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Stereoselective Synthesis of Biheterocycles Containing Indole and 5,6-Dihydropyridin-2(1H)-one or α-Methylene-β-butyrolactam Scaffolds

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Dedicated to Professor Joan Bosch on the occasion of his 75th birthday

Indium-mediated allylation of *N-tert*-butanesulfinyl imines derived from indole-2 and 3-carbaldehydes **3** and **5** with allylic bromides **6**, proceed with high diastereoselectivity. Homoallylic amide derivatives **13** and **14** are transformed into dihydropyridinones **15** and **16**, upon successive desulfinylation, *N*-acylation with acryloyl chloride and ring-closing-metathesis. Desulfinylation of amine ester derivatives **17** and **18**, obtained when ethyl 2-(bromomethyl)acrylate (**6b**) is used as the allylating reagent, lead to the corresponding α-methylene-γ-butyrolactams **19** and **20**, in modest yields.

Introduction

The indole moiety is widely represented in compounds with many applications in, for instance, material sciences, agriculture,[1] and most importantly, pharmaceutical industry.[2] These compounds are of both natural[3] and synthetic origin. There are two general types of methodologies leading to the synthesis of indole derivatives. Those comprising the formation of the condensed nitrogen-containing five membered ring (Scheme 1a),[4] and those in which a further functionalization in the indole unit occurs, taking advantage of the different site selectivity displayed by these systems. Among the latest ones, catalytic asymmetric processes for the construction of indole derivatives are of special interest, by means of asymmetric organocatalysis (Scheme 1b),[5] or under transition-metal catalysis, which allow the regioselective formation of carbon-carbon and carbon-heteroatom bonds (Scheme 1c).[6] Since the indole motif is present in many natural polycyclic products, annulation methodologies have also been developed to allow access to these compounds and their analogs.[7] At this respect, the nucleophilic character of indole C3 position uses to play a fundamental role by reacting with electrophiles, or by participating in tandem C3-electrophilic C2-nucleophilic annulations, the so-called dearomative annulations.[8]

On the other hand, we have reported the enantioselective synthesis of α-methylene-γ-butyrolactams[9] and 5,6-dihydropyridin-2(1*H*)-ones[10] by a diastereoselective indium-promoted allylation of chiral *N-tert*-butanesulfinyl imines[11] with ethyl 2-bromomethylacrylate and allyl bromide, respectively. Surprisingly, there are few examples of synthetic strategies involving indole derivatives bearing this type of chiral imines. The stereodivergent synthesis of pseudotabersonine alkaloids reported by Suna is one of these examples (Scheme 2a),[12] and the synthesis of Ma, Zhang and Xu of monoterpene indole alkaloid arbornamine is another one (Scheme 2b).[13]

Continuing our interest in the development of new methodologies for the stereoselective synthesis of nitrogen containing heterocyclic, we envisioned a synthetic strategy to access to biheterocycles bearing indole and methylenebutyrolactam or dihydropyridinone moieties. A diastereoselective indium-mediated allylation of indole-derived *N-tert*-butanesulfinyl imine is a key step in this strategy (Scheme 3). The resulting reaction products are of potential pharmacological interest since the methylenebutyrolactam[14] or

