Asymmetric Catalysis

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Enantioselective Thiourea-Catalyzed Acyl-Mannich Reactions of Isoquinolines**

*Mark S. Taylor, Norihito Tokunaga, and Eric N. Jacobsen**

Aromatic molecules represent an attractive class of feedstock compounds for organic synthesis because of their ready availability, their stability, and the wealth of classical and modern chemistry available for their preparation and manipulation. The development of enantioselective, catalytic methodologies that engage aromatic π systems as substrates offers particular promise for synthetic applications. Despite this potential, it is only recently that aromatic frameworks have been employed successfully as electrophiles[1] or nucleophiles[2] in asymmetric, catalytic reactions, and many important challenges in this area remain unmet. The addition of carbon-centered nucleophiles to nitrogen-containing heteroaromatic compounds is a particularly interesting problem, in light of the potential impact of such a methodology on alkaloid synthesis. Diastereoselective reactions controlled by chiral auxiliaries currently constitute the state-of-the-art methods for the majority of stereocontrolled transformations of this type.[3] The elegant alkaloid syntheses of Comins et al. based on diastereoselective nucleophilic additions to chiral (4-methoxy)acylpyridinium derivatives illustrate the utility of such approaches.[4] Only one enantioselective, catalytic method for the addition of carbon-centered nucleophiles to aromatic nitrogen heterocycles has been developed to date: the aluminum-catalyzed acylcyanation of quinolines, isoquinolines, and pyridines (the Reissert reaction) developed by Shibasaki and co-workers.[1a–d] Herein, we report the first example of an asymmetric, catalytic addition of enolate equivalents to heteroaromatic electrophiles. This acyl-Mannich reaction,[5] catalyzed by a chiral thiourea derivative, provides access to useful enantioenriched dihydroisoquinoline building blocks.[6]

N-Alkylations or *N*-acylations of nitrogen-containing heteroaromatic compounds give rise to highly electrophilic

[*] M. S. Taylor, N. Tokunaga, Prof. Dr. E. N. Jacobsen
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-496-1880
E-mail: jacobsen@chemistry.harvard.edu

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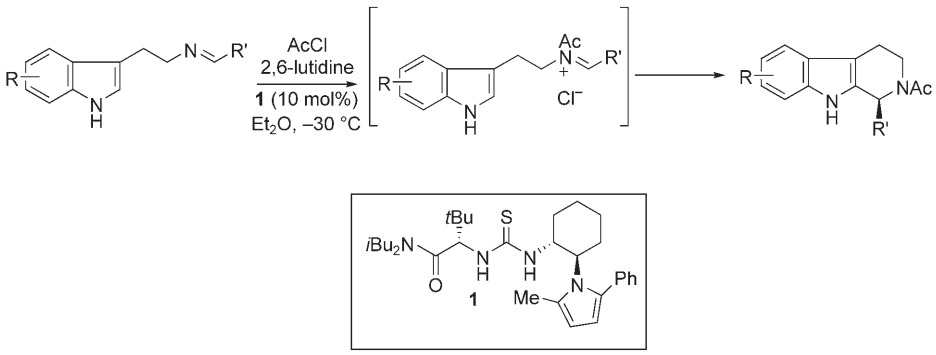
iminium or acyliminium ions that are susceptible to a variety of addition reactions. There are very few examples of the asymmetric catalysis of such additions,[1a–e] a fact that may reflect, to some extent, the difficulty in the development of catalysts capable of the activation of such intermediates. In that context, we were highly encouraged by the discovery that chiral thiourea **1** catalyzes an enantioselective acylative variant of the Pictet–Spengler reaction (Scheme 1). The



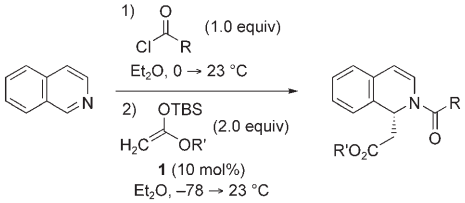
Scheme 1. Enantioselective acyl-Pictet–Spengler reaction catalyzed by **1**.

possibility that **1** can activate a putative intermediate acyliminium ion towards enantioselective cyclization by hydrogen-bond donation[7,8] prompted us to study its application to the reactions of acyliminium ions derived from nitrogen heterocycles.

