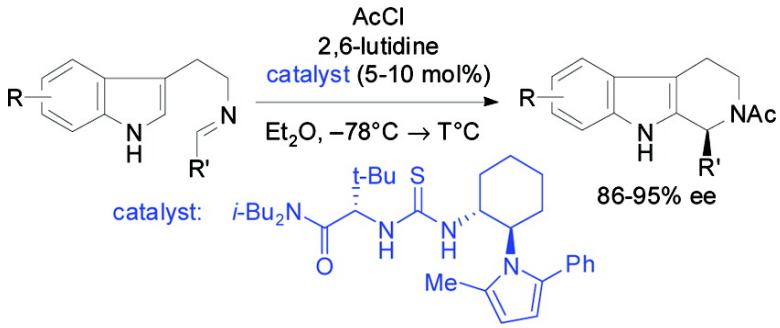
Communication

# Highly Enantioselective Catalytic Acyl-Pictet–Spengler Reactions

Mark S. Taylor, and Eric N. Jacobsen

*J. Am. Chem. Soc.*, **2004**, 126 (34), 10558-10559• DOI: 10.1021/ja046259p • Publication Date (Web): 07 August 2004






## More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 27 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 08/07/2004

# Highly Enantioselective Catalytic Acyl-Pictet−Spengler Reactions

Mark S. Taylor and Eric N. Jacobsen*

*Harvard University, Department of Chemistry and Chemical Biology, 12 Oxford Street, Cambridge, Massachusetts 02138*

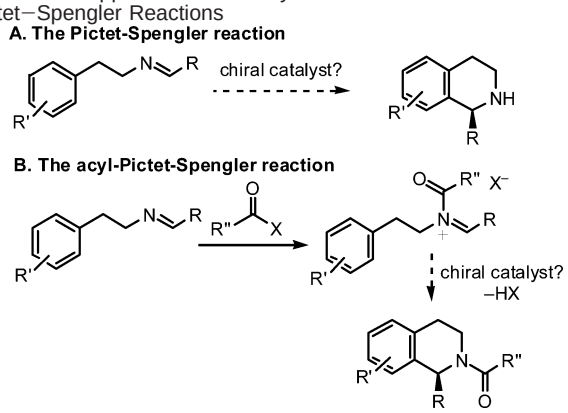
Received June 24, 2004; E-mail: jacobsen@chemistry.harvard.edu

Tetrahydroisoquinoline and tetrahydro-$\beta$-carboline ring systems are core structural elements in natural and synthetic organic compounds possessing a wide diversity of important biological activities.[1] The Pictet−Spengler reaction, involving the cyclization of electron-rich aryl or heteroaryl groups onto imine or iminium electrophiles (Scheme 1A), represents an established biosynthetic pathway and the laboratory method of choice for the preparation of these structural motifs.[2] Enantioselective variants of this transformation would be valuable, both for accessing useful chiral building blocks and in complex alkaloid synthesis. A number of elegant diastereoselective methods, including substrate-controlled Pictet−Spengler cyclizations,[3−5] have been developed to access this important class of compounds.[6] Enantioselective, catalytic approaches have, for the most part, been restricted to asymmetric hydrogenation of cyclic imines accessed by Bischler−Napieralski reaction.[7] The only reported example of a chiral Lewis acid-mediated Pictet−Spengler reaction requires the use of superstoichiometric quantities of an enantioenriched boron reagent, and its scope is restricted to $N_\beta$-hydroxytryptamine-derived nitrones.[8] Herein, we report asymmetric catalysis of the acyl-Pictet−Spengler reaction by chiral thiourea derivatives, providing access to a range of *N*-acetyl $\beta$-carbolines in high enantioselectivies.

The challenge of developing an asymmetric catalytic variant of the Pictet−Spengler reaction appears to be associated with the low reactivity of the imine substrate. Most often, strong Brønsted acids are employed to promote the racemic pathway; the few reported examples of Lewis acid catalysis involve highly reactive agents, unmodified by donor ligands.[9] In addition, high reaction temperatures are often required. We were thus not surprised to discover that a screen of potential chiral catalysts for this transformation did not afford any useful leads: all compounds tested were inactive except at high temperatures, and no enantiomerically enriched products were obtained under any conditions.[10] These results led us to conclude that the exploration of more reactive variants of the Pictet−Spengler reaction, which could proceed under relatively mild conditions, might be key to the development of an enantioselective, catalytic process.

