ORGANIC LETTERS

2012
Vol. 14, No. 10
2610–2613

Direct and Highly Enantioselective Iso-Pictet–Spengler Reactions with α-Ketoamides: Access to Underexplored Indole Core Structures

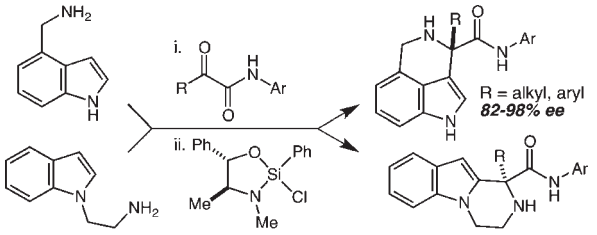
Heike Schönherr and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York 10027, United States

leighton@chem.columbia.edu

Received April 10, 2012

ABSTRACT



Direct, one-pot, operationally simple, and highly enantioselective iso-Pictet–Spengler reactions are reported. The reactions involve the condensation of either (1*H*-indol-4-yl)methanamine or 2-(1*H*-Indol-1-yl)ethanamine with a variety of α-ketoamides, followed by the addition of a simple and commercially available chiral silicon Lewis acid. These reactions are the first asymmetric examples of these cyclization modes and provide access to 3,3-disubstituted-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinolines and 1,1-disubstituted-1,2,3,4-tetrahydropyrazino[1,2-*a*]-indoles, respectively, two relatively underexplored indole-based core structure motifs in medicinal chemistry.

The indole version[1] of the venerable Pictet–Spengler reaction[2] provides access to tetrahydro-β-carbolines, and it is only recently that significant progress has been made toward the development of enantioselective variants.[3] Most notably, Jacobsen and co-workers have developed a suite of asymmetric Pictet–Spengler reactions based on the extraordinary and elegant concept of anion binding by chiral thiourea catalysts.[4] Despite these truly conceptually pioneering advances, however, the asymmetric Pictet–Spengler reaction remains an at least partly, if not largely, unsolved problem if success is defined as the ability to take an unmodified tryptamine (directness), react it with any aldehyde or ketone (scope) under operationally simple, inexpensive, and otherwise practical reaction conditions (practicality), and isolate the product in good yield and in highly enantiomerically enriched form (generality and applicability in complex settings). Such attributes are far more directly correlated with widespread adoption of a given asymmetric method than is, for example, the amount of chiral inducer employed.[5]

To that end, we reported in 2009 a direct asymmetric Pictet–Spengler reaction with unmodified tryptamines and α-ketoamides promoted by (*S*,*S*)-**1**,[6] a simple, versatile, and commercially available silicon Lewis acid[7] (Figure 1a).

(1) Tatsui, G. *J. Pharm. Soc. Jpn.* **1928**, *48*, 92.

(2) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (c) Youn, S. W. *Org. Prep. Proced. Int.* **2006**, *38*, 505.

(3) (a) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (c) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (d) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. (e) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 860. (f) Badillo, J. J.; Silva-Garciá, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. *Tetrahedron Lett.* **2011**, *52*, 5550.

(4) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (c) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.

(5) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(6) Bou-Hamdan, F. R.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2403.

(7) Leighton, J. L. *Aldrichimica Acta* **2010**, *43*, 3.

10.1021/ol300922b © 2012 American Chemical Society
Published on Web 04/27/2012

This method remains the only general way to access a variety of 1,1-disubstituted tetrahydro-β-carbolines[8,9] in a highly enantioselective fashion and at the same time is also one of the only direct and one of the more practical asymmetric Pictet–Spengler reactions reported to date. Given that we had in hand an operationally simple and practical method that can uniquely provide access to potentially valuable products, we decided to investigate whether the success of our method could be extended to indole-based core structures other than tetrahydro-β-carbolines. Here too, Jacobsen has provided the seminal contribution in the form of what was termed an "iso-Pictet–Spengler reaction" that provides the first and only enantioselective method to access tetrahydro-γ-carbolines.[10] This is not the only possible iso-Pictet–Spengler reaction, however, as at least two other variants, those employing amines **2** and **3**, may be imagined (Figure 1b and c). The only precedent at all for any asymmetric version of either of these two cyclization modes is a very recent report describing an enzymatic reaction between **3** and secologanin.[11] Because the hypothetical products of these reactions might therefore represent potentially interesting yet underexplored indole core structure space in medicinal chemistry terms, we decided to examine whether our asymmetric Pictet–Spengler methodology would be applicable in these contexts.

