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o-Benzenedisulfonimide as a reusable acid catalyst for an easy, efficient, and green synthesis of tetrahydroisoquinolines and tetrahydro-β-carbolines through Pictet–Spengler reaction

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ABSTRACT

The synthesis of tetrahydroisoquinolines and tetrahydro-β-carbolines, using the Pictet–Spengler reaction, was carried out in the presence of a catalytic amount of *o*-benzenedisulfonimide, which worked as a Brønsted acid organocatalyst. The reaction conditions were mild and green and good target product yields were achieved. The catalyst was easily recovered and purified, ready to be used in further reactions with economic and ecological advantages.

The Pictet–Spengler reaction[1a–d] is a useful and an important synthetic protocol for the preparation of tetrahydroisoquinoline[1e] and tetrahydro-β-carboline ring systems.[1f] These are present in numerous natural and synthetic organic compounds and posses various biological activities. For instance, tetrahydroisoquinolines show powerful anti-tumor, antimicrobial, anti-HIV activities;[1g,h] tetrahydro-β-carbolines are interesting hypnotic, anxiolytic, antimicrobial, antiviral, anti-tumor, and anti-convulsant compounds.[1i]

Usually, Brønsted acids (recent examples are: H^+ montomorillonite,[2] trifluoroacetic acid,[1g,3] carboxylic acids-thiourea,[4] *p*-toluenesulphonic acid,[5] perfluoroctansulphonic acid in water,[6] chiral phosphoric acids[7]) or Lewis acids (recent examples are: calcium complexes,[8] $Yb(OTf)_3$,[9] $AuCl_3/AgOTf$[10]) are employed as catalysts to promote this reaction, involving the cyclization of iminium ions (or imines) resulting from the dehydration reaction of 2-arylethylamine derivatives with aldehydes.

We have recently reported the use of *o*-benzenedisulfonimide (**1**, Fig. 1) in catalytic amounts as a safe, non-volatile, and non-corrosive Brønsted acid in some acid-catalyzed organic reactions, such as etherification,[11,12] esterification,[11–13] acetalization,[11,12] the Ritter reaction,[14] Nazarov electrocyclization,[15] disproportionation of dialkyl diarylmethyl ethers,[16] Hosomi–Sakurai reaction[17], and Friedlander annulation.[18]

In general, all synthetic methods were performed under mild reaction conditions and showed short reaction times, good selectivity, and the absence or minimal formation of by-products. Moreover, it is worthwhile highlighting another advantage of all the above reactions: **1** can be easily and almost completely recovered from the reaction mixtures in high yield, due to its complete solubility in water. This permits its reuse in other reactions, immediately or after a fast purification step on a cation-exchange resin without any loss of catalytic activity, with economic and ecological advantages.

In this Letter we wish to propose a simple, efficient, and green synthesis of tetrahydroisoquinolines and tetrahydro-β-carbolines under the Pictet–Spengler protocol in the presence of **1** which acts as a reusable Brønsted acid catalyst (Schemes 1 and 2).

Firstly, various aromatic and heteroaromatic aldehydes **3a**, **3c–g** were reacted with 2-(3,4-dimethoxyphenyl)ethanamine (**2a**); the reaction mixture was heated at 80 °C, in the presence of 10 mol % of **1** and in the absence of a solvent. The reaction times were between 6 and 12 h. As shown in Table 1 (entries 1 and 5–9), the target tetrahydroisoquinolines **5a**, **5e–i** were always obtained in

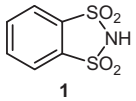

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Figure 1. *o*-Benzenedisulfonimide **1**.

