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AN ORGANOCATALYTIC ASYMMETRIC DIELS-ALDER STRATEGY FOR THE ENANTIOSELECTIVE SYNTHESIS OF SPIROCYCLIC OXINDOLE-CYCLOHEXENONES

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Abstract – An efficient method for the asymmetric synthesis of spirocyclic oxindole-cyclohexenone conjugates was developed. A chiral thiourea-catalyzed asymmetric Diels-Alder reaction between 3-alkylidene-oxindoles and Rawal's diene was used as the key strategy for construction of the desired products in moderate to good yields with good diastereo- and enantioselectivities.

Oxindoles bearing a tetrasubstituted carbon stereogenic center at the 3-position are an important family of compounds in the fields of natural products and pharmaceutical drugs.¹ In particular, spirocyclic oxindoles are fascinating scaffolds in potentially useful drug candidates and synthetic intermediates for biologically interesting alkaloids (Figure 1).² The construction of these frameworks by the use of several strategies, especially asymmetric approaches, offer considerable synthetic challenges.³

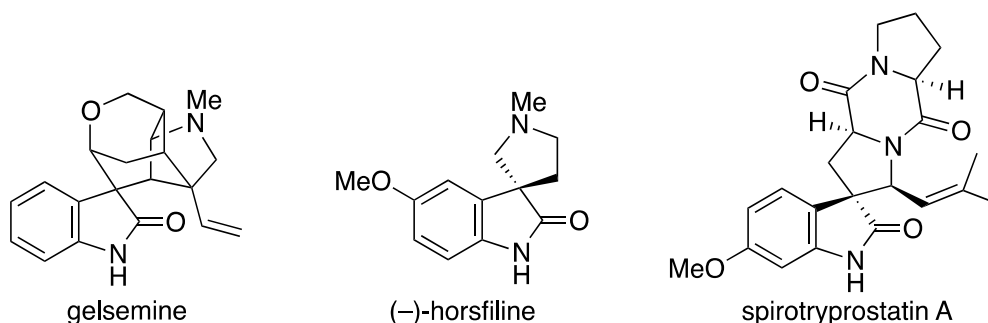
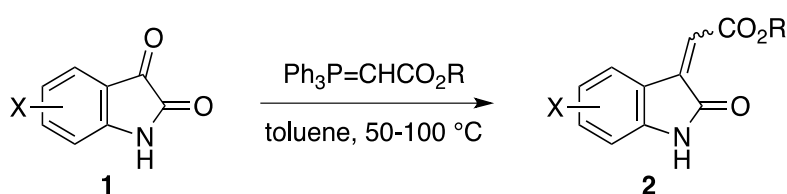


Figure 1. Examples of natural products having a spirooxindole scaffold

Organocatalytic asymmetric transformations have recently attracted a great deal of attention from synthetic chemists as effective and environmentally friendly methodologies and this is becoming one of

the most attractive fields in modern organic chemistry.⁴ In our ongoing projects on the synthesis of spirocyclic oxindoles via organocatalytic Diels-Alder strategies,⁵ we anticipated that the application of 3-alkylidene-oxindoles as dienophiles may provide an expedient route to spirocyclic oxindole-cyclohexenone conjugates. However, a search of the literature revealed that there are only a few precedents regarding transformations of this type through organocatalysis,⁶ and there is still strong interest in the identification of new convenient methods for obtaining these core skeletons in optically pure forms.^{3,7} In this paper, we describe our own approach based on the asymmetric Diels-Alder reaction of 3-alkylidene-oxindoles in the presence of a chiral thiourea catalyst.

