·3a** were selected to optimize the conditions for the Ugi-Joullié reaction (Table 1).

As expected for Ugi-type processes,[6] the reaction was found to be sluggish in aprotic solvents (dichloromethane and toluene, entries 1-2). The same reaction in MeOH (entry 3) afforded the desired thiazolidine product in 55% yield as a readily separable 1:1 mixture of *trans* and *cis* diastereomers. Switching to more acidic 2,2,2-trifluoroethanol (TFE) increased the reaction rate and yield (entry 4).

Table 1. Optimization of the Ugi-Joullié 3-CR.[a]



VI·1a VI·2a VI·3a VI·4a

(*major diastereoisomer*)

Entry	Solvent	Conc. [M]	Time [h]	Conversion (%)[b]	*dr* [*trans*:*cis*][c]
1	CH_2Cl_2	0.25	24	trace	nd
2	Toluene	0.25	24	trace	nd
3	MeOH	0.25	24	55	50:50
4	TFE	0.25	6	95	75:25
5	**TFE**	**0.5**	**4**	**95 (83)[d]**	**87:13**
6	TFE	0.125	6	85	76:24
7[e]	TFE	0.25	6	85	74:26

[a] Reactions conditions: thiazoline **V·1a** (0.30 mmol), isocyanide **V·2a** (0.30 mmol) and carboxylic acid **V·3a** (0.30 mmol) at rt, unless otherwise indicated. [b] Evaluated by ^{1}H NMR analysis of the crude mixture considering both diasteroisomers. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Isolated yield for the *trans* diasteroisomer. [e] Reaction performed at 0 °C. TFE = 2,2,2-trifluoroethanol. nd = not determined.

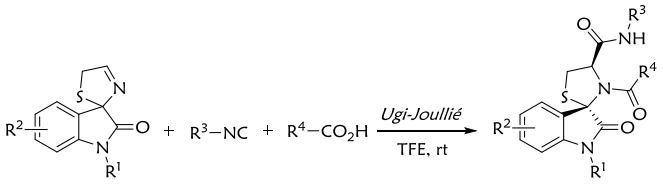
It also led to a more diastereoselective process affording *trans*-**V·4a** as the major product (dr 75:25).[7] The dr was further improved by increasing the concentration (0.5 M, entry 5), while lowering either the concentration (entry 6) or the temperature (entry 7) reduced the conversion without improving the dr.

With the optimal conditions in hand, we investigated the scope and limitations of the protocol, varying the three components one at a time (Scheme 2). Reaction of oxindole-based thiazolines **V·1a-h** with *tert*-butyl isocyanide (**V·2a**) and cyclohexanecarboxylic acid (**V·3a**) afforded the expected products **V·4a-4h** with good dr (up to 93:7 for compound **V·4e**) and in generally reasonable to good yield, although moderate yields were observed for **V·4b** and **V·4g**. Next,

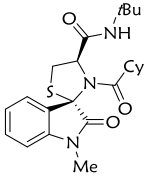
different isocyanides were combined with thiazoline **V·1a** and carboxylic acid **V·3a**. Compounds **V·4i-4n** were obtained in acceptable yields, with aliphatic isocyanides affording the best results (69% and 82% yield for compounds **V·4i** and **V·4j**, respectively). Due to their lower stability in acidic media, isocyanoacetates gave products **V·4k** and **V·4l** in lower yields. However, the highest dr was achieved in the reaction with *tert*-butyl isocyanoacetate (**V·4l**, dr 99:1). Good results were obtained with both phenyl and benzyl isocyanide (**V·4m** and **V·4n**), whereas no product **V·4o** was observed in the reaction with 2-morpholinoethyl isocyanide. As reported,[8] this reagent may undergo a facile internal cyclization reaction after protonation by the carboxylic acid, preventing the UJ-3CR.

Finally, twelve different carboxylic acids were tested in the reaction with thiazoline **V·1a** and *tert*-butyl isocyanide (**V·2a**). The resulting products **V·4p-z** were obtained in generally high yields (up to 80%) and with satisfactory dr (up to 86:14), except compound **V·4s** that was detected only in trace amounts. In this case, most likely the employed carboxylic acid [*N*-methylpiperidine-4-carboxylic acid] was present in its zwitterionic form and therefore not reactive. In support of this hypothesis, the reaction with the 1-(*tert*-butoxycarbonyl)-piperidine-4-carboxylic acid (structurally similar but lacking basicity) furnished the expected UJ-3CR product **V·4t** in good yield and dr. The wide variety of successfully tested carboxylic acids is noteworthy, ranging from phenylacetic acid to carboxylic acids containing both electron-rich and electron-deficient heterocycles (**V·4u-z**).

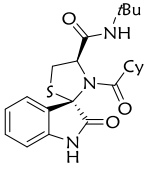
Scheme 3. Scope of components in the Ugi-Joullié 3-CR.[a]



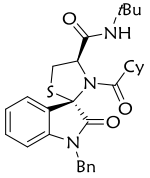
V·1a-h V·2a-h V·3a-l V·4a-z



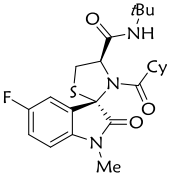
V·4a (83%)
dr 87:13



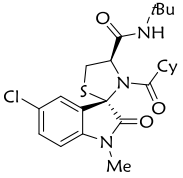
V·4b (34%)
dr 71:29



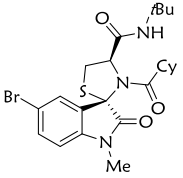
V·4c (53%)
dr 80:20



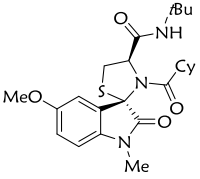
V·4d (54%)
dr 80:20



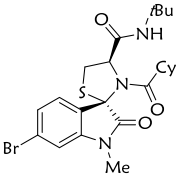
V·4e (48%)
dr 93:7



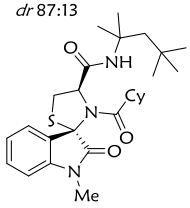
V·4f (61%)
dr 87:13



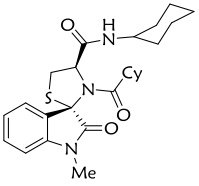
V·4g (30%)
dr 82:18



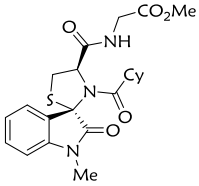
V·4h (55%)
dr 80:20



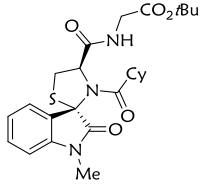
V·4i (69%)
dr 75:25



V·4j (82%)
dr 84:16

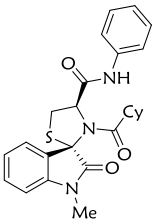


V·4k (47%)
dr 80:20

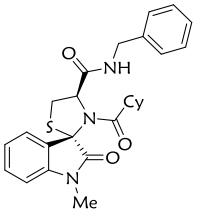


V·4l (41%)
dr 99:1

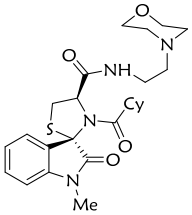
continued



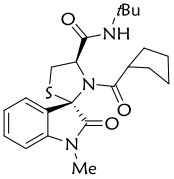
V·4m (43%)
dr 86:14



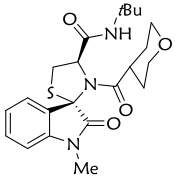
V·4n (57%)
dr 86:14



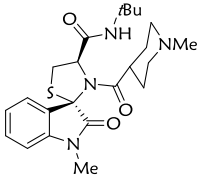
V·4o (trace)
dr nd



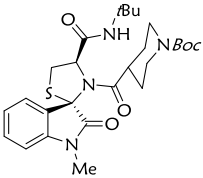
V·4q (80%)
dr 86:14



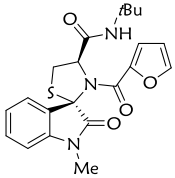
V·4r (79%)
dr 80:20



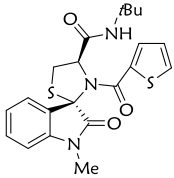
V·4s (trace)
dr nd



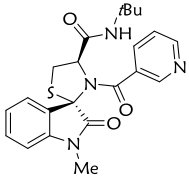
V·4t (79%)
dr 80:20



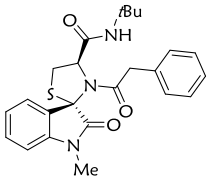
V·4u (78%)
dr 79:21



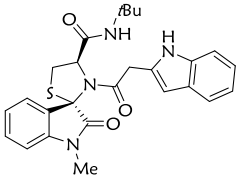
V·4v (76%)
dr 79:21



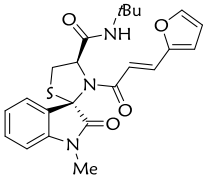
V·4w (56%)
dr 76:24



V·4x (55%)
dr 76:24



V·4y (72%)
dr 82:18

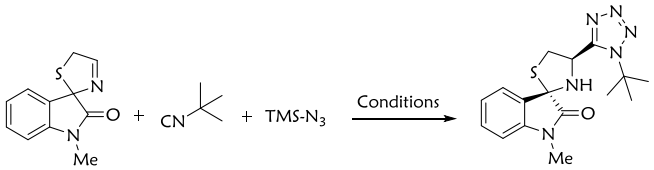


V·4z (42%)
dr 70:30

[a] Reactions conditions: thiazoline **V·1a-h** (0.30 mmol), isocyanide **V·2a-h** (0.30 mmol) and carboxylic acid **V·3a-l** (0.30 mmol) in TFE (600 µL) at rt. Isolated yield for the *trans* diasteroisomer are reported. The indicated *dr* was determined by ^{1}H NMR on the crude mixture. nd = not determined.

We then moved on to the azido-Ugi process, optimizing the reaction conditions using thiazoline **V·1a**, *tert*-butyl isocyanide (**V·2a**) and trimethylsilyl azide as the inputs (Table 2). Also in this case, the reaction was found to be sluggish in dichloromethane and toluene (entries 1-2), whereas excellent conversions to the target tetrazole derivative **V·5a** were observed in polar protic solvents (entries 3-5).

Table 3. Optimization of the azido-Ugi 3-CR.[a]



V·1a V·2a V·5a

Entry	Solvent	Conc. [M]	Time [h]	Conversion (%)[b]	dr [*trans:cis*][c]
1	CH_2Cl_2	0.5	24	<5	nd
2	Toluene	0.5	24	<5	nd
3	MeOH	0.5	2	95	56:44
4	TFE	0.5	1	99	81:19
5	HFIP	0.5	1	99	85:15
6	TFE	1.0	1	99	78:22
7	TFE[d]	0.5	1	99	83:17
8	TFE[e]	0.5	1	99	83:17
9	HFIP	1.0	1	99	84:16
10	HFIP	0.05	1	99	82:18
11	**HFIP[d]**	**0.5**	**1**	**99 (87)[f]**	**92:8**

[a] Reactions conditions: thiazoline **V·1a** (0.15 mmol), isocyanide **V·2a** (0.15 mmol) and $TMS\text{-}N_3$ (0.15 mmol) in solvent at rt, unless otherwise indicated. [b] Evaluated on the crude mixture considering both diasteroisomers. [c] Determined by ^1H NMR on the crude mixture. [d] Reaction performed at 0 °C. [e] Reaction performed at -18 °C. [f] Isolated yield for the *trans* diasteroisomer. TFE = 2,2,2-trifluoroethanol. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. nd = not determined.

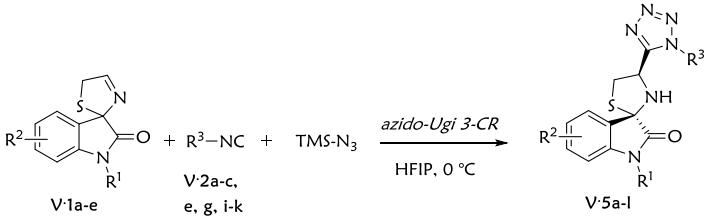
As for the above UJ-3CR, fluorinated solvents (TFE and 1,1,1,3,3,3-hexafluoro-2-propanol, HFIP) led to a more a diastereoselective transformation, affording the *trans* diastereoisomer **V·5a** as the major compound.

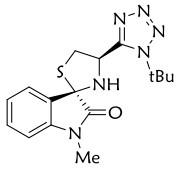
Aiming to further improve the *dr*, different concentrations and temperatures were screened. We found that increasing the concentration in TFE led to a slight decrease in *dr* (entry 6), whereas lowering the temperature only gave a small improvement in *dr* (entry 7). Similarly, varying the concentration in HFIP did not lead to an appreciable improvement (entries 9,10), while in this case excellent diastereoselectivity was achieved at 0 °C (entry 11). Aiming to further improve the *dr*, different concentrations and temperatures were screened. We found that increasing the concentration in TFE led to a slight decrease in *dr* (entry 6), whereas lowering the temperature only gave a small improvement in *dr* (entry 7). Similarly, varying the concentration in HFIP did not lead to an appreciable improvement (entries 9,10), while in this case an excellent *dr* was achieved at 0 °C (entry 11).

Next, we investigated the reaction scope, combining thiazolines **V·1a-e** and isocyanides **V·2a-h** with trimethylsilyl azide, leading to good results in nearly all cases (Scheme 3).

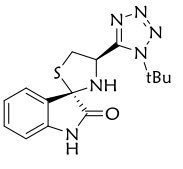
When aliphatic isocyanides were used, the corresponding products (**V·5a-j**; **5l**) were obtained in satisfactory yield and *dr*, with the exception of **V·5g** (67:33 *dr*). Unlike the case of the UJ-3CR, *tert*-butyl isocyanoacetate also worked well in the azido-Ugi reaction, affording the desired product **V·5j** in 72% yield and with 84:16 *dr*. Finally, phenyl isocyanide behaved similarly as in the UJ-3CR, giving the corresponding product **V·5k** in moderate yield and *dr*.

Scheme 3. Scope of components in the azido-Ugi 3-CR.[a]

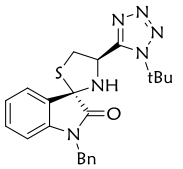




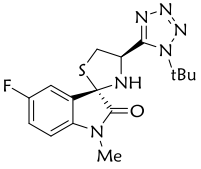
V·5a (87%)
dr 92:8



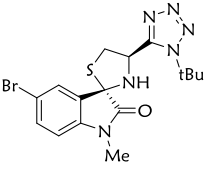
V·5b (69%)
dr 81:19



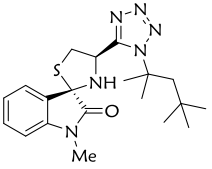
V·5c (80%)
dr 85:15



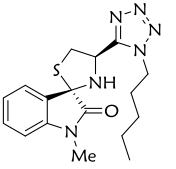
V·5d (78%)
dr 84:16



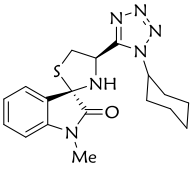
V·5e (81%)
dr 88:12



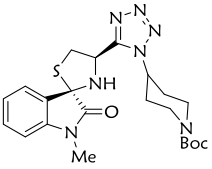
V·5f (84%)
dr 88:12



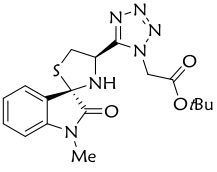
V·5g (59%)
dr 67:33



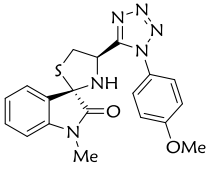
V·5h (75%)
dr 82:18



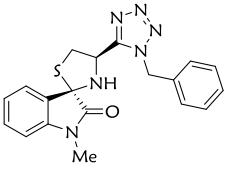
V·5i (69%)
dr 70:30



V·5j (72%)
dr 84:16



V·5k (37%)
dr 67:33



V·5l (70%)
dr 76:23

[a] Reactions conditions: thiazoline **V·1a-e** (0.30 mmol), isocyanide **V·2a-c,e,g,i-k** (0.30 mmol) and TMS-N_3 (0.30 mmol) in HFIP (600 µL) at 0 °C. Isolated yield for the *trans*

diasteroisomer are reported. Determined by ^{1}H NMR on the crude mixture. Compound **V·5i** was obtained as a mixture of inseparable diastereoisomers.

To determine the relative configuration for the two product types (**V·4** and **V·5**), single crystals of **V·4a** and **V·5a** were subjected to X-ray crystallographic analysis, leading to the unambiguous assignment of the trans stereochemistry for both compounds (Figure 2). Since all products **V·4** and **V·5** were obtained under the same conditions employed for compounds **V·4a** and **V·5a,** respectively, and given common trends in ^{1}H NMR chemical shifts as well as similarities in TLC retention times, he same relative *trans*-stereochemistry was assigned to all products **V·4** and **V·5**.

To provide a plausible explanation for the highly diastereo-selective outcome of both reactions, we consider the mechanism proposed in Figure 3 for the UJ-3CR. We presume that the preferred conformation of imine **V·1a** in solution is mainly

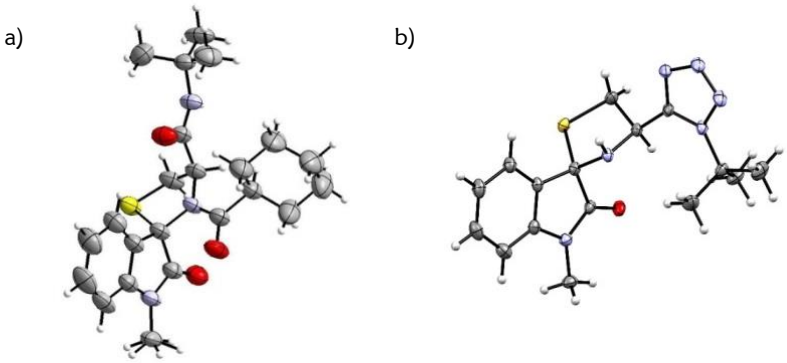


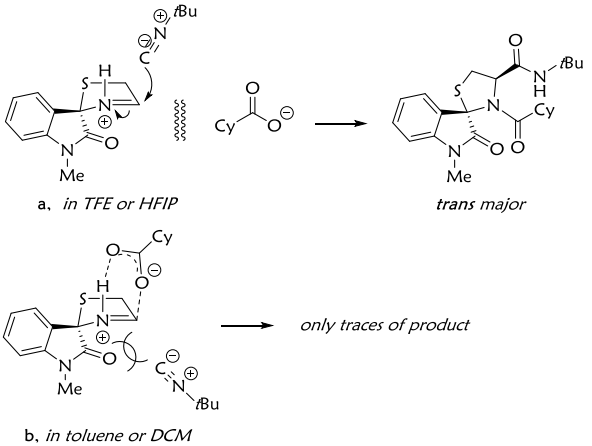
Figure 2. a) ORTEP view of compound **V·4a** at room temperature. The methyl group on the left is rotationally disordered. Thermal ellipsoids of non-*H* atoms were drawn at the 50% probability level. b) ORTEP view of compound **V·5a** at T = 105 K. Thermal ellipsoids of non-*H* atoms were drawn at the 50% probability level.

determined by the spiro junction between the oxindole and the thiazoline ring system, with the latter adopting an envelope-like conformation oriented nearly perpendicularly with respect to the oxindole. This spatial arrangement highlights the substantial shielding of the *Si*-face of the imine for both steric and electronic reasons, mainly due to the proximity of the oxindole carbonyl.

As a consequence, in strongly hydrogen-bonding solvents such as TFE and HFIP, the protonated imine exposes the *Re*-face to the incoming isocyanide, affording predominantly the *trans* isomer (Figure 3a).

Taking into account the effect of the solvent on the diastereoselectivity of the UJ-3CR involving a five-membered cyclic imine, as reported by Katsuyama *et al.*,[7a] we can also rationalize the poor reactivity observed in toluene. Indeed, in such nonpolar solvents, the protonation of the imine by the carboxylic acid likely results in the formation of a contact ion pair. This close interaction lowers the overall electrophilic reactivity of the imine and, more decisively, hinders the

Figure 3. Plausible explanation of the stereochemical outcome for the UJ-3CR.



approach of isocyanide, shielding the sterically more available *Re*-face (Figure 3b).

The use of MeOH as the solvent represents an intermediate scenario, providing sufficient activation for the reaction to occur, but very limited discrimination between the diastereotopic faces. Similar considerations on the molecular conformation of the imine component can be made to rationalize the high *dr* observed in the azido-Ugi 3-CR.

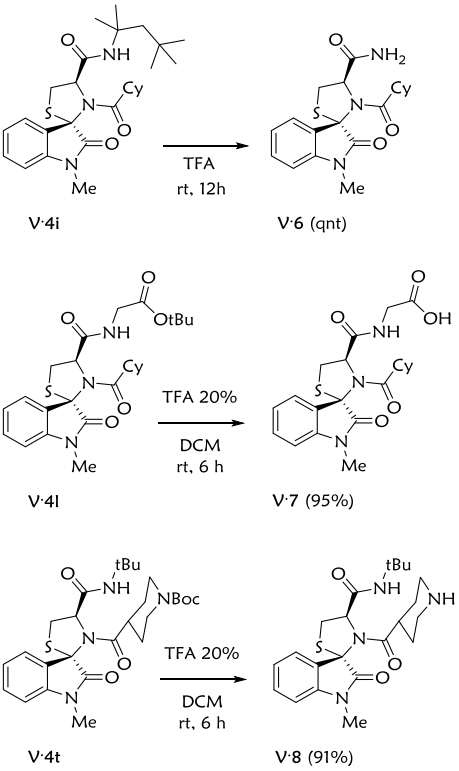
Having established the reaction scope, further transformations were examined to extend the library of potentially useful compounds. Selected post-transformations of Ugi-Joullié products **V·4** are depicted in Scheme 5. Primary amide **V·6** is readily obtained by treatment of compound **V·4i** with trifluoroacetic acid.

Starting from compound **V·4l**, cleavage of the *tert*-butyl ester afforded the free acid **V·7** in quantitative yield. Finally, the piperidine derivative **V·8** was obtained treating compound **V·4t** with 20% TFA in dichloromethane.

V.3 Conclusions

In conclusion, we have efficiently synthesized two structurally diverse libraries of highly functionalized spiooxindole thiazolidines, *via* Ugi-Joullié and azido-Ugi multicomponent reactions. The MCR-derived central spiro scaffold was effectively functionalized with a variety of lipophilic and polar appendages, as well as with tetrazole as a carboxylic acid isostere. The products were obtained in generally high yields, with simple workup procedures and straightforwardisolation. The observed high diastereoselectivity for both the transformations is particularly noteworthy. Further biological evaluation of compounds **V·4** and **V·5** is currently ongoing.

Scheme 5. Further post-transformation reactions on selected UJ-3 CR products.



V·4i V·6 (qnt)

V·4l V·7 (95%)

V·4t V·8 (91%)

V.4 Experimental Section

All commercial materials (Aldrich, Fluka, Fluorochem) were used without further purification. All solvents were of reagent grade or HPLC grade. Reactions requiring anhydrous conditions were performed under nitrogen atmosphere. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light (254 nm) or by treatment with $KMnO_4$ solution in water or ninhydrin solution in ethanol. Products were purified by flash chromatography on silica gel 60 (230–400 mesh). ^1H NMR spectra and ^{13}C NMR spectra were recorded on 300, 400 and 500 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^1H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra (HR-MS) were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Thiazolines **V·1a-h** were synthesized as described previously in *Chapter IV*.