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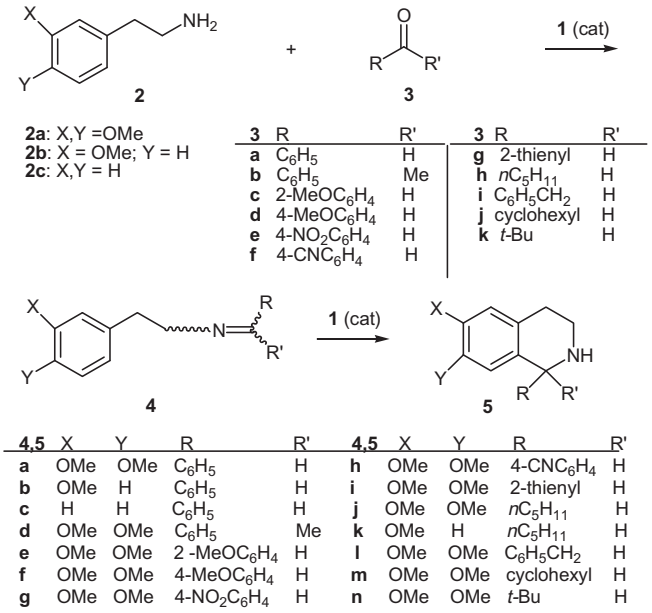
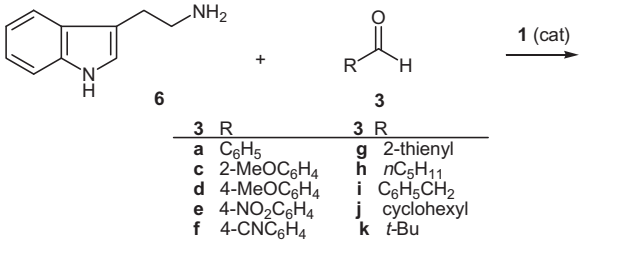


3	R	R'	3	R	R'
a	C_6H_5	H	g	2-thienyl	H
b	C_6H_5	Me	h	nC_5H_{11}	H
c	2-$MeOC_6H_4$	H	i	$C_6H_5CH_2$	H
d	4-$MeOC_6H_4$	H	j	cyclohexyl	H
e	4-$NO_2C_6H_4$	H	k	*t*-Bu	H
f	4-CNC_6H_4	H			

4,5	X	Y	R	R'	4,5	X	Y	R	R'
a	OMe	OMe	C_6H_5	H	h	OMe	OMe	4-CNC_6H_4	H
b	OMe	H	C_6H_5	H	i	OMe	OMe	2-thienyl	H
c	H	H	C_6H_5	H	j	OMe	OMe	nC_5H_{11}	H
d	OMe	OMe	C_6H_5	Me	k	OMe	H	nC_5H_{11}	H
e	OMe	OMe	2 -$MeOC_6H_4$	H	l	OMe	OMe	$C_6H_5CH_2$	H
f	OMe	OMe	4-$MeOC_6H_4$	H	m	OMe	OMe	cyclohexyl	H
g	OMe	OMe	4-$NO_2C_6H_4$	H	n	OMe	OMe	*t*-Bu	H

Scheme 1. Synthesis of tetrahydroisoquinolines **5**.



3	R	3	R
a	C_6H_5	g	2-thienyl
c	2-$MeOC_6H_4$	h	nC_5H_{11}
d	4-$MeOC_6H_4$	i	$C_6H_5CH_2$
e	4-$NO_2C_6H_4$	j	cyclohexyl
f	4-CNC_6H_4	k	*t*-Bu

7,8	R	7,8	R
a	C_6H_5	f	2-thienyl
b	2-$MeOC_6H_4$	g	*n*-C_5H_{11}
c	4-$MeOC_6H_4$	h	$C_6H_5CH_2$
d	4-$NO_2C_6H_4$	i	cyclohexyl
e	4-CNC_6H_4	j	*t*-Bu

Scheme 2. Synthesis of tetrahydro-β-carbolines **8**.

excellent yields, more than 80%. These high yields are independent of the type and the position of the substituents. The work-up was very simple: it was sufficient to add water to the crude residue, filter, and wash the resulting solid with additional water on a Buchner funnel.[19]

Furthermore, **1** was recovered in excellent yields (e.g., Table 2, entry 1, 89%), by simply evaporating the aqueous washings under reduced pressure.[19] Recovered **1** was reused as a catalyst in other two consecutive reactions between **2a** and **3a**. The results are listed in Table 2. The reaction time increased after each run, but the yields of **5a** and the recovery yield of **1** were always fairly good.