As described in the literature, the 3-alkylidene-oxindoles **2** as activated dienophiles were prepared from isatin precursors **1** via Wittig condensation in 70-80% yields (Scheme 1).⁸



Scheme 1

The olefin geometry of **2** was determined by NMR experiments (Figure 2).⁹ Thus, the vinyl proton of the (*Z*)-isomers of **2**, obtained exclusively from isatin precursors having a substituent at the 4-position as a result of peri-strain, was observed consistently at around δ 7.50-7.70 ppm. On the other hand, non-substituted isatins gave (*E*)-isomers of **2** with a characteristic vinyl proton signal at higher fields of δ 6.80-6.90 ppm. These stereochemical assignments were further confirmed by the examination of vicinal C,H-coupling constants between the vinyl proton and the amide carbonyl, e.g., 12.5 Hz for the (*Z*)-isomer **2a** and 7.1 Hz for the (*E*)-isomer **2g**.^{10,11}

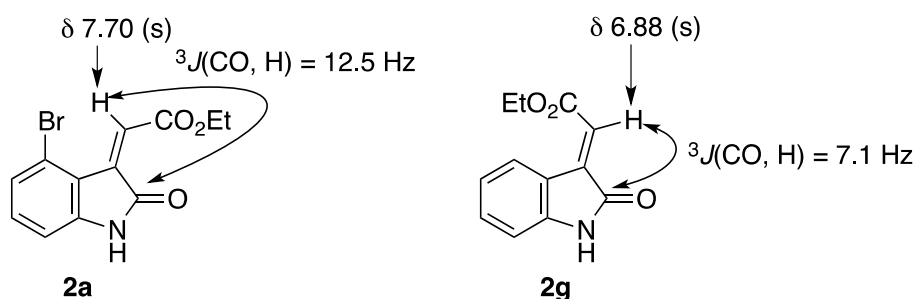
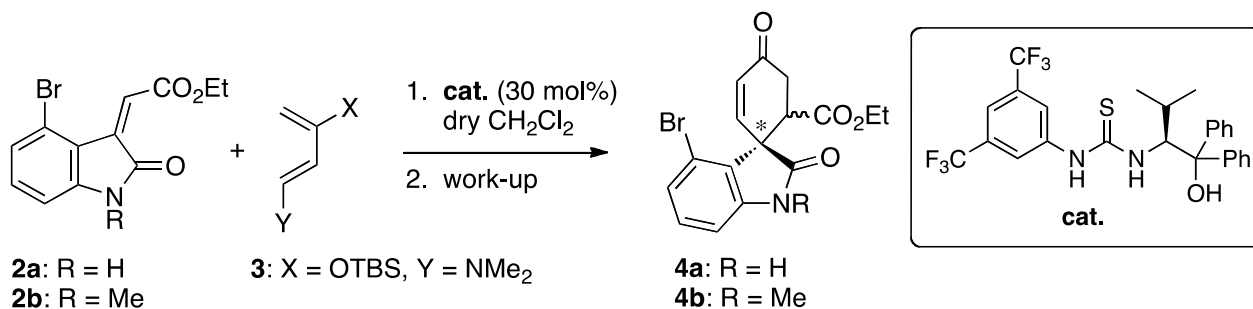


Figure 2. Olefin geometry of 3-alkylidene-oxindoles

Next, we examined the Diels-Alder reaction of dienophile **2a** using the chiral thiourea catalyst (30 mol%) in dry dichloromethane based on our previous findings (Table 1).^{5b} Although the reaction with

Danishefsky's diene was very sluggish at atmospheric pressure,¹² we were delighted to find that Rawal's diene **3**¹³ was sufficiently reactive in this transformation.

Table 1. Organocatalytic asymmetric Diels-Alder reactions: optimization^a



entry	2	conditions; work-up ^b	yield (%) ^c (dr) ^d	ee (%) (major / minor) ^e
1	2a	-110 °C, 5 min; A	14 (nd)	nd
2	2a	-110 °C, 5 min; B	57 (4 : 1)	76 / 60
3	2a	-110 °C, 5 min; C	71 (4 : 1)	85 / 83
4 ^f	2a	-110 °C, 5 min; C	64 (8 : 1)	79 / 68
5	2b	-110 °C, 5 min; C	58 (15 : 1)	69 / 70

^aConditions: **2** (0.2 mmol), diene **3** (0.3 mmol) in dry CH₂Cl₂ (2.5 mL) in the presence of 30 mol% of catalyst. ^bWork-up **A**: AcCl (1.3 eq), CH₂Cl₂, -78 °C; **B**: 1. silica gel, CH₂Cl₂, 2. MeI (excess), 3. pyridine, toluene, 110 °C; **C**: 1. silica gel, CH₂Cl₂, 2. MeI (excess), 3. 2,6-(*t*-Bu)₂pyridine, toluene, 110 °C. ^cIsolated yield. ^dDetermined by ¹H NMR. ^eDetermined by chiral HPLC analysis using a Chiralpak AD. ^f10 mol% of catalyst was used.

