Pictet–Spengler Reaction of Nitrones and Imines Catalyzed by Yb(OTf)$_3$–TMSCl

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The Pictet–Spengler reaction of nitrones and imines prepared from *N*-hydroxytryptamine and tryptamine gave the corresponding tetrahydro-*β*-carbolines in excellent yields in the presence of Yb(OTf)$_3$–TMSCl in a mixture of CH_2Cl_2 and THF.

The Pictet–Spengler reaction has been shown to be useful for the synthesis of tetrahydro-*β*-carbolines and has often been applied to the synthesis of natural products.[1] We succeeded in the total synthesis of natural products such as fumitremorgin[2] and eudistomins[3] using a diastereoselective Pictet–Spengler reaction. Although this reaction proceeds efficiently under the acidic conditions, other type of promoters are required to use acid-sensitive substrate and also to develop a chiral version of Pictet–Spengler reaction.[4]

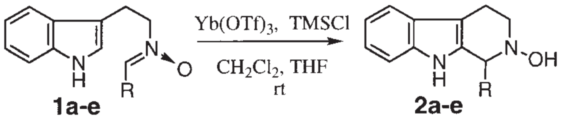
Rare-earth triflates have recently been recognized as stable, less-toxic, and environmentally harmonious Lewis acid catalysts. Various reactions have been developed using these catalysts, including the reactions of imines.[5] We have also reported that Yb(OTf)$_3$ is a powerful catalyst for imino-ene reaction in combination with a catalytic amount of TMSCl.[6,7] We report here the Pictet–Spengler reaction of imines catalyzed by the combination of Yb(OTf)$_3$ and TMSCl.

First, we tested the effectiveness of the catalyst system, Yb(OTf)$_3$–TMSCl, in the Pictet–Spengler reaction of nitrones (Scheme 1 and Table 1). The reaction of **1a** in CH_2Cl_2-THF (4 : 1) with only Yb(OTf)$_3$ (1.2 equiv) gave **2a** in 12% yield after 5 h at room temperature (entry 1). On the other hand, TMSCl (1.0 equiv) by itself promoted this reaction to give **2a** in 70% yield (entry 2) within 20 min. However, the reaction was considerably slow when only 0.12 equiv of TMSCl was used (entry 3). In contrast to these results, the reaction with both Yb(OTf)$_3$ and TMSCl proceeded efficiently and **1a** was cyclized to **2a** in quantitative yield within 20 min (entries 4 and 5).

Next, we investigated substituent effects under the conditions used for entry 5 in Table 1. The cyclization of *p*-anisyl nitrone **1b** required a prolonged reaction time and gave **2b** in only 36% yield (entry 6). On the other hand, the reaction of nitrone **1c**, which has an electron-defficient CN double bond by substitution of a nitro group, proceeded within 2 min and gave **2c** in high yield (entry 7). The methyl nitrone **1e** gave **2e** in only 30% yield (entry 9).

Then, we turned our attention to the Pictet–Spengler reaction of imines prepared from tryptamine and various aldehydes (Scheme 2 and Table 2). The Pictet–Spengler reaction of **3a** using 1.0 equiv of Yb(OTf)$_3$ gave only a trace amount of **3b**. However, the addition of 1.0 equiv of TMSCl together with Yb(OTf)$_3$ promoted the reaction and *β*-carboline **3b** was isolated in quantitative yield, whereas the reaction with 1.0 equiv of TMSCl gave **3b** in only 7% yield. TMSOTf did not promote the reaction. The similar reaction of **3b**, **3c**, and **3d** in the presence of Yb(OTf)$_3$ and TMSCl (1.0 equiv of each) gave the corresponding *β*-carbolines, **4b**, **4c** and **4d**, in quantitative yields. While **3e** gave only a trace amount of **4e** under the above conditions, the addition of 10 equiv of TMSCl improved the reaction.