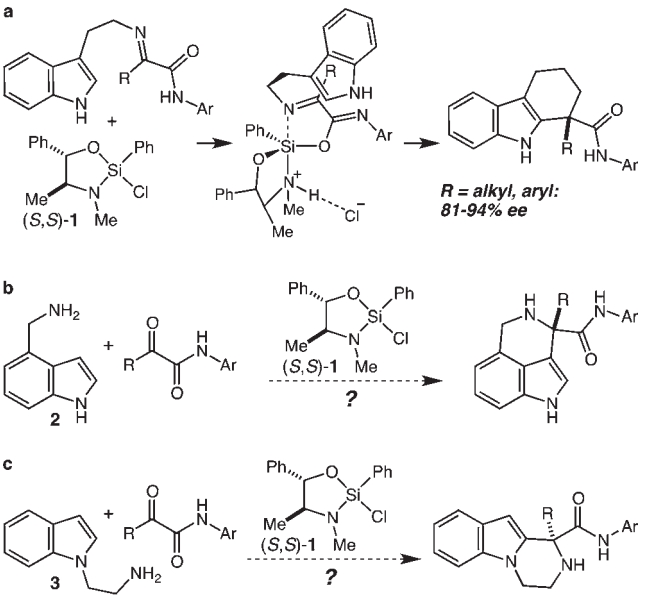
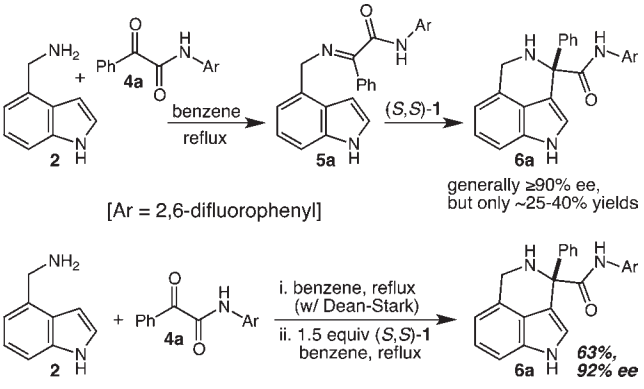


Figure 1. (a) Enantioselective Pictet–Spengler reactions with tryptamine and α-ketoamides. (b) A proposed iso-Pictet–Spengler reaction to access 3,3-disubstituted-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinolines. (c) A proposed iso-Pictet–Spengler reaction to access 1,1-disubstituted-1,2,3,4-tetrahydropyrazino-[1,2-*a*]indoles.

Our investigations began with (1*H*-indol-4-yl)methanamine **2**[12] and α-ketoamide **4a** (Ar = 2,6-diflourophenyl), as prior experience alerted us to the fact that the choice of the aryl group on the amide was critical to the successful optimization of both efficiency and enantioselectivity and 2,6-difluorophenyl had proven to be one of the more effective aryl groups in this regard (Scheme 1). Gratifyingly, we quickly found that the reaction was indeed feasible and provided the desired product **6a** with generally high levels of enantioselectivity (≥90% ee) depending on solvent and reaction temperature. However, these exploratory reactions, which involved isolation of the imine **5a** prior to the cyclization step, were also characterized by variable and generally low overall yields, a problem we attributed to the instability of the imine **5a**. We therefore turned our attention to the development of a one-pot procedure, and this proved straightforward and effective. Thus, simply heating **2** and **4a** in refluxing benzene with a Dean–Stark trap and then adding silane **1** led to the isolation of **6a** in 63% yield and 92% ee.

Scheme 1. Development of a One-Pot Enantioselective Iso-Pictet–Spengler Reaction with Amine **2** and α-Ketoamide **4a**



The one-pot procedure proved generally effective for a range of α-ketoamides as illustrated by the results described in Table 1. Both aromatic (entries 1–3) and aliphatic ketones (entries 4–8) generally reacted with excellent levels of enantioselectivity, while the aliphatic ketones generally provided higher yields. The only outlier in terms of enantioselectivity was the 3-pyridyl ketone **4c** (entry 3), but this was not completely unexpected as we have had prior indications that Lewis basic groups can interfere with the smooth operation of the silane Lewis acid.[13]

(8) One of the Jacobsen variants (see ref 4b) and the Bernardi and Bencivenni method (see ref 3e) allow the preparation of a limited set of 1,1-disubstituted tetrahydro-β-carbolines. Our claim to a greater degree of generality is based upon both the fact that R (see Figure 1a) can be a wide variety of both alkyl and aryl groups and the fact that the carboxamide moiety may be readily converted into a variety of other substituents.

