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Highly efficient Lewis acid-catalysed Pictet–Spengler reactions discovered by parallel screening†

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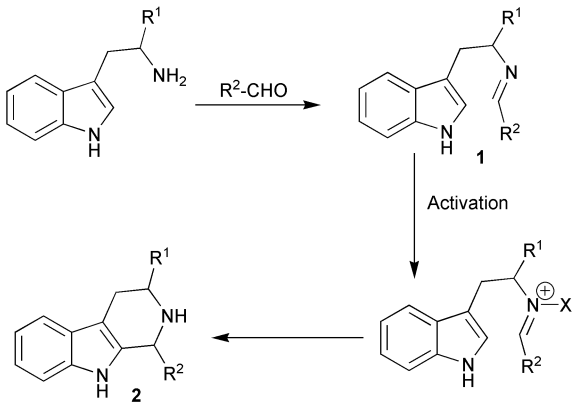
High yielding Lewis acid-catalysed one-pot Pictet–Spengler reactions of tryptophan methyl ester and tryptamine with aliphatic and aromatic aldehydes were achieved in short reaction times with the aid of microwave irradiation.

The tetrahydro-β-carboline ring system is present in numerous biologically active indole alkaloids as well as synthetic compounds. The World Drug Index, for instance, contains over 200 listings of this heterocycle, which is usually assembled by the Pictet–Spengler reaction[1] (Scheme 1). Activation of imine **1** is most commonly achieved via Brønsted acid catalysis (X = H). An alternative involves putative *N*-acyliminium ions (X = acyl group), and we have previously employed[2] this methodology for solution and solid-phase applications. Meanwhile, Lewis acid-catalysed Pictet–Spengler reactions yielding tetrahydro-β-carbolines are rare,[3,4] and largely limited to iminium species where X is a heteroatom containing coordinating group.



Scheme 1 The Pictet–Spengler reaction.

We carried out parallel screening to discover Lewis acids that efficiently catalyse Pictet–Spengler reactions of simple imines. A fixed amount (20 mg, corresponding to 9–45 mol%) of Lewis acid was added to reaction vessels containing 100 mg of imine **1a** (R_1 = CO_2Me, R_2 = Ph). Qualitatively, reactions were monitored by TLC using Dragendorff's staining reagent, which produces different colours for the starting imine and product tetrahydro-β-carboline **2a** (R_1 = CO_2Me, R_2 = Ph). Remarkably, many Lewis acids tested were found to be effective catalysts, although hitherto unreported for this transformation (Table 1).

Promising reactions were then analysed by HPLC analysis of the crude product mixture (Table 2). Based on the Kobayashi classification,[5] both aldehyde (e.g. Al, Ti) and aldimine selective (e.g. Sc, In, Cu(II), Yb, Y) Lewis acids were among those found to promote the Pictet–Spengler reaction. While $AlCl_3$ and the ionic liquid[6] [bmim]BF_4 (bmim = 1-butyl-3-methylimidazolium) were moderately effective, the ionic liquid chloroaluminate salt, [bmim]Cl–$AlCl_3$, N = 0.5,[7] was a highly active catalyst.

Table 1 Lewis acid catalysis of the Pictet–Spengler reaction of imine **1a**

Activity[a]	Lewis acid
High	$In(OTf)_3$, $Sm(OTf)_3$, $YbCl_3$, $Sc(OTf)_3$, YCl_3, $Ce(OTf)_3$, $Y(OTf)_3$, [bmim]Cl–$AlCl_3$, N = 0.5
Moderate	$InCl_3$, $Zn(OTf)_2$, $AlCl_3$, $TiCl_4$, $SiCl_4$, $Hg(OAc)_2$, $Cu(OTf)_2$, $Ho(OTf)_3$, $Tb(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, $Dy(OTf)_3$, $Eu(OTf)_3$, $Pr(OTf)_3$, [bmim][BF_4]
Poor	$Ba(OTf)_2$, AgOTf, CuOTf, $Sn(OTf)_2$, $La(OTf)_3$, $CoCl_2$, $BiCl_3$

[a] High activity: complete conversion in 24 h; moderate: 2.5 days needed; poor: incomplete reaction after 4 days.

As the reactions needed one day or longer at room temperature, we investigated the effects of microwave irradiation.[8] With metal chloride Lewis acids, imine hydrolysis was a competing reaction, possibly due to attack of chloride on the activated iminium species. Lewis acids with less nucleophilic triflate counterions were superior. Of these, $Yb(OTf)_3$ gave the best yields when tested with other imines, and was selected for further optimisation. Using only 5 mol% of catalyst and 30 minutes of microwave irradiation, high conversions were obtained with both aliphatic and aromatic imines.