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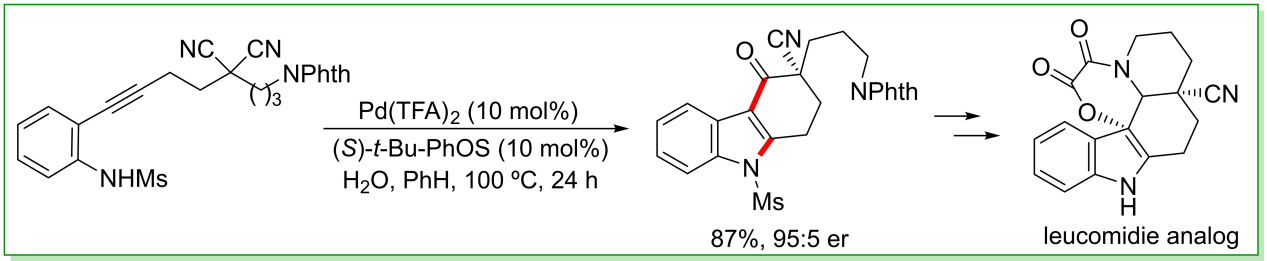
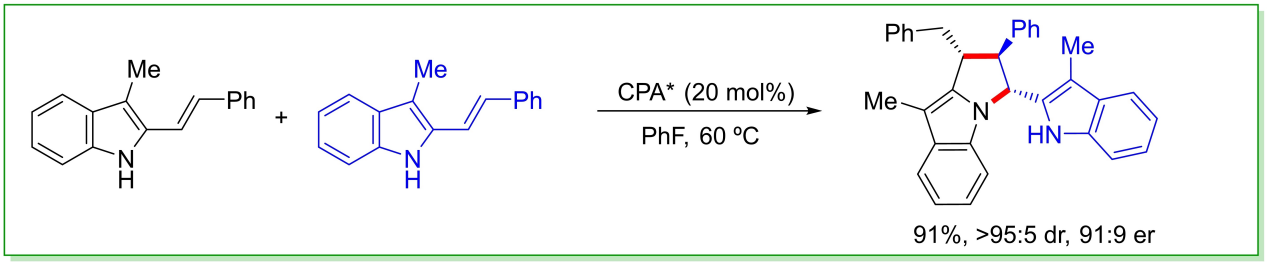
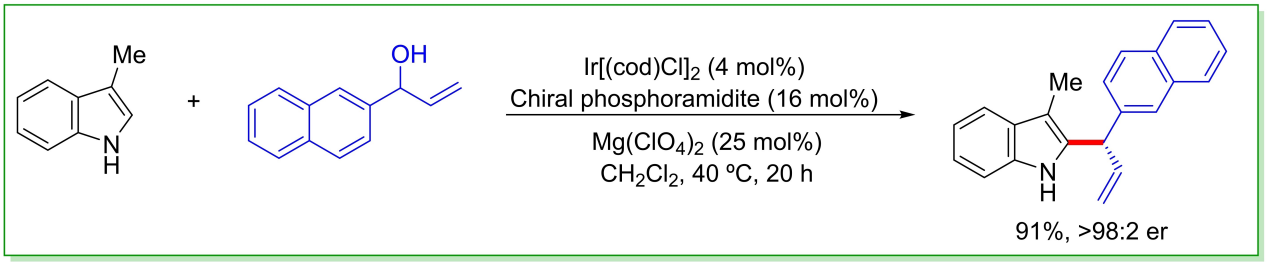
a) Previous report: Palladium(II)-catalyzed amino-cyclization (ref. 4c)



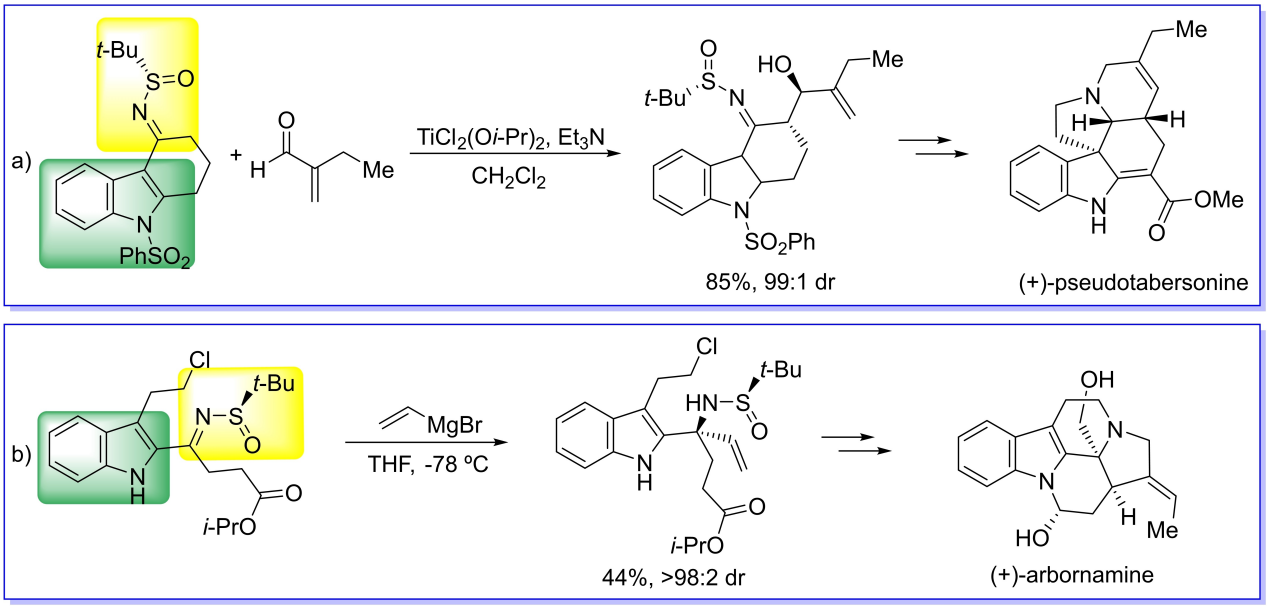
b) Previous report: Organocatalytic asymmetric [3 + 2] cyclodimerization of 3-alkyl-2-vinylindoles mediated by a chiral phosphoric acid (CPA) (ref. 5)