General procedure A (GP-A) for the synthesis of compounds V·4a-z via Ugi-Joullié 3-CR reaction. To a solution of thiazoline **V·1** (0.3 mmol, 1 eq) in TFE (0.62 mL), isocyanide **V·2** (0.3 mmol, 1 eq) and the carboxylic acid **V·3** (0.3 mmol, 1 eq) were added at room temperature. The reaction was stirred and the conversion was monitored by TLC. The solvent was removed under reduced

pressure and the crude was purified by flash chromatography (FC) as indicated below.

(3*S,4'*R**)-*N*-(*tert*-butyl)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4a).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 95:5; yield: 83%; grey foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 4:1 mixture of two rotamers) δ 7.43-7.18 (m, 2H), 7.11 (t, br, *J* = 7.8Hz, 0.2H), 7.14 (t, br, *J* = 7.8Hz, 0.8H), 6.95-6.86 (m, br, 0.4H), 6.83 (d, br, *J* = 7.8Hz, 0.8H), 6.52 (m, br, 0.8H), 5.42 (d, br, *J* = 4.9 Hz, 0.2H), 4.89 (d, *J* = 7.8 Hz, 0.8H), 4.04 (dd, *J* = 11.6 and 6.9 Hz, 0.8H), 3.69-3.57 (m, 0.4H), 3.45 (d, *J* = 11.6 Hz, 0.8H), 3.26 (s, 0.6H), 3.22 (s, 2.4H), 2.25 (t, br, *J* = 10.7Hz, 0.8H), 1.84-1.08 (m, 10 methylene protons + 0.2H), 1.47 (s, 7.2H), 1.40 (s, 1.8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 175.6 and 175.0 (1C), 169.2 and 168.8 (1C), 143.7 and 142.2 (1C), 130.8 and 130.1 (1C), 127.3 and 126.1 (1C), 124.3 and 123.8 (1C) 122.8 and 122.3 (1C), 109.1 and 108.9 (1C), 71.8, 66.8 and 66.2 (1C), 52.1 and 52.3 (1C), 44.1 and 42.7 (1C), 33.4, 29.9 and 29.6 (2C), 28.7 (3C), 26.6, 25.4 and 25.3 (3C); HR-MS (ESI) calcd for $C_{23}H_{31}N_3NaO_3S^+$ $[MNa]^+$ 452.1978, found 452.1987.

(3*S,4'R*)-*N*-(*tert*-Butyl)-3'-(cyclohexanecarbonyl)-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4b).** Prepared according to GP-A using thiazoline **V·1b**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: Hexane:EtOAc, 6:4; yield: 34%; grey foamy solid; ^{1}H NMR (400 MHz, DMSO-d_6, 9:1 mixture of rotamers) δ 10.87 (s, 0.1H), 10.34 (s, 0.9H), 7.93 (d, br, *J* = 7.7 Hz, 0.1H), 7.82 (s, br, 0.9H), 7.76 (d, br, *J* = 7.6 Hz, 0.9H), 7.54 (s, br, 0.1H), 7.33 (t, br, *J* = 7.7 Hz, 0.1H), 7.16 (t, br, *J* = 7.7 Hz, 0.9H), 7.11 (t, *J* =

7.6 Hz, 0.1H), 6.94 (t, br, *J* = 7.6 Hz, 0.9H), 6.75 (d, br, *J* = 7.7 Hz, 1H), 5.19 (d, *J* = 6.5 Hz, 0.1H), 5.11 (d, *J* = 6.8 Hz, 0.9H), 3.73 (dd, *J* = 12.0 and 6.8 Hz, 0.9H), 3.61 (dd, *J* = 12.0, 6.5 Hz, 0.1H), 3.37-3.22 (m, 1H), 2.24-2.12 (m, 1H), 1.77-1.52 (4H), 1.35 (*s*, 8.1H), 1.31 (*s*, 0.9H), 1.26-0.97 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.8 and 176.9 (1C), 174.2 and 173.1 (1C), 169.3 and 168.6 (1C), 141.8 and 140.7 (1C), 130.8 and 129.2 (1C), 128.9 and 128.8 (1C), 126.0 and 125.0 (1C), 123.1 and 122.1 (1C), 110.9 and 109.7 (1C), 71.9 and 69.9 (1C), 65.8 and 64.1 (1C), 50.8 and 50.6 (1C), 43.1 and 41.9 (1C), 35.3 and 33.3 (1C), 29.4 and 29.2 (1C), 28.9 and 28.7 (3C), 28.9 and 28.5 (1C), 25.7-25.3 (3C); HR-MS (ESI) calcd for $C_{22}H_{29}N_3NaO_3S^+$ $[MNa]^+$ 438.1822, found 438.1829.

(3*S,4'*R**)-1-Benzyl-*N*-(*tert*-butyl)-3'-(cyclohexanecarbonyl)-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4c).** Prepared according to GP-A using thiazoline **V·1c**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a.** FC: CH_2Cl_2:EtOAc, 95:5; yield: 53%; pale brown foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 4:1 mixture of two rotamers) δ 7.44-7.21 (m, 6.2H), 7.17 (t, br, J = 7.8 Hz, 0.8H), 7.09 (t, br, J = 7.8 Hz, 0.2H), 7.01 (t, br, J = 7.7 Hz, 0.8H), 6.94 (m, br, 0.2H), 6.71 (d, br, *J* = 7.6 Hz, 0.2H), 6.65 (d, br, *J* = 7.7 Hz, 0.8H), 6.58 (m, br, 0.8H), 5.47 (d, *J* = 5.9 Hz, 0.2H), 5.20 (d, *J* = 14.7 Hz, 0.2H), 5.02 (d, *J* = 15.6 Hz, 0.8H), 4.95 (d, *J* = 6.8 Hz, 0.8H), 4.85 (d, *J* = 15.6 Hz, 0.8H), 4.64 (d, *J* = 14.7 Hz, 0.2H), 4.10 (dd, *J* = 11.7 and 6.8 Hz, 0.8H), 3.72 (dd, *J* = 11.7 and 5.9 Hz, 0.2H), 3.63 (d, *J* = 11.7 Hz, 0.2H), 3.49 (d, *J* = 11.7 Hz, 0.8H), 2.30 (m, 1H), 1.89-0.92 (m, 10H, methylene protons) 1.49 (*s*, 7.2H), 1.41 (*s*, 1.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4-175.2 (2C), 169.2,and 168.8 (1C), 142.6 and 141.3 (1C), 135.6 and135.1 (1C), 130.7 and 130.0 (1C), 129.1 and 128.9 (2C), 128.1-127.1 (3C), 126.7 and 126.1 (1C), 124.3-122.3

(2C), 110.0, 72.1 and 70.3 (1C), 67.0 and 66.2 (1C), 52.1 and 51.3 (1C), 44.3 and 44.1 (1C), 44.0 and 42.5 (1C), 33.4-29.2 (3C), 28.8 (3C), 27.7-22.6 (3C); HR-MS (ESI) calcd for $C_{29}H_{35}N_3NaO_3S^+$ $[MNa]^+$ 528.2291, found 528.2302.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-3'-(cyclohexanecarbonyl)-5-fluoro-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4d).** Prepared according to GP-A using thiazoline **V·1d**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 95:5; yield: 54%; orange foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 17:3 mixture of two rotamers) δ 7.17-6.95 (m, 2H), 6.85 (dd, *J* = 7.8 and 3.9 Hz, 0.15H), 6.77 (dd, *J* = 8.6 and 3.9 Hz, 0.85H), 6.38 (m, br, 1H), 5.44 (t, *J* = 3.3 Hz, 0.15H), 4.89 (d, *J* = 6.8 Hz, 0.85H), 4.04 (dd, *J* = 11.7 and 6.8 Hz, 0.85H), 3.62 (d, *J* = 3.3 Hz, 0.3H), 3.48 (d, *J* = 11.7 Hz, 0.85H), 3.26 (*s*, 0.45H), 3.22 (*s*, 2.55H), 2.25 (tt, *J* = 10.7 and 3.5 Hz, 1H), 1.83-1.05 (m, 10H, methylene protons), 1.48 (*s*, 7.65H), 1.40 (*s*, 1.35H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 174.9, 168.9, 160.4 and 158.0 (1C), 139.6, 127.8, 116.4 and 116.2 (1C), 111.0 and 110.7 (1C), 109.4 and 109.3 (1C), 71.5, 66.0, 52.2, 44.0, 33.7, 29.5 (2C), 28.7 (3C), 26.7, 25.3(3C); HR-MS (ESI) calcd for $C_{23}H_{30}FN_3NaO_3S^+$ $[MNa]^+$ 470.1884, found 470.1872.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-5-chloro-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4e).** Prepared according to GP-A using thiazoline **V·1e**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: Hexane:EtOAc, 1:1; yield: 48%; grey foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 9:1 mixture of two rotamers) δ 7.40-7.33 (m, 0.2H), 7.29 (dd, *J* = 7.8 and 2.0 Hz, 0.9H), 7.24 (d, *J* = 2.0 Hz, 0.9H), 6.86-6.79 (m, 0.2H), 6.76 (d, *J* = 7.8 Hz, 0.9H), 6.40 (m, br, 0.9H), 5.45 (d, *J* = 4.9 Hz, 0.1H), 4.90 (d, *J* = 6.8 Hz, 0.9H), 4.00 (dd, *J* = 11.7 and 6.8 Hz, 0.9H), 3.65

(d, *J* = 10.7 Hz, 0.1H), 3.60 (dd, *J* = 10.7 and 4.9 Hz, 0.1H), 3.52 (d, *J* = 11.7 Hz, 0.9H), 3.26 (*s*, 0.3H), 3.22 (*s*, 2.7H), 2.25 (t, br *J* = 11.0 Hz, 1H), 1.83-1.04 (m, 10H, methylene protons), 1.49 (*s*, 8.1H), 1.42 (*s*, 0.9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0-174.7 (2C), 168.8 and 168.6 (1C), 142.2 and 140.6 (1C), 130.7 and 130.0 (1C), 129.6-128.0 (2C), 124.8 and 123.2 (1C), 110.2 and 109.8 (1C), 71.6 and 69.6 (1C), 66.8 and 66.0 (1C), 52.2 and 51.4 (1C), 44.0 and 42.9 (1C), 33.7, 30.3-25.3 (9C); HR-MS (ESI) calcd for $C_{23}H_{30}ClN_3NaO_3S^+$ $[MNa]^+$ 486.1589, found 486.1578.

(3*S,4'*R**)-5-Bromo-*N*-(*tert*-butyl)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4f).** Prepared according to GP-A using imine **V·1f**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 95:5; yield: 61%; pale brown foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 17:3 mixture of two rotamers) δ 7.54-7.48 (m, 0.3H), 7.43 (dd, *J* = 7.8 and 2.0 Hz, 0.85H), 7.36 (d, *J* = 2.0 Hz, 0.85H), 6.74 (d, *J* = 7.8 Hz, 0.15H), 6.72 (d, *J* = 7.8 Hz, 0.85H), 6.51 (m, br, 0.15H), 6.40 (m, br, 0.85H), 5.45 (d, *J* = 4.9 Hz, 0.15H), 4.90 (d, *J* = 6.8 Hz, 0.85H), 3.98 (dd, *J* = 11.7 and 6.8 Hz, 0.85H), 3.66 (d, *J* = 11.7 Hz, 0.15H), 3.59 (dd, *J* = 11.7 and 4.9 Hz, 0.15H), 3.53 (d, *J* = 11.7 Hz, 0.85H), 3.26 (*s*, 0.45H), 3.21 (*s*, 2.55H), 2.25 (t, br *J* = 11.2 Hz, 1H), 1.85-1.10 (m, 10H, methylene protons), 1.49 (*s*, 7.65H), 1.48 (*s*, 1.35H);); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 and 171.3 (1C), 171.2 and 170.2 (1C), 164.9 and 164.4 (1C), 138.4, 129.2 and 128.5 (1C), 124.2 and 124.0 (1C), 123.4 and 121.6 (1C), 123.0, 106.3 and 105.9 (1C), 69.7 and 69.4 (1C), 62.4 and 61.8 (1C), 48.9 and 47.8 (1C), 39.7 and 38.3 (1C), 29.2 and 29.1 (1C), 25.9-25.1 (2C), 24.4 (3C), 22.4, 21.4; HR-MS (ESI) calcd for $C_{23}H_{30}BrN_3NaO_3S^+$ $[MNa]^+$ 530.1083, found 530.1077.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-3'-(cyclohexanecarbonyl)-5-methoxy-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4g).** Prepared according to GP-A using thiazoline **V·1g**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 95:5; yield: 30%; pale orange foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of two rotamers) δ 6.96-6.88 (m, 0.5H), 6.85-6.79 (m, 1.5H), 6.75 (d, br, *J* = 7.8 Hz, 1H), 6.51 (m, br, 0.75H), 6.41 (m, br, 0.25H), 5.44 (m, br, 0.25H), 4.89 (d, *J* = 7.2 Hz, 0.75H), 4.05 (dd, *J* = 11.7 and 7.2 Hz, 0.75H), 3.76 (*s*, 3H), 3.63 (m, br, 0.5H), 3.46 (d, *J* = 11.7 Hz, 0.75H), 3.21 (*s*, 0.75H), 3.21 (*s*, 2.25H), 2.25 (t, br, *J* = 11.3 Hz, 1H), 1.35-1.09 (m, 10H, methylene protons), 1.48 (*s*, 6.75H), 1.40 (*s*, 2.25H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4-174.3 (2C), 169.1 and 168.8 (1C), 156.7 and 156.0 (1C), 136.9 and 135.2 (1C), 128.1 and 127.1 (1C), 115.9 and 113.3 (1C), 110.6 and 110.5 (1C), 109.9 and 109.1 (1C), 72.0 and 71.3 (1C), 66.6 and 66.1 (1C), 55.9 and 55.7 (1C), 52.3 and 52.0 (1C), 44.0 and 43.9 (1C), 33.5 and 33.3 (1C), 29.8- 29.5 (2C) , 28.8 (3C), 26.9 and 26.7 (1C), 27.7-25.3 (3C); HR-MS (ESI) calcd for $C_{24}H_{33}N_3NaO_4S^+$ $[MNa]^+$ 482.2084, found 482.2095.

(3*S,4'*R**)-6-Bromo-*N*-(*tert*-butyl)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4h).** Prepared according to GP-A using thiazoline **V·1h**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 95:5; yield: 55%; pale grey foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$, 17:3 mixture of two rotamers) δ 7.21 (dd, *J* = 7.5 and 1.9 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 1.9 Hz, 1H), 6.83 (m, br, 0.15H), 6.41 (m, br, 0.85H), 5.43 (d, *J* = 4.9 Hz, 0.15H), 4.92 (d, *J* = 6.7 Hz, 0.85H), 4.04 (dd, *J* = 12.0 and 6.7 Hz, 0.85H), 3.64 (dd, *J* = 11.7 and 4.9 Hz, 0.15H), 3.47 (d, *J* = 11.7 Hz, 0.85H), 3.27 (*s*, 0.45H), 3.23 (*s*, 2.55H), 2.30-2.22

(m, 1H), 1.84-1.56 (m, 4H), 1.48-1.10 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6-174.9 (2C), 168.9, 145.0, 126.6 and 125.7 (1C), 125.2, 123.9, 123.7, 112.6 and 112.4 (1C), 71.2, 66.7 and 66.0 (1C), 52,1 and 51.6 (1C), 44.0 and 42.8 (1C), 33.6, 30.1-29.5 (2C), 28.8 (3C), 26.8, 25.8-25.3 (3C); HR-MS (ESI) calcd for $C_{23}H_{30}BrN_3NaO_3S^+$ $[MNa]^+$ 530.1083, found 530.1090.

(3*S,4'*R**)-3'-(Cyclohexanecarbonyl)-1-methyl-2-oxo-*N*-(2,4,4-trimethylpentan-2-yl)spiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4i).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and 1,1,3,3-tetramethylbutyl isocyanide **V·2b**. FC: *c*-Hexane:EtOAc, from 4:1 to 1.5:1; yield: 69%; light yellow foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of two rotamers) δ 7.43-7.38 (m, 0.5H), 7.34 (t, *J* = 7.6 Hz, 0.75H), 7.30 (d, *J* = 7.6 Hz, 0.75H), 7.14 (t, *J* = 7.6 Hz, 0.25H), 7.07 (t, *J* = 7.6 Hz, 0.75H), 6.98 (m, br, 0.25H), 6.92 (d, *J* = 7.6 Hz, 0.25H), 6.87 (d, *J* = 7.6 Hz, 0.75H), 6.49 (m, br, 0.75H), 5.41 (d, *J* = 5.7 Hz, 0.25H), 4.90 (d, *J* = 6.9 Hz, 0.75H), 4.06 (dd, *J* = 11.8 and 6.9 Hz, 0.75H), 3.67 (dd, *J* = 11.4 and 5.7 Hz, 0.25H), 3.62 (d, *J* = 11.4Hz, 0.25H), 3.47 (d, *J* = 11.8 Hz, 0.75H), 3.28 (*s*, 0.75H), 3.24 (*s*, 2.25H), 2.26 (tt, *J* = 11.5 and 2.9 Hz, 1H), 2.05 (d, *J* = 14.8 Hz, 0.25H), 1.96 (d, *J* = 14.8 Hz, 0.75H), 1.92 (d, *J* = 14.8 Hz, 0.75H), 1.87-1.12 (m, 16.25H), 1.05 (*s*, 6.75H), 1.04 (*s*, 2.25H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3 and 175.7 (1C), 175.6 and 175.0 (1C), 168.8 and 168.3 (1C), 143.6 and 142.1 (1C), 130.8 and 130.1 (1C), 127.0 and 126.0 (1C), from 124.3 to 122.4 (2C), 109.1 and 108.8 (1C), 72.0 and 70.0 (1C), 67.0 and 66.1 (1C), 56.2 and 55.2 (1C), 51.4 and 51.3 (1C), 43.8 and 42.6 (1C), from 33.4 to 25.1 (13C); HR-MS (ESI) calcd for $C_{27}H_{40}N_3O_3S^+$ $[MH]^+$ 486.2785, found 486.2773.

(3*S,4'*R**)-3'-(Cyclohexanecarbonyl)-*N*-cyclohexyl-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4j).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and cyclohexyl isocyanide **V·2c**. FC: *c*-Hexane:EtOAc 1.5:1; yield: 80%; light pink foamy solid. ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of two rotamers) δ 7.40-7.35 (m, 0.5H), 7.32 (t, *J* = 7.6 Hz, 0.75H), 7.21 (d, *J* = 7.6 Hz, 0.75H), 7.11 (t, *J* = 7.6 Hz, 0.25H), 7.05 (t, *J* = 7.6 Hz, 0.75H), 6.94-6.88 (m, 0.5H), 6.86 (d, *J* = 7.6 Hz, 0.75H), 6.50 (d, br, *J* = 8.3 Hz, 0.75H), 5.45 (d, *J* = 5.7 Hz, 0.25H), 4.97 (d, *J* = 6.9 Hz, 0.75H), 4.04 (dd, *J* = 11.8 and 6.9 Hz, 0.75H), 4.00-3.86 (m, 1H), 3.69 (dd, *J* = 11.8 and 5.9 Hz, 0.25H), 3.62 (d, *J* = 11.8, 0.25H) 3.49 (d, *J* = 11.8 Hz, 0.75H), 3.27 (*s*, 0.75H), 3.23 (*s*, 2.25H), 2.23 (tt, *J* = 11.5 and 3.2 Hz, 1H), 2.11 (m, 0.75H), 2.00-1.86 (m, 1.25H), 1.85-1.52 (m, 6.75H), 1.51-1.07 (m, 11.25H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.3 and 175.0 (1C), 175.6, 168.8, 143.6 and 142.0 (1C), 130.8 and 130.1 (1C), 127.1 and 126.0 (1C), from 124.4 to 122.4 (2C), 109.1 and 108.8 (1C), 71.8 and 69.9 (1C), 66.4 and 65.6 (1C), 49.0 and 48.0 (1C), 43.9 and 42.6 (1C), from 33.3 to 24.3 (12C); HR-MS (ESI) calcd for $C_{25}H_{34}N_3O_3S^+$ $[MH]^+$ 456.2315, found 456.2303.

Methyl ((3*S,4'*R**)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carbonyl) glycinate (V·4k).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and methyl isocyanoacetate **V·2d**. FC: Hexane:EtOAc, 6:4; yield: 47%; light brown foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 7:3 mixture of two rotamers) δ 7.65 (d, *J* = 7.3 Hz, 0.3H), 7.45 (d, *J* = 7.3 Hz, 0.7H), 7.43- 7.28 (m, 1.3 H), 7.20-7.11 (m, br, 1H), 7.06 (t, *J* = 7.6 Hz, 0.7H), 6.90 (d, *J* = 7.6 Hz, 0.3H), 6.84 (d, *J* = 7.6 Hz, 0.7), 5.51 (d, *J* = 5.7 Hz, 0.3H), 5.06 (d, *J* = 6.8 Hz, 0.7H), 4.35 (dd, *J* = 18.5 and 6.8

Hz, 0.3H), 4.25 (d, *J* = 5.9 Hz, 1.4H), 4.10 (dd, *J* = 11.7 and 6.8 Hz, 0.7H), 3.95 (dd, *J* = 18.5 and 3.9 Hz, 0.3H), 3.83 (*s*, 2.1H), 3.78 (m, 0.3H), 3.79 (*s*, 0.9H), 3.61 (d, *J* = 11.7 Hz, 0.3H), 3.46 (d, *J* = 11.2 Hz, 0.7H), 3.28 (*s*, 0.9H), 3.24 (*s*, 2.1H), 2.29 (tt, *J* = 10.7 and 2.9 Hz, 1H), 1.87-0.99 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8 and 173.4 (1C), 174.0, 168.7, 168.5 and 168.0 (1C), 141.8 and 140.3 (1C), 129.1 and 128.3 (1C), 125.0 and 124.1 (1C), 123.3 and 122.4 (1C), 121.4 and 121.3 (1C), 107.2 and 106.9 (1C), 70.4 and 68.4 (1C), 64.7 and 63.7 (1C), 51.0 and 50.7 (1C), 42.1 and 41.0 (1C), 40.0 and 39.8 (1C), 31.6-23.4 (7C); HR-MS (ESI) calcd for $C_{22}H_{27}N_3NaO_5S^+$ [MNa]$^+$ 468.1564, found 468.1553.

***tert*-Butyl 2-((3*S**,4'*R**)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidin]-4'-ylcarboxamido)acetate (V·4l).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and *tert*-butyl isocyanoacetate **V·2e**. FC: *c*-Hexane:EtOAc, from 1:1 to 1:1.5; yield: 41%; beige foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$, 7:3 mixture of two rotamers) δ 7.69 (d, *J* = 7.6 Hz, 0.3H), 7.49 (d, *J* = 7.6 Hz, 0.7H), 7.41 (t, *J* = 7.6 Hz, 0.3H), 7.32 (t, *J* = 7.6 Hz, 0.7H), 7.24 (m, br, 0.3H), 7.18 (m, br, 0.7H), 7.14 (t, *J* = 7.6 Hz, 0.3H), 7.07 (t, *J* = 7.6 Hz, 0.7H), 6.91 (d, *J* = 7.6 Hz, 0.3H), 6.84 (d, *J* = 7.6 Hz, 0.7H), 5.52 (d, *J* = 6.3 Hz, 0.3H), 5.07 (d, *J* = 6.9 Hz, 0.7H), 4.19 (dd, *J* = 18.3 and 6.0 Hz, 0.3H), 4.14 (d, *J* = 4.7 Hz, 1.4H), 4.09 (dd, *J* = 11.7 and 6.9 Hz, 0.7H), 3.89 (dd, *J* = 18.3 and 4.1 Hz, 0.3H), 3.81 (dd, *J* = 11.7, 6.3 Hz, 0.3H), 3.60 (d, *J* = 11.7 Hz, 0.3H), 3.48 (d, *J* = 11.7 Hz, 0.7H), 3.29 (*s*, 0.9H), 3.25 (*s*, 2.1H), 2.31 (tt, br, *J* = 11.3 and 2.9 Hz, 1H), 1.98-0.99 (m, 10H, methylene protons), 1.51 (*s*, 6.3H), 1.50 (*s*, 2.7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2 and 175.7 (1C), 175.6 and 175.2 (1C), 170.1 and 169.9 (1C), 168.6 and 168.2 (1C), 143.4 and 142.0 (1C), 130.7 and 130.0 (1C), 126.7 and 125.8 (1C),

from 125.1 to 123.0 (2C), 108.9 and 108.6 (1C), 83.0 and 82.2 (1C), 72.0 and 70.1 (1C), 66.4 and 65.5 (1C), 43.8 and 42.7 (1C), 42.5, and 42.4 (1C), from 33.3 to 25.1 (10C); HR-MS (ESI) calcd for $C_{25}H_{34}N_3O_5S^+$ $[MH]^+$ 488.2214, found 488.2205.