In light of the prevalence of the 1-substituted tetrahydroisoquinoline motif in alkaloid architecture,[9] we selected isoquinoline as a model substrate (Table 1). The enantioselectivity of acyl-Mannich-type reactions catalyzed by **1** was found to depend strongly on the nature and structure of the acylating agent and nucleophile. A screen of acylating agents was performed using the *O*-*tert*-butyldimethylsilyl (TBS) ketene acetal derived from methyl acetate as the nucleophile.[10] Acetyl chloride, the optimal reagent for enantioselective Pictet–Spengler reactions, furnished the acyl-Mannich product in poor enantiomeric excess (28% *ee*; entry 1). More encouraging results were obtained using chloroformates (entries 2–5), with which tuning of the alkoxy substituent had a pronounced effect upon enantioselectivity. The dihydroisoquinoline product was obtained in a promising 82% *ee* by using 2,2,2-trichloroethyl chloroformate (TrocCl). Further improvement upon this result was realized by variation of the structure of the nucleophile (entries 5–7), with the best result provided by the silyl ketene acetal derived from isopropyl acetate. The acyl-Mannich reaction of isoquinoline proceeded in 80% yield with 86% *ee* under the optimized conditions.

Despite markedly different dependences of enantiomeric excess upon the structure of the acyl group, the acyl-Mannich and acyl-Pictet–Spengler reactions share several common features. Pronounced solvent effects were observed in both cases, with diethyl ether affording the highest enantioselectivity. In addition, **1** is the optimal catalyst identified to date for both reactions.[11] In particular, the *ee* values of both the acyl-Mannich and acyl-Pictet–Spengler reaction exhibit a dramatic dependence upon the substitution pattern of the pyrrole moiety (Table 2). The crystal structure of **1** may help to explain this behavior (Figure 1).[12] The orientation of the 2-methyl-5-phenylpyrrole structural motif places the phenyl group in position to interact closely with any species that undergoes hydrogen-bonding interactions with the acidic thiourea protons (Figure 1).[13] In the solid state, **1** exists as a dimeric structure through bifurcated hydrogen-

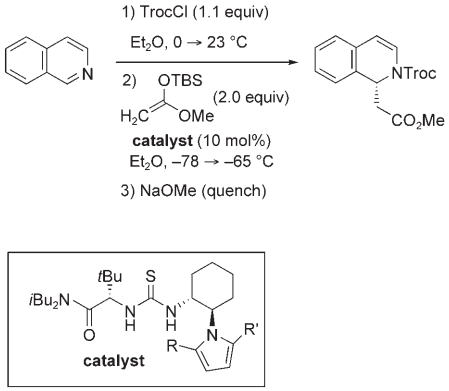
Table 1: Optimization of the acylating agent and nucleophile.



Entry	R	R′	Yield [%][a]	*ee* [%][b]
1	Me	Me	80	28
2	OBn	Me	60	41
3	$OC(CH_3)_2CCl_3$	Me	70	47
4	OCH_2(fluorenyl)	Me	75	64
5	OCH_2CCl_3	Me	65	82
6	OCH_2CCl_3	Bn	80	73
7	OCH_2CCl_3	*i*Pr	80	86[c]

[a] Yield of isolated product after column chromatography. [b] Enantiomeric excess determined by supercritical fluid chromatography (SFC) using commercially available chiral stationary-phase columns. [c] Reaction temperature was −70 °C.

Table 2: Dependence of reaction enantioselectivity on catalyst structure.



Entry	R	R′	Yield [%][a]	*ee* [%][b]
1	Me	Me	60	30
2	Ph	Ph	55	78
3	Me	Ph	55	85

[a] Yield of isolated product after column chromatography. [b] Enantiomeric excess determined by SFC using commercially available chiral stationary-phase columns.

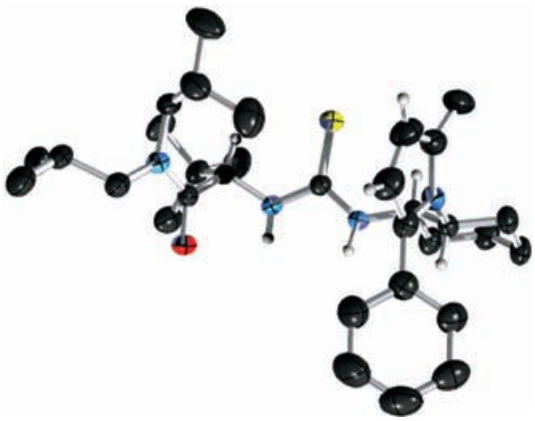
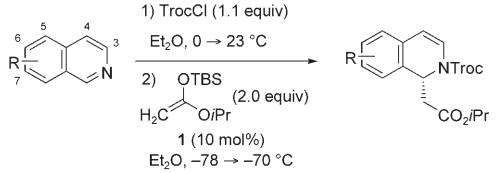


Figure 1. Solid-state structure of catalyst **1**.

bonding interactions between the thiourea N–H protons and the amide carbonyl group.[14]

A number of substituted dihydroisoquinolines are accessible through this new methodology (Table 3) and serve as

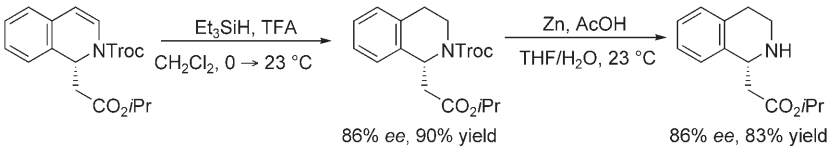
Table 3: Acyl-Mannich reaction of substituted isoquinolines.