(9) Maruoka has reported a non-Pictet–Spengler approach to the enantioselective preparation of 1,1-disubstituted tetrahydro-β-carbolines. See:Shirakawa, S.; Liu, K.; Ito, H.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 1515.

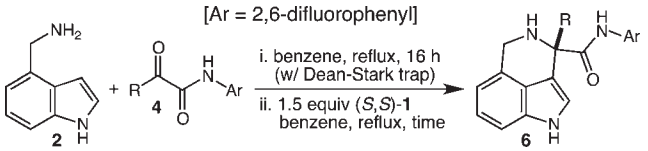
(10) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564.

(11) Wu, F.; Zhu, H.; Sun, L.; Rajendran, C.; Wang, M.; Ren, X.; Panjikar, S.; Cherkasov, A.; Zou, H.; Stöckigt, J. *J. Am. Chem. Soc.* **2012**, *134*, 1498.

(12) Robaa, D.; Enzensperger, C.; Abul Azm, S. D.; El Khawass, E. S.; El Sayed, O.; Lehmann, J. *J. Med. Chem.* **2010**, *53*, 2646.

Despite this reduced enantioselectivity, the reaction still facilitates access to the product **6c** with useful levels of enantioselectivity, and it is likely that, should the need arise, the enantiopurity of the product could be increased by recrystallization.

Table 1. Scope of the Iso-Pictet–Spengler Reaction of **2** with α-Ketoamides **4** Promoted by (*S*,*S*)-**1**

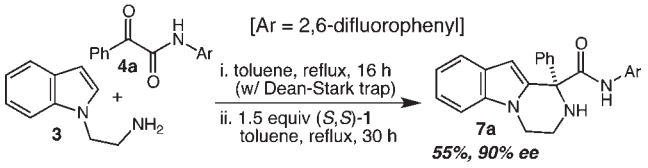


entry	α-ketoamide (R)	time (h)	product	yield (%)[a]	ee (%)[b]
1	**4a** (Ph)	24	**6a**	63	92
2	**4b** (*p*-BrC_6H_4)	24	**6b**	67	96
3	**4c** (3-pyridyl)	24	**6c**	66	82
4	**4d** (*n*-Pr)	8	**6d**	83	98
5	**4e** (*n*-Hex)	10	**6e**	86	98
6	**4f** (*i*-Bu)	8	**6f**	87	98
7	**4g** (*i*-Pr)	24	**6g**	77	94
8	**4h** (*c*-Hex)	24	**6h**	70	90

[a] Isolated yield after purification. [b] Determined by chiral HPLC analysis.

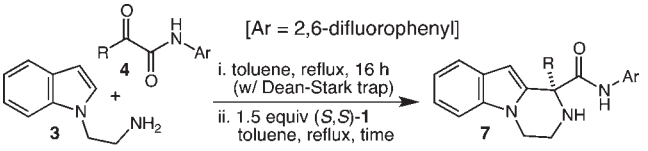
When we turned our attention to the use of (commercially available) 2-(1*H*-indol-1-yl)ethanamine **3** in the iso-Pictet–Spengler reaction, we were gratified to find that the reaction required almost no optimization. The only modification that proved necessary was to employ toluene as the solvent instead of benzene, to allow for a necessary increase in the reaction temperature due to the relative sluggishness of the reaction. Thus, simply heating **3** and **4a** in refluxing toluene with a Dean–Stark trap and then adding (*S*,*S*)-**1** produced **7a** in 55% yield and 90% ee (Scheme 2). This is not the first time we have observed high levels of enantioselectivity in refluxing toluene with this family of silane Lewis acids,[14] and this result stands as another testament to their robustness. The lower rate of reaction in this cyclization mode may presumably be attributed to the lower nucleophilicity of the 2-position of the indole.

Scheme 2. Optimization of an Iso-Pictet–Spengler Reaction with 2-(1*H*-Indol-1-yl)ethanamine **3** and α-Ketoamide **4**



An examination of the scope of the reaction with amine **3** revealed that, for the most part, the moderate efficiency of the reaction described in Scheme 2 was an outlier (Table 2). Thus, a variety of both aliphatic and aromatic ketones generally provided good to excellent yields and enantioselectivities (entries 1–7). It was also demonstrated in this series that the corresponding 5-bromo derivative of **3** provided good results with **4d** (entry 8), albeit with a drop in reaction efficiency relative to that of entry 4.