The above conditions were equally applicable to a one-pot version in which the imine is formed in situ, and these consistently gave higher yields and cleaner product mixtures than those with preformed imines (Table 3, entries **2a–2e**). To drive the reaction forward, 120 mol% of aldehyde was used, and the excess scavenged with amine functionalized resins. It is noteworthy that yields are equally good with electron-poor and electron-rich aromatic imines, as the latter are less reactive in Pictet–Spengler cyclizations. The mechanisms[9] by which microwave irradiation influence organic reactions remain controversial. In our case, a conventionally heated (oil bath) reaction gave incomplete conversion, but increasing the time and temperature (120 °C, 50 minutes) resulted in similar yields to the microwave experiments.

Table 2 Quantitative analysis of promising Lewis acid catalysts for the Pictet–Spengler reaction of imine **1a**

Lewis acid	Mol%	Yield (%)[a]	Cis/trans[a]
$In(OTf)_3$	15	78	1:1.2
$Sm(OTf)_2$	15	80	1:1.4
$YbCl_3$	15	80	1:1.4
$Yb(OTf)_3$	9	85	1:1.6
$Sc(OTf)_3$	10	86	1:1.7
$Ce(OTf)_3$	10	80	1:1.2
YCl_3	15	82	1:1.3
$Y(OTf)_3$	10	82	1:1.4
[bmim]Cl–$AlCl_3$, N = 0.5	20	80	1:1.6
$InCl_3$	20	69	1:1.4
$Zn(OTf)_2$	20	72	1:1.2
$AlCl_3$	45	70	1:1.2
$TiCl_4$	40	65	1:1.1

[a] Crude yield of **2a**, cis/trans ratio determined by HPLC.

† Electronic supplementary information (ESI) available: full experimental procedures. See http://www.rsc.org/suppdata/cc/b2/b212063a/

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Table 3 One-pot synthesis of tetrahydro-ß-carbolines from aldehydes and tryptophan methyl ester (**2a–2e**)[a] or tryptamine (**2f–2j**)[b] using microwave irradiation

	R^1	R^2	Yield (%)[c]	Cis/trans[c]
2a	CO_2Me	Ph	96 (90)	1:1.2
2b	CO_2Me	*p*-NO_2–Ph	92 (90)	1:1.1
2c	CO_2Me	*p*-OMe–Ph	97 (92)	1:1.4
2d	CO_2Me	3,4,5$(OMe)_3$–Ph	93 (92)	1:1.4
2e	CO_2Me	*c*-C_6H_{11}	92 (86)	1:1.2
2f	H	Ph	92 (93)	–
2g	H	*p*-NO_2–Ph	85 (84)	–
2h	H	*p*-OMe–Ph	90 (92)	–
2i	H	3,4,5$(OMe)_3$–Ph	89 (85)	–
2j	H	*c*-C_6H_{11}	95 (82)	–

[a] Reactions carried out with tryptophan methyl ester (200 mg), $Yb(OTf)_3$ (20 mg), and aldehyde (120 mol%) in dichloromethane (2.5 ml) heated at 100 °C for 30 minutes in a Smith Synthesizer microwave instrument. [b] Reactions carried out with tryptamine (200 mg), $Yb(OTf)_3$ (40mg), [bmim]Cl–$AlCl_3$, N = 0.5 (200 mg), and aldehyde (120 mol%) in dichloromethane (2.5 ml) heated at 120 °C for 60 minutes in a Smith Synthesizer microwave instrument. [c] Isolated yields of purified product by the one-pot method, or by using preformed imine (yield in parentheses), with *cis*/*trans* ratio for **2a–2e** determined by HPLC analysis.

Extending these results to tryptamine (**1**, R_1 = H) was less straightforward. Due to the absence of the inductively electron-withdrawing carbonyl group in tryptophan, tryptamine imines are significantly less reactive. In the literature,[10] protic acid catalysed Pictet–Spengler reactions of tryptamine often feature harsher conditions and poorer yields than their tryptophan counterparts. Indeed, those Lewis acids successful in the tryptophan cyclizations were unable to promote the analogous conversion of **1f** (R_1 = H, R_2 = Ph) to **2f** under a number of experimental conditions.

Various additives were tested to boost the reactivity of $Yb(OTf)_3$: no reaction occurred with 100 mol% of benzoic acid[11] or TMSOTf,[12] HCl[13] led to extensive decomposition, and TMSCl gave low yields. Encouraged by the activity of ionic liquids in Table 2, these were tested as well. It was found that the combination of 10 mol% $Yb(OTf)_3$ and 50 mol% [bmim]Cl–$AlCl_3$, N = 0.5, resulted in a very active catalyst which gave uniformly high yields, either with preformed imines **1f–1j** or in one-pot condensations with the aldehydes (Table 3, entries **2f–2j**). The ionic liquid is integral to the additive's effects, as substitution by 50 mol% $AlCl_3$ alone resulted in lower yields. Although ionic liquids are often employed as solvents, and have been used as such in lanthanide triflate catalyzed reactions,[14] we believe this is the first example where they are beneficial as a substoichiometric additive. While this work was in progress, Nakagawa reported[15] the one-pot Pictet–Spengler reaction of tryptamine with *p*-nitrobenzaldehyde using 5 mol% $Yb(OTf)_3$ and 100 mol% TMSCl. The reaction did not proceed with benzaldehyde, whereas our ionic liquid assisted conditions are applicable to even more electron-rich aldehydes (**2h,2i**).

