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Calcium-Catalyzed Pictet−Spengler Reactions

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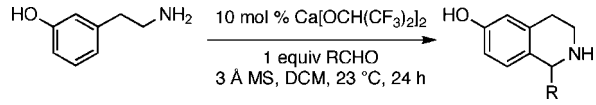
ABSTRACT



Pictet−Spengler reactions of *m*-tyramine and aldehydes produced tetrahydroisoquinolines in the presence of a catalytic amount of $Ca[OCH(CF_3)_2]_2$. This reaction occurs with a variety of aryl, heteroaryl, and alkyl aldehydes, producing tetrahydroisoquinolines in high yield and with high regioselectivity. This calcium-promoted Pictet−Spengler reaction provides a mild alternative to the traditional Brønsted acids typically employed in these reactions.

The use of calcium complexes as catalysts for organic transformations has seen a slow but steady growth over the past decade. Calcium is an attractive Lewis acid catalyst because of its low toxicity and cost. However, calcium is not traditionally thought of as a catalyst for organic transformations.[1] Recently, groups have employed calcium catalysts to promote alkene hydroaminations[2] and hydrophosphinations,[3] and aldol,[4] Michael,[5] epoxidation,[6] and Tishcenko reactions.[7] In addition, chiral complexes of calcium have been used as catalysts in enantioselective processes.[8]

Recently, we have begun a program in our laboratories to expand the use of calcium complexes in organic synthesis. Although the role of calcium has been studied greatly in biochemical processes,[9] there are not enough studies related to the behavior of calcium complexes in organic processes. However, as a greater awareness of the utility of calcium is displayed, more chemists will be attracted to study and employ this underutilized Lewis acid in organic chemistry.

The Pictet−Spengler reaction has been used in the synthesis of alkaloids as the key step in the formation of tetrahydroisoquinolines and β-carbolines.[10] Typically, strong Brønsted acids are used to promote this reaction, and in some cases, poor regioselectivities are observed. Although activated substrates containing a catechol functionality undergo Pictet−Spengler reactions under mildly acidic conditions,[11] other less activated substrates provide low conversions (vide infra).

Lewis acid catalyzed Pictet−Spengler reactions have been previously reported in the literature.[12] Although a large

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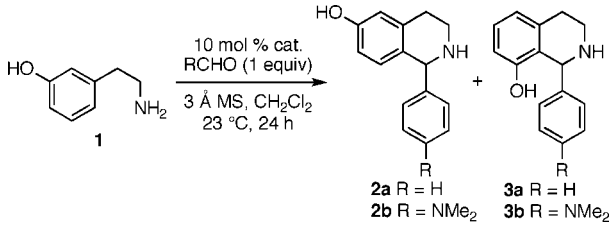
Table 1. Screening of Calcium Complexes



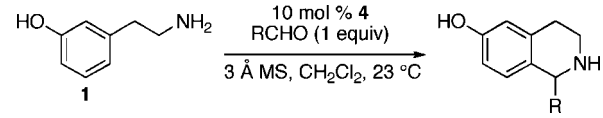
entry	catalyst	R	yield (%)[a]	ratio (**2**:**3**)
1	no catalyst	H	19	9:1
2	2 M NaOH	H	57	16:1
3	$Ca(OH)_2$	H	16	12:1
4	CaF_2	H	40	8:1
5	CaCI	H	17	5:1
6	CaI_2	H	43	5:1
7	$Ca(OTf)_2$	H	22	6:1
8	$Ca(OMe)_2$	H	92	25:1
9	$Ca(O\textit{i}\text{-}Pr)_2$	H	93	38:1
10	$Ca(THF)_2(HMDS)_2$	H	97	100:0
11	Ca(BDI)	H	>99	100:0
12	$Ca(O\textit{i}\text{-}Pr)_2$	NMe_2	0	
13	$Ca(THF)_2(HMDS)_2$	NMe_2	0	
14	Ca(BDI)	NMe_2	7	
15	Ca(hexafluoroisopropoxide)$_2$	H	>99	100:0
16	Ca(hexafluoroisopropoxide)$_2$	NMe_2	>99	100:0

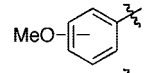
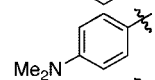
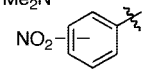
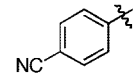
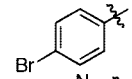
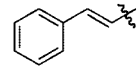
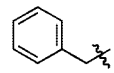
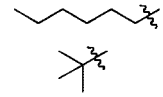
[a] Yield and ratio determined by ^{1}H NMR spectroscopy.

number of Lewis acids were screened in those papers, calcium complexes were not included in any of the studies. Kobayashi showed the use of 10 mol % of $Yb(OTf)_3$ in the presence of 3Å molecular sieves; however, the reaction scope was narrow, with only three examples reported in 55−98% yield.[12c]

Using Kobayashi's conditions as a starting point, *m*-tyramine (**1**) and benzaldehyde were combined in the presence of 3Å MS and 10 mol % catalyst in CH_2Cl_2 and monitored by ^{1}H NMR spectroscopy (Table 1). Although activated toward the cyclization reaction, **1** is converted to the desired product in 19% yield in the absence of catalyst (entry 1). The addition of sodium hydroxide to the reaction gave 57% yield of **2a** and **3a** in a 16:1 ratio. We then screened a wide range of calcium complexes that were commercially available or easily prepared.[13] Low yields and selectivity were observed when calcium halides were employed to promote the reaction (entries 4−6). Calcium alkoxides, $Ca(HMDS)_2(THF)_2$,[14] and Ca(BDI)[15] gave tetrahydroisoquinoline product in high yields and with complete selectivity as determined by ^{1}H NMR spectroscopy (entries 8−11). The best catalysts were then subjected to similar