(3*S,4'*R**)-3'-(Cyclohexanecarbonyl)-1-methyl-2-oxo-*N*-phenylspiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4m).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and isocyanobenzene **V·2f**. FC: Hexane:EtOAc, 1.5:1; yield: 43%; grey foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 11:9 mixture of two rotamers) δ 9.25 (m, br, 0.45 H), 8.47 (m, br, 0.55H), 7.64 (d, br, *J* = 7.7 Hz, 1H), 7.58 (d, br, *J* = 7.8 Hz, 1H), 7.48-7.19 (m, 4.55H), 7.13 (t, br, *J* = 7.7 Hz, 0.45H), 7.05 (t, br, *J* = 7.7 Hz, 1H), 6.88 (m, 1H), 5.64 (d, *J* = 4.9 Hz, 0.45H), 5.16 (d, *J* = 6.8 Hz, 0.55H), 4.12 (dd, *J* = 11.7, 6.8 Hz, 0.55H), 3.78 (dd, *J* = 11.7 and 4.9 Hz, 0.45H), 3.71 (d, *J* = 11.7 Hz, 0.45H), 3.59 (d, *J* = 11.7 Hz, 0.55H), 3.29 (*s*, 1.35H), 3.26 (*s*, 1.65H), 2.37 (tt, br, *J* = 11.6 and 2.9 Hz, 1H), 1.93-0.90 (m, 10H, methylene protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2 and 175.6 and 175.1 (2C), 168.1 and 167.8 (1C), 143.7 and 142.1 (1C), 138.1 and 136.9 (1C), 131.0 and 130.3 (1C), 129.5 (2C), 129.1 (2C), 126.8 and 126.1 (1C), 125.4-122.8 (3C), 119.9 and 119.8 (1C), 109.1 and 19.0 (1C), 72.1, and 70.1 (1C), 67.1 and 66.1 (1C), 44.0 and 42.8 (1C), 33.8-25.4 (7C); HR-MS (ESI) calcd for $C_{25}H_{27}N_3NaO_3S^+$ $[MNa]^+$ 472.1665, found 472.1653.

(3*S,4'*R**)-*N*-Benzyl-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4n).** Prepared according to GP-A using thiazoline **V·1a**, cyclohexanecarboxylic acid **V·3a** and benzyl isocyanide **V·2g**. FC: Hexane:EtOAc, 1:1; yield: 57%; light pink foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$, 7:3 mixture of two rotamers) δ 7.45-7.22 (m, 6H), 6.98-6.77 (m, 4H),

5.53 (d, *J* = 5.8 Hz, 0.3H), 5.08 (d, *J* = 6.8 Hz, 0.7H), 4.78 (dd, *J* = 14.7 and 6.8 Hz, 0.3H), 4.72 (dd, *J* = 14.3 and 6.2 Hz, 0.7H), 4.59 (dd, *J* = 14.3 and 5.5 Hz, 0.7H), 4.32 (dd, *J* = 14.7 and 4.8 Hz, 0.3H), 4.06 (dd, *J* = 12.0 and 6.8 Hz, 0.7H), 3.75 (dd, *J* = 11.6 and 5.8 Hz, 0.3H), 3.65 (d, *J* = 11.6 Hz, 0.3H), 3.56 (d, *J* = 12.0 Hz, 0.7H), 3.27 (s, 0.9H), 3.22 (s, 2.1H), 2.26 (tt, br, *J* = 11.3 and 3.4 Hz, 1H), 1.95-0.98 (m, 10H, methylene protons); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2 and 177.5 (1C), 175.6 and 175.0 (1C), 169.7, 143.6 and 142.1 (1C), 138.5 and 137.3 (1C), 130.8-127.5 (6C), 126.9 and 125.9 (1C), 124.5-122.7 (2C), 109.0 and 108.7 (1C), 72.0 and 70.0 (1C), 66.4 and 65.7 (1C), 44.4 and 43.7 (1C), 43.9 and 42.7 (1C), 33.5-25.2 (10C); HR-MS (ESI) calcd for $C_{26}H_{29}N_3NaO_3S^+$ $[MNa]^+$ 486.1822, found 486.1833.

(3*S,4'*R**-3'-Acetyl-*N*-(tert-butyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4p).** Prepared according to GP-A using thiazoline **V·1a**, acetic acid **V·3b** and *tert*-butyl isocyanide **V·2a**. FC: Hexane:EtOAc, 1:9; yield: 52%; yellow foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$, 9:1 mixture of two rotamers) δ 7.43-7.23 (m, 2.1H), 7.14 (t, br, *J* = 7.7 Hz, 0.1H), 7.07 (t, br, *J* = 7.7 Hz, 0.9H), 6.89 (m, br, 0.1H), 6.85 (d, br, *J* = 7.8 Hz, 0.9H), 6.49 (m, br, 0.9H), 5.36 (d, *J* = 5.8 Hz, 0.1H), 4.83 (d, *J* = 6.8 Hz, 0.9H), 4.08 (dd, *J* = 11.7 and 6.8 Hz, 0.9H), 3.69 (dd, *J* = 11.7 and 5.8 Hz, 0.1H), 3.59 (d, *J* = 11.7 Hz, 0.1H), 3.46 (d, *J* = 11.7 Hz, 0.9H), 3.26 (s, 0.3H), 3.24 (s, 2.7H), 2.12 (s, 2.7H), 2.03 (s, 0.3H), 1.52 (s, 0.9H), 1.49 (s, 8.1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 169.5, 168.7, 143.7 and 142.3 (1C), 130.9 and 130.2 (1C), 126.3 and 126.0 (1C), 124.5-122.8 (2C), 109.2 and 108.9 (1C), 74.2 and 72.1 (1C), 67.5 and 67.0 (1C), 52.2 and 51.4 (1C), 33.9, 28.8 (3C), 26.8 and 26.6 (1C), 23.6 and 21.4 (1C); HR-MS (ESI) calcd for $C_{18}H_{23}N_3NaO_3S^+$ $[MNa]^+$ 384.1352, found 384.1360.

(3*S,4'*R**)-*N*-(tert-Butyl)-3'-(cyclopentanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4q).** Prepared according to GP-A using thiazoline **V·1a**, cyclopentanecarboxylic acid **V·3c** and *tert*-butyl isocyanide **V·2a**. FC: *c*-Hexane:EtOAc, 1:1; yield: 80%; yellow foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$, 9:1 mixture of two rotamers) δ 7.38 (d, br, *J* = 7.8 Hz, 0.1H), 7.32 (t, br, *J* = 7.8 Hz, 0.9H), 7.28-7.22 (m, 1H), 7.12 (t, *J* = 7.7 Hz, 0.1H), 7.05 (t, br, *J* = 7.7 Hz, 0.9H), 6.96 (m, br, 0.1H), 6.86 (d, br, *J* = 7.8 Hz, 0.1H), 6.84 (d, br, *J* = 7.8 Hz, 0.9H),, 6.54 (m, br, 0.9H), 5.44 (d, *J* = 5.4 Hz, 0.1H), 4.94 (d, *J* = 6.9 Hz, 0.9H), 4.03 (dd, *J* = 12.0 and 6.9 Hz, 0.9H), 3.65 (dd, *J* = 11.3 and 5.4 Hz, 0.1H), 3.60 (d, *J* = 11.3 Hz, 0.1H), 3.46 (d, *J* = 12.0 Hz, 0.9H), 3.25 (s, 0.3H), 3.23 (s, 2.7H), 2.71 (m, 1H), 1.91 (m, 1H), 1.78-1.45 (m, 7H), 1.48 (s, 8.1H), 1.41 (s, 0.9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178,4 and 176.4 (1C) 175.5 and 175.0(1C), 169.1 and 168.7 (1C), 143.6 and 141.9 (1C), 130.4 and 130.1 (1C), 127.1 and 126.0 (1C), 123.8-122.3 (2C), 109.1 and 108.9 (1C), 72.0 and 70.0 (1C), 67.3 and 66.2 (1C), 52.1 and 51.2 (1C), 43.5 and 42.2 (1C), 33.4-26.0 (9C); HR-MS (ESI) calcd for $C_{22}H_{30}N_3O_3S^+[MH]^+$ 416.2002, found 416.1993.

(3*S,4'*R**)-*N*-(tert-Butyl)-1-methyl-2-oxo-3'-(tetrahydro-2H-pyran-4-carbonyl)spiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4r).** Prepared according to GP-A using thiazoline **V·1a**, tetrahydropyran-4-carboxylic **V·3d** and acid *tert*-butyl isocyanide **V·2a**. FC: *c*-Hexane:EtOAc, 1:1; yield: 79%; white foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 mixture of two rotamers) δ 7.44-7.37 (m, 0.5H), 7.33 (t, *J* = 7.6 Hz, 0.75H), 7.23 (d, *J* = 7.6 Hz, 0.75H), 7.12 (t, *J* = 7.6 Hz, 0.25H), 7.06 (t, *J* = 7.6 Hz, 0.75H), 6.93 (d, *J* = 7.6 Hz, 0.25H), 6.90-6.81 (m, 1H), 6.52 (m, b, 0.75H), 5.41 (d, *J* = 5.4 Hz, 0.25H), 4.90 (d, *J* = 6.9 Hz, 0.75H), 4.06 (dd, *J* = 11.7, 6.9 Hz, 0.75H), 4.00-3.83 (m,

1.75H), 3.69-3.56 (m, 0.75H), 3.47-3.28 (m, 2.25H), 3.28 (*s*, 0.9H), 3.24 (*s*, 2.1H), 2.90 (t, br, *J* = 11.3 Hz, 0.25H), 2.54 (m, 1H), 2.44 (t, *J* = 11.4 Hz, 0.25H), 1.84-1.48 (m, 4H), 1.47 (*s*, 6.75H), 1.40 (*s*, 2.25H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6-173.7 (2C), 169.0 and 168.4 (1C), 143.5 and 142.0 (1C), 131.1 and 130.3 (1C), 127.1 and 125.7 (1C), 124.4-122.3 (2C), 109.2 and 109.0 (1C), 72.0 and 69.9 (1C), 67.2-66.7 (2C), 66.9 and 66.0 (1C), 52.1 and 51.3 (1C), 41.1 and 39.9 (1C), 33.5 (1C), 30.2-26.7 (6C); HR-MS (ESI) calcd for $C_{22}H_{30}N_3O_4S^+$ $[MH]^+$ 432.1952, found 432.1947.

***tert*-Butyl 4-((3*S**,4'*R**)-4'-(*tert*-butylcarbamoyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidin]-3'-ylcarbonyl)piperidine-1-carboxylate (V·4t).** Prepared according GP-A using thiazoline **V·1a**, 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid **V·3f** and *tert*-butyl isocyanoacetate **V·2a**; FC: *c*-Hexane:EtOAc, gradient from 1:1, gradually changed to 1:1.5; yield: 59%; white foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$, 7:3 mixture of two rotamers) δ 7.45-7.39 (m, 0.6H), 7.36 (t, br, *J* = 7.7 Hz, 0.7H), 7.25 (d, br, *J* = 7.7 Hz, 0.7H), 7.16 (t, *J* = 7.7 Hz, 0.3H), 7.08 (t, br, *J* = 7.7 Hz, 0.7H), 6.93 (d, br, *J* = 7.7 Hz, 0.3H), 6.88 (d, br, *J* = 7.7 Hz, 0.7H), 6.85 (m, br, 0.3H), 6.55 (m, br, 0.7H), 5.44 (d, *J* = 5.7 Hz, 0.3H), 4.92 (d, *J* = 6.9 Hz, 0.7H), 4.24 – 3.97 (m, br, 1.4H), 4.10 (dd, *J* = 12.0 and 6.9 Hz, 0.7H) 3.83 (m, br, 0.6H), 3.71 (dd, *J* = 11.8, 5.7 Hz, 0.3H), 3.62 (d, *J* = 11.8, 0.3H), 3.43 (d, *J* = 11.8 Hz, 0.7H), 3.29 (*s*, 0.9H), 3.25 (*s*, 2.1H), 2.69 (m, br, 1.4H), 2.47 (m, 1H), 2.21 (m, br, 0.6H), 1.83-1.68 (m, 1.7H), 1.64-1.52 (m, 2.3H), 1.50 (*s*, 6.3H), 1.43 (*s*, 2.7H), 1.42 (*s*, 6.3H), 1.40(*s*, 2.7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6 and 175.5 (1C), 174.8 and 174.0 (1C), 169.0 and 168.4 (1C), 154.4 and 154.3 (1C), 143.5 and 141.9 (1C), 131.1 and 130.3 (1C), 127.0 and 125.6 (1C), 124.3-122.3 (2C), 109.2 and 108.9 (1C), 79.7 and 79.6 (1C), 71.9 and 69.9

(1C), 66.8 and 66.0 (1C), 52.1 and 51.3 (1C), 43.2-42.3 (br, 2C), 41.9 and 40.8 (1C), 33.6, 30.0-26.6 (9C); HR-MS (ESI) calcd for $C_{27}H_{39}N_4O_5S^+$ [MH^+] 531.2636, found 531.2615.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-3'-(furan-2-carbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4u).** Prepared according to GP-A using thiazoline **V·1a**, 2-furoic acid **V·3g** and *tert*-butyl isocyanide **V·2a**. FC: *c*-Hexane:EtOAc, 1:1; yield: 78%; light pink foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, br, 1H), 7.40-7.31 (m, 2H), 7.16 (d, br, *J* = 3.4 Hz, 1H), 7.07 (t, br, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.49 (dd, *J* = 3.5 and 1.6 Hz, 1H), 6.45 (m, br, 1H), 5.40 (d, *J* = 6.3 Hz, 1H), 4.10 (dd, *J* = 11.9 and 6.3 Hz, 1H), 3.59 (d, *J* = 11.9 Hz, 1H), 3.29 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 169.5, 158.1, 146.4, 145.2, 143.9, 130.4, 125.3, 122.9, 122.8, 119.8, 112.3, 108.8, 73.1, 67.1, 52.0, 29.7, 28.7 (3C), 26.7; HR-MS (ESI) calcd for $C_{21}H_{24}N_3O_4S^+$ [MH^+] 414.1482, found 414.1478.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-1-methyl-2-oxo-3'-(thiophene-2-carbonyl)spiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4v).** Prepared according to GP-A using thiazoline **V·1a**, thiophene-2-carboxylic acid **V·3h** and *tert*-butyl isocyanide **V·2a**. FC: *c*-Hexane:EtOAc, 1:1; yield: 76%; light yellow foamy solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 4.8 Hz, 1H), 7.47 (m, br, 1H), 7.38 (d, br, *J* = 7.6 Hz, 1H), 7.35 (d, br, *J* = 7.6 Hz, 1H), 7.07 (t, br, *J* = 7.7 Hz, 1H), 7.05 (m, br, 1H), 6.88 (d, br, *J* = 7.8 Hz, 1H), 6.71 (m, br, 1H), 5.27 (d, *J* = 6.7 Hz, 1H), 4.11 (dd, *J* = 11.8, 6.7 Hz, 1H), 3.54 (d, *J* = 11.8 Hz, 1H), 3.29 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 169.0, 162.5, 143.8, 137.2, 132.3, 130.7, 130.4, 127.6, 125.4, 122.8, 122.7, 108.9, 73.3, 68.1, 52.3, 29.7, 28.6 (3C), 26.7; HR-MS (ESI) calcd for $C_{21}H_{24}N_3O_3S_2^+$ [MH^+] 430.1254, found 430.1258.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-1-methyl-3'-nicotinoyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4w).** Prepared according to GP-A using thiazoline **V·1a**, nicotinic acid **V·3i** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 56%; orange foamy solid; ^{1}H NMR (300 MHz, DMSO-d_6, 3:1 mixture of two rotamers) δ 8.70 (d, br, *J* = 4.9 Hz, 0.75H), 8.53 (s, br, 0.75H), 8.07 (d, br, *J* = 7.8 Hz, 1H), 7.94 (s, br, 0.25H), 7.88 (d, br, *J* = 4.8 Hz, 0.25H), 7.79-7.70 (m, br, 2H), 7.47 (m, 0.75H), 7.42-7.32 (m, 1.25H), 7.14 (t, br, *J* = 7.6 Hz, 1H), 7.04 (t, br, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 6.3 Hz, 0.25H), 4.78 (d, *J* = 5.8 Hz, 0.75H), 3.76 (m, 1H), 3.45-3.32 (m, 1H), 3.21 (s, 2.25H), 3.13 (s, 0.75H), 1.36 (s, 2.25H), 1.31 (s, 6.75H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1-175.3 (2C), 169.4, 152.1 (br), 148.2 (br), 142.9, 135.2, 131.4 and 130.6 (1C), 131.0 (br), 128.8, 128.7, 125.5 and 123.9 (1C), 125.1 (br), 110.5, 72.2, 67.4 and 66.7 (1C), 52.9 and 52.8 (1C), 34.7 and 34.4 (1C), 29.4 (3C), 27.4; HR-MS (ESI) calcd for $C_{22}H_{24}N_4NaO_3S^+$ $[MNa]^+$ 447.1461, found 447.1457.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-1-methyl-2-oxo-3'-(2-phenylacetyl)spiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4x).** Prepared according to GP-A using thiazoline **V·1a**, phenylacetic acid **V·3j** and *tert*-butyl isocyanide **V·2a**. FC: Hexane:EtOAc, 7:3; yield: 55%; yellow foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.11 (m, 7H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.43 (m, br, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 3.99 (dd, *J* = 11.7 and 6.8 Hz, 1H), 3.69 (s, 2H), 3.43 (d, *J* = 11.7 Hz, 1H), 3.24 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 170.1, 168.8, 143.9, 133.3, 130.4, 129.9, 129.1 (2C), 129.0 (2C), 127.5, 123.1 (2C), 109.1, 72.5, 66.6, 52.3, 42.5, 34.1, 28.9 (3C), 26.9; HR-MS (ESI) calcd for $C_{24}H_{27}N_3NaO_3S^+$ $[MNa]^+$ 460.1665, found 460.1657.

(3*S,4'*R**)-3'-(2-(1*H*-Indol-3-yl)acetyl)-*N*-(*tert*-butyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4y).** Prepared according to GP-A using thiazoline **V·1a**, 3-indoleacetic acid **V·3k** and *tert*-butyl isocyanide **V·2a**. FC: *c*-Hexane:EtOAc, 1:1; yield: 72%; white foamy solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (*s*, br, 1H), 7.90-7.85 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.15 (*s*, br, 1H), 7.10-7.05 (m, 2H), 6.96-6.91 (m, 2H), 5.18 (d, *J* = 6.7 Hz, 1H), 3.73 (dd, *J* = 12.1 Hz and 6.7, 1H), 3.62 (d, *J* = 16.0 Hz, 1H), 3.47 (d, *J* = 16.0 Hz, 1H), 3.42 (d, *J* = 12.1 Hz, 1H) 3.10 (*s*, 3H), 1.33 (*s*, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.5, 168.9, 168.8, 143.4, 136.5, 129.7, 127.9, 127.6, 125.1, 123.8, 122.9, 121.6, 118.9, 118.7, 111.8, 108.8, 107.6, 71.6, 64.9, 55.4, 51.1, 35.9, 28.8 (3C), 26.7; HR-MS (ESI) calcd for $C_{26}H_{29}N_4O_3S^+$ $[MH]^+$ 477.1955, found 477.1942.

(3*S,4'*R**)-*N*-(*tert*-Butyl)-3'-((*E*)-3-(furan-2-yl)acryloyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·4z).** Prepared according to GP-A using thiazoline **V·1a**, 3-(2-furyl)acrylic acid **V·3l** and *tert*-butyl isocyanide **V·2a**. FC: CH_2Cl_2:EtOAc, 19:1; yield: 42%; grey foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.23 (m, 4H), 7.10 (t, br, *J* = 7.5 Hz, 1H), 6.91 (d, br, *J* = 7.6 Hz, 1H), 6.64-6.40 (m, 4H), 5.08 (d, *J* = 7.0 Hz, 1H), 4.13 (dd, *J* = 11.6 and 7.0 Hz, 1H), 3.59 (d, *J* = 11.6 Hz, 1H), 3.31 (*s*, 3H), 1.52 (*s*, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 168.9, 165.3, 150.8, 143.9, 132.4, 130.3 (2C), 125.8, 122.8, 122.7, 116.0, 114.0, 112.5, 108.8, 72.3, 66.4, 52.3, 33.6, 28.8 (3C), 26.7; HR-MS (ESI) calcd for $C_{23}H_{25}N_3NaO_4S^+$ $[MNa]^+$ 462.1458, found 462.1446.

General procedure B (GP-B) for the synthesis of compounds V·5a-l via azido-Ugi 3-CR reaction. To a solution of thiazoline **V·1** (0.3 mmol, 1 eq) in HFIP (0.68 mL) cooled to 0 °C, isocyanide **V·2** (0.3 mmol, 1 eq) and trimethylsilyl azide (0.3 mmol, 1 eq) were added. The reaction was stirred at room temperature and the conversion was monitored by TLC. The solvent was evaporated under reduce pressure and the crude was purified by flash chromatography (FC) or triturated as reported below.

(3*S,4'*R**)-4'-(1-(tert-butyl)-1H-tetrazol-5-yl)-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (V·5a).** Prepared according to GP-B using thiazoline **V·1a**, *tert*-butyl isocyanide **V·2a** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0, to 96:4; yield: 87%; amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.6, 1.3 Hz, 1H), 7.38 (td, J = 7.6, 1.3 Hz, 1H), 7.15 (td, J = 7.6, 1.3 Hz, 1H), 6.88 (d, J = 7.6, 1H), 5.80 (dd, J = 9.5, 6.3 Hz, 1H), 4.00 - 3.90 (m, 1H), 3.75 (dd, J = 9.5, 6.3 Hz, 1H), 3.22 (*s*, 3H), 2.85 (br *s*, 1H), 1.81 (*s*, 9H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 176.4, 152.6, 143.3, 130.7, 126.4, 124.1, 123.6, 108.7, 75.5, 62.1, 57.3, 41.0, 30.0 (3C), 29.8; HR-MS (ESI) calcd for $C_{16}H_{21}N_6OS^+$ [MH]+ 345.1492, found 345.1512.