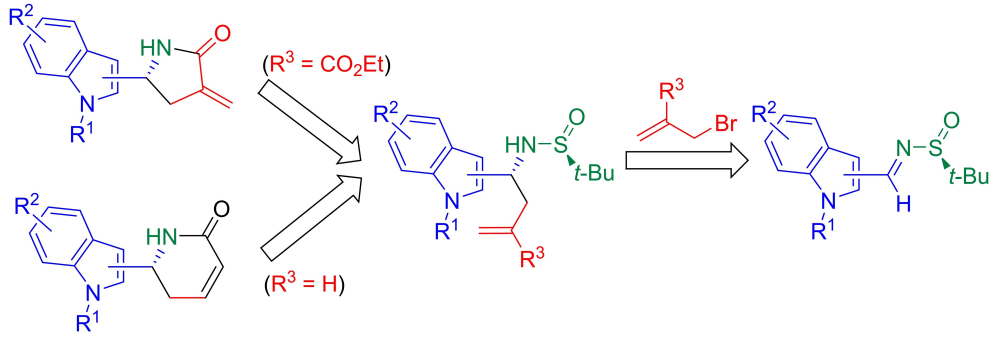
c) Previous report: Iridium-catalyzed enantioselective intermolecular indole C2-allylation with allylic alcohols (ref. 6d)



Scheme 1. Stereoselective synthesis of indole derivatives.



Scheme 2. Selected synthesis of alkaloids involving indole derivatives bearing chiral sulfinyl imines.



Scheme 3. Retrosynthetic analysis for indolyl α-methylene-β-butyrolactams and 5,6-dihydropyridin-2(1*H*)-ones.

dihydropyridinone[15] motifs, themselves display a wide range of biological activities.

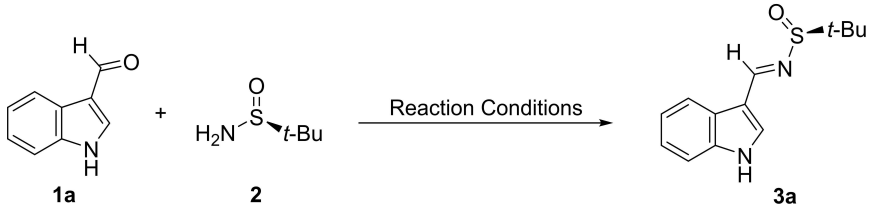
Results and Discussion

Our strategy to reach biheterocycles with the indole and the lactam moieties, started with the synthesis of chiral *N-tert*-butanesulfinyl imines **3** derived from indole carbaldehydes **1**. In order to find the best reaction conditions for this purpose, we choose indole-3-carbaldehyde **1 a**, and (*S*)-*N-tert*-butanesulfinamide (**2**) as the model starting materials. Surprisingly, direct condensation of these reactants, in the presence of a Lewis acid and a water scavenger at room temperature, did not produce the expected imine (Table 1, entries 1, 3, 4). Those are typical conditions for the formation of *N-tert*-butanesulfinyl imines derived from aliphatic and aromatic aldehydes.[16] Performing the condensation with titanium tetraethoxide in refluxing THF, which worked well for less reactive ketimines,[17] only traces of the imine **3 a** were detected in the crude of the reaction (Table 1, entry 2). The use of *p*-toluenesulfonic acid supported in silica gel was not effective for the imine formation under ultrasound activation (Table 1, entry 5). Fortunately, the condensation worked well under microwave irradiation for 10 minutes, in the presence of titanium tetraethoxide, without additional solvents (Table 1, entry 6).[18] Even, a highest yield was obtained under solvent-free conditions and thermal activation (80 °C) for 1 hour (Table 1, entry 7).