Thus, the reaction of **2a** with 1.5 equiv of **3** using 30 mol% of chiral thiourea catalyst in dry dichloromethane proceeded even at -110 °C and was complete within 5 min, but the adduct **4a** was obtained in a disappointingly low yield after treatment with acetyl chloride according to the procedure in the literature (entry 1).¹³ We thought that the initial adduct could be rather sensitive towards the acidic work-up conditions and might be decomposed under these conditions. After numerous trials, we devised a fairly convenient three-step procedure, as follows: 1. desilylation (by exposure to silica gel), 2. Conversion to the corresponding trimethylammonium salt by treatment with an excess amount of MeI, and 3. Hofmann elimination by heating in toluene in the presence of a small amount of pyridine, most favorably 2,6-di-*t*-butylpyridine (entries 2 and 3). Consequently, under the optimized conditions, the adduct **4a** was obtained in 71% yield with good diastereoselectivity (ca. 4 : 1) and high enantioselectivity (85% ee for the major and 83% ee for the minor). In contrast, an NH-protected compound such as **2b** was less effective, suggesting that the presence of a free NH function plays an important role in this asymmetric catalysis probably through a hydrogen-bonding interaction with the catalyst (entry 5). With respect to the

catalyst loading, we found that the use of at least 30 mol% of the catalyst was necessary to achieve good results (entry 3 vs. 4).¹⁴

At this stage, the relative and absolute stereochemistries of the cyclohexenone **4** were unknown.¹⁵ To solve these problems, the major stereoisomer **4a** was converted to the corresponding *p*-bromobenzamide **5** by treatment with *p*-bromobenzoyl chloride in Et₃N. Fortunately, **5** was obtained as a highly crystalline substance (mp 187-189 °C) and its structure was determined by X-ray crystallographic analysis (Figure 3).¹⁶ As evident from this result, the absolute configuration of **5** concerning the newly formed stereogenic centers was assigned to be (1*S*,6*R*). On the other hand, upon treatment with DBU, the minor isomer could be converted to the major isomer through isomerisation of an ester function, and chiral HPLC analysis revealed that this compound was enantiomeric with the major one; therefore, we can deduce that the minor one should possess a (1*R*,6*R*)-configuration.