(3*S,4'*R**)-4'-(1-(tert-butyl)-1H-tetrazol-5-yl)spiro[indoline-3,2'-thiazolidin]-2-one (V·5b).** Prepared according to GP-B using thiazoline **V·1b**, *tert*-butyl isocyanide **V·2a** and trimethylsilyl azide. Triturated in MeOH; yield: 69%; pale yellow amorphous solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.55 (br *s*, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.4 Hz, 1H), 5.52 (ddd, J = 11.9, 9.3, 6.0 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.00 (t, J = 9.3 Hz, 1H), 3.73 (dd, J = 9.3, 6.0 Hz, 1H), 1.72 (*s*, 9H); ^{13}C NMR (76 MHz, DMSO-d_6) δ 178.0, 152.6, 141.8, 130.6, 127.8, 126.1, 122.5, 110.2, 76.2, 62.7,

58.1, 29.5 (3C); HR-MS (ESI) calcd for $C_{15}H_{19}N_6OS^+$ $[MH]^+$ 331.1336, found 331.1321.

(3*S,4'*R**)-1-benzyl-4'-(1-(tert-butyl)-1H-tetrazol-5-yl)spiro[indoline-3,2'-thiazolidin]-2-one (V·5c).** Prepared according to GP-B using thiazoline **V·1c**, *tert*-butyl isocyanide **V·2a** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 80%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.25 (m, 6H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 5.65 – 5.48 (m, 1H), 5.04 – 4.75 (m, 3H), 4.25 – 4.3.90 (m, 1H), 3.80 (dd, *J* = 9.5, 5.8 Hz, 1H), 1.73 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.4, 152.5, 142.2, 136.6, 130.6, 129.1 (2C), 128.0, 127.6 (2C), 127.1, 126.1, 123.3, 109.9, 75.9, 62.8, 58.1, 42.8, 39.7, 29.5 (3C); HR-MS (ESI) calcd for $C_{22}H_{25}N_6OS^+$ $[MH]^+$ 421.1805, found 421.1799.

(3*S,4'*R**)-4'-(1-(tert-butyl)-1H-tetrazol-5-yl)-5-fluoro-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (V·5d).** Prepared according to GP-B using thiazoline **V·1d**, *tert*-butyl isocyanide **V·2a** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 78%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 1H), 6.80 (dt, *J* = 8.5, 3.9 Hz, 1H), 6.79 (dd, *J* = 8.5, 3.9 Hz, 1H), 5.90 – 5.75 (m, 1H), 4.00 – 3.89 (m, 1H), 3.75 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.22 (*s*, 3H), 3.07 (br *s*, 1H), 1.81 (*s*, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 160.5 and 158.6 (1C), 152.4, 139.3 and 139.2 (1C), 128.0 and 127.9 (1C), 117.2 and 117.0 (1C), 112.5 and 112.3 (1C), 109.5 and 109.4 (1C), 75.4, 62.1, 57.4, 41.0, 30.0 (3C), 26.6; HR-MS (ESI) calcd for $C_{16}H_{20}FN_6OS^+$ $[MH]^+$ 363.1398, found 363.1417.

(3*S,4'*R**)-5-bromo-4'-(1-(tert-butyl)-1H-tetrazol-5-yl)-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (V·5e).** Prepared according to GP-B using thiazoline **V·1f**, *tert*-

butyl isocyanide **V·2a** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 81%; white amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.7 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 5.92 – 5.66 (m, 1H), 4.00 – 3.89 (m, 1H), 3.77 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.22 (s, 3H), 3.00 (br s, 1H), 1.82 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 152.4, 142.4, 133.6, 128.4, 127.5, 116.0, 110.2, 75.0, 62.1, 57.4, 41.1, 30.0 (3C), 26.6; HR-MS (ESI) calcd for $C_{16}H_{20}BrN_6OS^+$ $[MH]^+$ 423.0597, found 422.0524.

(3*S,4'*R**)-1-methyl-4'-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)spiro[indoline-3,2'-thiazolidin]-2-one (V·5f).** Prepared according to GP-B using imine **V·1a**, 1,1,3,3-tetramethylbutyl isocyanide **V·2b** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 84%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 5.96 – 5.75 (m, 1H), 4.00 – 3.83 (m, 1H), 3.81 – 3.69 (m, 1H), 3.22 (s, 3H), 2.16 (d, *J* = 15.5 Hz, 1H), 2.01 (d, *J* = 15.5 Hz, 1H), 1.89 (d, *J* = 14.1 Hz, 4H), 0.77 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 153.2, 143.4, 130.7, 126.4, 124.1, 123.5, 108.7, 75.5, 65.4, 57.4, 53.2, 41.3, 31.7, 30.8, 30.6 (3C), 30.1, 26.4; HR-MS (ESI) calcd for $C_{20}H_{29}N_6OS^+$ $[MH]^+$ 401.2118, found 401.2130.

(3*S,4'*R**)-1-methyl-4'-(1-pentyl-1H-tetrazol-5-yl)spiro[indoline-3,2'-thiazolidin]-2-one (V·5g).** Prepared according to GP-B using imine **V·1a**, 1-pentyl isocyanide **V·2i** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 59%; pale yellow foam; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 – 7.29 (m, 2H), 7.18 – 6.78 (m, 2H), 5.40 (ddd, J = 11.5, 8.7, 6.3 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.61 – 4.23 (m, 2H), 4.11 – 3.67 (m, 2H), 3.15 (s, 3H), 1.82 (p, J = 7.2 Hz, 2H), 1.32 – 1.17 (m, 4H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ

176.5, 153.5, 143.3, 130.7, 127.3, 125.4, 123.2, 109.4, 75.8, 57.2, 47.7, 38.6, 28.5, 28.3, 26.6, 21.8, 14.1; HR-MS (ESI) calcd for $C_{17}H_{23}N_6OS^+$ $[MH]^+$ 359.1649, found 359.1629.

(3S*,4'R*)-4'-(1-cyclohexyl-1H-tetrazol-5-yl)-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (V·5h). Prepared according to GP-B using imine **V·1a**, cyclohexyl isocyanide **V·2c** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 76%; white foam; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 – 7.27 (m, 2H), 7.14 – 6.94 (m, 2H), 5.65 – 5.37 (m, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.57 (t, J = 11.1 Hz, 1H), 3.96 – 3.85 (m, 1H), 3.82 – 3.70 (m, 1H), 3.15 (s, 3H), 2.07 (d, J = 11.7 Hz, 1H), 1.96 (d, J = 11.7 Hz, 1H), 1.90 – 1.70 (m, 4H), 1.69 – 1.56 (m, 1H), 1.40 – 1.15 (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.6, 152.9, 143.3, 130.6, 127.5, 125.3, 123.2, 109.4, 75.7, 57.8, 57.2, 38.5, 32.7, 32.6, 26.6, 25.3, 25.2, 24.9; HRMS (ESI) calcd for $C_{18}H_{23}N_6OS^+$ $[MH]^+$ 371.1649, found 371.1632.

***tert*-butyl 4-(5-((3S*,4'R*)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidin]-4'-yl)-1H-tetrazol-1-yl)piperidine-1-carboxylate (V·5i).** Prepared according to GP-B using imine **V·1a**, *tert*-butyl 4-(methylidyne-λ4-azanyl)piperidine-1-carboxylate **V·2j** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 69%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, DMSO-d_6, disteroisomeric mixture 7:3) δ 7.62 (d, J = 7.4 Hz, 0.3H), 7.42 – 7.30 (m, 1.3H), 7.14 (t, J = 7.4 Hz, 0.3H), 7.10 – 6.99 (m, 1.3H), 5.55 – 5.35 (m, 1H), 5.24 – 5.09 (m, 0.3H), 4.87 – 4.78 (m, 0.7H), 4.74 (d, J = 11.0 Hz, 0.7H), 4.57 (d, J = 11.0 Hz, 0.3H), 4.19 – 3.69 (m, 4H), 3.14 (*s*, 2.1H), 3.09 (*s*, 0.9H), 3.00 – 2.70 (br m, 2H), 2.19 – 1.76 (m, 4H), 1.41 (*s*, 2.7H) 1.40 (*s*, 6.3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.5 and 175.8 (1C), 154.3 and 154.2 (1C), 154.1 and 153.4 (1C), 143.3 and 143.0 (1C),

130.6 and 130.5 (1C), 129.3 and 127.4 (1C), 125.3 and 125.0 (1C), 123.3 and 123.2 (1C), 109.5 and 109.4 (1C), 79.6 and 79.5 (1C), 75.7 and 75.0 (1C), 59.2 and 57.3 (1C), 55.8 and 55.2 (1C), 38.9 and 38.5 (1C), 32.1 and 31.7 (2C), 28.6 and 28.5 (3C), 26.8 (2C), 26.7 and 26.6 (1C); HR-MS (ESI) calcd for $C_{22}H_{30}N_7O_3S^+$ $[MH]^+$ 472.2125, found 472.2121.

***tert*-butyl 2-(5-((3S*,4'R*)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidin]-4'-yl)-1H-tetrazol-1-yl)acetate (V·5j).** Prepared according to GP-B using imine **V·1a**, *tert*-butyl isocyanoacetate **V·2e** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc from 100:0 to 96:4; yield: 72%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 5.48 – 5.24 (m, 3H), 4.65 (d, J = 11.6 Hz, 1H), 3.94 – 3.66 (m, 2H), 3.13 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 165.5, 154.4, 143.3, 130.7, 127.2, 125.4, 123.2, 109.3, 83.2, 75.4, 57.1, 49.7, 38.3, 27.8 (3C), 26.5; HR-MS (ESI) calcd for $C_{18}H_{23}N_6O_3S^+$ $[MH]^+$ 403.1547, found 403.1538.

(3S*,4'R*)-4'-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (V·5k). Prepared according to GP-B using imine **V·1a**, 4-methoxyphenyl isocyanide **V·2k** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc from 100:0 to 96:4; yield: 37%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 7.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 8.3 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 5.50 – 5.32 (m, 1H), 4.64 (d, J = 11.2 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.83 (s, 3H), 3.75 – 3.64 (m, 1H), 3.08 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.1, 160.7, 153.7, 143.3, 130.7, 126.9 (2C), 126.8, 125.5, 123.1, 115.1 (2C), 109.3,

75.8, 56.9, 56.1, 39.0, 26.5; HR-MS (ESI) calcd for $C_{19}H_{19}N_6O_2S^+$ $[MH]^+$ 395.1285, found 395.1272.

(3*S,4'*R**)-4'-(1-benzyl-1H-tetrazol-5-yl)-1-methylspiro[indoline-3,2'-thiazolidin]-2-one (V·5l).** Prepared according to GP-B using imine **V·1a**, benzyl isocyanide **V·2g** and trimethylsilyl azide. FC: CH_2Cl_2:EtOAc, from 100:0 to 96:4; yield: 70%; pale yellow amorphous solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 16.8 Hz, 5H), 7.12 – 6.88 (m, 2H), 5.68 (s, 2H), 5.42 (q, J = 8.3, 7.7 Hz, 1H), 4.86 (d, J = 11.4 Hz, 1H), 3.82 (dt, J = 27.6, 8.8 Hz, 2H), 3.15 (*s*, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.5, 153.7, 143.3, 134.8, 130.7, 129.3 (2C), 128.9, 128.8 (2C), 127.3, 125.4, 123.2, 109.4, 75.7, 57.2, 51.0, 38.6, 26.6; HR-MS (ESI) calcd for $C_{19}H_{19}N_6OS^+$ $[MH]^+$ 379.1336, found 379.1321.

Post-transformations

(3*S,4'*R**)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·6).** Compound **V·4i** (0.11 mmol, 1 eq) was dissolved in TFA (0.22 mL) and stirred overnight at room temperature. The mixture was diluted in EtOAc (5 mL) and washed with water (1x5 mL) and brine (1x5 mL). The solvent was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure affording product **V·6** (37 mg, quantitative yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67 (m, br, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.44 (m, br, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 3.70 (dd, *J* = 12.3 and 6.5 Hz, 1H), 3.48 (d, *J* = 12.3 Hz, 1H), 3.09 (s, 3H), 1.02 (m, br, 1H), 1.71-1.51 (m, 4H), 1.40-0.93 (m, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.9, 173.0, 171.1, 143.0, 129.1, 127.7, 124.4, 122.3, 108.3, 64.9, 63.8, 42.5, 34.5, 28.7, 28.6, 26.3, 25.3,

25.1, 25.0; HR-MS (ESI) calcd for $C_{19}H_{24}N_3O_3S^+$ $[MH]^+$ 374.1538, found 374.1526.

((3*S,4'*R**)-3'-(cyclohexanecarbonyl)-1-methyl-2-oxospiro[indoline-3,2'-thiazolidine]-4'-carbonyl)glycine (V·7).** To a solution of **V·4l** (0.1 mmol, 1 eq) in CH_2Cl_2 (0.4 mL), TFA (0.1 mL) was added and the mixture stirred for 6 hours at room temperature. The reaction was diluted in EtOAc and washed with saturated aq. $NaHCO_3$ (2x5 mL) and then with HCl 1M (2x5 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvents were evaporated. Product **V·7** (42 mg, 95%) was obtained as a grey foamy solid. ^{1}H NMR (300 MHz, DMSO-d_6, 9:1 mixture of two rotamers) δ 13.46-12.16 (m, br, 1H), 8.58 (m, br, 0.9H), 8.35 (m, br, 0.1H), 8.03 (d, br, *J* = 7.6 Hz, 0.1H), 7.76 (d, br, *J* = 7.6 Hz, 0.9H), 7.46 (t, br, *J* = 7.7 Hz, 0.1H),7.29 (d, br, *J* = 7.6 Hz, 0.9H), 7.17 (m, br, 0.2H), 7.10-6.91 (m, 1.8H), 5.77 (m, br, 0.1H), 5.30 (d, *J* = 6.6 Hz, 0.9H), 4.19-3.24 (m, 4H), 3.18 (*s*, 0.3H), 3.12 (*s*, 2.7H), 2.26 (m, br, 1H), 1.80-1.42 (m, 4H), 1.38-0.62 (m, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.5 and 174.9 (1C), 173.7 and 173.2 (1C), 171.3 and 171.1 (1C), 170.1 and 169.5 (1C), 143.0 and 141.8 (1C), 130.7 and 129.2 (1C), 127.6 and 127.5 (1C), 125.4 and 124.5 (1C), 123.5 and 122.4 (1C) 109.6 and 108.3 (1C), 71.0 and 69.2 (1C), 64.9 and 63.7 (1C), 42.4 and 41.8 (1C), 41.2 and 41.0 (1C), 34.5 and 32.8 (1C), 28.7 (2C), 26.6 and 26.3 (1C), 25.3, 25.1, 24.7; HR-MS (ESI) calcd for $C_{21}H_{26}N_3O_5S^+$ $[MH]^+$ 432.1588, found 432.1581.

(3'*S,4'*R**)-*N*-(tert-butyl)-1-methyl-2-oxo-3'-(piperidine-4-carbonyl)spiro[indoline-3,2'-thiazolidine]-4'-carboxamide (V·8).** To a solution of **V·4t** (0.084 mmol, 1 eq) in CH_2Cl_2 (0.4 mL), TFA (0.1 mL) was added and the mixture was stirred for 2 hours at room temperature. The reaction was diluted with CH_2Cl_2 and washed

with saturated aq. $NaHCO_3$ (2x5 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduce pressure affording compound **V·8** (37 mg, 91%) as a yellow foamy solid. ^1H NMR (500 MHz, $CDCl_3$, mixture of two rotamers 73:27) δ 7.44 – 7.39 (m, *J* = 7.4 Hz, 0.44H), 7.35 (t, *J* = 7.7 Hz, 0.73H), 7.27 (d, *J* = 9.8 Hz, 1.01H), 7.15 (t, *J* = 7.6 Hz, 0.25H), 7.08 (t, *J* = 7.5 Hz, 0.66H), 6.94 (d, *J* = 8.1 Hz, 0.24H), 6.90 – 6.84 (m, *J* = 6.7 Hz, 0.75H), 6.55 (br s, 0.43H), 6.52 (br s, 0.09H), 5.44 (d, *J* = 5.7 Hz, 0.25H), 4.91 (dd, *J* = 18.0, 7.0 Hz, 0.66H), 4.08 (dd, *J* = 11.9, 7.2 Hz, 0.70H), 3.71 – 3.65 (m, 0.26H), 3.65 – 3.60 (m, *J* = 11.5 Hz, 0.26H), 3.47 (dd, *J* = 17.9, 9.5 Hz, 0.67H), 3.30 (s, 0.47H), 3.26 (s, *J* = 8.0 Hz, 1.39H), 3.24 (s, 0.27H), 3.15 – 3.02 (m, 1.14H), 2.82 – 2.40 (m, 2.12H), 2.08 (br s, *J* = 30.9, 20.7 Hz, 1.41H), 1.83 – 0.64 (m, 29.11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 175.6, 175.0 and 174.3 (2C), 169.1 and 168.6 (1C), 143.6 and 142.1 (1C), 131.1 and 130.2 (1C), 127.1 and 125.9 (1C), 124.4, 124.0, 122.9 and 122.4 (2C), 109.3 and 109.0 (1C), 71.9 and 70.0 (1C), 66.9 and 66.0 (1C), 52.1 and 51.3 (1C), 45.8, 45.6, 45.3 and 45.3 (2C), 42.3 and 41.1 (1C), from 33.67 to 26.70 (7C). HR-MS (ESI) calcd for $[C_{22}H_{31}N_4O_3S^+]$ 431.2111, found 431.2112.

V.5 References

(1) (a) Rainoldi, G.; Faltracco, M.; Lo Presti, L.; Silvani, A.; Lesma, G. *Chem. Commun.* **2016**, *52*, 11575. (b) Rainoldi, G.; Sacchetti, A.; Silvani, A.; Lesma, G. *Org. Biomol. Chem.* **2016**, *14*, 7768. (c) Stucchi, M.; Lesma, G.; Meneghetti, F.; Rainoldi, G.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2016**, *81*, 1877. (d) Lesma, G.; Meneghetti, F.; Sacchetti, A.; Stucchi, M.; Silvani, A. *Beilstein J. Org. Chem.* **2014**, *10*, 1383. Sacchetti, A.; Silvani, A.; Gatti, F. G.; Lesma, G.; Pilati, T.; Trucchi, B. *Org. Biomol. Chem.* **2011**, *9*, 5515. (e) Lesma, G.; Landoni, N.; Sacchetti, A.; Silvani, A. *Tetrahedron* **2010**, *66*, 4474. Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537.

(2) Rainoldi, G.; Begnini, F.; Silvani, A.; Lesma, G. *Synlett* **2016**, *27*, 2831.

(3) (a) Saraswat, P.; Jeyabalan, G.; Ansari, Z. H.; Rahman, M. U.; Nyola, N. K. *Synt. Commun. Rev.* **2016**, *46*, 1643. (b) Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. *Eur. J. Med. Chem.* **2016**, *123*, 858. (c) Surmiak, E.; Neochoritis, C. G.; Musielak, B.; Twarda-Clapa, A.; Kurpiewska, K.; Dubin, G.; Camacho, C.; Holak, T. A.; Dömling, A. *Eur. J. Med. Chem.* **2016**, *126*, 384. (d) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673. (e) Zheng, Y. J.; Tice, C. M. *Expert Opin. Drug Discov.* **2016**, *11*, 831.

(4) (a) Zhu, D.; Xia, L.; Pan, L.; Li, S.; Chen, R.; Mou, Y.; Chen, X. *J. Org. Chem.* **2012**, *77*, **3**, 1386. (b) Chèron, N.; Ramozzi, R.; El Kaim, L.; Grimaud, L.; Fleurat-Lessard, P. *J. Org. Chem.* **2012**, *77*, 1361. (c) Nutt, R. F.; Joullié, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5852.

(5) Osborn, H.; Schneider, J. F. *e-EROS*, **2012**, DOI: 10.1002/047084289X.rm291.pub2.

(6) Katsuyama, A.; Matsuda, A.; Ichikawa, S. *Org. Lett.* **2016**, *18*, 2552.

(7) Bertamino A.; Soprano M.; Musella S.; Rusciano M. R.; Sala M.; Vernieri E.; Di Sarno V.; Limatola A.; Carotenuto A.; Cosconati S.; Grieco P.; Novellino E.; Illario M.; Campiglia P.; Gomez-Monterrey I.; *J. Med. Chem.* **2013**, *56*, 5407.

VI. Spirooxindole-fused 4-Methylene azetidines: Formal [2+2] Annulation Reaction

A diastereoselective, DABCO-catalyzed reaction of isatin-derived ketimines and allenoates is described. Exploiting the stereodirecting effect of the bulky tert-butanesulfinyl chiral auxiliary, the method provides an efficient access to single diastereoisomers of unprecedented spirocyclic oxindoles, bearing a 4-methyleneazetidine ring at the spiro junction. The versatility of the method is fully demonstrated by further transformations including the conversion to relevant spirocyclic oxindolo-β-lactams.

Moreover, a β-ICD-based catalysed enantioselective approach is undergoing in order to obtain enantioenriched spirooxindole-fused 4-methylene azetidines.

Published in *Chem. Commun.* **2016**, *52*, 11575-11578.

Published in *Molecules*, **2017**, *22*, 2016.

VI.1 Introduction

The strained four-membered ring system of azetidines[1] is present as a partial structure of a number of natural products[2] and pharmaceutical agents[3] (Figure 1). Owing to their strong molecular rigidity and, at the same time, to their reasonable stability, azetidines are of special interest, being able to potentially provide improved physicochemical properties in their interaction with biological systems.

They have had enormous application in medicinal chemistry in the form of azetidin-2-ones (β-lactams), that are the key components of many biologically active compounds showing antibacterial, antifungal, and anti-inflammatory properties.[4] Various multifunctional spiro β-lactam derivatives have also been reported recently,[5] among which spirooxindolyl β-lactams are particularly relevant.[6] Despite this interest for azetidin-2-ones, in general azetidines have received much less attention with respect to their lower and higher small-ring homologues, and their application in the context of drug discovery is not so common. In particular, only few novel spirocyclic azetidine scaffolds have been recently proposed,[7] able to access unexplored chemical space and to act as

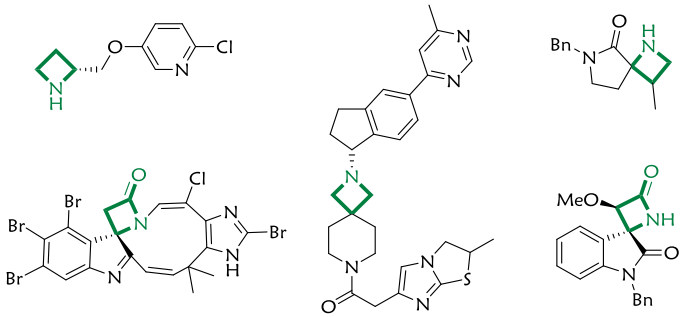
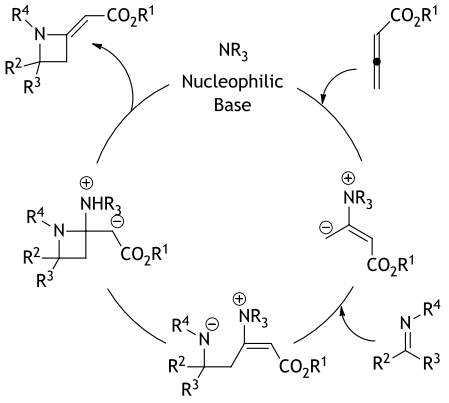


Figure 1. Examples of biologically relevant compounds containing azetidines and azetidin-2-ones moieties.