Table 2. Scope of Reaction Catalyzed by $Ca[(OC(H)(CF_3)_2]_2$



entry	R	time (h)	yield (%)[a]
1		5	97
2-4		24	2-OMe = 92 3-OMe = 97 4-OMe = 92
5		18	89
6-8		5	2-NO_2 = 94 3-NO_2 = 98 4-NO_2 = 96
9		18	90
10		24	97
11		24	89[b]
12		18	96
13		24	65
14		24	92
15		24	91
16		24	0

[a] Isolated yields. [b] Isolated as an 8:1 mixture of isomers.

reaction conditions, with benzaldehyde being replaced with 4-(dimethylamino)benzaldehyde. Suprisingly, none of these cataylsts were reactive using the electron-rich benzaldehyde. From the simple assumption that increasing the Lewis acidity at the calcium center should generate a more reactive catalyst, we synthesized Ca(hexafluoroisopropoxide)$_2$ (**4**) and applied it to our reaction conditions. In both cases of aldehydes, catalyst **4** provided the corresponding products (**2a**, **2b**) in excellent yield and regioselectivity (entries 15 and 16).

To probe the utility of this catalyst system, we explored the substrate scope of this process (Table 2). As shown in the table, the reaction of *m*-tyramine with various aldehydes in the presence of **4**, produces a variety of 6-hydroxy-tetrahydroisoquinolines in high yields and regioselectivities. The existence of electron-donating (entries 2−5) and electron-withdrawing groups (entries 6−9) on the arenes did not have an effect on yield or regioselectivity. Interestingly, 2-pyridine carboxaldehyde was the lone substrate that produced appreciable amounts of both regioisomers (8:1, 6-ol:8-ol) (entry 11). One explanation for the appearance of the 8-ol regioisomer in this example may be simultaneous coordination of the calcium center to the pyridine nitrogen and oxygen of

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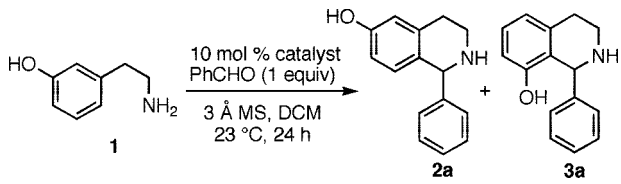
Table 3. Cation Effect



entry	catalyst	yield[a]	ratio (**2**:**3**)
1	2 M NaOH	57	16:1
2	2 M KOH	55	10:1
3	$LiOH{\cdot}H_2O$	61	30:1
4	$Ba(OH)_2$	50	16:1
5	$Ca(OH)_2$	15	15:2
6	Na(hexafluoroisopropoxide)	35	25:2
7	Li(hexafluoroisopropoxide)	22	27:2
8	K(hexafluoroisopropoxide)	15	8:1
9	$Ba(hexafluoroisopropoxide)_2$	88	100:0
10	$Ca(hexafluoroisopropoxide)_2$	>99	100:0

[a] Yield and ratio were determined by ^{1}H NMR spectroscopy.

the phenol. This catalyst also promoted the reaction of *trans*-cinnamaldehyde with *m*-tyramine in 96% yield (entry 12), whereas the $Yb(OTf)_3$ catalyst system gave a complex mixture of products under similar conditions. The imines of alkyl aldehydes also underwent cyclization to the corresponding products in high yields (entries 13−15). The use of pivaldehyde did not allow product formation, and we attribute this unreactivity to obvious steric reasons (entry 16).

In an effort to further understand the role of calcium in these reactions, we investigated the influence that other cations invoked on this reaction. We evaluated a number of Group I and Group II metal hydroxides under our optimized reaction conditions (Table 3). The yields observed for all metal hydroxides did not appear to vary greatly as they ranged between 50−60%, except for the low yield of calcium hydroxide, which we attribute to the poor solubility of calcium hydroxide in dichloromethane. We then synthesized the corresponding metal hexafluoroisopropoxide complexes and compared their catalytic ability to **4**. These complexes all gave low yields (entries 6−8), except for barium hexafluoroisopropoxide, which gave the desired product regioselectively in 88% yield. However, barium bis(hexafluoroisopropoxide) does not catalyze the conversion of **1** and *p*-dimethylaminobenzaldehyde to **2b**. These results suggest the calcium cation has a large effect on this transformation and this is not simply a base-promoted process.

Currently, the exact role of calcium in this process is unclear. The use of less reactive Pictet−Spengler substrates such as tryptamine did not produce cyclization to the desired product under our conditions, as we only observed their corresponding imines by ^{1}H NMR spectroscopy. A similar result was reported by Kobayashi.[12c]

In summary, we report a practical method to synthesize 1,2,3,4-tetrahydroisoquinolines that is mediated by a novel calcium hexafluoroisopropoxide complex. This method provides a mild alternative to the typical conditions requiring strong Brønsted acids. Future work in this area involves identifying the exact role of the calcium catalyst, which should assist us in expanding the scope of this reaction to include less reactive tryptamine and tryptophan substrates. We are also investigating the use of chiral calcium complexes to effect an enantioselective version of this Pictet−Spengler reaction.

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

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