The scope of the reaction under the optimized conditions shown in entry 7 of Table 1 was studied next. The expected imines **3** and **5** were obtained in relatively high yields after column chromatography purification. Halogens, electron-withdrawing and electron-donating groups were well tolerated at different positions. Alkyl substituents at the nitrogen atom of the indole did not affect the imine formation, since compounds **3 a** and **3 h** (the corresponding *N*-methyl derivative) were obtained in similar yields. Better result was obtained for indole-2-carbaldehyde (**4**), with the formyl group at C2 position of the indole system in comparison with **1 a** (imine **5**, 87% yield *vs.* imine **3 a**, 75% yield, Table 2).

We envisioned homoallylamine derivatives **7** and **8** as synthetic intermediates in the way to the target biheterocycles depicted on Scheme 3. These compounds were easily prepared in excellent enantiopurity under reaction conditions developed in our research group.[19] Chiral imines **3** and **5** were treated

Table 1. Optimization of imine **3 a** formation from aldehyde **1 a** and (*S*)-*tert*-butanesulfinamide **2**.[a]

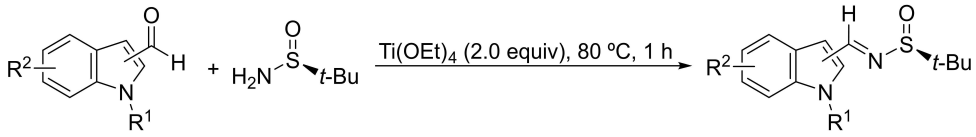


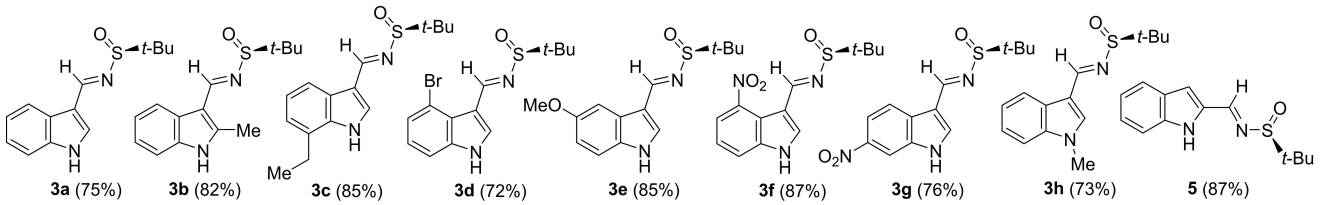
1a **2** **3a**

Entry	Reaction Conditions Additive	Solvent	Activation	Temperature (°C)	Time	Yield (%)[b]
1	$Ti(OEt)_4$ (2.0 equiv)	THF	–	23	4 h	NR
2	$Ti(OEt)_4$ (2.0 equiv)	THF	–	66	4 h	>5
3	$Mg(SO_4)_2$ (1.5 equiv)	CH_2Cl_2	–	23	12 h	NR
4	$Cu(SO_4)_2$ (1.5 equiv)	CH_2Cl_2	–	23	12 h	NR
5	$TsOH{\cdot}SiO_2$ (0.16 mol%)	–	US))))	23-50	12 h	NR
6	$Ti(OEt)_4$ (2.0 equiv)	–	MW (40 W)	70	10 min	68
7	$Ti(OEt)_4$ (2.0 equiv)	–	Thermal	80	1 h	75

[a] All reactions were carried out with 1.0 mmol of 1a and 1.0 mmol of 2 in 1.0 mL of the corresponding solvent. [b] Yield was determined after column chromatography purification based on the starting aldehyde 1a.

Table 2. Scope of imines **3** and **5** formation from aldehydes **1** and **4**, and (*S*)-*tert*-butanesulfinamide **2**.[a]