Scheme 1. Proposed mechanism for the formal [2+2] annulation reaction catalysed by a nucleophilic amine.

potential new lead compounds.[8]Our long-standing interest in the asymmetric synthesis of 3,3-disubstituted oxindoles derivatives and related spiro compounds,[9] unitely to the growing interest in hybrid drugs as therapeutic agents, inspired us to combine the two biologically active oxindole and azetidine moieties, by means of a spiro arrangement of the two ring systems.[10] We conceived the synthesis of chiral spirooxindole-based 4-methyleneazetidines, as an unprecedented, intriguing combination of pharmacologically relevant motifs. Such methyleneazetidines can be also seen as key intermediates for the synthesis of particularly relevant spirooxindolyl β-lactams derivatives.

Relying on our previous experience with isatin-derived ketimines, we looked at the formal [2+2] annulation reactions of such compounds with allenoates, as a practical and direct strategy to obtain highly functionalized target compounds, with a good level of atom-economy (Scheme 1).

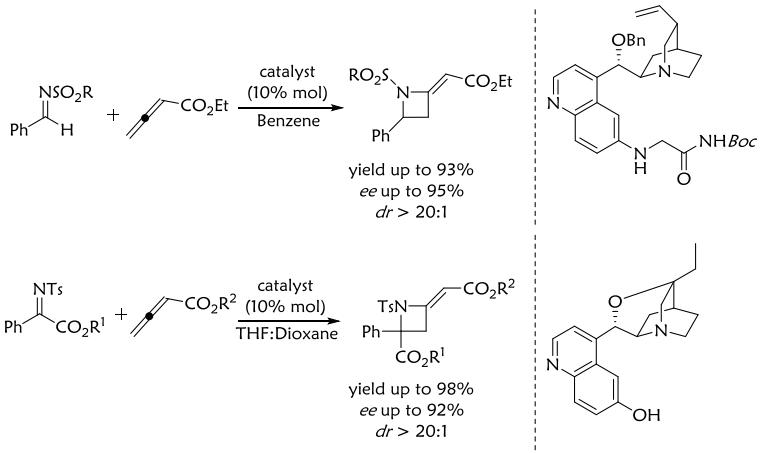
Since Shi's pioneer work[11] disclosing an abnormal aza-Baylis-Hillman reaction of *N*-tosylated imines with allenoates to give azetidine derivatives in the presence of

the strong Lewis base DABCO (1,4-diazabicyclo[2.2.2]octane), additional examples of such [2+2] annulation were reported, both on electron-deficient aldimines and ketimines. A detailed investigation on the effect of different Lewis bases in the reaction of allenoates with cyclic trifluoromethyl ketimines was accomplished by Ma and co-workers.[12]

Remarkable is also the application of this strategy from Ye and co-workers,[13] affording functionalized biologically relevant sultam-fused azetidines. The asymmetric approach to this [2+2] annulation is more challenging, with only two reports reporting enantioselective, organocatalytic versions employing Cinchona alkaloid-derived catalysts (Scheme 2).[14] Finally, a diasteroselective synthesis of 2-azetidines was exploited by Santos and co-workers,[15] based on allenoates bearing a chiral auxiliary on the ester moiety.

At the best of our knowledge, no diastereoselective [2+2] annulation-based strategies employing chiral imines have been described for the preparation of methyleneazetidines.

Herein we first demonstrate the suitability of chiral, isatin-derived *tert*-butanesulfinyl ketimines for reaction with allenoates, applying this reaction to the synthesis of unprecedented, enantiopure spirooxindole-based 4-methyleneazetidines.



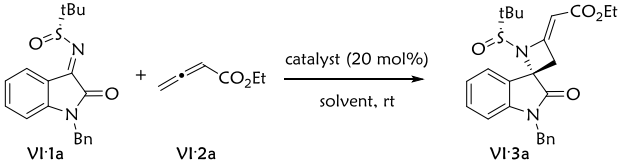
Scheme 2. Reported examples of enantioselective synthesis of methyleneazetidines using cinchona-based catalysts.

VI.2 Results and Discussion

We began our investigation by catalyst screening and reaction optimization using the known 1-benzyl-isatin-derived *N*-tert-butanesulfinyl ketimine **VI·1a** and ethyl buta-2,3-dienoate **VI·2a** (Table 1). A number of amines as diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N*,*N*-dimethyl-4-aminopyridine (DMAP) and pyridine were screened at room temperature in THF for 24 hours (entries 1-4). Only DABCO promoted efficiently the reaction to give the desired azetidine **VI·3a**. DBU proved to be quite ineffective, while with pyridine or DMAP the reaction afforded complex mixtures, from which only traces of the probable aza-Morita-Baylis-Hillman adduct could be tentatively identified by NMR. Next, solvent screening revealed that the reaction with DABCO also worked in toluene, dioxane and dichloromethane, but in slightly lower yields with respect to THF (entries 5-7).

Using a greater excess of ethyl buta-2,3-dienoate **VI·2a** had positive effects on the chemical yield, with 2.0 equivalents performing best (entries 8-9). Finally, lowering the substrate concentration elongated the reaction time reducing the conversion, while increasing the concentration gave a less clean reaction, however with a good isolated yield for **VI·3a** (entries 10-11). With respect to the stereochemical outcome, we were delighted to realize that, in all reactions, only the *E*-double bond isomer was formed, bearing, at the best of ^{1}H NMR sensitivity, only a single *C*-3 relative configuration with respect to the chiral auxiliary.

Table 1. Survey of the reaction conditions for the formal [2+2] annulation reaction of isatin ketimine **VI·1a** with ethyl buta-2,3-dienoate **VI·2a**.[a]

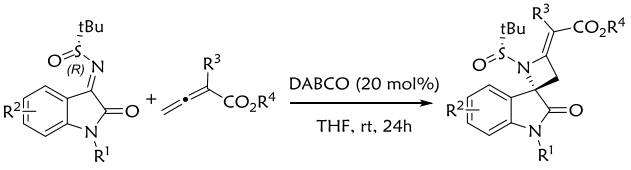


Entry	Catalyst	Solvent	Eq VII·2a	Conc [M]	Time [h]	Yield (%)[b]
1	DABCO	THF	1.5	0.1	24	76
2	DBU	THF	1.5	0.1	24	nd
3	DMAP	THF	1.5	0.1	24	-
4	Pyridine	THF	1.5	0.1	24	-
5	DABCO	toluene	1.5	0.1	24	67
6	DABCO	dioxane	1.5	0.1	24	57
7	DABCO	CH_2Cl_2	1.5	0.1	24	72
8	DABCO	THF	2.0	0.1	8	83
9	DABCO	THF	2.5	0.1	8	69
10	DABCO	THF	2.0	0.05	24	48
11	DABCO	THF	2.0	0.2	8	79

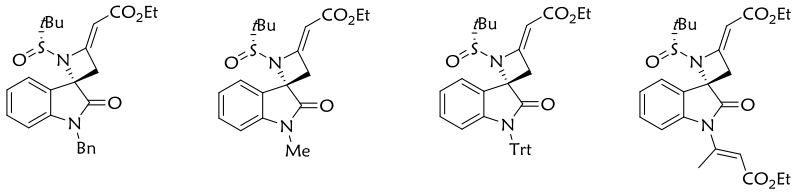
[a] Reaction conditions: ketimine **VII·1a** (0.15 mmol). [b] Isolated yields. nd = no detected.

With the optimized reaction conditions in hand, a variety of *N*-tert-butanesulfinyl ketimines **VI·1** were next explored, to investigate the substrate scope of this novel, DABCO-catalyzed formal [2+2] annulation reaction. The generality was also evaluated with respect to allenoates **VI·2** (Scheme 3). The protecting group on oxindole nitrogen atom was found to have a moderate effect on the reactivity, with best yields obtained with R^1= Bn, Me, Trt and PBB (*p*-Bromobenzyl).

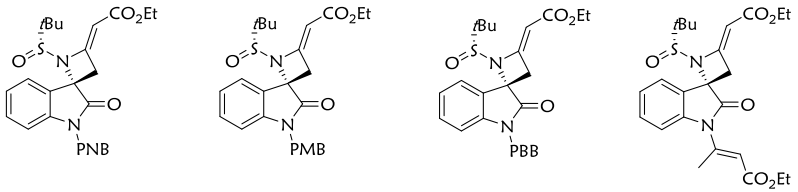
Scheme 3. Diastereoselective formal [2+2] annulation reaction of various isatin ketimines **VI·1** with allenoates **VI·2**, catalyzed by DABCO.[a]



VI·1a-m VI·2a-c VI·3a-o

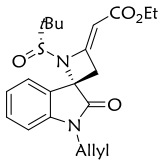


VI·3a (83%) *dr* >99:1 | VI·3b (85%) *dr* >99:1 | VI·3c (97%) *dr* 74:26 | VI·3d from *NH* (75%)[a] *dr* >99:1

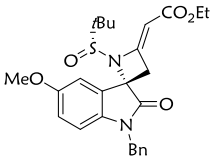


VI·3e (36%) *dr* >99:1 | VI·3f (51%) *dr* >99:1 | VI·3g (95%) *dr* >99:1 | VI·3d from *N-Ac* (68%)[a] *dr* >99:1

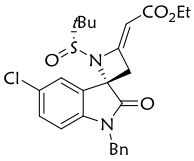
continued



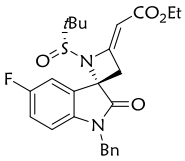
VI·3i (66%)
dr >99:1



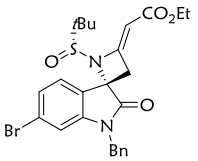
VI·3j (81%)
dr >99:1



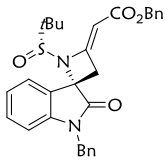
VI·3k (59%)
dr >99:1



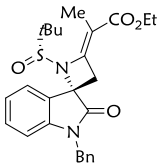
VI·3l (47%)
dr >99:1



VI·3m (71%)
dr >99:1



VI·3n (22%)
dr >99:1



VI·3o (nd)

[a] Reactions conditions: ketimine **VI·1** (0.15 mmol), **VI·2** (0.30 mmol), DABCO (0.030 mmol) in THF (1.5 mL). Isolated yields are reported. *dr* was determined by ^{1}H NMR analysis of crude mixture. [a] Reaction performed with 4 equiv of **VI·2a**. Trt = Trityl; PNB = *p*-Nitrobenzyl; PMB = *p*-Methoxybenzyl; PBB = *p*-Bromobenzyl; nd = not detected.

Surprisingly, ketimine **VI·1c**, bearing the *N*-trityl protecting group, afforded the corresponding azetidine **VI·3c** with the highest yield, but definitely lower stereocontrol, probably due to a steric mismatching effect of the bulky trityl group with the chiral auxiliary *tert*-butanesulfinyl moiety. Unprotected ketimine **VI·1d** also gave the reaction, affording the unexpected compound **VI·3d**, deriving from both the [2+2] annulation and the competitive *NH* participation with allenoate. The same compound **VI·3d** could be also recovered from the reaction of *N*-Ac ketimine **VI·1h**, probably as a result of the lability of the *N*-acetyl protecting group.

Next, *N*-benzylisatin ketimines with various substituents on the aromatic ring were explored. Moderate to good yields of the corresponding azetidines were obtained in the presence of a variety of substituents

including electron-donating groups, and halogen substituents at the 5- or 6-position on the oxindole aromatic ring. Finally, we investigated the formal [2+2] annulation with two different allenoates, namely benzyl buta-2,3-dienoate **VI·2b** and ethyl 2-methylbuta-2,3-dienoate **VI·2c**. Employing **VI·2b**, the corresponding azetidine **VI·3n** could be easily obtained, albeit in moderate yield. On the other hand, α-substituted allenoate **VI·2c** proved to be completely unreactive under the reaction conditions and the corresponding azetidine could not be detected, even after a longer reaction time. This result can be ascribed both to the stereoelectronic influence of the methyl group on the allenoate **VI·2c**, and to the high steric challenge inherent to the formation of the tetrasubstituted double bond, joint to the spiroazetidine ring.

As usual for such kinds of studies, we also proceeded to a scale-up experiment, employing 1 mmol of ketimine **VI·1a** (reaction conditions as reported in Scheme 3). After 24 hours, the desired azetidine **VI·3a** could be obtained in yield quite similar to that obtained on the small scale, still as a single diastereoisomer (yield 80%, dr >99:1).

To determine the absolute stereochemistry of the oxindole *C*-3 spiro center, a single crystal of 4-methyleneazetidine **VI·3a** was subjected to X-ray crystallographic analysis. This experiment unambiguously confirmed the *E*-double bond configuration and assigned the absolute configuration of the spiro center as (*S*), derived from (*R*)-*tert*-butanesulfinyl ketimine **VI·1a** (Figure 2).

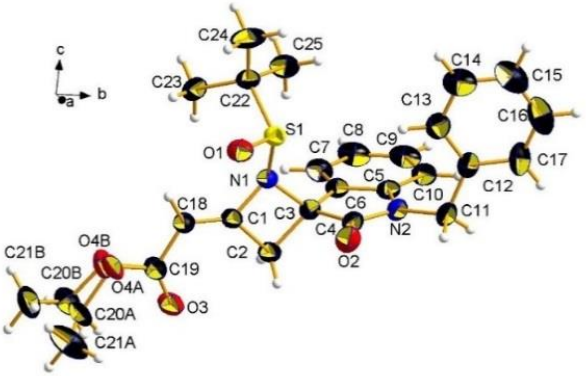


Figure 2. ORTEP view of compound **VI·3a**, with the atom-numbering scheme and the crystallographic reference system. Thermal ellipsoids of non-H atoms were drawn at the 25 % probability level. The two equiprobable conformations of the disordered ethoxy chain of the ester moiety are shown.

In order to explain this stereochemical outcome, we refer to the established mechanism of Lewis base-catalysed similar formal [2+2] annulations.[11] Accordingly, the nitrogen base DABCO acts as a nucleophilic activator, producing a zwitterionic allylic carbanion from the allenoate reagent. Such intermediate undergoes a γ-addition to the ketimine, followed by intramolecular nucleophilic attack to give the azetidine ring with regeneration of DABCO. On this basis, a plausible transition state for the formation of (3,*S*)-**VI·3a** is illustrated in Figure 3. In the working model, the stereochemical outcome can be explained assuming a *syn*-periplanar relationship between the imine and the S=O double bond,[16] which favors the shown conformation for starting ketimine **VI·1a**. The excellent diastereoselectivity observed in the azetidine formation may be due to the high stereodirecting effect of the bulky *tert*-butanesulfinyl group.

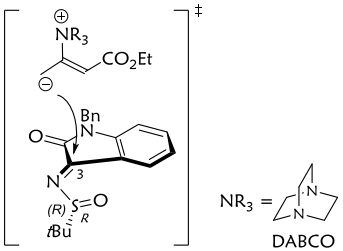


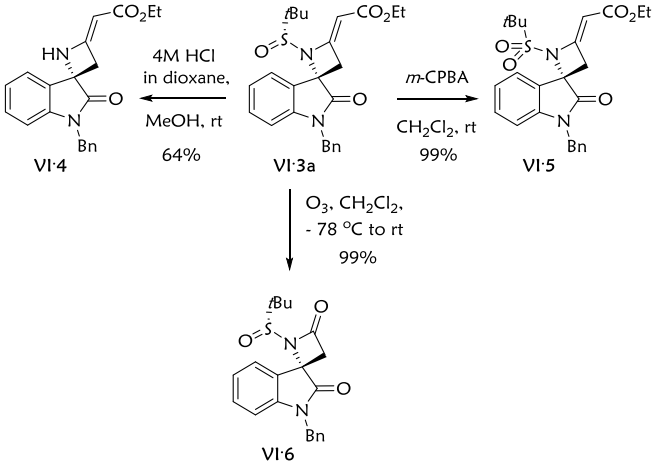
Figure 3. Plausible explanation of the stereochemical outcome.

Consequently, the delivery of the DABCO-activated nucleophile would occur from the less hindered *re*-face, resulting in the formation of the (3*S*)-azetidine.

To demonstrate the synthetic utility of highly functionalized azetidines, we subjected compound **VI·3a** to cleavage of *N-tert*-butanesulfinyl chiral auxiliary, to sulfur oxidation and to ozonolysis (Scheme 4).

Treatment of sulfinyl amide **VI·3a** with anhydrous HCl in dioxane at room temperature afforded the secondary amine **VI·4** in acceptable yield. Whereas, by action of *m*-chloroperbenzoic acid at room temperature, the sulfinyl amide **VI·3a** was readily oxidized to the corresponding sulfonamide **VI·5**. Finally, β-lactam **VI·6** was obtained in quantitative yield by treatment with ozone. This last result can be considered particularly relevant, given the interest in the spirocyclic oxindolo-β-lactam skeleton, which, combining two privileged heterocycles such as indole and β-lactam, is a motif strictly related to natural products and synthetic compounds with significant biological activities.[17]

Scheme 4. Further transformations of azetidine **VI·3a**.



VI.3 Conclusion

In conclusion, an efficient asymmetric approach for the preparation of unprecedented, chiral spirooxindole-fused 4-methyleneazetidines has been developed, based on a diastereoselective, DABCO-catalysed formal [2+2] annulation reaction. The method provides easy access to a range of highly functionalized compounds, which are obtained as single diastereoisomers, under mild conditions. By taking advantage of the functional groups transformations, a rapid asymmetric construction of the relevant spirocyclic oxindolo-β-lactam has been also achieved.

Further work is underway, aimed to establish spirooxindole-fused 4-methyleneazetidines as possible lead compounds for drug discovery programs.

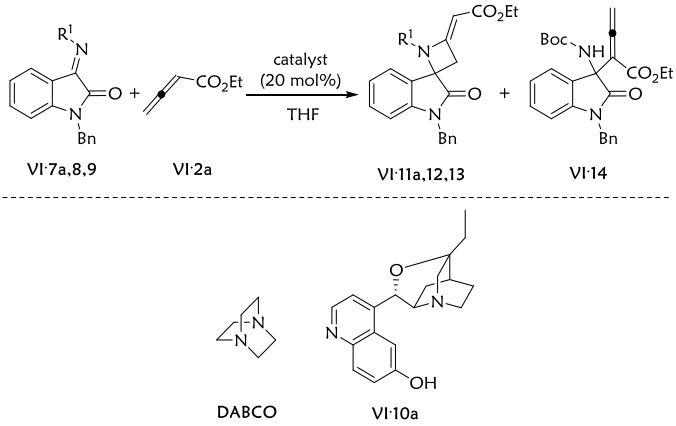
VI.4 Update work

Moreover, considering the importance of asymmetric catalytic approaches over chiral auxiliary strategies, we investigated the possibility of carried out the synthesis of enantiomerically enriched spirooxindole-fused 4-methyleneazetidines using cinchona-based catalysts.

We started our investigation evaluating the reaction of ethyl buta-2,3-dienoate **VI·2a** with different *N*-benzyl isatin-derived ketimines, namely *N-tert* butanesulfonyl imine **1a**, *N-p*-toluensulfonyl imine **2** and *N*-Boc imine **3** (Table 2).

All substrates **VI·7a**, **VI·8** and **VI·9** afforded the corresponding azetidines **VI·11a**, **VI·12** and **VI·13** in presence of DABCO (entries 1-3). In the case of *N*-Boc ketimine **VI·9**, also the aza-Morita-Baylis-Hillman (AMBH) product **VI·14** was isolated in low yield. Then the same ketimines **VI·7a**, **VI·8** and **VI·9** have been tested in the organocatalytic reaction, employing the quinidine-derived alkaloid *β*-isocupridine (*β*-ICD) catalyst **VI·10a**. Both *N-tert* butanesulfonyl imine **VI·7a** and tosyl imine **VI·8** afforded the expected azetidines **VI·11a** and **VI·12** in good yield and enantiomeric ratio (*er*) (entries 4 and 5), whereas in this condition the *N*-Boc ketimine **VI·9** provided only the AMBH product **VI·14** (entry 6).

Table 2. Preliminary screening for the isatin-derived ketimine selection.[a]

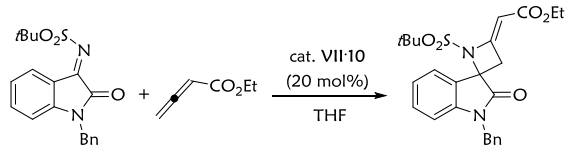


Entry	Imine (R^1)	Catalyst	Yield (%)[b]	*er*[c]
1	VI·7a (SO_2tBu)	DABCO	VI·11a (90)	-
2	VI·8 (Ts)	DABCO	VI·12 (77)	-
3	VI·9 (Boc)	DABCO	VI·13 (48), VI·14 (28)	-
4	VI·7a (SO_2tBu)	VI·10a	VI·11a (91)	70:30
5	VI·8 (Ts)	VI·10a	VI·12 (80)	61:39
6	VI·9 (Boc)	VI·10a	VI·14 (52)	-

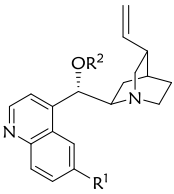
[a] Reaction conditions: ketimine **VI·7a,8,9** (0.15 mmol), **VI·2a** (0.30 mmol) and catalyst (0.030 mmol) in THF (1.5 mL) at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

N-tert butanesulfonyl imine **VI·7a** was selected for further optimization of the reaction conditions, as reported in Table 3. Starting our screening testing different catalysts, we observed that typical quinidine-derived catalysts **VI·10b-f** were unable to promote the reaction even for prolonged reaction times (entries 1-5). In all cases only degradation of the starting ketimine was observed. Instead, using *6*-isocupridine-based catalysts (**VI·105g-l**), the desired azetidine **VI·11a** was obtained in all cases, with the exception of reaction with catalyst **VI·10h** (entries 6-12).

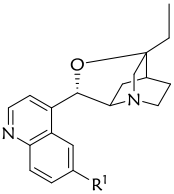
Table 3. Catalyst and solvent screen for the reaction of **VI·7a** with **VI·2a**.[a]



VI·7a VI·2a VI·11a



VI·10b: R^1= NHCOCH$_2$NH*Boc*, R^2= Bn
VI·10c: R^1= H, R^2= H
VI·10d: R^1= OMe, R^2= H
VI·10e: R^1= OH, R^2= Bn
VI·10f: R^1= OH, R^2= H



VI·10a: R^1=OH
VI·10g: R^1= NHCOCH$_2$NH*Boc*
VI·10h: R^1= 1-(3,5-bis(trifluorometil)fenil)tiourea
VI·10i: R^1= 2-(3-(3,5-bis(trifluorometil)fenil)tiourea)acetamide
VI·10j: R^1= (*S*)-NHCOCHBnNH*Boc*
VI·10k: R^1= (*R*)-NHCOCHBnNH*Boc*
VI·10l: R^1= 2-naphtamide

Entry	Solvent	Catalyst	Time [h]	Yield (%)[b]	*er*[c]
1	THF	VI·10b	48	nd	-
2	THF	VI·10c	48	nd	-
3	THF	VI·10d	48	nd	-
4	THF	VI·10e	48	nd	-
5	THF	VI·10f	48	nd	-
6	THF	VI·10a	1	91	70:30
7	**THF**	**VI·10g**	**3**	**90**	**80:20**
8	THF	VI·10h	48	nd	-
9	THF	VI·10i	3	64	74:26
10	THF	VI·10j	3	87	70:30
11	THF	VI·10k	3	86	77:23
12	THF	VI·10l	3	83	70:30
13	CH_2Cl_2	VI·10g	24	12	-
14	Toluene	VI·10g	24	16	-
15[d]	THF	VI·10g	24	78	80:20
16[e]	THF	VI·10g	48	nd	-
17[f]	THF	VI·10g	24	68	80:20

[a] Reaction conditions: ketimine **VI·7a** (0.15 mmol), **VI·2a** (0.30 mmol) and catalyst **VI·10** (0.03 mmol) in solvent (1.5 mL) unless otherwise noted. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Reaction performed at 0 °C. [e] Reaction performed at -20 °C. [f] Catalyst loading 10% mol. nd = no detected.

