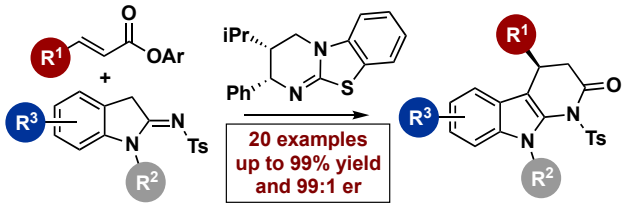
Isothiourea-Catalyzed Enantioselective Synthesis of Tetrahydro-α-carbolinones

Honglei Liu,[a] Alexandra. M. Z. Slawin,[a] Andrew D. Smith [a]*

[a] EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK

Supporting Information Placeholder

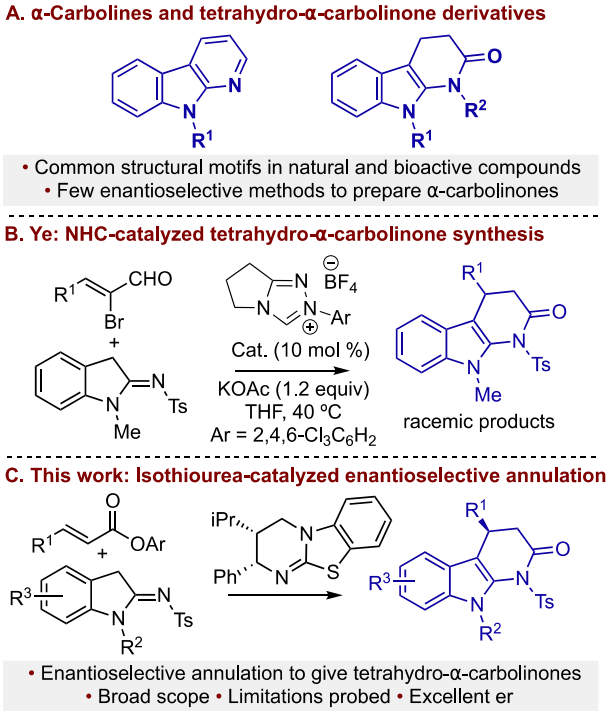


ABSTRACT: An isothiourea-catalyzed enantioselective annulation protocol using indolin-2-imines with a series of α,β-unsaturated *p*-nitrophenyl esters for the synthesis of tetrahydro-α-carbolinones has been developed. Using 5 mol% of the isothiourea HyperBTM as the Lewis base catalyst, this process allows 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 US 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 co-workers have 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 co-workers have 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 co-workers reported an elegant oxidative NHC-catalyzed annulation of indolin-2-imines with *in situ* generation 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]

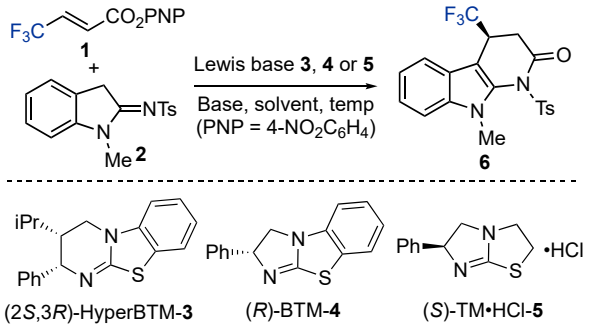
Isothioureas are versatile and powerful Lewis base catalysts of broad synthetic utility,[9] and have been utilized for the *in situ* generation of chiral α,β-unsaturated acyl ammonium species for use in a range of reaction processes.[10] In previous work, we and others have harnessed this intermediate in Michael addition and subsequent lactonization or lactamization processes to generate carbo- and heterocycles.[10a,f,l,m] 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).

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 (2*S*,3*R*)-HyperBTM **3** (20 mol %) and an equivalent of iPr_2NEt 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 optimisation varied both base and solvent (entries 4–10). Variation of base showed that $NaHCO_3$ gave improved yield and excellent er in THF. A screen of solvents showed that an excellent 91% isolated yield of **6** with 97:3 er was observed in acetonitrile (entry 10). Carrying out the reaction without additional base provided a lower isolated yield (65%, entry 11). Decreasing the catalyst loading to 5 mol% gave **6** in still excellent yield and enantioselectivity (entry 12). Finally, improved yield while maintaining high enantioselectivity was observed (up to 99% yield and 97:3 er) when using a small excess (1.2 equiv) of imine **2** at room temperature or at 0 °C (entries 13–14).