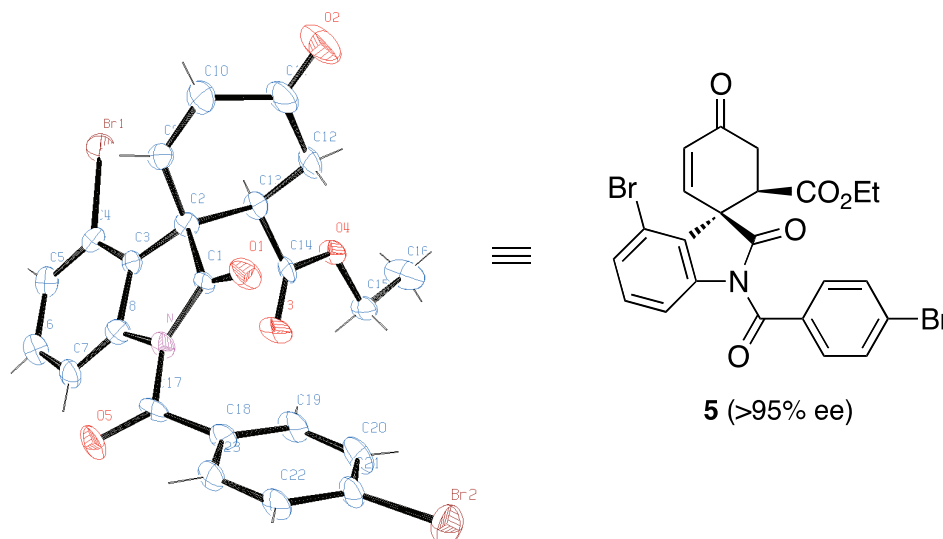
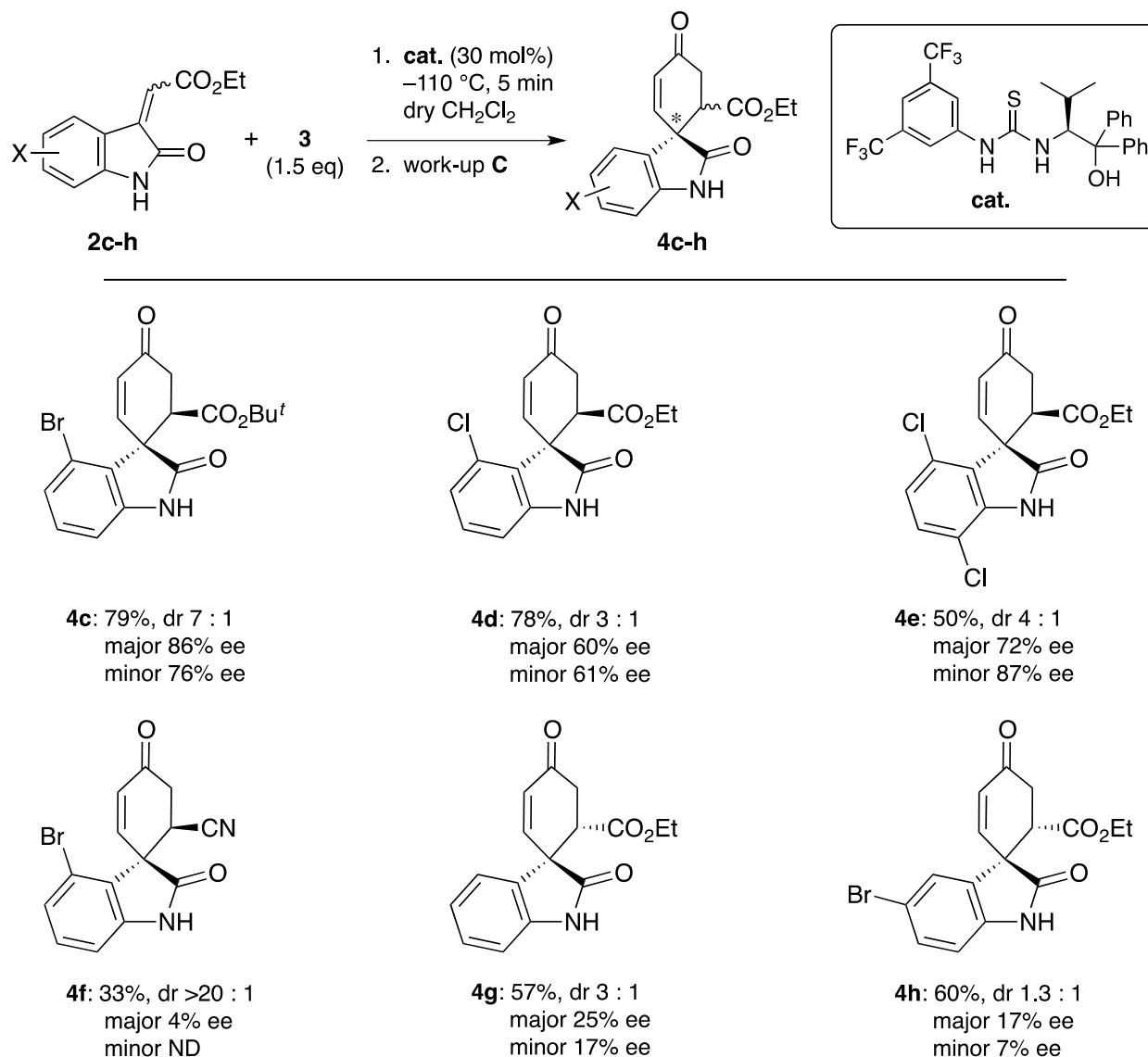


Figure 3. Structure of the *p*-bromobenzamide **5** by X-ray crystallographic analysis