In summary, we demonstrate for the first time that the one-pot Pictet–Spengler cyclization to tetrahydro-β-carbolines can be catalysed by a wide variety of Lewis acids. This should facilitate the future evaluation of *chiral* Lewis acids for the development of reagent-controlled asymmetric versions of these reactions. In the present study, the achiral Lewis acid $Yb(OTf)_3$ is shown to be highly effective in catalysing the Pictet–Spengler reactions of tryptophan and tryptamine. The latter needed the addition of 50 mol% [bmim]Cl–$AlCl_3$, N = 0.5, and suggests that such ionic liquids may be effective additives for other slow Lewis acid-catalysed processes.

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Notes and references

1 For reviews, see (*a*) W. M. Whaley and T. R. Govindachari in *Organic Reactions*, **Vol. 6** Ed. R. Adams, Wiley, New York, 1951, p. 151; (*b*) E. D. Cox and J. M. Cook, *Chem. Rev*., 1995, **95**, 1797.
2 (*a*) H. Wang and A. Ganesan, *Tetrahedron Lett.*, 1997, **38**, 4327; (*b*) H. Wang and A. Ganesan, *Org. Lett.*, 1999, **1**, 1647; (*c*) H. Wang and A. Ganesan, *J. Org. Chem.*, 2000, **65**, 4685; (*d*) D. Bonnet and A. Ganesan, *J. Comb. Chem.*, 2002, **4**, 546.
3 (*a*) T. Kawate, M. Nakagawa, K. Ogata and T. Hino, *Heterocycles*, 1992, **33**, 801; (*b*) T. Kawate, H. Yamada, T. Soe and M. Nakagawa, *Tetrahedron: Asymmetry*, 1996, **7**, 1249; (*c*) T. Kawate, H. Yamada, M. Matsumizu, A. Nishida, K. Yamaguchi and M. Nakagawa, *Synlett*, 1997, 761; (*d*) H. Yamada, T. Kawate, M. Matsumizu, A. Nishida, K. Yamaguchi and M. Nakagawa, *J. Org. Chem.*, 1998, **63**, 6348.
4 (*a*) H. Waldmann, G. Schmidt, H. Henke and M. Burkard, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2402; (*b*) G. Schmidt, H. Waldmann, H. Henke and M. Burkard, *Chem. Eur. J.*, 1996, **2**, 1566.
5 S. Kobayashi, T. Busujima and S. Nagayama, *Chem. Eur. J.*, 2000, **6**, 3491.
6 For reviews, see: (*a*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*b*) R. Sheldon, *Chem. Commun.*, 2001, 2399.
7 Prepared by the following procedure: J. S. Wilkes, J. A. Levisky, R. A. Wilson and C. L. Hussey, *Inorg. Chem.*, 1982, **21**, 1263.
8 For a recent example of microwave accelerated Pictet–Spengler reactions, see: C.-Y. Wu and C.-M. Sun, *Synlett*, 2002, 1709.
9 For a discussion, see: (*a*) N. Kuhnert, *Angew. Chem., Int. Ed.*, 2002, **41**, 1863; (*b*) C. R. Strauss, *Angew. Chem., Int. Ed.*, 2002, **41**, 3589.
10 For example: (*a*) W. A. Skinner and R. M. Parkhurst, *Can. J. Chem.*, 1965, **43**, 2251; (*b*) R. Grigg, H. Q. N. Gunaratne and E. McNaghten, *J. Chem. Soc., Perkin Trans. 1*, 1983, 185; (*c*) H. C. Hiemstra, H. Bierangel, M. Wijnberg and U. K. Pandit, *Tetrahedron*, 1983, **39**, 3981.
11 H. C. Aspinall, N. Greeves and E. G. McIver, *Tetrahedron Lett.*, 1998, **39**, 9283.
12 A. Kakuuchi, T. Taguchi and Y. Hanzawa, *Tetrahedron Lett.*, 2001, **42**, 1547.
13 K. Manabe and S. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 3773.
14 S. Lee, J. H. Park, J. Kang and J. K. Lee, *Chem. Commun.*, 2001, 1698.
15 R. Tsuji, M. Yamanaka, A. Nishida and M. Nakagawa, *Chem. Lett.*, 2002, 428.

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