A general strategy for enhancing the reactivity in processes involving imine or iminium intermediates involves generation of the corresponding *N*-acyliminium ions.[11] These highly active electrophiles form the basis for a wealth of useful synthetic transformations, and their application in variants of the Pictet−Spengler reaction has been known for some time.[12] We chose to investigate the possibility that the acyl-Pictet−Spengler reaction might be amenable to catalysis by a relatively mild Lewis or Brønsted acid catalyst (Scheme 1B).[13] Recent results from our group have demonstrated that chiral thiourea catalyst **1a** and related compounds promote highly enantioselective additions of nucleophiles to *N*-alkyl[14] and *N*-*tert*-butoxycarbonyl (Boc) imines.[15] The ability of these catalysts to activate such electronically distinct imine derivatives with high enantioselectivity prompted us to investigate

***Scheme 1.*** Approaches to Catalysis of Enantioselective Pictet−Spengler Reactions




their application in the activation of *N*-acyliminium ions. Limited precedent exists for such an approach: the enantioselective acylcyanation of quinolines (Reissert reaction) discovered by Shibasaki is the only reported example of *N*-acyliminium ion activation by a chiral catalyst.[16]

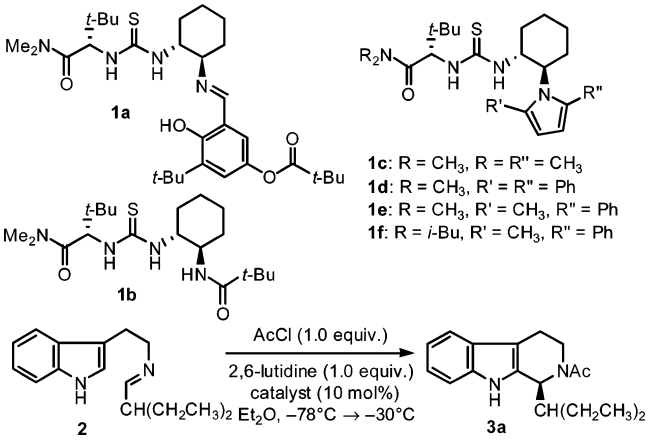
Preliminary screening experiments along these lines unearthed promising results: tryptamine-derived imine **2** underwent cyclization in the presence of acetyl chloride, 2,6-lutidine, and catalyst **1a** in diethyl ether at −30 °C to provide the $N_\beta$-acetyl-tetrahydro-$\beta$-carboline **3a** in 59% ee (Table 1). This lead result emerged from careful evaluation of each of the reaction parameters: the reaction enantioselectivity exhibited a strong dependence upon the structure of the acylating agent,[17] as well as the reaction solvent and temperature.[18] Taking advantage of the modular structure of **1a**, we investigated catalyst optimization. Substantial variation of the diaminocyclohexane-derived portion of the catalyst was tolerated: for example, catalyst **1b**, in which the salicylaldimine moiety was replaced by a bulky *N*-pivaloyl amide, imparted enantioselectivity similar to that obtained using **1a**. Catalyst **1c**, containing a 2,5-dimethylpyrrole group, afforded an especially promising result, which could be improved dramatically by tuning of the pyrrole substituents.[19] Unsymmetrically substituted 2-methyl-5-phenylpyrrole derivative **1e** emerged as a highly efficient catalyst, providing the cyclization product in 93% ee. Fine-tuning of the amide moiety demonstrated that the *N*,*N*-diisobutyl amide **1f** was optimal across a wide range of imine substrates.[20]

This new methodology provides access to a range of substituted tetrahydro-$\beta$-carbolines in high enantiomeric excess (Table 2). Imines obtained by condensation of tryptamine with 1.05 equiv of aldehyde may be used without further purification, and the yields of cyclized products for the two-step procedure are generally good.[21] Variation of the indole moiety is also tolerated; the ability to access products bearing methoxy groups at the 5- or 6-position is particularly significant in light of the ubiquity of these substitution patterns in indole alkaloids. Limitations of the current system include substrates derived from aromatic aldehydes or trimethylacetaldehyde, which display lower reactivity.[22]