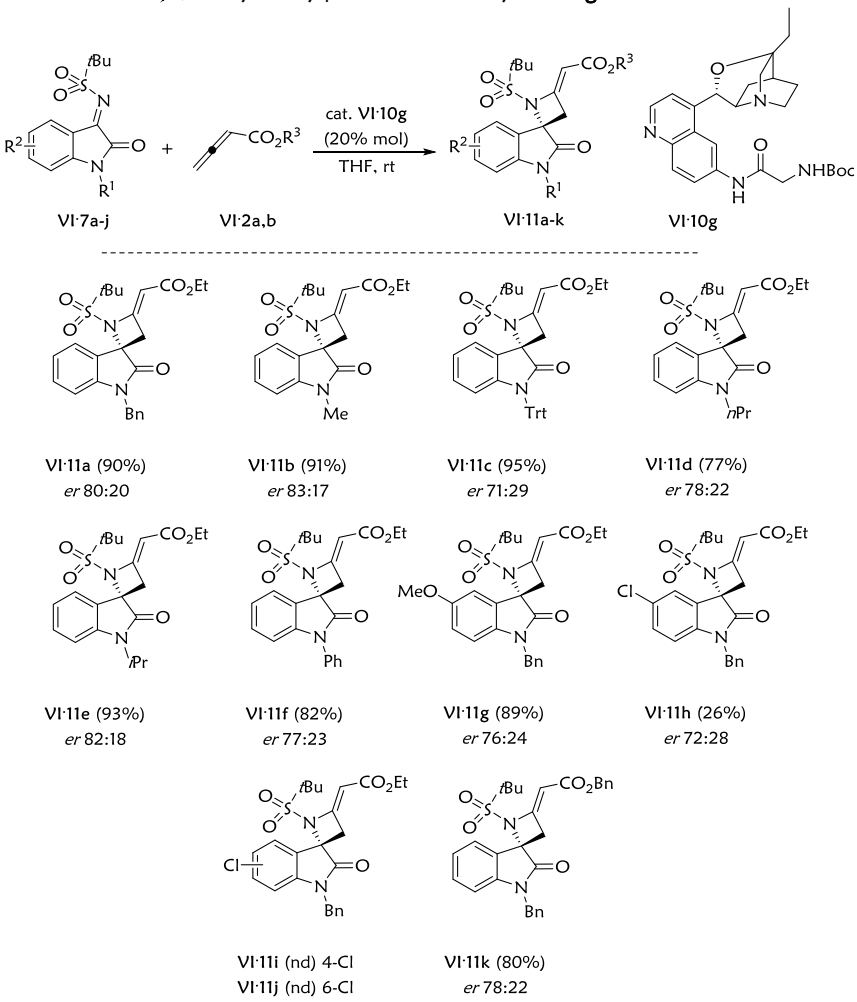
The high conformational bias of *β*-ICD and its derivatives, as well as the presence of at least a hydrogen bond donor group at the C6 position of the quinoline ring, seem to be necessary requirements to coordinate the substrate and therefore to catalyse the reaction. Best results in terms of both er and chemical yield have been obtained employing catalyst **VI·10g**, which was then used for a further screening of solvents and temperature.

Performing the reaction in apolar solvents such as dichloromethane and toluene, the desired product was observed just in very low yields (entries 13 and 14). Lowering the temperature to 0 °C no appreciable improvement of er was observed and prolonged reaction time was needed to obtain the desired azetidine in good yield (entry 15). At - 20 °C the reaction is completely inhibited (entry 16). Finally, reducing the catalyst amount (entry 17) no improved er was observed, but just elongation of reaction time with reduction of the chemical yield.

With the best conditions in hands, we planned to screen *N-tert* butanesulfonyl ketimines bearing different *N*-substituents at the oxindole ring (**VI·7b-f**, Scheme 5). Such starting compounds have been prepared by *m*-cloroperbenzoic acid-mediated oxidation of the corresponding *N-tert*-butanesulfinyl ketimines and immediately used without purification.

General good yields and *er* were observed in the reaction with allenoate **VI·2a**, under the catalysis of **VI·10g**. The presence of the bulky trityl substituent at the oxindole nitrogen leads to the corresponding spiroazetidine derivative **VI·11c** with the best yield, but with the lowest enantioselectivity.

Scheme 5. Substrate scope for the reaction of various ketimines **VI·7a-j** with allenoates **VI·2a,b**, catalyzed by β-ICD-based catalyst **VI·10g** .[a]



[a] Reactions conditions: ketimine **VI·7a-j** (0.15 mmol), **VI·2a,b** (0.30 mmol), **VI·10g** (0.030 mmol) in THF (1.5 mL). Isolated yields are reported. *er* was determined by chiral HPLC analysis. Trt = Trityl; nd = not detected.

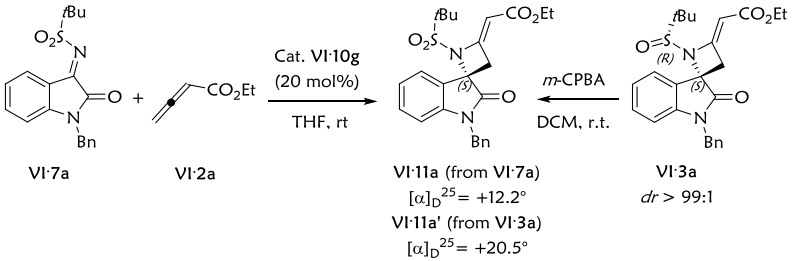
The best result in terms of er was obtained performing the reaction with *N*-methyl substituted ketimine **VI·7b**, leading to product **VI·11b**.

Depending on whether electron-withdrawing or electron-donating group was introduced at 4-,5- or 6-position of the benzene ring of starting ketimines (**VI·7g-j**), the reactions proceeded in a different way. Good yield and enatioselectivity were observed for the synthesis of 5-OMe substituted spiroazetidine **VI·11g**. In the presence of the electron withdrawing Cl-substituent at C5 position, a very low yield was achieved (**VI·11h**). Finally, compounds **VI·11i** and **VI·11j** were not detected in the crude, but just degradation of the ketimine starting material was observed.

At the end, we investigated the formal [2+2] annulation with a different allenoate. Considering the possibility of a favourable π-π interaction with the aromatic portion of the catalyst, we selected benzyl buta-2,3-dienoate **VI·2b**. Indeed, the corresponding azetidine **VI·11k** could be easily obtained in good yield, even if in quite similar *er*.

The absolute configuration of the major enantiomer of compound **VI·11a** was determined through chemical correlation, exploiting a proper conversion of reference compound **VI·3a** (Scheme 6). More precisely, performing a selective sulfur oxidation, enantiopure compound **VI·11a'** could be easily obtained from compound **VI·3a**. Relying on comparison of both optical rotation signs and chiral HPLC chromatograms, the (*S*)-configuration at the quaternary stereocenter of product **VI·11a** could be assigned with certainty.

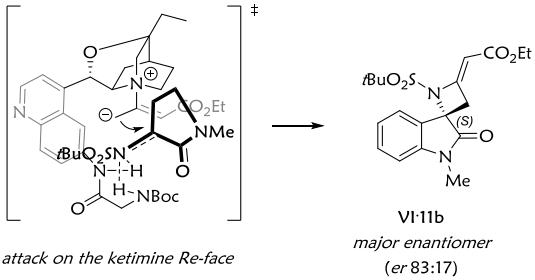
Scheme 6. Chemical correlation for the assignment of absolute configuration of compound **VI·11a.**



VI·7a VI·2a VI·11a (from VI·7a) $[\alpha]_D^{25}$= +12.2° VI·11a' (from VI·3a) $[\alpha]_D^{25}$= +20.5° VI·3a *dr* > 99:1

To rationalize the stereochemical outcome, we referred to the proposed mechanism for similar cinchona-base catalysed [2+2] annulation reactions.[18] Accordingly, the basic quinuclidine moiety acts as a nucleophile activator, producing a zwitterionic allylic carbanion from the allenoate reagent. The activated γ-position of this intermediate undergoes addition to the ketimine, followed by an intramolecular attack back from the ketimine's nitrogen atom, leading to azetidine ring formation and catalyst regeneration. From our experimental data, it results that the peculiar skeleton of β-ICD-type catalysts (e.g. **VI·10g**), more rigid with respect to that of corresponding quinidine-catalysts (e.g. **VI·10b**), seems the only one able to bring the reactants to the correct distance for a productive reaction. Moreover, the presence of the *N*-Boc glycinamide unit at C6' position in catalyst **VI·10g** ensures a proper activation of the ketimine, through up to two hydrogen bonds. Relying on this disposition, to minimize the steric hindrance with the catalyst's residue, ketimine offers its *Re*-face to the incoming γ-carbanion, leading to the corresponding spiroazetidine derivative in the prevailing (*S*)-configuration at the C3 of the oxindole ring.

Figure 4. Possible transition state for reaction of ketimine **VI·7b** with allenoate **VI·2a**, under catalysis of **VI·10g**. Ketimine **VI·7b** is reported without the condensed phenyl ring for clarity.



attack on the ketimine Re-face

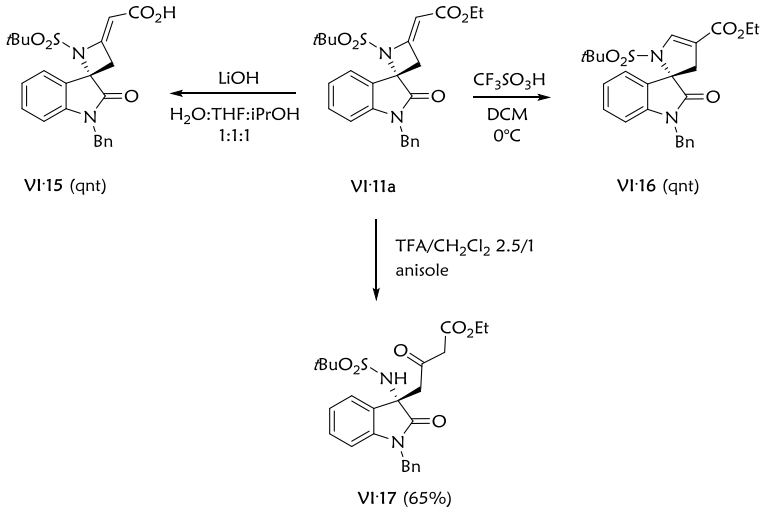
VI·11b
major enantiomer
(*er* 83:17)

On this basis, a plausible transition state for the reported reaction is illustrated in Figure 3, where ketimine **VI·7b** is shown coordinated to the catalyst **VI·10g** by double H-bonding, so explaining the found superiority of the amide N-H over the O-H group in this kind of process.

To demonstrate the synthetic utility of obtained compounds, some post-transformation reactions have been performed (Scheme 7). Starting from compound **VI·11a**, acid **VI·15** could be quantitatively obtained by reaction with LiOH.

Aiming to selectively remove the *tert*-butylsulfonyl group, we refer to a milestone literature procedure,[19] reporting the cleavage of such protecting groups to the parent amines by mild acidic solvolysis. Surprisingly, exposure of **VI·11a** to 0.075 N TfOH/CH_2Cl_2 at 0 °C for two hours afforded quantitatively the rearranged product **VI·16**, without trace of the expected spiroazetidine *N*-deprotected derivative. The spiropyrroline ring system of compound **VI·16** was disclosed by careful

Scheme 7. Post-Trasformation Reactions Performed from Compound **VI·11a**.



VI·15 (qnt) **VI·11a** **VI·16** (qnt)

VI·17 (65%)

analysis of mono- and bidimensional NMR spectra. In particular, the HMBC (Heteronuclear Multiple Bond Correlation) experiment allowed a complete and confident assignment of all ^{1}H and ^{13}C NMR signals. Changing the acid to trifluoroacetic acid (TFA) and adding anisole as scavenger, the reaction followed a different course, affording the unprecedented 3-*tert*-butylsulfonylamino, 3-substituted derivative **VI·17**, as the result of the acid catalyzed azetidine ring opening. Evidently, the presence of the methylene acetic ester moiety as substituent in compound **VI·11a** diverts from the expected cleavage of the *tert*-butylsulfonyl group, addressing the reaction toward less predictable pathways. Anyway, preserving the integrity at the oxindole C3 stereogenic centre, compounds **VI·16** and **VI·17** can be considered relevant examples of almost unexplored spiro and 3,3-disubstituted oxindole derivatives.

VI.5 Experimental Section

All commercial materials (Aldrich, Fluka) were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with ninhydrin solution in ethanol. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source. Chiral HPLC analysis was performed on a Jasco PU-2080 (UV Detector and binary HPLC pump) at 254 nm. Chiralcel AD columns were purchased from Daicel Chemical Industries®. Optical rotator power [α]T D was measured with a Jasco P-1030 polarimeter, endowed with a cell of 1 dm pathlength and 1 mL capacity. The light used has a wavelength of 589 nm (sodium D line).

General procedure A (GP-A) for the synthesis of isatin-derived (R)-sulfinyl ketimines VI·1a-m. To a solution of *N*-substituted isatin (1.17 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (2.9 mL, 0.4M), $Ti(O\mathit{i}Pr)_4$ (2.34 mmol, 2.0 eq) and (*R*)-2-methyl-2-propanesulfinamide (1.4 mmol, 1.2 eq) were added. The

solution was refluxed until complete disappearance of the starting materials (monitored by TLC). The reaction was quenched by adding saturated aq. $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (15 mL). The biphasic solution was filtered through a pad of Celite and the organic phase washed with water (2 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude was purified by FC as indicated below.

(*R*,*E*)-2-Methyl-N-(1-(4-nitrobenzoyl)-2-oxoindolin-3-ylidene)propane-2-sulfinamide (VI·1e). Prepared according to GP-A using *N*-*p*-nitrobenzyl isatin. FC: CH_2Cl_2:EtOAc, 49:1; yield: 180 mg, 40%; brown solid; m.p.: 104-106 °C; $[\alpha]_D^{25}$ = - 124.9 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 4.99 (d, *J* = 16.6 Hz, 1H), 5.05 (d, *J* = 16.6 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.37 (t, br, *J* = 7.7 Hz, 1H), 7.49 (d, br, *J* = 7.8 Hz, 2H), 8.21 (d, *J* = 7.8 Hz, 2H), 8.32-8.64 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 (3C), 43.4, 51.6, 109.6, 123.6 (2C), 124.2, 124.3 (2C), 128.2 (2C), 135.5, 142.2 (2C), 146.5, 147.8, 162.2; HRMS-ESI: $[M+Na]^+$, calcd for $C_{19}H_{19}N_3NaO_4S^+$ 408.0988, found 408.0980.

(*R*,*E*)-N-(1-Allyl-2-oxoindolin-3-ylidene)-2-methylpropane-2-sulfinamide (VI·1i). Prepared according to GP-A using *N*-allyl isatin. FC: CH_2Cl_2:EtOAc, 49:1; yield: 248 mg, 73%; red foam; $[\alpha]_D^{25}$ = - 147.5 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 4.25 (d, *J* = 4.8 Hz, 2H), 5.11-5.24 (m, 2H), 5.73 (m, 1H), 6.72 (d, br, *J* = 7.7 Hz, 1H), 6.94 (t, br, *J* = 7.7 Hz, 1H), 7.31 (t, br, *J* = 7.7 Hz, 1H), 8.07-8.58 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (3C), 42.6, 66.8, 109.9, 118.4, 123.1, 123.5 (2C),

130.6, 135.4, 148.0 (2C), 160.7; HRMS-ESI: $[M+Na]^+$, calcd for $C_{15}H_{18}N_2NaO_2S^+$ 313.0981, found 313.0993.

General procedure B (GP-B) for diasteroselective formal [2+2] annulation reaction for the synthesis of compounds VI·3a-n. To a solution of ketimine **VI·1a-m** (0.15 mmol, 1.0 eq) and DABCO (0.03 mmol, 0.2 eq) in THF (1.5 mL), 2a-c was added (0.30 mmol, 2.0 eq) and the reaction was stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure to provide an oily residue that was purified by FC as reported below.

Ethyl-(*E*)-2-((*S*)-1'-benzyl-1-((*R*)-*tert*-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3a). Prepared according to GP-B using **VI·1a** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 56 mg, 83%; pale yellow solid; m.p.: 126.4-127.6 °C; $[\alpha]_D^{25}$ = - 90.0 (c 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.26 (t, *J* = 7.3 Hz, 3H), 3.56 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.83 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.14 (m, 2H), 4.85 (d, *J* = 15.6 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 5.55 (t, *J* = 1.9 Hz, 1H), 6.73 (d, br, *J* = 7.6 Hz, 1H), 7.07 (t, br, *J* = 7.6 Hz, 1H), 7.18-7.36 (m, 6H), 7.51 (d, br, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 14.0, 22.1 (3C), 41.3, 44.1, 59.3, 60.2, 70.7, 95.0, 110.6, 123.9, 125.9, 127.9 (2C), 128.2, 129.1 (2C), 130.4, 131.5, 136.2, 141.6, 157.3, 168.8, 173.0; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{28}N_2NaO_4S^+$ 475.1662 found 475.1655.

Ethyl (*E*)-2-((*S*)-1-((*R*)-*tert*-butylsulfinyl)-1'-methyl-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3b). Prepared according to GP-B using **VI·1b** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 47 mg, 85%; pale yellow foam; $[\alpha]_D^{25}$ = - 96.9 (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H),

1.22 (t, *J* = 7.1 Hz, 3H), 3.23 (*s*, 3H), 3.50 (dd, J = 15.9 and 1.9 Hz, 1H), 3.74 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.10 (m, 2H), 5.51 (t, *J* = 1.9 Hz, 1H), 6.83 (d, br, *J* = 7.5 Hz, 1H), 7.10 (t, br, *J* = 7.5 Hz, 1H), 7.35 (d, br, *J* = 7.5 Hz, 1H), 7.49 (d, br, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 26.6, 41.6, 58.7, 59.5, 71.0, 94.2, 108.7, 123.2, 125.1, 125.7, 130.9, 143.3, 159.47, 167.3, 173.2; HRMS-ESI: $[M+Na]^+$, calcd for $C_{19}H_{24}N_2NaO_4S^+$ 399.1349, found 399.1354.

Ethyl (*E*)-2-((*S*)-1-((*R*)-*tert*-butylsulfinyl)-2'-oxo-1'-tritylspiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3c). Prepared according to GP-B using **VI·1c** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 88 mg, 97%; pale yellow foam; $[\alpha]_D^{25}$ = - 55.2 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (*s*, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 3.55 (dd, *J* = 15.7 and 1.8 Hz, 1H), 3.81 (dd, *J* = 15.7 and 1.8 Hz, 1H), 4.11 (m, 2H), 5.48 (t, *J* = 1.8 Hz, 1H), 6.29 (d, br, *J* = 7.5 Hz, 1H), 6.82-7.08 (m, 2H), 7.06-7.37 (m, 10H), 7.31-7.52 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.5, 22.6 (3C), 42.0, 58.4, 59.5, 71.6, 75.4, 94.3, 116.4, 122.7, 124.8, 126.4, 127.1 (3C), 127.8 (6C), 129.2 (6C), 129.4, 141.6 (3C), 143.3, 159.3, 167.5, 174.8; HRMS-ESI: $[M+Na]^+$, calcd for $C_{37}H_{36}N_2NaO_4S^+$ 627.2288, found 627.2293.

(*E*)-Ethyl 3-((*S*,*E*)-1-((*R*)-*tert*-butylsulfinyl)-4-(2-ethoxy-2-oxoethylidene)-2'-oxospiro[azetidine-2,3'-indolin]-1'-yl)but-2-enoate (VI·3d). Prepared according to GP-B using **VI·1d** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 18 mg, 38%; brown foam; $[\alpha]_D^{25}$ = - 31.5 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (*s*, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.3 Hz, 3H), 2.58 (d, *J* = 0.9 Hz, 3H), 3.59 (dd, *J* = 16.1 and 2.0 Hz, 1H), 3.83 (dd, *J* = 16.1 and 2.0 Hz, 1H), 4.17 (m, 2H), 4.27 (q, *J* = 7.3 Hz, 2H), 5.55 (t, *J*

= 2.0 Hz, 1H), 6.05 (q, br, *J* = 0.9 Hz, 1H), 6.99 (d, br, *J* = 7.6 Hz, 1H), 7.19 (td, br, *J* = 7.7 and 0.9 Hz, 1H), 7.38 (td, br, *J* = 7.6 and 0.9 Hz, 1H), 7.60 (d, br, *J* = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1, 17.3, 22.3 (3C), 41.8, 42.7, 56.6, 59.4, 60.3, 70.6, 93.7, 110.3, 118.4, 123.7, 125.0, 125.4, 130.6, 141.2, 147.7, 159.2, 165.3, 171.8, 171.9; HRMS-ESI: $[M+Na]^+$, calcd for $C_{24}H_{30}N_2NaO_6S^+$ 497.1717, found 497.1724.

ethyl (*E*)-2-((*S*)-1-((*R*)-*tert*-butylsulfinyl)-1'-(4-nitrobenzoyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3e). Prepared according to GP-B using **VI·1e** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 27 mg, 36%; pale yellow foam; $[\alpha]_D^{25}$ = - 70.4 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.58 (dd, *J* = 15.8 and 1.9 Hz, 1H), 3.82 (dd, *J* = 15.8 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.92 (d, *J* = 16.6 Hz, 1H), 5.15 (d, *J* = 16.6 Hz, 1H), 5.53 (t, *J* = 1.9 Hz, 1H), 6.64 (d, br, *J* = 7.1 Hz, 1H), 7.12 (t, br, J = 7.2 Hz, 1H), 7.25 (t, br, *J* = 7.2 Hz, 1H), 7.47 (d, br, *J* = 8.8 Hz, 2H), 7.55 (d, br, *J* = 7.1 Hz, 1H), 8.18 (d, br, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.6, 43.6, 59.1, 59.7, 70.8, 94.6, 109.3, 121.7, 123.8, 124.2 (2C), 125.4, 128.2 (2C), 130.9, 141.8, 142.5, 147.8, 159.1, 167.3, 175.0; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}N_3NaO_6S^+$ 520.1513, found 520.1521.

Ethyl (*E*)-2-((*S*)-1-((*R*)-*tert*-butylsulfinyl)-1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3f). Prepared according to GP-B using **VI·1f** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 37 mg, 51%; pale yellow foam; $[\alpha]_D^{25}$ = - 87.7 (c 0.5, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.53 (dd, *J* = 15.9 and 1.8 Hz, 1H), 3.76 (s, 3H), 3.80 (dd, *J* = 15.9 and 1.8 Hz, 1H), 4.14 (m,

2H), 4.77 (d, *J* = 15.6 Hz, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 5.54 (t, *J* = 1.8 Hz, 1H), 6.75 (d, br, *J* = 7.3 Hz, 1H), 6.82 (d, br, *J* = 8.7 Hz, 2H), 7.06 (t, br, *J* = 7.3 Hz, 1H), 7.18-7.33 (m, 3H), 7.49 (d, br, *J* = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.6, 43.7, 55.3, 58.7, 59.6, 71.0, 94.3, 109.8, 114.2 (2C), 123.1, 125.1, 125.8, 127.2, 128.9 (2C), 130.7, 142.4, 159.2, 159.3, 167.4, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{26}H_{30}N_2NaO_5S^+$ 505.1768 found 505.1759.