Using acetophenone (**3b**) as a carbonyl partner, we also obtained good results (Table 1, entry 4). Using the less reactive 2-(3-methoxyphenyl)ethanamine (**2b**), the yield of **5b** was lower and the reaction time was longer (24 h, Table 1, entry 2). Reacting 2-phenylethanamine (**2c**), no traces of **5c** were detected; only the intermediate *N*-benzyliden-2-phenylethyl amine (**4c**) formed. This intermediate cannot cycle due to the lack of electron donating groups on the aromatic ring (Table 1, entry 3).

To further explore the synthetic usefulness of **1** in Pictet–Spengler reactions we reacted tryptamine **6** with aromatic aldehydes **3a**, **3c–g** in order to obtain tetrahydro-β-carbolines **8** (Scheme 2).

These reactions needed 20 mol % of **1**, reaction times between 8 and 16 h and heating to 80 °C; however, the yields of **8** and the recovery yield of **1** were always good (Table 3, entries 1–6). It was always possible to recover **1** in good yields (e.g., Table 3 entry 1, 85%).

It is worth noting that the Pictet–Spengler reactions, performed with other Brønsted acids as catalysts, usually require the presence of a solvent, either during the reaction or the work-up[3–5,7–10] or harsher reaction conditions.[4,5,8,10]

We then examined the extension of this procedure to aliphatic aldehydes. However, the reaction of **2a** with primary aldehyde **3h** gave a small amount of product **16a**, which arises from homo-aldol condensation and imine formation (Table 1, entry 10; Scheme 3) as well as the target product **5j**.[7] The amount of **16b** significantly increased when **2b** was reacted with **3h** (Table1, entry 11). Furthermore, the reactions of **6** with **3h** furnished only **16c** (Table 3, entry 7).

The mechanism of the Pictet–Spengler reaction, described in Scheme 3, implies the formation of the iminium salt **11**, its cyclization, and subsequent deprotonation to give the final product **12**.

However, when tautomerism between imine **13** and amine **14** is possible (probably favoured by **1**; Scheme 3), **14** can react with a protonated aldehyde initially furnishing the intermediate **15** and then the product of the homo-aldol condensation **16**.[7] Since the cyclization reaction is greatly facilitated by the presence of electron donating groups on the aromatic ring, we could suppose that in the presence of two methoxy groups the speed of the cyclization reaction is greater than the speed with which **13** can tautomerize. In the presence of only one methoxy group, however, since the speed of cyclization decreases, the possibility of tautomery between **13** and **14** increases and accordingly increases the yield of

Table 1
Synthesis of tetrahydroisoquinolines **5**

Entry	Reactants[a]		Products and yields[b] (%)	Time (h)	Tetrahydroisoquinolines **5**[c]		
					Mp[d] (°C)	Lit. mp (°C)	EI–MS: *m*/*z* (%)
1	**2a**	**3a**	**5a**, 89	6	111–112	110–111[20]	269 [M$^+$,5]
2	**2b**	**3a**	**5b**, 72	24	75–76	73–74[21]	239 [M$^+$,8]
3	**2c**	**3a**	**4c**, 85	24	Viscous oil	—[22]	209 [M$^+$,25]
4	**2a**	**3b**	**5d**, 85	8	96–97	94–96[23]	283 [M$^+$,10]
5	**2a**	**3c**	**5e**, 86	8	Waxy solid	Viscous oil[1g]	299 [M$^+$,5]
6	**2a**	**3d**	**5f**, 85	6	94–95	95–96[24]	299 [M$^+$,12]
7	**2a**	**3e**	**5g**, 84	10	142–143	140–141[24]	314 [M$^+$,5]
8	**2a**	**3f**	**5h**, 87	12	114–115	110–112[1g]	294 [M$^+$,10]
9	**2a**	**3g**	**5i**, 87	8	64–65	[e]	275 [M$^+$,5]

