Isothiourea-Catalyzed Enantioselective Synthesis of Tetrahydro-α-carbolinones

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ABSTRACT: An isothiourea-catalyzed enantioselective annulation protocol using indolin-2-imines with a series of α,β-unsaturated ω-nitrophenyl esters for the synthesis of tetrahydro-α-carbolinones was developed. Using 5 mol % of the isothiourea HyperBTM as the Lewis base catalyst, this process allows the enantioselective preparation of a range of C(4)-substituted tetrahydro-α-carbolinones in good to excellent yield and with high enantioselectivity (20 examples, 32−99% yield and up to 99:1 er).

Nitrogen-containing heterocycles are important structural motifs prevalent in a diverse range of natural products and medicinal agents. Their importance is readily quantified as 59% of United States FDA approved small-molecule drugs contain a nitrogen heterocycle,1 with these heterocycles commonly incorporated into molecules to improve physicochemical properties.2 α-Carbolines and their tetrahydro-α-carbolinone derivatives (Figure 1A) are a representative class of N-heterocycle that are frequently found in natural compounds with diverse biological activities.3 Although a range of methods for the construction of β- and γ-carbolinone skeletons has been reported,4 limited synthetic routes to α-carbolinones have been developed, with enantioselective methods rare. For example, Zhou and coworkers developed a sequential Michael addition/amidation/reductive cyclization process using oxindole nucleophiles with Michael acceptors to give tetrahydro-α-carbolinones in racemic form.5,6 Alternatively, Li and coworkers demonstrated the enantioselective synthesis of tetrahydro-α-carbolinones through an NHC-catalyzed formal [4 + 2] cyclization of aza-dienes with an azolium enolate derived from α-chloroaldehydes.7 Recently, Ye and coworkers reported an elegant oxidative NHC-catalyzed annulation of indolin-2-imines with in situ generation of α,β-unsaturated acyl azolium intermediates for the preparation of racemic tetrahydro-α-carbolinones bearing C(4)-aryl and C(4)-alkyl groups (Figure 1B) that served as precedent for this work.8

Isothioureas are versatile and powerful Lewis base catalysts of broad synthetic utility9 and have been utilized for the in situ generation of chiral α,β-unsaturated acyl ammonium species for use in a range of reaction processes.10 In previous work, we and others have harnessed this intermediate in Michael addition and subsequent lactonization or lactamization processes to generate carbo- and heterocycles.11 Building upon these precedents, this manuscript showcases the use of isothioureas for the enantioselective synthesis of tetrahydro-α-carbolinones using indolin-2-imines and α,β-unsaturated esters as starting materials (Figure 1C).

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Figure 1. Synthesis of tetrahydro-α-carbolinones.
Initial investigations studied the proposed annulation between indolin-2-imine 2 and β-trifluoromethyl α,β-unsaturated p-nitrophenyl (PNP) ester 1 using (2S,3R)-HyperBTM 3 (20 mol %) and an equivalent of iPr2NEt in THF at room temperature. The desired C(4)-trifluoromethyl substituted tetrahydro-α-carbolinone product 6 was afforded in 53% yield with 98:2 er (Table 1, entry 1). Use of alternative isothiourea catalysts (R)-BTM 4 and (S)-tetramisole hydrochloride 5 gave lower product conversion and yield, despite promising enantioselectivity with BTM (entries 2–3). Further optimization varied both base and solvent (entries 4–10). Variation of base showed that NaHCO₃ gave improved yield and excellent er at room temperature. The desired C(4)-trifluoromethyl substituted tetrahydro-α-carbolinone product 6 was afforded in 53% yield but poor 57:43 er, the use of the corresponding C(3)-phenyl-substituted ester provided 25 in 38% yield but excellent 96:4 er. While the corresponding C(3)-phenyl-substituted ester contained C(3)-ester and C(3)-amide functional groups gave the corresponding products 26–27 in good yield and excellent enantioselectivity. Notably, challenging C(3)-aliphatic substituents that are typically recalcitrant when using α,β-unsaturated PNP esters are also tolerated, giving the desired products 22–24 in moderate yield (38–59%) but with excellent enantioselectivity. While the corresponding C(3)-phenyl-substituted ester provided 25 in 53% yield but poor 57:43 er, the use of the corresponding isopropyl carbionic anhydride using iPr2NEt as base in THF gave 25 in 40% yield and improved 88:12 er. Other C(3)-substituted esters containing C(3)-ester and C(3)-amide functional groups gave the corresponding products 26–27 in good yield and good to excellent enantioselectivity.