A two-component Pictet–Spengler reaction, which should



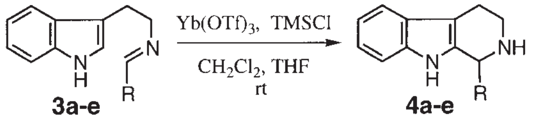
a: R=Ph, b: R=*p*-$MeOC_6H_4$, c: R=*p*-$O_2NC_6H_4$,
d: α-Naphthyl, e: R=Me

Scheme 1.

Table 1. Pictet–Spengler reaction of nitrones promoted by Yb(OTf)$_3$–TMSCl

Entry	Substrate	Yb(OTf)$_3$ /equiv	TMSCl /equiv	Time /min	Yield[a] /%
1	**1a**	1.2	- -	300	12
2	**1a**	- -	1.0	20	70
3	**1a**	- -	0.12	20	30
4	**1a**	1.0	0.12	20	>99
5	**1a**	0.25	1.0	20	>99
6	**1b**	0.25	1.0	300	36
7	**1c**	0.25	1.0	2	84
8	**1d**	0.25	1.0	90	98
9	**1e**	0.25	1.0	50	30

[a]Isolated yield.



a: R=Ph, b: R=*p*-BrC_6H_4, c: R=*p*-$O_2NC_6H_4$,
d: α-Naphthyl, e: R=*p*-$MeOC_6H_4$

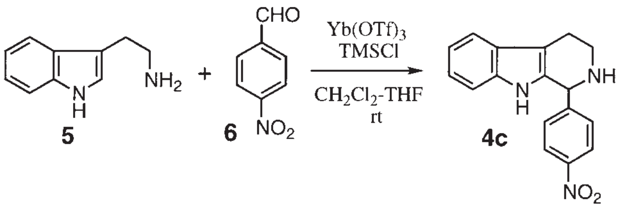
Scheme 2.

Table 2. Pictet–Spengler reaction of imines promoted by Yb(OTf)$_3$–TMSCl

Entry	Substrate	Yb(OTf)$_3$ /equiv	TMSCl /equiv	Time /h	Yield[a] /%
1	**3a**	1.0	- -	41	trace
2	**3a**	- -	1.0	1.3	7
3	**3a**	1.0	1.0	5	>99
4	**3b**	1.0	1.0	4	>99
5	**3c**	1.0	1.0	10 min	>99
6	**3d**	1.0	1.0	16	>99
7	**3e**	1.0	1.0	2	trace
8	**3e**	1.0	10.0	20	>99

[a]Isolated yield.

proceed without isolation of an imine, is desirable when the imine is unstable. However, most Lewis acids are not effective for such a two-component reaction because the reaction involves highly reactive amines and water. Thus, using a water-tolerant Lewis acid, Yb(OTf)$_3$,[8] we examined two-component coupling between tryptamine (**5**) and *p*-nitrobenzaldehyde (**6**) in the presence of Yb(OTf)$_3$ and TMSCl (Scheme 3 and Table 3).



Scheme 3.

Table 3. Two-component Pictet–Spengler reaction

Entry	Yb(OTf)$_3$ /equiv	TMSCl /equiv	Time /h	Yield[a] /%
1	1.0	1.0	10	25
2	0.3	1.0	3.5	40
3	0.2	1.0	3.5	56
4	0.1	1.0	3.5	61
5	0.05	1.0	3.5	76
6	- -	1.0	18	16

[a]Isolated yield.

When a mixture of **5** and **6** (1 : 1) was stirred under the same conditions as for entry 2 in Table 2, the reaction proceeded slowly and gave β-carboline **4c** in 25% yield after 10 h. When 1.0 equiv of Yb(OTf)$_3$ is used, tryptamine may coordinate with Yb(OTf)$_3$ and prevent imine formation. Therefore, reactions using less than 1.0 equiv of Yb(OTf)$_3$ were examined. The yield of **4c** increased dramatically up to 76%. The reaction without Yb(OTf)$_3$ gave the product in only 16% yield, and the two-component reaction was only successful using **6**.[9]

In summary, we have developed an efficient Yb(OTf)$_3$–TMSCl-mediated Pictet–Spengler reaction using mild conditions. Further studies to investigate the mechanism of this reaction and its application in asymmetric processes are under investigation.[10]

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