Table 1. Optimization of Reaction Conditions[a]

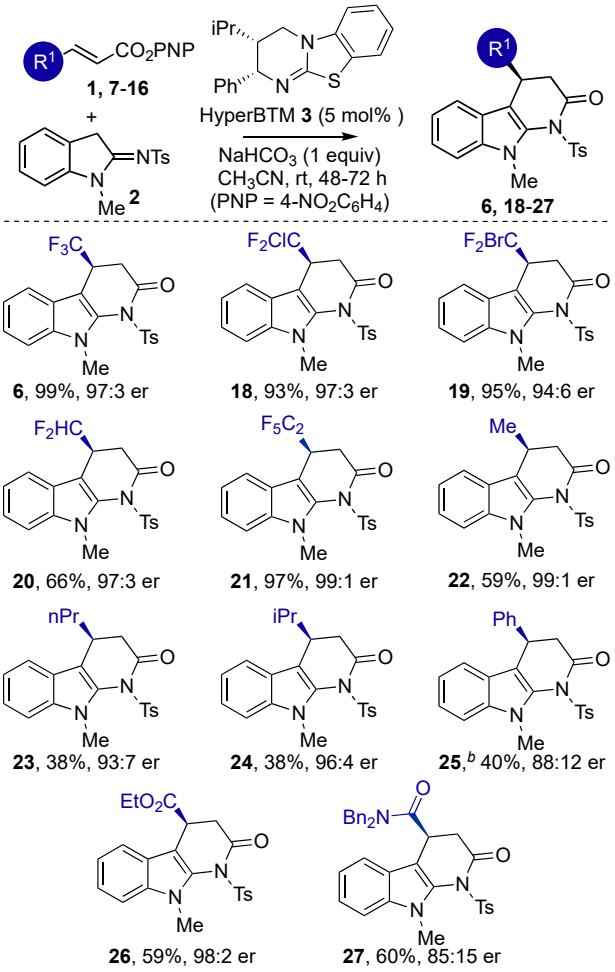


entry	cat.	base	solvent	yield (%)[b]	er (%)[c]
1	**3**	iPr_2NEt	THF	53	98:2
2	**4**	iPr_2NEt	THF	37	98:2
3	**5**	iPr_2NEt	THF	6	15:85
4	**3**	Et_3N	THF	40	98:2
5	**3**	Na_2CO_3	THF	12	>99:1
6	**3**	$NaHCO_3$	THF	68	>99:1
7	**3**	$NaHCO_3$	toluene	81	98:2
8	**3**	$NaHCO_3$	CH_2Cl_2	80	98:2
9	**3**	$NaHCO_3$	dioxane	80	83:17
10	**3**	$NaHCO_3$	CH_3CN	91	97:3
11	**3**	-	CH_3CN	65	97:3
12[d]	**3**	$NaHCO_3$	CH_3CN	83	96:4
13[d,e]	**3**	$NaHCO_3$	CH_3CN	99	97:3
14[d,f]	**3**	$NaHCO_3$	CH_3CN	99	97:3

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

Using the optimal reaction conditions, variation of the C(3)-substituent within the α,β-unsaturated PNP ester to construct C(4)-substituted tetrahydro-α-carbolinones was explored (Scheme 1). C(3)-Chlorodifluoromethyl-, -bromodifluoromethyl-, -difluoromethyl-, and -perfluoroethyl-substituted esters gave the corresponding products **18**–**21** in good to excellent yields and with high enantioselectivity. Notably,[10g] 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 carbonic anhydride using iPr_2NEt 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.

Scheme 1. Variation of the α,β-Unsaturated Aryl Ester[a]

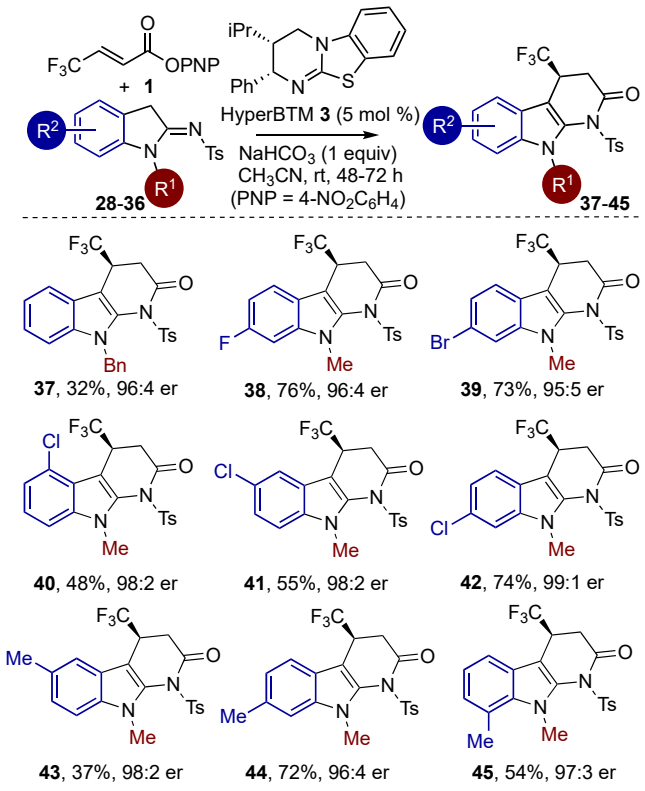


[a] Isolated yield given; er determined by HPLC analysis on a chiral stationary phase. [b] Carried out in THF using (*E*)-cinnamic (isopropyl carbonic) anhydride **17** and iPr_2NEt.