**10.1021/ja046259p CCC: $27.50** 

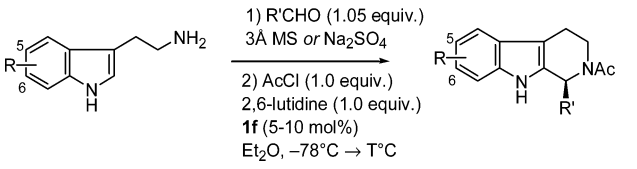
***Table 1.*** Optimization of Catalyst Structure




| catalyst | yield (%)[a] | ee (%)[b] |
|---|---|---|
| **1a** | 65 | 59 |
| **1b** | 45 | 61 |
| **1c** | 65 | 77 |
| **1d** | 55 | 71 |
| **1e** | 70 | 93 |
| **1f** | 70 | 93 |

[a] Determined by HPLC using benzophenone as an internal quantitative standard, from reactions carried out on a 0.1 mmol scale. [b] Determined by HPLC (Pirkle (*S*,*S*)-Whelk-01 column, 10% ethanol/hexanes).

***Table 2.*** Asymmetric Acyl-Pictet−Spengler Reactions Catalyzed by **1f**




| product | R | R′ | *T* (°C) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| **3a** | H | $CH(CH_2CH_3)_2$ | −30 | 65[c] | 93 |
| **3b** | H | $CH(CH_3)_2$ | −40 | 67[d] | 85 |
| **3c** | H | *n*-$C_5H_{11}$ | −60 | 65[d] | 95 |
| **3d** | H | $CH_2CH(CH_3)_2$ | −60 | 75[d] | 93 |
| **3e** | H | $CH_2CH_2OTBDPS$ | −60 | 77[d] | 90 |
| **3f** | 5-MeO | $CH(CH_2CH_3)_2$ | −40 | 81[c] | 93 |
| **3g** | 6-MeO | $CH(CH_2CH_3)_2$ | −50 | 76[d] | 86 |

[a] Isolated yield over two steps after chromatography, from reactions performed on a 0.25 mmol scale. [b] Enantiomeric excess by HPLC using commercially available chiral columns (see Supporting Information for details). The absolute configuration of products **3b** and **3d** was determined by deacetylation to the corresponding known tetrahydro-$\beta$-carbolines with lithium amidotrihydroborate. Other assignments are by analogy. [c] Performed with 5 mol % catalyst. [d] Performed with 10 mol % catalyst.

The ability to activate a weakly Lewis basic *N*-acyliminium ion toward enantioselective transformations using a chiral hydrogen bond donor presents new opportunities for catalysis and raises intriguing questions as to the nature of this interaction. Our current efforts include examination of the mechanism of this transformation, further exploration of the reaction scope, and application of the enantioselective Pictet−Spengler reaction in indole alkaloid synthesis.

**Acknowledgment.** This work was supported by the NIH (GM-43214).

**Supporting Information Available:** Complete experimental procedures, characterization data, and chromatographic analyses of racemic and enantiomerically enriched products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) For reviews: (a) Brown, R. T. In *Indoles*; Saxton, J. E., Ed.; Wiley-Interscience: New York, 1983; Part 4 (The Monoterpenoid Indole Alkaloids). (b) Bentley, K. W. *Nat. Prod. Rep*. **2004**, *21*, 395−424 and references therein.

(2) (a) Pictet, A.; Spengler, T. *Ber*. **1911**, *44*, 2030−2036. (b) Tatsui, G. *J. Pharm. Soc. Jpn*. **1928**, *48*, 92. (c) For a review: Cox, E. D.; Cook, J. M. *Chem. Rev*. **1995**, *95*, 1797−1842.

(3) Diastereoselective Pictet−Spengler reactions of tryptophan esters: Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M. *J. Org. Chem*. **1997**, *62*, 44−61 and references therein.