With the optimal conditions in hand, we then examined a variety of alkylidene-oxindoles **2** to explore the general scope of this synthetic methodology (Table 2). All reactions were performed in dry dichloromethane¹⁷ at -110 °C in the presence of 30 mol% of chiral thiourea catalyst; the adducts were converted to the final products, cyclohexenones **4**, following the work-up procedure **C** as described above.¹⁴ The relative and absolute configurations of unknown products **4** were surmised by analogy to **4a**. As expected, all substrates reacted smoothly with **3** in moderate yields (up to 79%) with good diastereo- (ca. 4 : 1) and enantioselectivities (up to 86% ee for major). This method is particularly useful for 3-alkylidene-oxindoles with a (*Z*)-olefin geometry such as **2c-2e** except for the nitrile homolog **2f**. In contrast, (*E*)-olefin substrates such as **2g** and **2h** proved to be less efficient with regard to diastereo- and enantioselectivity.

Table 2. Organocatalytic asymmetric Diels-Alder reactions: generality^a

^aConditions: **2** (0.2 mmol), diene **3** (0.3 mmol) in dry CH₂Cl₂ (2.5 mL) in the presence of 30 mol% of catalyst. Work-up **C**: 1. silica gel, CH₂Cl₂, 2. MeI (excess), 3. 2,6-*t*-Bu₂pyridine, toluene, 110 °C. All yields were isolated yields. Diastereomeric ratio (dr) were determined by ¹H NMR. Enantioselectivities were determined by chiral HPLC analysis using a Chiralpak AD.

The role of a free NH function in **2a** was noted above (Table 1). In conjunction with this evidence and the observed chiral dictation in this asymmetric Diels-Alder process, we postulated a hydrogen-bonding activation mode composed of the dienophile **2a** and the diene **3** with the thiourea catalyst, as exemplified in Figure 4. This spatial arrangement minimizes repulsion with the bulky diphenylcarbinol substituent and determines the selective attack to the less-hindered *Si*-face of the dienophile component.¹⁸ In addition, the lower efficiency for the nitrile homolog **2f** or (*E*)-isomers **2g** and **2h** suggests that a well-organized hydrogen-bonding network extending to both an oxindole part and an ester carbonyl side chain of the (*Z*)-dienophiles **2a-2e** plays a significant role.