Entry	R	Yield [%][a]	*ee* [%][b]
1	H	80	86
2	3-Me	75	92
3	4-Br	78	91
4	5-Br	77	87
5	5-OTBS	77	83
6	5-NO_2	71	71
7	6-OSO_2CF_3	67	83
8	7-OTBS	86	60

[a] Yield of isolated product after column chromatography. [b] Enantiomeric excess determined by SFC or HPLC using commercially available chiral stationary-phase columns.

precursors to enantioenriched 1-substituted tetrahydroisoquinolines: hydrogenation of the enamide moiety and reductive cleavage of the trichloroethyl carbamate group occur in good yield without detectable racemization (Scheme 2).[15] Thus, this method represents a straightforward approach to the preparation of enantioenriched heterocycles with potential utility for alkaloid synthesis from stable, readily accessible aromatic starting materials. For certain applications, this methodology may prove complementary to the Pictet–Spengler reaction, both in terms of electronic requirements (both electron-rich and electron-poor products may be accessed) and regioselectivity (the substitution pattern of the product is determined only by the choice of the isoquinoline starting material). In addition, this study demonstrates that thiourea catalyst **1** mediates two distinct enantioselective transformations of *N*-acyliminium ions: intramolecular Friedel–Crafts reactions of acyliminium ions derived from acyclic, aliphatic imines (the acyl-Pictet–Spengler reaction) and intermolecular Mannich reactions of acylisoquinolinium ions. Further extension of this mode of catalysis to encompass other reactions of *N*-acyliminium intermediates and investigation of the mechanism by which these electron-poor species are activated by a hydrogen-bond donor are the focus of future study.



Scheme 2. Synthesis of an enantioenriched tetrahydroisoquinoline. TFA = trifluoroacetic acid.

Experimental Section

General procedure for acyl-Mannich reactions catalyzed by **1**: 1-Isopropoxycarbonylmethyl-1*H*-isoquinoline-2-carboxylic acid 2,2,2-trichloroethyl ester (Table 3, entry 1): Isoquinoline (61 μL, 0.50 mmol; 97% purity) was dissolved in diethyl ether (5.0 mL) in a flame-dried round-bottomed flask and cooled to 0 °C. 2,2,2-Trichloroethyl chloroformate (76 μL, 0.55 mmol, 1.1 equiv; 98% purity) was added dropwise by syringe, and the resulting white suspension was warmed to 23 °C, stirred for 30 min, and then cooled to −78 °C (dry ice/isopropanol bath). Catalyst **1** (26.9 mg, 0.050 mmol, 10 mol%) in diethyl ether (4.0 mL + 1.0 mL rinse volume) and then 1-(*tert*-butyldimethylsilyloxy)-1-isopropoxyethene (216 mg, 1.0 mmol, 2.0 equiv) were added. The reaction mixture was warmed to −70 °C (isopropanol bath equipped with immersion cooler) and stirred for 14 h. Cooling was stopped and the bath allowed to warm to 23 °C over 3 h. After the solvent was removed in vacuo, the residue was purified by chromatography on silica gel (0→5% ethyl acetate/hexanes), thus yielding a colorless oil (161 mg, 0.40 mmol, 80% yield). The enantiomeric excess was determined to be 86% by SFC using a commercial chiral stationary phase (Chiralpak OD-H, 5% methanol/CO_2, 5 mL min^{-1}, 50 °C, 285 nm; t_r(minor): 2.23 min, t_r(major): 2.66 min); α_D −240° (c = 1.1 g 100 mL^{-1}, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): the compound exists as a 1.7:1 mixture of carbamate rotamers; signals corresponding to the major rotamer: δ = 7.26–7.17 (3H, m), 7.10 (1H, d, J = 7.5 Hz), 6.90 (1H, d, J = 7.5 Hz), 5.99 (1H, d, J = 8.0 Hz), 5.84–5.82 (1H, m), 4.97–4.88 (2H, m), 4.78 (1H, d, J = 12.0 Hz), 2.67–2.58 (2H, m), 1.20 (3H, d, J = 6.0 Hz), 1.16 ppm (3H, d, J = 6.5 Hz); representative signals corresponding to the minor rotamer: δ = 6.90 (1H, d, J = 7.5 Hz), 6.04 (1H, d, J = 8.0 Hz), 4.82 (1H, d, J = 11.5 Hz), 2.77 (1H, dd, J = 14.0, 9.0 Hz), 1.11 ppm (3H, d, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), signals corresponding to both rotamers: δ = 169.6, 169.5, 151.6, 151.2, 131.4, 131.2, 129.9, 129.8, 128.6, 128.5, 127.7, 127.5, 126.7, 126.6, 125.5, 125.3, 124.5, 123.6, 110.7, 110.6, 95.2, 95.2, 75.7, 75.6, 68.4, 68.4, 53.3, 53.1, 40.8, 40.1, 22.0, 22.0, 21.9, 21.9 ppm; IR (neat): $\tilde{\nu}$ = 3063 (w), 2980 (m), 2936 (w), 1728 (s), 1651 (s), 1452 (m), 1262 (m), 1109 (m), 968 cm^{-1} (w); HRMS (ES): m/z calcd for $[C_{17}H_{18}C_{13}NO_4+H]^+$: 406.0380; found: 406.0380.