Further work probed the scope of this transformation through structural variation of the N-substituent andaryl substitution pattern within the indolin-2-imine component (Scheme 2). N-Benzyl substitution led to decreased yield over the N-Me variant, giving 37 in 32% yield but excellent 96:4 er. Aryl substituent variation proved more tolerant to steric and electronic variation, with various indolin-2-imines incorporating both electron-withdrawing halogen or electron-donating methyl substituents tolerated. Notably, the substitution pattern has an interesting influence on the observed reactivity. 6-Substituted indolin-2-imines gave the products 38–39, 42, and

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**Table 1. Optimization of Reaction Conditions**

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<th>er (%)</th>
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**Scheme 1. Variation of the α,β-Unsaturated Aryl Ester**

**Notes:**

1. Unless indicated otherwise, reactions were carried out in 1 mL of solvent using 0.1 mmol of 1, 0.1 mmol of 2, and 0.1 mmol of base in the presence of 20 mol % of catalysts 3–5 at rt. 
2. Isolated yield given. 
3. Determined by HPLC analysis on a chiral stationary phase and given as a ratio of (S):(R). 
4. S mol % of 3 used. 
5. 0.12 mmol of 3 used. 
6. Carried out at 0 °C.

Esters gavè the corresponding products 18–21 in good to excellent yields and with high enantioselectivity.
in good 72–76% yield with 95:5−99:1 er. In contrast, incorporation of substituents into the 4-, 5-, or 7-position of the indolin-2-imine substrate led to the corresponding products 40, 41, 43, and 45 in moderate 37–54% yield but with good enantioselectivity (up to 98:2 er).

The scalability of this process was demonstrated by performing the reaction of indolin-2-imine 2 with β-trifluoromethyl α,β-unsaturated PNP ester 1 on a gram scale, giving 6 in excellent 87% yield and 97:3 er (Scheme 3A). To further demonstrate the utility of the α-carbolinone products, 6 was derivatized to a range of compounds (Scheme 3B).

Treatment of 6 with Mg/methanol gave ring-opened product 46 in 99% yield and 97:3 er.8 Oxidation of 6 with m-CPBA gave the corresponding epoxide in situ with subsequent rearrangement yielding spirolactone 47 as a single diastereoisomer in moderate isolated yield but high er. The absolute configuration of 47 was determined by single crystal X-ray diffraction, which also served to assign the absolute configuration at C(4) within 6, with all other α-carbolinone products assigned by analogy.11 Alternatively, sequential reduction with LiAlH4 and triethylsilane gave tetrahydropryranoindole 48 in 68% yield and 97:3 er,7 while dehydrogenation of 6 was also readily achieved with Pd/C, giving 49 in 57% yield.8

Based upon our previous mechanistic investigations in this area, a simple catalytic cycle is proposed (Figure 2).10a Catalysis is initiated through rapid and reversible acylation of HyperBTM 3 by the α,β-unsaturated ester 1 to give α,β-unsaturated acyl isothiouonium ion pair 50. The addition of enamine anion 51, generated from indoline-2-imine 2, to the α,β-unsaturated acyl isothiouonium 50 gives isothiouonium enolate 52. Subsequent proton transfer gives zwitterion 53. Finally, lactamization yields the product 6 and regenerates the isothiourea HyperBTM 3. The stereochemical outcome of the reaction can be rationalized by the α,β-unsaturated acyl isothiouonium 50 adopting an s-cis conformation with a 1,5-S···O interaction between the acyl O and catalyst S providing a conformational lock.12 Enantioselective conjugate addition of the enamine anion to the α,β-unsaturated acyl isothiouonium 50 takes place anti to the stereodirecting pseudoaxial phenyl substituent of the acylated HyperBTM isothiourea catalyst and determines the configuration at C(4) within the products.

In conclusion, an isothiourea-catalyzed enantioselective annulation protocol of indolin-2-imines with a series of α,β-unsaturated p-nitrophenyl esters for the synthesis of tetrahydroα-carbolinones was developed. Using 5 mol % of isothiourea HyperBTM 3, this protocol allows the enantioselective preparation of a range of C(4)-substituted tetrahydroα-carbolinones.

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Scheme 2. Variation of Indolin-2-imine Componenta

Scheme 3. Gram-Scale Experiment and Derivatizations

Figure 2. Proposed mechanism.
carbolines in moderate to excellent yield and with excellent enantioselectivity (20 examples, 32–99% yield and up to 99:1 er). The scope of the process was demonstrated through variation in C(3) substitution within the α,β-unsaturated p-nitrophenyl ester, as well as with the α-N substituent and aryl substitution pattern within the indolin-2-imine component. Further investigations from within our laboratory are concerned with alternative applications of isothioureas and harnessing the utility of α,β-unsaturated acyl ammonium intermediates.

### References


(3) For selected examples of α-carboline derivatives, see:


(11) The relative and absolute configuration of 47 was confirmed by X-ray crystallographic analysis followed by HPLC analysis. CCDC 1973369 contains the supplementary crystallographic data for compound 47. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.


(13) The research data underpinning this publication can be found at DOI: 10.17630/46afe239-6329-434e-b590-f536e3f7de66.