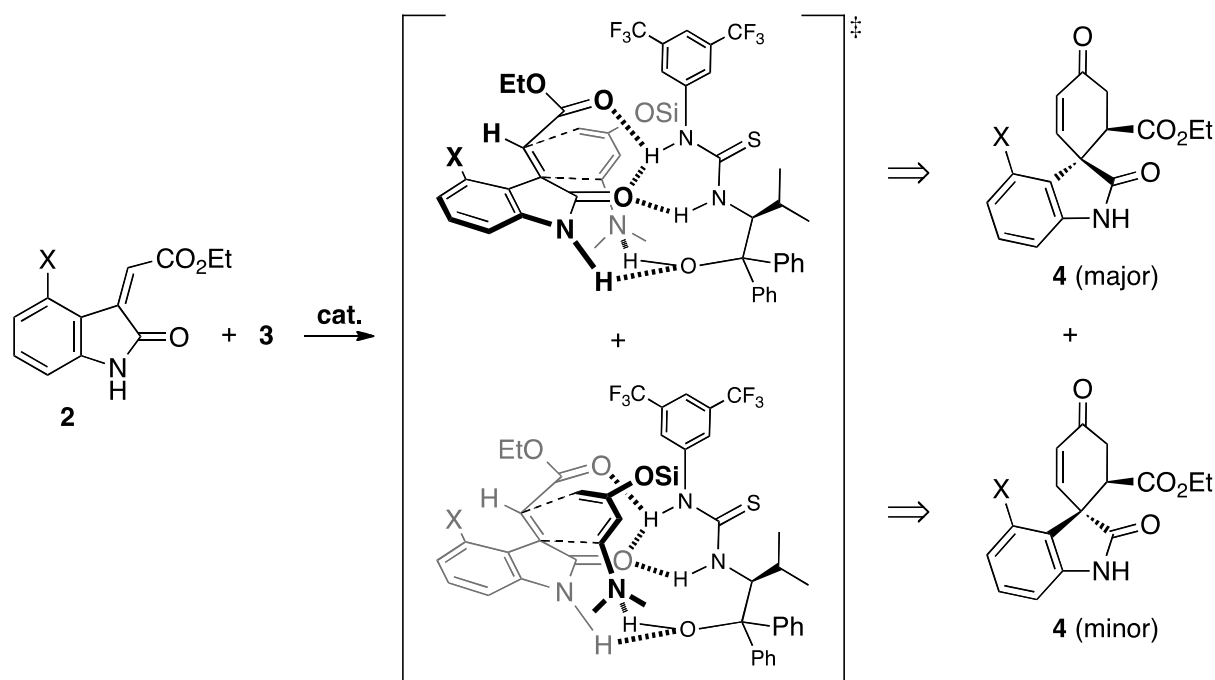


Figure 4. Proposed activation mode of chiral thiourea organocatalysis

In conclusion, we have developed a new efficient method for the asymmetric synthesis of spirocyclic oxindole-cyclohexenone conjugates by taking advantage of a chiral thiourea-catalyzed asymmetric Diels-Alder reaction between 3-alkylidene-oxindoles and Rawal's diene. We believe that this method should provide an expeditious route to a significant class of spirooxindole derivatives. Further studies to extend the scope of this method are now in progress in our laboratory.

ACKNOWLEDGEMENTS

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11. Crystallographic data of *N*-Boc-protected **2a** have been deposited with the accession number CCDC 1489400, and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures. See also the Supporting Information.
12. The reaction with Danishefsky's diene in place of **3** (rt, 18 h) gave **4a** in 21% yield (dr = 99 : 1) with 43% ee.
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14. **General Procedure for the Diels-Alder Reaction of 2:** To a solution of 3-alkylidene-oxindole **2** (0.20 mmol) and the thiourea cat. (0.060 mmol) in CH₂Cl₂ (2.5 mL) was added Rawal's diene **3** (0.30 mmol) at -110 °C under Ar, and the resulting orange-colored mixture was stirred at this

temperature for a few minutes. The mixture was then exposed to silica gel (ca. 10 mg) at rt and stirred for 15 min, filtered and concentrated. The residue was treated with an excess of MeI (ca. 10 eq) at 50 °C for 15 min. After concentration, the mixture was diluted with toluene (1.5 mL) containing 2,6-di(*t*-Bu)₂pyridine (20 mg), and the mixture was stirred at 110 °C for 15 h. After concentration, the residue was purified by silica gel column chromatography (benzene/acetone) to afford the desired product in a pure form, and its ee was determined by chiral HPLC analysis. The results are summarized in Tables 1 and 2.

15. Unfortunately, NOESY experiments for both major and minor adducts did not provide any stereochemical information.
16. Crystallographic data of **5** have been deposited with the accession number CCDC 1489401, and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures. See also the Supporting Information.
17. We briefly checked the same reaction in toluene as a solvent, but the yields were invariably low compared to the case in CH₂Cl₂.
18. To confirm this speculation, ¹H and ¹³C NMR experiments were performed by mixing dienophile **2g** with catalyst **A** in C₆D₆ (Figure 5). Downfield shifts of 0.69 ppm for the free NH proton (¹H) and 0.86 ppm for the lactam C=O (¹³C) were observed, clearly indicating that **2g** formed a complex with catalyst **A**.

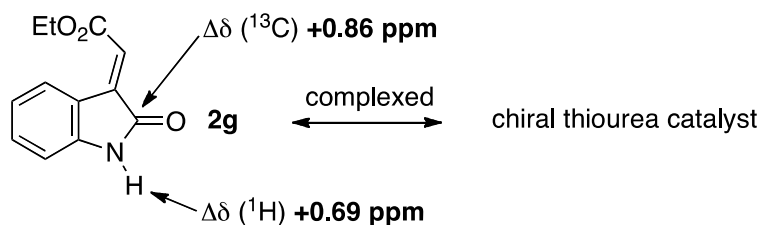


Figure 5. Chemical shift changes ($\Delta\delta$) observed for the ¹H and ¹³C NMR signals (500 and 125.8 MHz, C₆D₆) for **2g** complexed with the thiourea catalyst (40 mol%)