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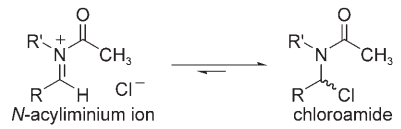
[10] A preliminary survey of ketone enolates did not yield satisfactory results; for example, 2-(trimethylsilyloxy)propene underwent addition to isoquinoline in the presence of TrocCl and **1** to yield the corresponding dihydroisoquinoline in 14% *ee* (unoptimized).

[11] A list of solvents and other catalysts tested may be found in the Supporting Information.

[12] Slow evaporation of a solution of **1** in hexanes/diethyl ether yielded crystals suitable for X-ray analysis; crystal data for **1**: $C_{32}H_{50}N_4OS$, $M_r = 538.82$, colorless prism, $0.20 \times 0.18 \times 0.14$ mm, orthorhombic, $a = 16.590(3)$, $b = 17.202(3)$, $c = 22.411(4)$ Å, $V = 6396(2)$ Å^3, $T = 193(2)$ K, space group $C222_1$, $Z = 8$, $\rho_{calcd} = 1.119$ g cm^{-3}, $\mu = 0.130$ mm^{-1}; a total of 22451 reflections were measured, 7659 independent, final residuals were $R1 = 0.0394$ and $wR2 = 0.0877$ for 7659 observed reflections with $I > 2\sigma(I)$, 543 parameters, GOF = 0.960, maximum residual electron density 0.438 e Å^{-3}; data were collected on a Bruker SMART CCD (charge-coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus; data were measured by using scans of 0.3° per frame for 45 s, such that a hemisphere was collected; a total of 1271 frames were collected with a maximum resolution of 0.76 Å; the first 50 frames were recollected at the end of data collection to monitor for decay; the structure was solved by the direct method (G. M. Sheldrick, SHELXL-97, Program for the Solution of Crystal Structures, University of Göttingen, Germany, **1997**) followed by refinement by the least-squares method on F^2 (SHELXL-97); all non-hydrogen atoms were refined anisotropically; the positions of hydrogen atoms were found by difference Fourier methods and refined isotropically. CCD-275454 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] A neutral chloroamide structure, rather than an ion pair, may represent a more accurate depiction of the bonding interactions in *N*-acyliminium chlorides in nonpolar organic solvents (for an NMR spectroscopic study that supports this assertion, see: A. K. Bose, G. Spiegelman, M. S. Manhas, *Tetrahedron Lett.* **1971**, 3167 – 3170). Calculations that use the density-functional theory



N-acyliminium ion chloroamide

(B3LYP/6-31G++(d,p)) predict substantial chloroamide character for *N*-acylisoquinolinium chloride (M. S. Taylor, E. N. Jacobsen, unpublished results), and the strong dependence of enantioselectivity upon solvent polarity observed in both acyl-Mannich and acyl-Pictet–Spengler reactions may be a reflection of the importance of the pairing of the *N*-acyliminium ions in these processes. These reactions are also subject to dramatic leaving-group effects upon reactivity and enantioselectivity, a phenomenon that seems difficult to reconcile with a fully ionized *N*-acyliminium ion as the reactive species. The possibility that **1** activates intermediate chloroamides toward substitution reactions by hydrogen-bonding interactions with the carbonyl group represents an intriguing, albeit speculative, mechanistic hypothesis that is consistent with these observations.

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[15] Transesterification of the resulting product permitted the absolute configuration to be assigned (see the Supporting Information for details).