(*continued on next page*)

Table 1 (*continued*)

Entry	Reactants[a]		Products and yields[b] (%)	Time (h)	Tetrahydroisoquinolines **5**[c]		
					Mp[d] (°C)	Lit. mp (°C)	EI–MS: *m*/*z* (%)
10	**2a**	**3h**	**5j**, 75[f]	8	Viscous oil	Oil[26]	263 [M$^+$,15]
11	**2b**	**3h**	**5k**, —[g]	12	—	—	—
12	**2a**	**3i**	**5l**, 82[h]	6	Viscous oil	Oil[27]	283 [M$^+$,12]
13	**2a**	**3j**	**5m**, 88[h]	10	Viscous oil	[28]	275 [M$^+$,5]
14	**2a**	**3k**	**5n**, 88	8	51–52	50–51[30]	249 [M$^+$,10]

[a] All the reactions were performed with 10 mol % of **1** and at 80 °C.
[b] Yields refer to the pure products.
[c] Structures and purity of all the products were confirmed by comparison of their physical (mp) and spectral data with those reported in the literature.
[d] Crystallization solvent: MeOH.
[e] In the literature[25] only spectral data are reported.
[f] The reaction mixture was dissolved in Et_2O (5 ml) and washed with H_2O (5 ml). After solvent removal under reduced pressure, the crude residue was chromatographed on a short flash column, (eluent: CH_2Cl_2/MeOH 9:1) to provide pure **5j**. In the GC and GC/MS analyses of the crude residue **16a**, EI–MS, *m*/*z* (%) = 345 [M$^+$,45], was also detected. However, it was impossible to isolate it as pure product.
[g] On the GC and GC/MS analyses of the crude residue **4k**, EI–MS, *m*/*z* (%) = 233 [M$^+$,35], **5k**, EI–MS, *m*/*z* (%) = 233 [M$^+$,15], and **16b** EI–MS, *m*/*z* (%) = 315 [M$^+$,20] were detected (**5k** and **16b** about 1:1 ratio). However, it was impossible to separate them by flash chromatography.
[h] Cold water (5 ml) was added to the reaction mixtures, which were cooled to 0–5 °C, under vigorous stirring. The resulting gummy solids were filtered on a Buchner funnel, placed in a flask and dried under vacuum at room temperature. The resulting viscous oils were pure **5l** or **5m**.

Table 2
Consecutive reactions with **1**

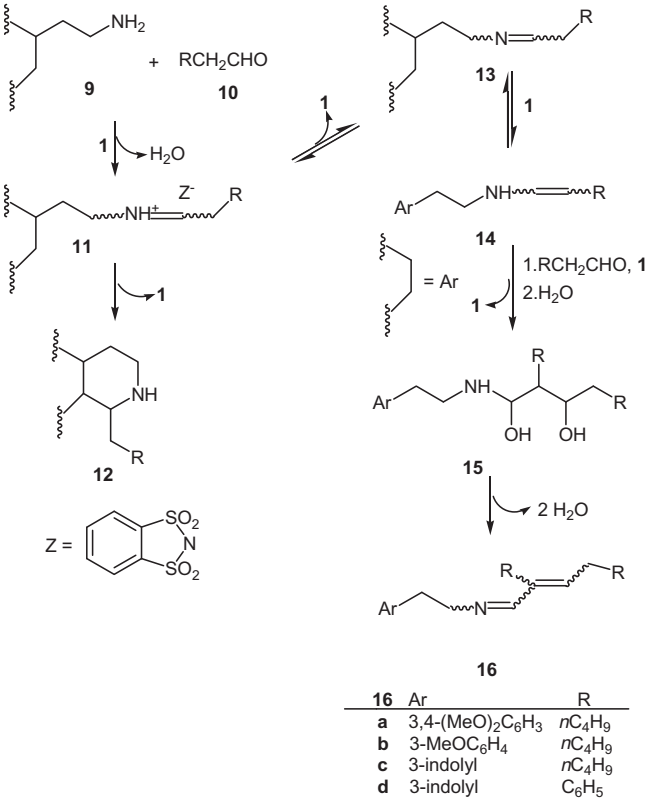
Entry	Time (h)	Yield (%) of **5a**[a]	Recover (%)of **1** (mg)
1	6	89[b]	84, 92[c]
2	9	81	80, 74[d]
3	10	78	80, 59