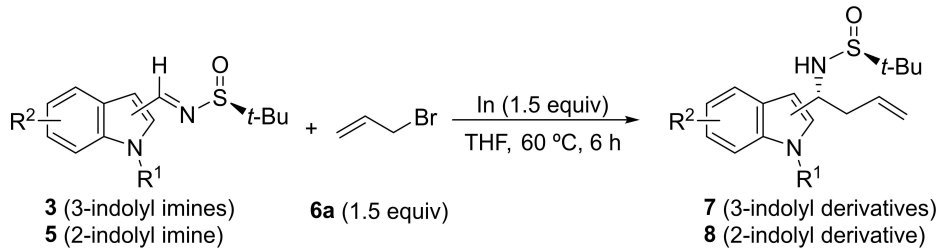


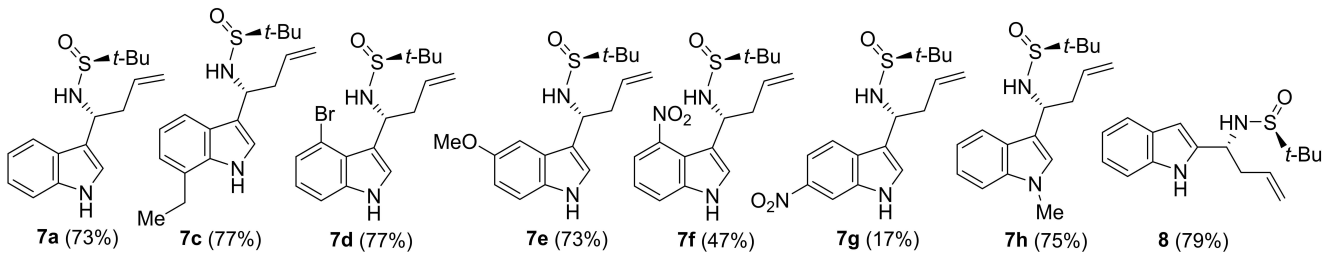
[a] All reactions were carried out with 1.0 mmol of aldehydes 1 or 4, and 1.0 mmol of 2. Isolated yield after column chromatography purification is given in parenthesis.

with an excess (1.5 equiv) of allyl bromide (**6a**), in the presence of indium metal, in THF at 60°C for 6 hours (Table 3). Homoallylamine derivatives **7** and **8** were obtained in variable yields (ranging from 17% for 6-nitro indole derivative **7g**, to 79% for 2-substituted homoallyl amine derivative **8**), and excellent diastereoselectivities, after column chromatography purification (>95:5 dr). Only the more sterically hindered imine **3b**, derived from the corresponding 2-methylindole-3-carbaldehye (**1b**), did not give the expected allylated product **7b**. The stereochemical outcome of these allylations is well known. The nucleophilic attack takes place to the *Re* face of imines **3** and **5** with the *S* configuration at the sulfur atom, leading to reaction products **7** and **8** with *R* configuration at the new formed stereogenic center (Table 3). Unfortunately, decomposition of the ammonium salt intermediate in a relatively large extension was observed after removal of the sulfinyl group under acidic conditions, previous to the planed *N*-acylation with acryloyl chloride. Probably, nitrogen atom of the indole facilitates release of ammonia as leaving group attached at the carbon bonded to C3 position furnishing a highly conjugated system.

In order to avoid decomposition of the ammonium salt, and with the aim of mitigate the nucleophilic character of the C3 position, we decided to place an electron-withdrawing group on the indolic nitrogen. For that reason, representative *N*-Boc-protected imines **9a**, **9c**, **9e**, **9f**, **9g** and **10** were prepared first from the corresponding *N*-*tert*-butanesulfinyl imines **3** and **5**, respectively, in high to excellent yields (Table 4). Further indium-promoted allylation of imines **9** and **10** under the previously commented reaction conditions provided the expected homoallylamine derivatives **11** and **12**, in moderate (**11c** and **11e**) to high yields (**11a** and **12**) (Table 4).

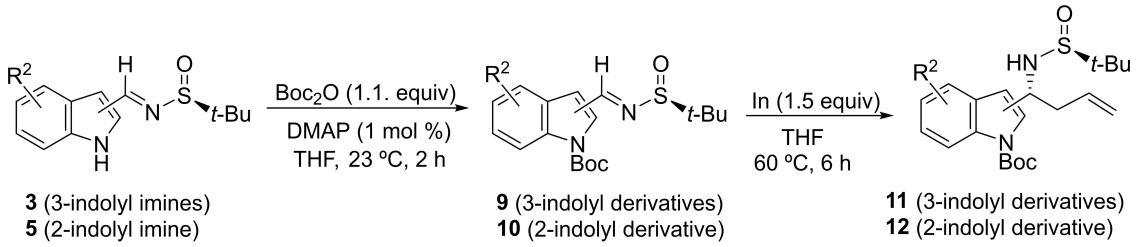
Table 3. Diastereoselective indium-mediated allylation with allyl bromide (**6a**) of sulfinyl imines **3** and **5**.[a]