Further work probed the scope of this transformation through structural variation of the N-substituent and aryl 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 elec-

tron-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 **44** 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).

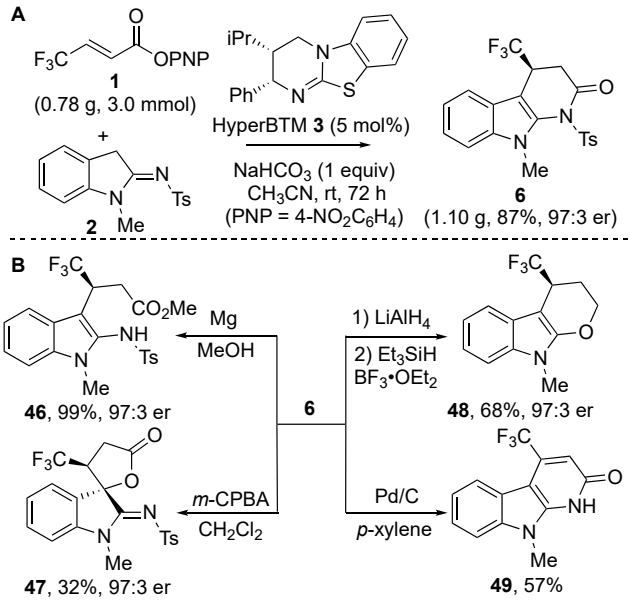
Scheme 2. Variation of Indolin-2-imine component[a]



[a] Isolated yield given; er was determined by HPLC analysis on a chiral stationary phase.

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 $LiAlH_4$ and triethylsilane gave tetrahydropyranoindole **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]

Scheme 3. Gram-Scale Experiment and Derivatizations



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 isothiouronium ion pair **50**. The addition of enamine anion **51**, generated from indoline-2-imine **2**, to the α,β-unsaturated acyl isothiouronium **50** gives isothiouronium 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 rationalised by the α,β-unsaturated acyl isothiouronium **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 isothiouronium **50** takes place *anti*- to the stereodirecting pseudo-axial phenyl substituent of the acylated HyperBTM isothiourea catalyst and determines the configurarion at C(4)-within the products.

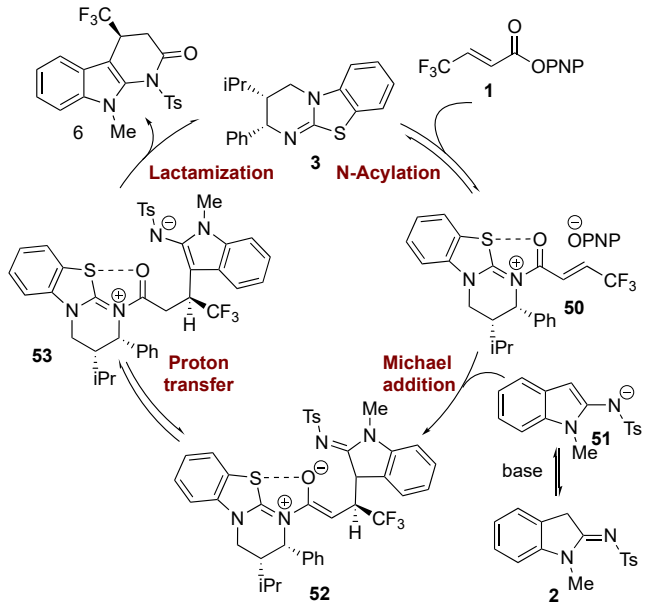


Figure 2. Proposed Mechanism

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 tetrahydro-α-carbolinones has been developed. Using 5 mol% of isothiourea HyperBTM **3**, this protocol allows the enantioselective preparation of a range of C(4)-substituted tetrahydro-α-carbolinones 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 has been demonstrated through variation in both C(3)-substitution within the α,β-unsaturated *p*-nitrophenyl ester, as well as the 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.[13]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, compound characterization, NMR spectra, HPLC traces (PDF).

AUTHOR INFORMATION

Corresponding Author

* ads10@st-andrews.ac.uk

Author Contributions

The manuscript was written by H. L. and A. D. S. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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

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