Table 2. Scope of the Iso-Pictet–Spengler Reaction with 2-(1*H*-Indol-1-yl)ethanamine **3** and α-Ketoamides Promoted by (*S*,*S*)-**1**



entry	α-ketoamide (R)	time (h)	product	yield (%)[a]	ee (%)[b]
1	**4a** (Ph)	30	**7a**	55	90
2	**4b** (*p*-BrC_6H_4)	30	**7b**	70	88
3	**4c** (3-pyridyl)	30	**7c**	60	86
4	**4d** (*n*-Pr)	8	**7d**	89	92
5	**4f** (*i*-Bu)	10	**7f**	90	92
6	**4g** (*i*-Pr)	24	**7g**	57	96
7	**4i** ($CH_3(CH_2)_{13}$)	5	**7i**	89	90
8[c]	**4d** (*n*-Pr)	8	**8**[d]	65	90

[a] Isolated yield after purification. [b] Determined by chiral HPLC analysis. [c] 2-(5-Bromo-1*H*-indol-1-yl)ethanamine was used in this experiment in place of **3**. [d] The product of this reaction (**8**) is the 5-bromo derivative of **7d**. See the Supporting Information.

Finally, in an effort to alleviate any concerns about the use of 1.5 equiv of the silane Lewis acid,[15] we have revisited the reactions of **2** and **3** with **4d** on a 10 and 8 mmol scale, respectively, and with a reduced silane loading of 1.3 equiv (Scheme 3). The products **6d** and **7d** were isolated by recrystallization in 92% and 94% yields and 99% and 98% ee, respectively. Importantly, and as we have demonstrated in other contexts,[6,16] the pseudoephedrine was recovered by simple extraction in both experiments. Thus, by any objective measure, these reactions score very highly for practicality, efficiency, atom-economy, and user-friendliness, all while providing unique access to novel and interesting enantiomerically highly enriched structures that may be of use in medicinal chemistry applications.

We have devised two new asymmetric iso-Pictet–Spengler reactions of aminoindoles **2** and **3** with a variety of α-ketoamides promoted by the simple and commercially

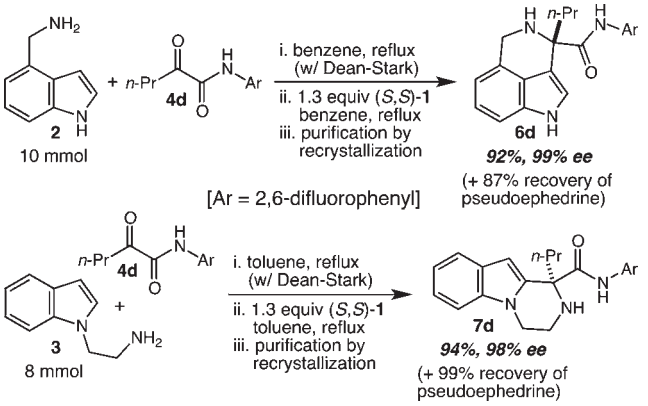
(13) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596.

(14) Rabbat, P. M. A.; Valdez, S. C.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119.

(15) On the smaller scale (0.30 mmol of α-ketoamides **4**) used for the reactions described in Tables 1 and 2, we observed a small but noticeable drop in enantioselectvity when we used less than 1.5 equiv of silane **1**. This problem is mitigated substantially as the scale of the reactions increases.

(16) (a) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (b) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858. (c) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974.

Scheme 3. "Large" Scale (8−10 mmol) Reactions with Product Isolation by Recrystallization and Pseudoephedrine Recovery by Extraction Demonstrate the Utility and Practicality of the Iso-Pictet−Spengler Reactions



available chiral silane Lewis acid **1**. These operationally simple, practical, and scalable reactions facilitate unique access to two relatively underexplored indole core structure motifs (3,3-disubstituted-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-isoquinolines and 1,1-disubstituted-1,2,3,4-tetrahydro-pyrazino[1,2-*a*]indoles) and provide additional examples of the remarkable generality and versatility of silane **1**.[7]

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-11-52949). We thank the Deutsche Forschungsgemeinschaft for a Postdoctoral Fellowship (SCHO 1403/1-1) to H.S. We thank Professor Ged Parkin and Mr. Aaron Sattler (Columbia University) for two X-ray structure analyses (see Supporting Information), and the National Science Foundation (CHE-0619638) is thanked for acquisition of an X-ray diffractometer.

Supporting Information Available. Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare the following competing financial interest(s): Columbia University holds a patent on silane Lewis acid **1**, and Columbia has licensing deals in place with Sigma-Aldrich and Gelest, Inc. The authors have no official relationship with either company otherwise and receive no honoraria or fees of any kind from either of them.