Ethyl (*E*)-2-((*S*)-1'-(4-bromobenzyl)-1-((*R*)-tert-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3g). Prepared according to GP-B using **VI·1g** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 59 mg, 95%; pale yellow foam; $[\alpha]_D^{25}$ = - 70.7 (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 3H), 3.54 (dd, *J* = 16.6 and 1.9 Hz, 1H), 3.81 (dd, *J* = 16.6 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 5.53 (t, *J* = 1.9 Hz, 1H), 6.69 (d, br, *J* = 7.1 Hz, 1H), 7.08 (t, br, *J* = 7.2 Hz, 1H), 7.18 (d, br, *J* = 8.8 Hz, 2H), 7.25 (t, br, *J* = 7.2 Hz, 1H), 7.42 (d, br, *J* = 8.8 Hz, 2H) , 7.51 (d, br, *J* = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.6, 43.6, 58.9, 59.6, 70.9, 94.6, 109.6, 121.9, 123.5, 125.3, 125.8, 129.3 (2C), 130.9, 132.0 (2C), 134.2, 142.1, 159.1, 167.4, 173.4; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}BrN_2NaO_4S^+$ 553.0767 found 553.0769.

Ethyl (*E*)-2-((*S*)-1'-allyl-1-((*R*)-*tert*-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3i). Prepared according to GP-B using **VI·1i** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 40 mg, 66 %; pale yellow foam; $[\alpha]_D^{25}$ = - 62.3 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (*s*, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 3. 49 (dd, *J* = 15.6 and 1.9 Hz, 1H), 3.76 (dd, *J* =

15.6 and 1.9 Hz, 1H), 4.11 (m, 2H), 4.29 (dd, *J* = 16.6 and 4.9 Hz, 1H), 4.42 (dd, *J* = 16.6 and 4.9 Hz, 1H), 5.16-5.29 (m, br, 2H), 5.50 (m, br, 1H), 5.80 (m, 1H), 6.82 (d, br, *J* = 7.6 Hz, 1H), 7.09 (t, br, *J* = 7.7 Hz, 1H), 7.31 (t, br, *J* = 7.7 Hz, 1H), 7.50 (d, br, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.7, 42.7, 58.8, 59.6, 70.9, 94.2, 109.7, 118.2, 123.2, 125.1, 125.8, 130.9 (2C), 142.5, 159.6, 167.4, 173.0; HRMS-ESI: $[M+Na]^+$, calcd for $C_{21}H_{26}N_2NaO_4S^+$ 425.1505, found 425.1513.

Ethyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-*tert*-butylsulfinyl)-5'-methoxy-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3j). Prepared according to GP-B using **VI·1j** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 57 mg, 81%; pale yellow foam; $[\alpha]_D^{25}$ = - 79.6 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.53 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.74 (s, 3H), 3.82 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.81 (d, *J* = 15.6 Hz, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 5.54 (t, *J* = 1.9 Hz, 1H), 6.60 (d, br, *J* = 8.6 Hz, 1H), 6.74 (dd, *J* = 8.6 and 2.5 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 7.21-7.35 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.7 (3C), 41.8, 44.3, 55.9, 58.75, 59.6, 71.3, 94.3, 110.3, 111.9, 115.5, 127.0, 127.5 (2C), 127.8, 128.8 (2C), 135.2, 135.6, 156.4, 159.4, 167.35, 173.1; HRMS-ESI: $[M+Na]^+$, calcd for $C_{26}H_{30}N_2NaO_5S^+$ 505.1768, found 505.1757.

Ethyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-*tert*-butylsulfinyl)-5'-chloro-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3k). Prepared according to GP-B using **VI·1k** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 43 mg, 59%; pale yellow foam; $[\alpha]_D^{25}$ = - 29.8 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.53 (dd, *J* = 15.9

and 1.8 Hz, 1H), 3.82 (dd, *J* = 15.9 and 1.8 Hz, 1H), 4.12 (m, 2H), 4.81 (d, *J* = 15.6 Hz, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 5.52 (t, *J* = 1.8 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.23-7.38 (m, 5H), 7.48 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.7, 44.3, 58.9, 59.7, 71.1, 94.5, 110.9, 125.4, 127.4 (2C), 128.1, 128.8, 128.9 (2C), 130.6, 134.6, 135.2, 144.3, 158.9, 167.2, 174.8; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}ClN_2NaO_4S^+$ 509.1272, found 509.1279.

Ethyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-*tert*-butylsulfinyl)-5'-fluoro-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3l). Prepared according to GP-B using **VI·1l** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 33 mg, 47%; pale yellow foam; $[\alpha]_D^{25}$ = - 82.4 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (*s*, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 3.57 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.86 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.18 (m, 2H), 4.87 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.56 (t, *J* = 1.9 Hz, 1H), 6.68 (dd, *J* = 8.6 and 3.9 Hz, 1H), 6.97 (td, *J* = 8.8 and 2.6 Hz, 1H), 7.26-7.41 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.9, 44.4, 58.9, 59.7, 70.9, 94.4, 110.6 (d, *J* = 7.7 Hz), 113.1 (d, *J* = 24.5 Hz), 117.2 (d, *J* = 23.0 Hz), 127.5 (2C), 127.6, 128.1, 129.0 (2C), 134.8, 138.2, 158.2, 159.8 (d, *J* = 150.3 Hz) , 167.2, 173.2; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}FN_2NaO_4S^+$ 493.1568, found 493.1559.

Ethyl (*E*)-2-((*S*)-1'-benzyl-6'-bromo-1-((*R*)-*tert*-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3m). Prepared according to GP-B using **VI·1m** and **VI·2a**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 56 mg, 71%; pale yellow foam; $[\alpha]_D^{25}$ = - 43.7 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (*s*, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.52 (dd, *J* =

15.9 and 1.9 Hz, 1H), 3.81 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.13 (m, 2H), 4.81 (d, *J* = 15.6 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 5.52 (t, *J* = 1.9 Hz, 1H), 6.88 (m, br, 1H), 7.21 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.24-7.35 (m, 5H), 7.37 (d, br, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 22.6 (3C), 41.8, 44.3, 58.8, 59.6, 70.6, 94.3, 113.2, 124.5, 124.7, 126.2, 126.4, 127.5 (2C), 128.1, 129.0 (2C), 134.6, 143.6, 159.2, 167.2, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{27}BrN_2NaO_4S^+$ 553.0767, found 553.0772.

Benzyl (*E*)-2-((*S*)-1'-benzyl-1-((*R*)-*tert*-butylsulfinyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·3n). Prepared according to GP-B using **VI·1a** and **VI·2b**. FC: CH_2Cl_2:EtOAc, 49:1; yield: 40 mg, 52%; pale orange foam; $[\alpha]_D^{25}$ = - 57.9 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 3.58 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.85 (dd, *J* = 15.9 and 1.9 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 5.17 (s, 2H), 5.64 (t, *J* = 1.9 Hz, 1H), 6.76 (d, br, *J* = 8.1 Hz, 1H), 7.10 (td, *J* = 8.1 and 1.0 Hz, 1H), 7.27 (td, *J* = 8.2 and 1.2 Hz, 1H), 7.28-7.43 (m, 10H), 7.53 (dd, *J* = 8.1 and 1.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.7 (3C), 41.8, 44.3, 58.8, 65.6, 71.1, 93.9, 109.8, 123.2, 125.2, 125.8, 127.6-128.9 (10C), 130.8, 135.1, 136.5, 142.5, 160.0, 167.1, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{30}H_{30}N_2NaO_4S^+$ 537.1818, found 537.1811.

Post-transformation reactions

Ethyl (*S,E*)-2-(1'-benzyl-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·4). To a solution of compound **VI·3a** (0.11 mmol, 1.0 eq) in 1:1 mixture of anhydrous 1,4-dioxane and anhydrous MeOH (550 μL), HCl in dioxane (4 M solution, 0.44 mmol, 0.4 eq) was added. After the mixture was

stirred at room temperature for 1 h, all volatiles were removed under reduced pressure, and the residue was dissolved in water (2 mL) and extracted with EtOAc (1 x 1 mL). The water layer was basified to pH 8 with aqueous concentrated NH_4OH and extracted with EtOAc (2 x 2 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by FC (CH_2Cl_2:EtOAc, 49:1) affording product **VI·4** as a pale orange foam (25 mg, yield = 64%); $[\alpha]_D^{25}$ = - 47.4 (c 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.21 (d, br, *J* = 14.2 Hz, 1H), 3.44 (dd, *J* = 14.1 and 2.8 Hz, 1H), 4.15 (m, 2H), 4.80 (s, br, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.95 (d, *J* = 15.6 Hz, 1H), 6.76 (m, br, 1H), 6.78 (d, br, *J* = 7.8 Hz, 1H), 7.11 (t, br, *J* = 7.7 Hz, 1H), 7.27 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.29-7.37 (m, 5H), 7.56 (d, br, *J* = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.6, 41.6, 44.2, 59.0, 65.6, 83.6, 109.5, 123.4, 124.2, 127.4, 127.5 (2C), 127.9, 128.9 (2C), 130.4, 135.4, 142.6, 162.7, 169.2, 175.1; HRMS-ESI: $[M+Na]^+$, calcd for $C_{21}H_{20}N_2NaO_3^+$ 371.1366, found 371.1360.

(*S,E*)-ethyl 2-(1'-benzyl-1-(*tert*-butylsulfonyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·5). A solution of compound **VI·3a** (0.11 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (1.1 mL, 0.1M) was cooled to 0°C, and *m*-CPBA (0.11 mmol, 1.0 eq) was added in small portions. Stirring was continued for 15 min, then the solution was diluted with CH_2Cl_2 (10 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (3 x 5 mL) and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by FC (CH_2Cl_2:EtOAc, 49:1) affording product **VI·5** as a pale yellow foam (54 mg, yield = 99%); $[\alpha]_D^{25}$

= + 20.5 (c 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 9H), 3.44 (dd, *J* = 15.6 and 1.9 Hz, 1H), 3.71 (dd, *J* = 15.6 and 1.9 Hz, 1H),4.16 (q, *J* = 7.1 Hz, 2H), 4.83 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.68 (s, br, 1H), 6.69 (d, br, *J* = 7.8 Hz, 1H), 7.08 (t, br, *J* = 7.7 Hz, 1H), 7.19-7.38 (m, 6H), 7.50 (d, br, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.5, 22.7 (3C), 41.8, 44.4, 58.9, 59.7, 70.6, 94.3, 113.2, 124.6, 126.2, 126.4, 127.5 (2C), 128.2, 129.0 (3C), 134.6, 143.6, 159.2, 167.3, 173.3; HRMS-ESI: $[M+Na]^+$, calcd for $C_{25}H_{28}N_2NaO_5S^+$ 491.1611, found 491.1604.

(*S*)-1'-benzyl-1-((*R*)-*tert*-butylsulfinyl)spiro[azetidine-2,3'-indoline]-2',4-dione (VI·6). A solution of compound **VI·3a** (0.11 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (13.75mL) was bubbled with ozone at -78°C for 10 minutes. Then Me_2S (1.21 mmol, 11.0 mmol) was added at the same temperature and the reaction was warmed up to room temperature and stirred for 10 minutes. The solvent was evaporated under reduced pressure and the residue was purified by FC (CH_2Cl_2:EtOAc, 49:1) to afford compound **VI·6** as a pale yellow foam (45 mg, yield = 99%); $[\alpha]_D^{25}$ = - 47.8 (c 0.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H), 3.37 (d, J = 15.1 Hz, 1H), 3.69 (d, J = 15.1 Hz, 1H), 4.93 (d, J = 15.6 Hz, 1H), 5.03 (d, J = 15.6 Hz, 1H), 6.82 (d, br, J = 7.6 Hz, 1H), 7.14 (t, br, J = 7.6 Hz, 1H), 7.23-7.39 (m, 6H), 7.50 (d, br, J = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.6 (3C), 44.4, 49.9, 59.2, 60.9, 109.9, 123.4, 124.3, 125.1, 127.5, 128.0 (2C), 128.9, 130.6 (2C), 135.0, 142.5, 165.7, 173.4; HRMS-ESI: $[M+Na]^+$, calcd for $C_{21}H_{22}N_2NaO_3S^+$ 405.1243, found 405.1251.

General procedure C (GP-C) for the synthesis of N-tert butanesulfonyl ketimines VI·7a-j. To a solution of *N*-substituted isatin (1.17 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (2.9 mL, 0.4 M), $Ti(O_iPr)_4$ (2.34 mmol, 2.0 eq) and 2- methyl-2-propanesulfinamide (1.4 mmol, 1.2 eq) were added. The solution was refluxed until complete disappearance of the starting materials (monitored by TLC). The reaction was quenched by adding saturated aq. $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (15 mL). The biphasic solution was filtered through a pad of Celite and the organic phase washed with water (2 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (FC), using Hexane/EtOAc/CH_2Cl_2 (gradient from 9:1:10 to 5/5/10) as eluent. To a solution of the desired sulfinamide in CH_2Cl_2 (6 mL), *m*-CPBA (1.5 equiv) was slowly added at room temperature and the mixture was stirred until completion of the reaction (monitored by TLC). The reaction was quenched by adding saturated aq. $NaHCO_3$ (15 mL) and diluted with CH_2Cl_2 (15 mL). The organic phase was washed with sat. $NaHCO_3$ (2×40 mL), dried (Na_2SO_4), and concentrated. The corresponding sulfonamide was used without further purification.

(*E*)-2-methyl-*N*-(2-oxo-1-tritylindolin-3-ylidene)propane-2-sulfonamide (VI·7c). Prepared according to GP-C starting from *N*-trityl substituted isatin. Red foamy solid, yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.37 (m, 6H), 7.37 – 7.19 (m, 9H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 151.5, 144.5, 141.7 (3C), 136.9, 130.1 (6C), 128.6 (6C), 128.0 (3C), 123.9, 123.8, 117.9, 114.9, 75.9, 60.7, 24.5 (3C); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{31}H_{28}N_2NaO_3S^+$ 531.1716, found 531.1709.

(*E*)-2-methyl-*N*-(2-oxo-1-propylindolin-3-ylidene)propane-2-sulfonamide (VI·7d). Prepared according to GP-C starting from *N*-propyl substituted isatin. Red foamy solid, yield: 95%. ^{1}H NMR (300 MHz, , $CDCl_3$, 7:3 mixture of two rotamers) δ 8.40 (m, br, 0.3H), 8.06 (d, *J* = 7.8 Hz, 0.7H), 7.50 (t, *J* = 7.8 Hz, 0.3H), 7.45 (t, *J* = 7.8 Hz, 0.7H), 7.11 (t, *J* = 7.8 Hz, 0.7H), 7.07 (t, *J* = 7.8 Hz, 0.3H), 6.93 (d, *J* = 7.8 Hz, 0.7H), 6.82 (t, *J* = 7.8 Hz, 0.3H), 3.74 – 3.62 (m, 2H), 1.74 (sext, br, *J* = 6.8 Hz, 2H), 1.62 (s, 6.3H), 1.60 (s, 2.7H), 0.99 (t, br, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 150.4, 147.4, 139.0 and 138.5 (1C), 124.0 (2C), 116.2, 110..4 and 110.3 (1C), 60.6, 43.1 and 42.7 (1C), 24.5 (3C), 21.2 and 20.8 (1C), 12.0; HRMS (ESI): $[M+Na]^+$, Calcd for $C_{15}H_{20}N_2NaO_3S^+$ 331.1087, found 331.1096.

(*E*)-2-(1-isopropyl-2-oxoindolin-3-ylidene)-2-methylpropane-2-sulfonamide (VI·7e). Prepared according to GP-C starting from *N*-isopropyl substituted isatin. Red foamy solid, yield: 99%. ^{1}H NMR (400 MHz, $CDCl_3$, 17:3 mixture of two rotamers) δ 8.19 (dd, *J* = 7.8 and 1.7 Hz, 0.15H), 8.12 (dd, *J* = 7.8 and 1.7 Hz, 0.85H), 7.76 (ddd, *J* = 8.2, 7.5 and 1.7 Hz, 0.15H), 7.73 (ddd, *J* = 8.2, 7.5 and 1.7 Hz, 0.85H), 7.34 – 7.21 (m, 2H), 4.77 (hept, *J* = 6.8 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 6H), 1.62 (s, 1.35H) 1.57 (s, 7.65H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 158.0, 149.9, 138.9 and 138.5 (1C), 124.9 and 124.7 (1C), 124.0 and 123.7 (1C), 113.3, 112.0 and 111.3 (1C), 60.0, 45.7 and 45.5 (1C), 24.7 and 24.5 (3C), 19.9 (2C); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{15}H_{20}N_2NaO_3S^+$ 331.1087, found 331.1081.

(*E*)-2-methyl-*N*-(2-oxo-1-phenylindolin-3-ylidene)propane-2-sulfonamide (VI·7f). Prepared according to GP-C starting from *N*-phenyl substituted isatin. Red foamy solid, yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$, 7:3 mixture of two rotamers) δ

8.21 (dd, *J* = 7.9 and 1.4 Hz, 0.7H), 8.00 (d, br, *J* = 7.9 Hz, 0.3H), 7.69 - 7.53 (m, 4H), 7.44 (t, *J* = 7.8 Hz, 0.3H), 7.41 – 7.26 (m, 2.7H), 6.58 (d, *J* = 7.8 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 150.9, 143.1, 138.5 and 137.5 (1C), 133.7, 130. 6(3C), 129.6 and 129.5 (2C), 127.1, 125.0 and 124.7 (1C), 115.9, 111.4, 60.8, 24.9-24.5(3C); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{18}H_{18}N_2NaO_3S^+$ 365.0930, found 365.0939.

(*E*)-*N*-(1-benzyl-5-methoxy-2-oxoindolin-3-ylidene)-2-methylpropane-2-sulfonamide (VI·7g). Prepared according to GP-C starting from 5-OMe-*N*-benzyl substituted isatin. Red foamy solid, yield: 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 6H), 6.99 (dd, *J* = 8.2 and 2.6 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 4.89 (s, 2H), 3.79 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.7, 145.2, 144.1, 135.3, 129.7 (2C), 128.8, 128.0 (2C), 126.7, 125.6, 116.7, 111.9, 60.7, 56.7, 44.9, 24.6 (3C); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{20}H_{22}N_2NaO_4S^+$ 409.1192, found 409.1186.

(*E*)-*N*-(1-benzyl-5-chloro-2-oxoindolin-3-ylidene)-2-methylpropane-2-sulfonamide (VI·7h). Prepared according to GP-C starting from 5-Cl-*N*-benzyl substituted isatin. Red foamy solid, yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$, 4:1 mixture of two rotamers) δ 7.42 - 7.26 (m, 7H), 6.76 (d, *J* = 8.2 Hz, 0.2H), 6.68 (d, *J* = 8.2 Hz, 0.8H), 4.93 (s, 2H), 1.67 (s, 1.8H), 1.65 (s, 7.2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 148.2, 145.6, 138.3 and 137.9 (1C), 134.7, 130.7 and 129.8(2C), 129.9, 129.0 (2C), 128.0 (2C), 116.9, 112.2, 63.9, 45.5 and 45.0 (1C), 24.6 and 24.5 (3C); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{19}H_{19}ClN_2NaO_3S^+$ 413.0697, found 413.0674.

General procedure D (GP-D) for enantioselective formal [2+2] annulation reaction for the synthesis of compounds VI·11a-k. To a solution of the proper *N-tert* butanesulfonyl ketimine **VI·7a-j** (0.10 mmol) and catalyst **VI·10g** (0.02 mmol) in THF (1.5 mL), allenoate **VI·2a** (**or 2b**, for spiroazetidine **VI·11k**) was added (0.20 mmol). The mixture was stirred at room temperature and the conversion was monitored by TLC. The solvent was evaporated under reduced pressure and the crude was purified by FC, using CH_2Cl_2/EtOAc 9/1 as eluent.

(*S,E*)-ethyl-2-(1'-benzyl-1-(*tert*-butylsulfonyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11a). Prepared according to GP-D using imine **VI·7a** and allenoate **VI·2a**. Pale orange foam; yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, br, *J* = 7.8 Hz, 1H), 7.19-7.38 (m, 6H), 7.08 (t, br, *J* = 7.7 Hz, 1H), 6.69 (d, br, *J* = 7.8 Hz, 1H), 5.68 (*s*, br, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.71 (dd, *J* = 15.6 and 1.9 Hz, 1H), 3.44 (dd, *J* = 15.6 and 1.9 Hz, 1H), 1.33 (*s*, 9H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 167.3, 159.2, 143.6, 134.6, 129.0 (3C), 128.2, 127.5 (2C), 126.4, 126.2, 124.6, 113.2, 94.3, 70.6, 59.7, 58.9, 44.4, 41.8, 22.7 (3C), 14.5; $[\alpha]^{D}_{25}$= + 12.2 (c 0.90, $CHCl_3$); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{25}H_{28}N_2NaO_5S^+$ 491.1611, found 491.1604; enantiomeric ratio: 80:20 , determined by HPLC (C-AD, Hexane/iPrOH 7:3, flux: 0.7 mL/min, λ = 254 nm): t_R = 16.80 min (major) t_R = 23.38 min (minor).

(*S,E*)-ethyl 2-(1-(*tert*-butylsulfonyl)-1'-methyl-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (6b). Prepared according to GP-D using imine **VI·7b** and allenoate **VI·2a**. Pale orange foam; yield: 91%. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 5.66 (t, *J* = 1.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.66 (dd, *J* = 16.0, 1.9 Hz, 1H), 3.41 (dd, *J* = 16.0, 1.9 Hz, 1H), 3.24 (s, 3H), 1.32 (s, 9H), 1.23 – 1.30 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 167.7, 159.4, 144.7, 131.8, 125.9, 125.0, 123.7, 109.5, 95.9, 71.7, 62.2, 60.5, 39.8, 27.3, 24.5 (3C), 15.0; $[\alpha]^{D}_{25}$= + 19.3 (c 0.80, $CHCl_3$); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{19}H_{24}N_2NaO_5S^+$: 415.1298, found 415.1303; enantiomeric ratio: 83:17, determined by HPLC (C-AD, Hexane/iPrOH 7:3, flux: 0.7 mL/min, λ = 254 nm): t_R = 24.96 min (major) t_R = 29.58 min (minor).

(*S,E*)-ethyl 2-(1-(*tert*-butylsulfonyl)-2'-oxo-1'-tritylspiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11c). Prepared according to GP-D using imine **VI·7c** and allenoate **VI·2a**. Pale orange foam; yield: 95%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.50 (m, 7H), 7.14 – 7.30 (m, 9H), 6.89 – 7.03 (m, 2H), 6.28 (d, *J* = 7.4 Hz, 1H), 5.62 (t, *J* = 1.9 Hz, 1H), 4.05 – 4.19 (m, 2H), 3.58 (dd, *J* = 15.7, 1.9 Hz, 1H), 3.31 (dd, *J* = 15.7, 1.9 Hz, 1H), 1.34 (s, 9H), 1.20 – 1.30 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.1, 158.9, 143.9, 141.6 (3C), 129.5 (7C), 127.6 (6C), 127.0 (3C), 125.6, 123.9, 122.5, 116.6, 94.9, 74.9, 71.6, 61.7, 59.8, 40.1, 24.0 (3C), 14.4; $[\alpha]^{D}_{25}$= - 0.67 (c 1.5, $CHCl_3$); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{37}H_{36}N_2NaO_5S^+$: 643.2237, found 643.2240; enantiomeric ratio: 71:29, determined by HPLC (C-AD, Hexane/iPrOH 7:3, flux: 0.7 mL/min, λ = 254 nm): t_R = 8.00 min (major) t_R = 11.84 min (minor).