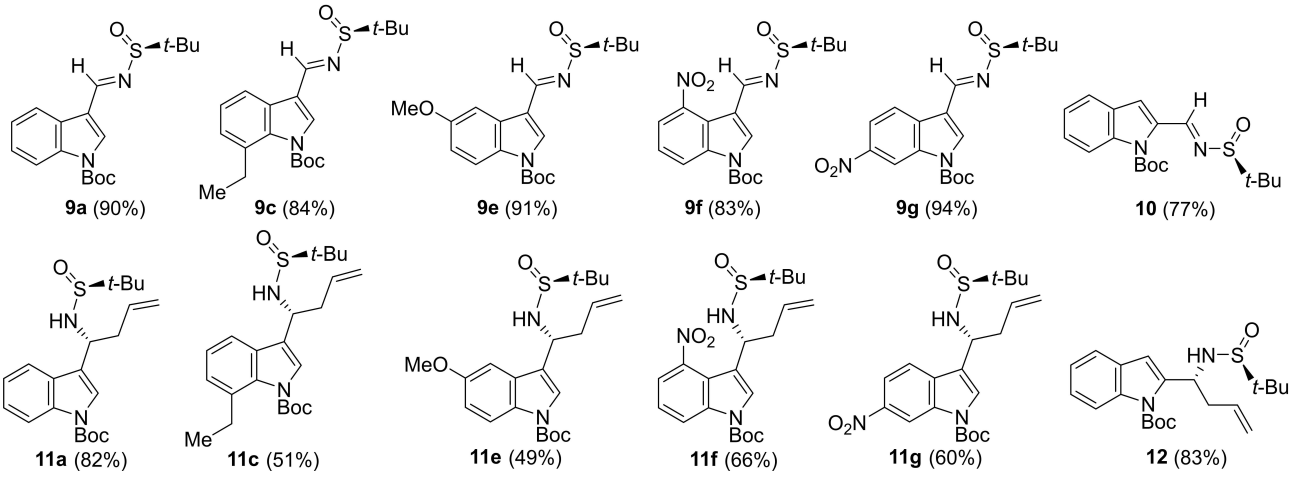




[a] All reactions were carried out with 1.0 mmol of imines 3 or 5, and 1.5 mmol of **6a**. Isolated yield after column chromatography purification is given in parenthesis.

Table 4. Synthesis and diastereoselective allylation of *N*-Boc protected sulfinyl imines **9** and **10**.[a]





[a] All reactions were carried out with 1.0 mmol of imines 3 or 5, and 0.5 mmol of *N*-Boc protected imines 9 and 10. Isolated yield after column chromatography purification is given in parenthesis.

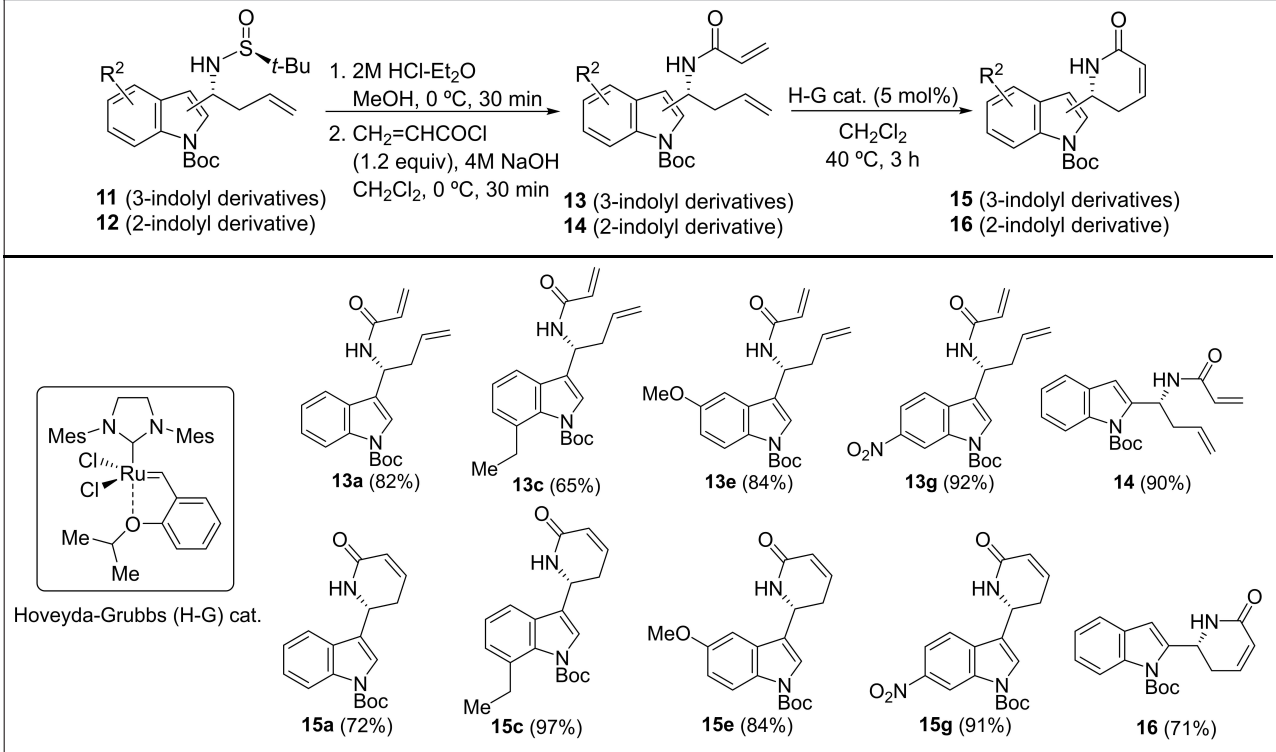
The removal of *tert*-butanesulfinyl group in *N*-Boc-protected homoallylamine derivatives **11** and **12** was carried out under acidic conditions in MeOH, and the resulting ammonium salt was treated with acryloyl chloride at 0 °C in a two-phase solvent system consisting of 4 M aqueous sodium hydroxide and dichloromethane. The expected acrylamides **13** and **14** were isolated in excellent yields in most of the cases (Table 5).