(4) Diastereoselective Pictet−Spengler reactions of chiral aldehydes: (a) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *Can. J. Chem*. **1986**, *64*, 2205−2210. (b) Czarnocki, Z.; Suh, D.; MacLean, D. B.; Hultin, P. G.; Szarek, W. A. *Can. J. Chem*. **1992**, *70*, 1555−1561. (c) Czarnocki, Z.; Mieckzkowsi, J. B.; Kiegiel, J.; Araźny, Z. *Tetrahyedron: Asymmetry* **1995**, *6*, 2899−2902.

(5) Chiral *N*-protective groups: (a) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2402−2403. (b) Schmidt, G.; Waldmann, H.; Henke, H.; Burkard, M. *Chem. Eur. J*. **1996**, *2*, 1566−1571. (c) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett*. **2000**, *2*, 1955−1958. (d) Gremmen, C.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett*. **2001**, *42*, 8885−8888. (e) Tsuji, R.; Nakagawa, M.; Nishida, A. *Tetrahedron: Asymmetry* **2003**, *14*, 177−180.

(6) A more comprehensive list of methods for the preparation of enantioenriched tetrahydroisoquinolines and tetrahydro-$\beta$-carbolines is provided in Supporting Information.

(7) (a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc*. **1986**, *108*, 7117−7119. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *116*, 8952−8965. (c) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1996**, *118*, 4916−4917.

(8) (a) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem*. **1998**, *63*, 6348−6354. (b) Hino, T.; Nakagawa, M.; *Heterocycles* **1998**, *49*, 499−531.

(9) (a) Ytterbium triflate/chlorotrimethylsilane: Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett*. **2002**, 428. (b) Ytterbium triflate: Srinivasan, N.; Ganesan, A. *Chem. Commun*. **2003**, *7*, 916−917.

(10) Catalysts screened included chiral ureas and thioureas, (salen)aluminum complexes, as well as other chiral ligand/metal combinations. Substrates included imines derived from condensation of aromatic and aliphatic aldehydes with tryptamines and electron-rich arylethylamines.

(11) For reviews of cyclizations of *N*-acyliminium ions: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev*. **2004**, *104*, 1431−1628.

(12) (a) Venkov, A. P.; Mollov, N. M. *Synthesis* **1982**, *82*, 216−2217. (b) Yamanaka, E.; Shibata, N.; Sakai, S. *Heterocycles* **1984**, *22*, 371−374. (c) Venkov, A. P.; Lukanov, L. K. *Synthesis* **1989**, *89*, 59−61. (d) Venkov, A. P.; Boyadjieva, A. K. *Synth. Commun*. **1999**, *29* (3), 487−494.

(13) Acceleration of acyl-Pictet−Spengler reactions by achiral Lewis acids has been reported. (a) aluminum trichloride: See refs 12a,c. (b) Titanium isopropoxide: See refs 5a,b.

(14) (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 4901−4902. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2000**, *39* (7), 1279−1281. (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 10012−10014. (d) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 4102−4103.

(15) (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 12964−12965. (b) Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. *Synlett* **2003**, *12*, 1919−1922. See also: (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett*. **2004**, *4*, 625−627.

(16) (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2000**, *122*, 6327−6328. (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 6801−6802. (c) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 10784−10785.

(17) Acylating agents screened included acyl halides, anhydrides, and chloroformates.

(18) Majority of solvents tested (toluene, dichloromethane, tetrahydrofuran) afforded poor enantioselectivity. Other ethereal solvents such as *tert*-butyl methyl ether and diisopropyl ether provided comparable but slightly inferior results to diethyl ether. Temperature optimization was required to suppress competing uncatalyzed cyclization.

(19) A variety of (*R*,*R*)-2-pyrrolylcyclohexylamines was prepared in good yield by Paal−Knorr condensation of diaminocyclohexane and 1,4-diketones (1.0 equiv). See Supporting Information for details.

(20) Use of catalyst **1e** provides products **3d** and **3e** (Table 2) in 89 and 84% ee, respectively.

(21) Catalyst **1f** may be recovered in quantitative yield by chromatography and reused to produce **3a** without deterioration of cyclization yield or enantiomeric excess. See Supporting Information for details.

(22) Catalyst undergoes decomposition by acetylation of the thiourea moiety at the temperatures required for efficient cyclization of such substrates, resulting in low enantioselectivity.

JA046259P