(*S,E*)-ethyl 2-(1-(*tert*-butylsulfonyl)-2'-oxo-1'-propylspiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11d). Prepared according to GP-D using imine

VI·7d and allenoate **VI·2a**. Pale orange foam; yield: 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 1H), 7.35 (td, *J* = 7.4 and 1.1 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 5.65 (t, *J* = 1.9 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.75 (dt, *J* = 14.6 and 6.8 Hz, 1H), 3.63 (dd, *J* = 15.6 and 1.9 Hz, 1H), 3.58 (dt, *J* = 14.6 and 6.8 Hz, 1H), 3.39 (dd, J = 15.6 and 1.9 Hz, 1H), 1.72 (sext, *J* = 6.8 Hz, 2H), 1.32 (s, 9H), 1.27 – 1.22 (m, 3H) 0.97 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 167.8, 159.6, 142.9, 131.6, 126.2, 125.1, 123.5, 109.8, 95.7, 71.8, 60.5, 42.7, 40.0, 30.4, 24.6 (3C), 21.2, 15.1, 12.0; $[\alpha]^{D}_{25}$ = + 5.5 (c 1.02, $CHCl_3$); HRMS (ESI) calculated for $C_{21}H_{28}N_2NaO_5S^+$ $[M+Na]^+$ 443.1611, found 443.1617; enantiomeric ratio: 78:22, determined by HPLC (C-AD, Hexane/iPrOH 7:3, flux: 0.7 mL/min, λ = 254 nm): t_R = 7.73 min (major) t_R = 9.85 min (minor).

(*S,E*)-ethyl 2-(1-(*tert*-butylsulfonyl)-1'-isopropyl-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11e). Prepared according to GP-D using imine **VI·7e** and allenoate **VI·2a**. Pale orange foam; yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 5.64 (t, *J* = 2.0 Hz, 1H), 4.56 (hept, J = 6.8 Hz, 1H), 4.15 (q, *J* = 7.6 Hz, 2H), 3.64 (dd, *J* = 15.9 and 2.0 Hz, 1H), 3.40 (dd, *J* = 15.9, 2.0 Hz, 1H), 1.50 (d, *J* = 6.8, 3H), 1.48 (d, *J* = 6.8, 3H), 1.30 (s, 9H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 167.2, 159.1, 143.2, 130.9, 125.6, 124.8, 122.5, 110.4, 95.0, 71.1, 61.5, 59.9, 44.7, 39.1, 23.9 (3C), 19.2 (2C), 14.5; $[\alpha]^{D}_{25}$ = + 14.7 (c 0.99, $CHCl_3$); HRMS (ESI) calculated for $C_{21}H_{28}N_2NaO_5S^+$ $[M+Na]^+$ 443.1611, found 443.1616; enantiomeric ratio 82:18, determined

by HPLC (C-AD, Hexane/iPrOH 7:3, flux: 0.7 mL/min, λ = 254 nm): t_R = 7.32 min (major) t_R = 9.33 min (minor).

(*S,E*)-ethyl 2-(1-(*tert*-butylsulfonyl)-2'-oxo-1'-phenylspiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11f). Prepared according to GP-D using imine **VI·7f** and allenoate **VI·2a**. Pale orange foam; yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.39 (m, 6H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.68 (t, J = 2.0 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.77 (dd, J = 16.0, 2.0 Hz, 1H), 3.52 (dd, J = 16.0, 2.0 Hz, 1H), 1.33 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 167.2, 158.9, 144.6, 134.0, 131.2, 129.8 (2C), 128.5, 126.6 (2C), 125.8, 124.9, 123.5, 110.2, 95.4, 71.3, 61.6, 60.0, 39.2, 24.0 (3C), 14.5; $[\alpha]^D_{25}$ = + 10.3 (c 1.04, $CHCl_3$); HRMS (ESI) calculated for $C_{24}H_{26}N_2NaO_5S^+$ $[M+Na]^+$ 477.1455, found 447.1460; enantiomeric ratio: 77:23, determined by HPLC (C-AD, Hexane/iPrOH 4:1, flux: 0.7 mL/min, λ = 254 nm): t_R = 9.63 min (major) t_R = 14.79 min (minor).

(*S,E*)-ethyl 2-(1'-benzyl-1-(*tert*-butylsulfonyl)-5'-methoxy-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11g). Prepared according to GP-D using imine **VI·7g** and allenoate **VI·2a**. Pale orange foam; yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.78 (dd, *J* = 8.4 and 2.7 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.71 (t, *J* = 1.9 Hz, 1H), 5.05 (d, *J* = 15.8 Hz, 1H), 4.81 (d, *J* = 15.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.75 (dd, *J* = 15.9 and 1.9 Hz, 1H), 3.45 (dd, *J* = 15.9 and 1.9 Hz, 1H), 1.38 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 167.1, 158.8, 156.4, 136.4, 135.2, 128.8 (2C), 127.7, 127.3 (2C), 127.0, 115.4, 111.4, 110.5, 95.2, 71.5,

61.8, 59.9, 55.9, 44.3, 39.7, 24.0 (3C), 14.4; $[\alpha]^{D}_{25}$ = + 8.9 (c 0.95, $CHCl_3$); HRMS (ESI) calculated for $C_{26}H_{30}N_2NaO_5S^+$ $[M+Na]^+$ 521.1717, found 521.1720; enantiomeric ratio: 76:24, determined by HPLC (C-AD, Hexane/iPrOH 4:1, flux: 0.7 mL/min, λ = 254 nm): t_R = 15.00 min (major) t_R = 20.63 min (minor).

(*S,E*)-ethyl 2-(1'-benzyl-1-(*tert*-butylsulfonyl)-5'-chloro-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11h). Prepared according to GP-D using imine **VI·7h** and allenoate **VI·2a**. Pale orange foam; yield: 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.26 (m, 5H), 7.23 (dd, *J* = 8.2 and 2.1 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 5.71 (t, *J* = 2.1 Hz, 1H), 5.07 (d, *J* = 16.0 Hz, 1H), 4.82 (d, *J* = 16.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.74 (dd, *J* = 15.9 and 2.1 Hz, 1H), 3.47 (dd, *J* = 15.9 and 2.1 Hz, 1H), 1.39 (*s*, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 166.9, 158.2, 141.6, 136.7, 134.6, 130.8, 129.0 (2C), 128.7, 127.9, 127.2 (2C), 124.7, 111.0, 95.6, 70.7, 61.8, 60.0, 44.4, 39.5, 23.9 (3C), 14.4; $[\alpha]^{D}_{25}$ = + 9.8 (c 1.05 , $CHCl_3$); HRMS (ESI) calculated for $C_{25}H_{27}ClN_2NaO_5S^+$ $[M+Na]^+$ 525.1221, found 525.1229; enantiomeric ratio: 72:28, determined by HPLC (C-AD, Hexane/iPrOH 4:1, flux: 0.7 mL/min, λ = 254 nm): t_R = 10.31 min (major) t_R = 16.59 (minor).

(*S,E*)-Benzyl-2-(1'-benzyl-1-(*tert*-butylsulfonyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetate (VI·11k). Prepared according to GP-D using imine **VI·7a** and allenoate **VI·2b**. Pale yellow foam; yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, br, *J* = 7.8 Hz, 1H), 7.44-7.23 (m, 11H), 7.11 (t, br, *J* = 7.7 Hz, 1H), 6.72 (d, br, *J* = 7.8 Hz, 1H), 5.78 (*s*, br, 1H), 5.19 (*s*, br, 2H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.84 (d, *J* = 15.8 Hz, 1H), 3.74 (d, br, *J* =

16.0 Hz, 1H), 3.47 (d, br, *J* = 16.0 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 167.5, 160.0, 143.9, 136.9, 135.7, 131.7, 129.5 (3C), 129.3, 129.0, 128.8, 128.4 128.0 (3C), 126.0, 125.1, 123.8, 110.7, 95.5, 71.8, 66.6, 62.3, 44.9, 40.3, 24.6 (3C); $[\alpha]^{D}_{25}$ = + 15.0 (c 0.8, $CHCl_3$); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{30}H_{30}N_2NaO_5S^+$ 553.1768, found 553.1772; enantiomeric ratio: 78:22, determined by HPLC (C-AD, Hexane/iPrOH 7:3, flux: 0.7 mL/min, λ = 254 nm): t_R = 16.80 min (major) t_R = 23.38 min (minor).

Post-transformation reactions

(*S,E*)-2-(1'-benzyl-1-(*tert*-butylsulfonyl)-2'-oxospiro[azetidine-2,3'-indolin]-4-ylidene)acetic acid (VI·15).

To a solution of **VI·11a** (0.21 mmol) in water/THF/*i*PrOH (1:1:1, 1.5 mL), LiOH (0.63 mmol) was added and the mixture was stirred at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched with a 1M aqueous solution of HCl and extracted with CH_2Cl_2. The organic layer was collected, dried over anhydrous sodium sulfate, and concentrated under reduced pressure affording the product as a white foam (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 1H), 7.41 – 7.23 (m, 6H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.4 Hz, 1H), 5.71 (t, *J* = 1.9 Hz, 1H), 5.07 (d, *J* = 15.8 Hz, 1H), 4.87 (d, *J* = 15.8 Hz, 1H), 3.76 (dd, *J* = 16.3 and 2.0 Hz, 1H), 3.49 (dd, *J* = 16.3 and 2.0 Hz, 1H), 2.05 (m, br, 1H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 172.5, 161.3, 143.2, 135.0, 131.1, 128.9 (2C), 127.8, 127.3 (2C), 125.1, 124.4, 123.2, 110.1, 94.4, 71.2, 61.8, 44.3,

39.7, 23.9 (3C); $[\alpha]^{D}_{25}$ = + 5.7 (c 0.79, $CHCl_3$); HRMS (ESI) calculated for $C_{23}H_{24}N_2NaO_5S^+$ $[M+Na]^+$ 463.1298, found 463.1289.

(*S*)-Ethyl 1-benzyl-1'-(*tert*-butylsulfonyl)-2-oxo-1',3'-dihydrospiro[indoline-3,2'-pyrrole]-4'-carboxylate (VI·16). To a stirred solution of **VI·11a** (0.21 mmol) in CH_2Cl_2 (9 mL) at 0 °C, CF_3SO_3H (0.68 mmol) was added. After stirring at 0 °C for 2 h, the mixture was neutralized with 0.1 M NaOH and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo, affording the product as a white foam (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, br, *J* = 7.8 Hz, 1H), 7.40-7.25 (m, 6H), 7.05 (t, br, *J* = 7.7 Hz, 1H), 6.79 (d, br, *J* = 7.8 Hz, 1H), 6.15 (s, br, 1H), 4.97 (d, *J* = 15.5 Hz, 1H), 4.91 (d, *J* = 15.5 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.49 (d, br, *J* = 16.4 Hz, 1H), 2.63 (d, br, *J* = 16.4 Hz, 1H), 1.46 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.5, 169.7, 142.3, 134.7, 131.6, 129.1 (2C), 128.1, 127.3 (2C), 126.4, 125.1, 124.0, 81.2, 79.7, 66.6, 58.5, 44.2, 38.4, 24.0 (3C), 14.2; $[\alpha]^{D}_{25}$ = + 6.3 (c 0.53, $CHCl_3$); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{25}H_{28}N_2NaO_5S^+$ 491.1611, found 491.1617.

(*S*)-ethyl 4-(1-benzyl-3-(1,1-dimethylethylsulfonamido)-2-oxoindolin-3-yl)-3-oxobutanoate (VI·17). To a solution of **VI·11a** (0.20 mmol) in trifluoroacetic acid (5 mL) and CH_2Cl_2 (2 mL), anisole (4 mmol) was added, and the mixture was stirred for 1h at 60 °C. To this saturated Na_2CO_3 was added and organic materials were extracted with EtOAc. Dried and concentrated extract was subjected to FC (Hexane/ EtOAc 1/1) to give the product as a pale yellow foam (yield: 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, br, *J* = 7.8 Hz, 1H), 7.43-7.24 (m, 5H), 7.21 (t, br, *J* = 7.7 Hz, 1H), 7.04 (t, *J* =

7.7 Hz, 1H), 6.72 (d, br, *J* = 7.8 Hz, 1H), 5.75 (*s*, br, 1H), 5.04-4.90 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.60 (d, *J* = 17.4 Hz, 1H), 3.47-3.38 (m, 2H), 3.07 (d, *J* = 17.4 Hz, 1H), 1.34 (*s*, 9H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 174.7, 166.1, 142.4, 135.6, 129.7, 128.8 (2C), 128.7, 127.7, 127.3 (2C), 125.3, 122.9, 109.7, 61.7, 60.6, 60.3, 50.1, 49.2, 44.4, 24.1 (3C), 14.0; $[\alpha]^{D}_{25}$ = - 57.4 (c 0.50, $CHCl_3$); HRMS (ESI): $[M+Na]^+$, Calcd for $C_{25}H_{30}N_2NaO_6S^+$ 509.1717, found 509.1711.

VI.6 References

1. (a) Brandi A.; Cicchi S.; Cordero F. M.; *Chem. Rev.* **2008**, *108*, 3988-4035. (b) Dejaegher Y.; Kuz'menok N. M.; Zvonok A. M.; De Kimpe N.; *Chem. Rev.* **2002**, *102*, 29-60.

2. For examples, see: (a) Rubenstein E.; Zhou H.; Krasinska K. M.; Chien A.; Becker C. H.; *Phytochemistry* **2006**, *67*, 898-903. (b) Aoyagi Y.; *Phytochemistry* **2006**, *67*, 618-621.

3. For examples, see: (a) Lowe J. T.; Lee IV M. D.; Akella L. B.; Davoine E.; Donckele E. J.; Durak L.; Duvall J. R.; Gerard B.; Holson E. B.; Joliton A.; Kesavan S.; Lemercier B. C.; Liu H.; Marié J. C.; Mulrooney C. A.; Muncipinto G.; Welzel-O'Shea M.; Panko L. M.; Rowley A.; Suh B. C.; Thomas M.; Wagner F. F.; Wei J.; Foley M. A.; Marcaurelle L. A. *J. Org. Chem.* **2012**, *77*, 7187-7211. (b) Evans G. B.; Furneaux R. H.; Greatrex B.; Murkin A. S.; Schramm V. L.; Tyler P. C. *J. Med. Chem.* **2008**, *51*, 948-956.

4. (a) Van Brabandt W.; Vanwalleghem M.; D'hooghe M.; De Kimpe N. *J. Org. Chem.* **2006**, *71*, 7083-7086. (b) von Nussbaum F.; Brands M.; Hinzen B.; Weigand S.; Habich D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072-5129. (c) Singh G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 69-92. (d) Singh G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 93-109. (e) Buynak J. D. *Curr. Med. Chem.* **2004**, *11*, 1951-1964.

5. (a) Hatano M.; Horibe T.; Ishihara K. *J. Am. Chem. Soc.* **2010**, *132*, 56-57. (b) Bhalla A.; Venugopalan P.; Bari S. S. *Eur. J. Org. Chem.* **2006**, *71*, 4943-4950.

6. (a) Jain R.; Sharma K.; Kumar D. *J. Heterocyclic Chem.* **2013**, *50*, 315-319. (b) Subba Reddy B. V.; Karthik G.; Rajasekaran T.; Antony A.; Sridhar B. *Tetra. Lett.* **2012**, 53, 2396-2401. (c) Cheng Y.; Wang B.; Cheng L. Q. *J. Org. Chem.* **2006**, *71*, 4418-4427.

7. (a) Orr S. T. M.; Beveridge R.; Bhattacharya S. K.; Cameron K. O.; Coffey S.; Fernando D.; Hepworth D.; Jackson M. V.; Khot V.; Kosa R.; Lapham K.; Loria P. M.; McClure K. F.; Patel J.; Rose C.; Saenz J.; Stock I. A.; Storer G.; von Volkenburg M.; Vrieze D.; Wang G.; Xiao J.; Zhang Y. *ACS Med. Chem. Lett.* **2015**, *6*, 156-161. (b) Karlsson S.; Bergman R.; Löfberg C.; Moore P. R.; Pontén F.; Tholander J.; Sörensen H. *Org. Process Res. Dev.* **2015**, *19*, 2067-2074. (c) Xu R.; Czarniecki M.; de Man J.; Pan J.; Qiang L.; Root Y.; Ying S.; Su J.; Sun X.; Zhang Y.; Yu T.; Zhang Y.; Hu T.; Chen S. H. *Tetrahedron Lett.* **2011**, *52*, 3266-3270. (d) Meyers M. J.; Muizebelt I.; van Wiltenburg J.; Brown D. L.; Thorarensen A. *Org. Lett.* **2009**, *11*, 3523-3525. (e) Deguest G.; Bischoff L.; Fruit C.; Marsais F.; *Org. Lett.* **2007**, *9*, 1165-1167.

8. Lüthy M.; Wheldon M. C.; Haji-Cheteh C.; Atobe M.; Bond P. S.; O'Brien P.; Hubbard R. E.; Fairlamb I. J. S. *Bioorg. Med. Chem.* **2015**, *23*, 2680-2694.

9. (a) Stucchi M.; Lesma G.; Meneghetti F.; Rainoldi G.; Sacchetti A.; Silvani A. *J. Org. Chem.* **2016**, *81*, 1877-1884. (b) Lesma G.; Meneghetti F.; Sacchetti A.; Stucchi M.; Silvani A. *Belstein J. Org. Chem.* **2014**, *10*, 1383-1389. (c) Sacchetti A.; Silvani A.; Gatti F. G.; Lesma G.; Pilati T.; Trucchi B. *Org. Biomol. Chem.* **2011**, *9*, 5515-5522. (d) Lesma G.; Landoni N.; Sacchetti A.; Silvani A. *Tetrahedron* **2010**, *66*, 4474-4478. (e) Lesma G.; Landoni N.; Pilati T.; Sacchetti A.; Silvani A. *J. Org. Chem.* **2009**, *74*, 4537-4541.

10. For reviews on bioactive spirooxindoles, see: (a) Ye N.; Chen H.; Wold E. A.; Shi P.-Y.; Zhou J. *ACS Infect. Dis.* **2016**, *2*, 382-392. (b) Saraswat P.; Jeyabalan G.; Ansari Z. H.; Rahman M. U.; Nyola N. K. *Synth. Comm.* **2016**, DOI: 10.1080/00397911.2016.1211704. (c) Yu B.; Yu D.-Q.; Liu H-M. *Eur. J. Med. Chem.* **2015**, *97*, 673-698. For examples, see: (a) Wang S.; Jiang Y.; Wu S.; Dong

G.; Miao Z.; Zhang W.; Sheng C. *Org. Lett.* **2016**, *18*, 1028-1031. (b) Bertamino A.; Soprano M.; Musella S.; Rusciano M. R.; Sala M.; Vernieri E.; Di Sarno V.; Limatola A.; Carotenuto A.; Cosconati S.; Grieco P.; Novellino E.; Illario M.; Campiglia P.; Gomez-Monterrey I. *J. Med. Chem.* **2013**, *56*, 5407-5421.

11. (a) Zhao G.-L.; Shi M. *J. Org. Chem.* **2005**, *70*, 9975-9984. (b) Zhao G.-L.; Huang J. W.; Shi M. *Org. Lett.* **2003**, *5*, 4737-4739.

12. Yang L. J.; Li S.; Wang S.; Nie J.; Ma J. A. *J. Org. Chem.* **2014**, *79*, 3547-3558.

13. Chen X. Y.; Lin R. C.; Ye S. *Chem. Commun.* **2012**, *48*, 1317-1319.

14. (a) Takizawa S.; Arteaga F.; Yoshida Y.; Suzuki M.; Sasai H. *Org. Lett.* **2013**, *15*, 4142-4145. (b) Denis J. B.; Masson G.; Retailleau P.; Zhu J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5356-5360.

15. Santos B. S.; Cardoso A. L.; Matos Beja A.; Ramos Silva M.; Paixão J. A.; Palacios F.; Pinho e Melo T. M. V. D. *Eur. J. Org. Chem.* **2010**, *17*, 3249-3256.

16. (a) Bhaskara Rao V. U.; Jadhav A. P.; Garad D.; Singh R. P. *Org. Lett.* **2014**, *16*, 648-651. (b) Chen D.; Xu M. H. *Chem. Commun.* **2013**, *49*, 1327-1329.

17. (a) Zhang H. M.; Gao Z. H.; Ye S. *Org. Lett.* **2014**, *16*, 3079-3081. (b) Sato S.; Shibuya M.; Kanoh N.; Iwabuchi Y. *Chem. Comm.* **2009**, 6264-6266.

18. Denis, J.-B.; Masson, G.; Retailleau, P.; Zhu, J.; *Angew. Chem. Int. Ed.* **2011**, *50*, 5356 -5360.

19. Sun, P.; Weinreb, S.M.; *J. Org. Chem.* **1997**, *62*, 8604-8608.

VII. Conclusion and Future Perspective

In conclusion, I exploited the potentialities of various convergent approaches, mostly based on multicomponent reactions (MCRs), for the synthesis of small libraries of highly functionalized oxindoles, also taking into particular attention the issue of stereochemical induction.

I successfully applied BINOL-derived phosphoric acids to the vinylogous-Mannich reaction between trimethylsiloxyfuran and isatin-derived ketimines, obtaining a small library of chiral quaternary 3-aminooxindole butenolides. Unable to obtain good crystals for the X-ray analysis, the configurational assignment of the obtained compounds was performed by chemical correlation. For this project, a computational study of the transition state allowed to rationalize the stereochemical outcome, highlighting the possible binding modes of the catalyst-imine-nucleophile transition complex.

Still aiming to combine MCRs with asymmetric organocatalysis, I developed the first BINOL-derived phosphoric acid catalysed Biginelli-like reaction on a ketone. In particular, I achieved the synthesis of a small library of biologically relevant enantioenriched spiro[indoline-pyrimidine]-diones derivatives by employing *N*-substituted isatins as carbonyl substrates. The assignment of the configuration at the new oxindole C-3 stereocenter was assessed through quantum-mechanical methods and NMR spectroscopy, while computational studies on the reaction transition state allowed to rationalize the enantioselectivity and the stereochemical outcome.

In the context of diversity-oriented synthesis, I focused my attention on the possibility of combining two diverse MCRs, namely Asinger and Ugi-type

reactions. In particular, I developed the first Asinger reaction involving isatin as the oxo component and leading to large a family of spirooxindole-fused 3-thiazoline derivatives. The resulting thiazolines proved to be optimal substrates for Ugi-Joullié 3-CR and azido-Ugi 3-CR reactions leading to spirooxindole-fused 3-thiazolidine-carboxamide and tetrazole-containing derivatives, respectively. These reactions were surprisingly high *trans*-diasteroselective due to a particular envelope-like conformation of the spirothiazoline. The relative stereochemistry was confirmed for both classes of products by X-ray analysis and some post-transformations were also performed, in order to increase the chemical diversity.

Finally, I explored the synthesis of enantiopure compounds bearing the small-size azetidine ring spiro-fused with the oxindole moiety. In this work, I developed the first effective application of chiral imines for the preparation of methyleneazetidines. In particular the suitability of chiral, isatin-derived *tert*-butanesulfinyl ketimines for a diastereoselective [2+2] annulation-based strategy, is fully demonstrated for the first time. Considering the importance of asymmetric catalytic approaches over chiral auxiliary strategies, I also successfully investigated the possibility of carrying out the synthesis of such spirooxindole-fused 4-methyleneazetidines in an enantioenriched form, by using cinchona-based catalysts.

In my opinion, the results presented here clearly highlight the high potential of the multicomponent approach when applied to the synthesis of small libraries of oxindole-based products. To this regard, the discovery of novel MCRs, as well as their combination with asymmetric organocatalysis, will be the key point in the next future of this rapidly growing research area.

Most of the compound libraries presented in this thesis have been submitted to a preliminary computational and biological evaluation, in collaboration with Merck Pharma.