Fortunately, decomposition of ammonium salts intermediates did not take place in *N*-Boc-protected indoles. Target biheterocycles **15** and **16**, based on the indole and dihydropyridinone scaffolds, were accessed through ring-closing metathesis of acrylamides **13** and **14**, under Hoveyda-Grubbs (H–G) second-generation ruthenium catalyst in high yields (Table 5).

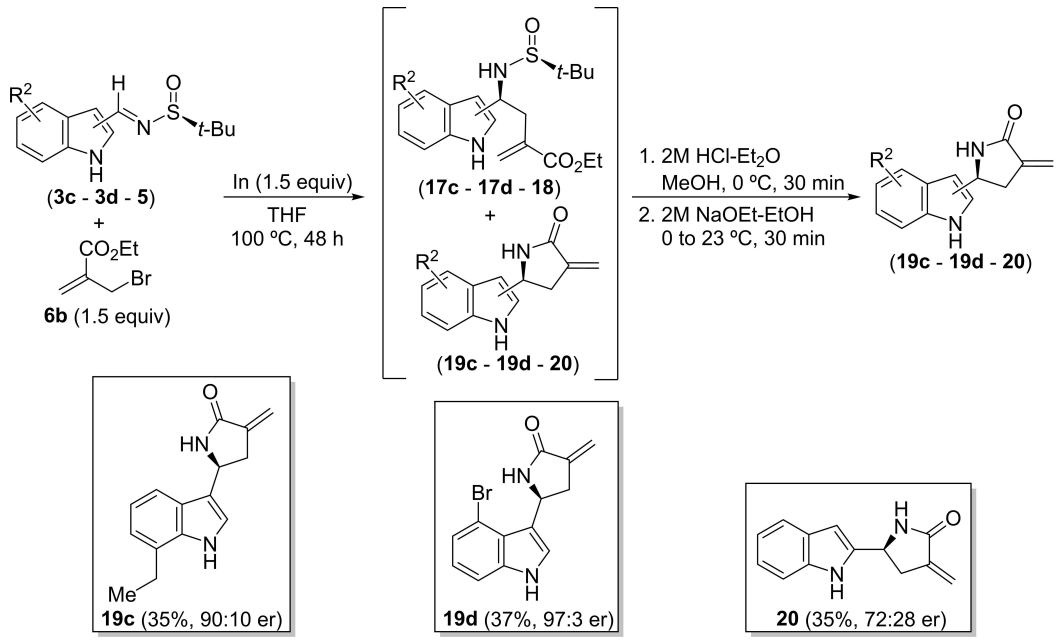
The allylation of indolylsulfinyl imines **3** and **5** with ethyl 2-(bromomethyl)acrylate (**6b**) in a saturated aqueous sodium bromide solution in the presence of 4 equivalents of indium at room temperature for 48 h did not afford amino esters **17** and **18**. We found that these conditions worked well for aliphatic and aromatic *N*-*tert*-butanesulfinyl aldimines,[9,20] and when the reaction was performed at higher temperature, decomposition of the imine took place. Fortunately, complete conversion was achieved in THF at 100 °C after 48 hours to give a mixture of the expected amino ester derivatives **17** and **18**, and the butyrolactams **19** and **20** (Scheme 4).[21] Under these reaction conditions, the initially formed amino esters could partially cyclized to give α-methylene-γ-butyrolactams. From the reaction mixture, amino esters **17** and **18** were converted into butyrolactams **19** and **20**, upon removal of the *tert*-butanesulfinyl group under acidic conditions at low temperature, and final basic workup. Relatively low yields were obtained, due probably to partial decomposition of the ammonium salt resulting after removal of the sulfinyl group under acidic conditions. Through HPLC analysis using columns with a chiral packing, er values of the reaction products were determined, ranging from 97:3 (**19d**) to 72:28 (**20**).