[a] Yields refer to the pure products.
[b] The reaction was performed with 5 mmol of **2a** and **3a** and 10 mol % of **1** (110 mg, 0.5 mmol).
[c] Recovered **1** was used as catalyst in entry 2.
[d] Recovered **1** was used as catalyst in entry 3.

Table 3
Synthesis of tetrahydro-β-carbolines **8**

Entry	Reactants[a]	Products and yields[b] (%)	Time (h)	Tetrahydro-β-carbolines **8**[c]		
				Mp[d] (°C)	Lit. mp (°C)	EI–MS: *m*/*z* (%)
1	**3a**	**8a**, 82[e]	12	161–162	160–161[3]	248 [M$^+$,5]
2	**3c**	**8b**, 86	12	95–96	[32]	278 [M$^+$,8]
3	**3d**	**8c**, 80	14	204–205	205–206[34]	278 [M$^+$,10]
4	**3e**	**8d**, 85	12	170–171	172–173[3]	293 [M$^+$,10]
5	**3f**	**8e**, 86	16	159–160	[35]	273 [M$^+$,12]
6	**3g**	**8f**, 82	16	172–173	169–170[37]	254 [M$^+$,10]
7	**3h**	**8g**, —[f]	12	—	—	—
8	**3i**	**8h**, —[g]	14	—	—	—
9	**3j**	**8i**, —[h]	16	—	—	—
10	**3k**	**8j**, 78	12	93–94	94.5–95.5[38]	228 [M$^+$,8]

[a] All the reactions were performed with **6** and 20 mol % of **1** at 80 °C.
[b] Yields refer to the pure products.
[c] Structures and purity of all the products were confirmed by comparison of their physical (mp) and spectral data with those reported in the literature.
[d] Crystallization solvent: MeOH.
[e] The reaction carried out with 10 mol % of **1**, after 24 h was not complete, due to the presence of intermediate **7a** EI–MS, *m*/*z* (%) = 248 [M$^+$,20].
[f] On the GC and GC/MS analyses of the crude residue, **16c**, EI–MS, *m*/*z* (%) = 324 [M$^+$,10] was detected. However, it was impossible to purify by flash chromatography. No traces of **8g** were detected.
[g] On the GC and GC/MS analyses of the crude residue, **16d**, EI–MS, *m*/*z* (%) = 364 [M$^+$,25] was detected. However, it was impossible to purify by flash chromatography. No traces of **8h** were detected.
[h] On the GC and GC/MS analyses of the crude residue no significant products were detected. No traces of **8i** were detected.



16	Ar	R
a	3,4-$(MeO)_2C_6H_3$	nC_4H_9
b	3-$MeOC_6H_4$	nC_4H_9
c	3-indolyl	nC_4H_9
d	3-indolyl	C_6H_5

Scheme 3. Mechanism of Pictet–Spengler reaction.

16. On the other hand, when the indolyl ring is present, tautomerization is faster than cyclization and the only product is **16**. To further the examination of aliphatic aldehydes, it is worth noting that the reactions of **2a** with **3i–k**, under the same conditions as described above for aromatic aldehydes, provided excellent yields of **5l–n** (Table 1, entries 12–14).The greater steric hindrance of aldehydes **3i** and **3j** probably made their electrophilic attack on **14** more difficult, therefore cyclization was favored. On the other hand, only **16d** was formed and no traces of **8h** were detected when **6** was reacted with **3i** (Table 3, entry 8). The reaction between **6** and **3j** also failed (Table 3, entry 9). Obviously, the only positive result was obtained by reacting **6** with tertiary aldehyde **3k** (Table 3, entry 10).