Based on previous studies,[21] the configuration of the newly created stereogenic center in the major diastereoisomer of compounds **19** and **20** was assigned to be *S*. In order to explain this stereochemical outcome, we proposed that the nucleophilic attack of the allylindium intermediate upon the *Si*-face of the imine with S_S configuration occurred preferentially through an open transition state **A**, in a kind of *s-cis* configuration, which is more stable (Figure 1a). On the contrary, a six-membered ring model **B** (Figure 1b), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety, has been proposed for the indium-promoted allylation of these chiral aldimines with allyl bromide (**6a**)[19] and it would lead to the opposite configuration (see allylated products in Tables 3 and 4). Intermolecular indium chelation of allylindium intermediate resulting from ethyl 2-(bromomethyl)acrylate (**6b**) with the sulfinyl group of the imine may be hampered by a more favorable intramolecular chelation with the ester group,

Table 5. Synthesis of acrylamides **13** and **14**, and indolyldihydropyridin-2-ones **15** and **16**.[a]



[a] All reactions were carried out with 0.2 mmol of compounds **11**, **12**, **13** and **14**. Isolated yield after column chromatography purification is given in parenthesis.



Scheme 4. Synthesis of indolyl-α-methylene-β-butyrolactams **19** and **20** from sulfinyl imines **3c**, **3e** and **5**.

facilitating the addition through an open transition state **A** (Figure 1a).

Conclusion

In summary, 2- and 3-indolyl dihydropyridinones (**15** and **16**) and α-methylene-γ-butyrolactams (**19** and **20**) were prepared

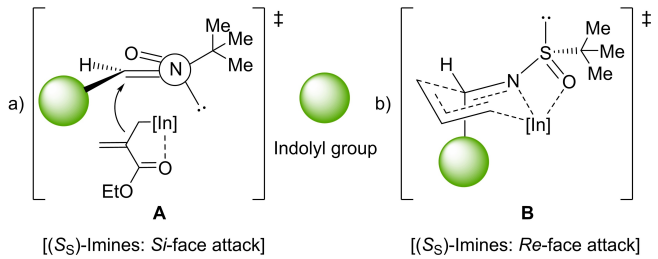


Figure 1. Proposed working models in the allylation of sulfinyl imines.

in a highly enantioselective manner, using as precursors *N-tert*-butanesulfinyl imines **3** and **5**, derived from the corresponding indole carbaldehyde. Indium-mediated diastereoselective allylations of the chiral imines, as well as ring closing metathesis for lactams **15** and **16**, are key steps of the presented methodologies, showing opposite configuration the formed stereogenic centers when the allylation was carried out with allyl bromide or with ethyl 2-(bromomethyl)acrylate. Biheterocycles **15**, **16**, **19** and **20**, based on indole on one side, and α-methylene-γ-butyrolactam or dihydropyridin-2-one scaffolds on the other side, could be of potential interest since these heterocyclic motifs are known to display biological activities by themselves.

Supporting Information Summary

The experimental section is provided in the supporting information, and copies of ^{1}H, ^{13}C NMR and DEPT spectra for compounds **3a**–**f**[22,23] **5**,[24] **7a**, **7c**–**f**, **8**, **9a**, **9c**, **9e**, **10**, **11a**, **11c**, **11e**, **12**, **13a**, **13c**, **13e**, **14**, **15a**, **15c**, **15e**, **16**, **19c**, **19d** and **20**. Copies of chiral HPLC chromatograms for compounds **19c**, **19d** and **20**.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: allylation · chiral sulfinyl imines · dihydropyridinones · functionalized indoles · lactams

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