In conclusion, we have proposed a mild, easy, efficient, and green method for the synthesis of tetrahydroisoquinoline and tetrahydro-β-carboline through the Pictet–Spengler reaction in the presence of *o*-benzenedisulfonimide (**1**) used as a reusable homogeneous catalyst. The advantages of performing the Pictet–Spengler reaction in the presence of **1** as a catalyst can be summarized as follows: (1) the use of a safe, non-volatile, non-corrosive Brønsted acid, (2) good recovery yields of **1** at the end of the reactions by simply evaporating aqueous washings, (3) the target products are obtained generally in excellent yields (4) the reactions are carried out under easy, mild, and green conditions with economic and ecological benefits.

Acknowledgment

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19. *6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline* (**5a**): *representative procedure for the preparation of tetraydroisoquinolines* **5**: o-Benzenedisulfonimide (**1**; 10 mol %; 110 mg, 0.5 mmol) was added to a mixture of 2-(3,4-dimethoxyphenyl)ethanamine (**2a**; 0.91 g, 5 mmol) and benzaldehyde (**3a**; 0.53 g, 5 mmol). The mixture was stirred and heated at 80 °C. The reaction was monitored by GC and GC/MS. First, the complete disappearance of **2a** and **3a**, then the formation of intermediate **4a** and product **5a** were observed (30 min), and finally the total interconversion of **4a** to **5a** (6 h). Cold water (20 ml) was added to the reaction mixture, which was cooled to 0–5 °C, under vigorous stirring. The resulting solid was filtered on a Buchner funnel and washed with additional cold water (5 ml). It was virtually pure (GC, GC–MS, ^{1}H NMR, ^{13}C NMR) title compound **5a**, white solid; yield: 89% (1.61 g). The aqueous washings were collected and evaporated under reduced pressure. After removal of the water, virtually pure (^{1}H NMR) *o*-benzenedisulfonimide (**1**) was recovered (92 mg, 84% yield). The same procedure was employed in the preparation of tetrahydro-β-carbolines **8**.
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28. 1-Cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5m**) is known in the literature[29] but no physical and spectral data are reported. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.64 (s, 1H), 6.55 (s, 1H), 3.95 (d, J = 7.0 Hz, 1H) 3.69 (s, 3H), 3.68 (s, 3H), 3.25–3.18 (m,2H), 2.71–2.64 (m, 2H), 2.10–1.86 (m, 2H), 1.60–1.46 (m, 5H), 1.10–0.97 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.8, 147.4, 131.1, 127.8, 111.6, 109.5, 56.5, 56.1, 55.9, 43.4, 37.0, 32.1, 29.8, 26.1, 25.6.
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30. 1-(*t*-Butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5n**) is known in the literature[31] but no NMR data are reported. ^{1}H NMR (200 MHz, $CDCl_3$): 6.61 (s, 1H), 6.57 (s, 1H), 3. 99 (s, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.28–3.20 (m, 2H), 2.69–2.60 (m, 2H), 1.99 (br s, 1H), 0.86 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.5, 146.1, 131.9, 128.9, 112.4, 110.2, 56.4, 56.1, 55.7, 42.3, 25.0.
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35. 1-(4-Cyanophenyl)-1,2,3,4-tetrahydro-β-carboline (**8e**) is known in the literature[36] but no physical and spectral data are reported. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.93 (br s, 1H), 7.72–7.57 (m, 5H), 7.32–7.28 (m, 1H), 7.20–7.01 (m, 2H), 3.27–3.18 (m, 2H), 2.75–2.64 (m, 2H), 1.99 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.6, 140.3, 136.5, 132.6, 132.4, 128.6, 127.6, 122.3, 122.2, 119.5, 119.1, 118.6, 113.9, 56.9, 41.7, 22.2.
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