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Calcium-Promoted Pictet-Spengler Reactions of Ketones and Aldehydes

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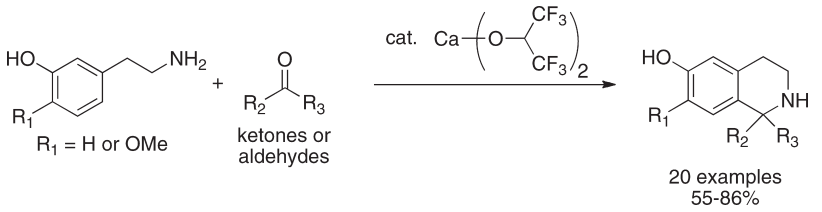

Calcium *bis*-1,1,1,3,3,3-hexafluoroisopropoxide is shown to be an effective catalyst for Pictet−Spengler reactions of 3-hydroxyphenethylamine and 3-hydroxy-4-methoxyphenethylamine with various aldehydes and ketones. Previous Lewis acid catalyzed Pictet−Spengler reactions of unactivated ketones typically require two separate reactions (imine formation, cyclization) to obtain the same results. The reactions described within directly provide 1,1′-disubstituted tetrahydroisoquinolines from the corresponding amine and ketone. These rare examples of Pictet−Spengler reactions of unactivated ketones demonstrate the unique nature of calcium as a Lewis acid catalyst.

Introduction

Calcium salts are highly abundant in nature and have a wide variety of industrial and commercial uses. Though calcium salts are often used as drying agents in organic chemistry, the use of calcium as a Lewis acid in organic synthesis is slowly gaining widespread attention because of the interesting reactivity of calcium, along with its low cost and low toxicity.[1] Calcium is a versatile metal as it catalyzes a variety of reactions including hydroaminations[2] and -phosphinations,[3] ring-opening polymerizations of lactides,[4] asymmetric epoxidations,[5] aldol reactions,[6] 1,4 additions,[7] and C−H activation reactions.[8]

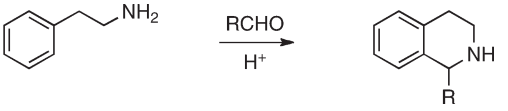

FIGURE 1. Classical Pictet−Spengler reaction.

The Pictet−Spengler reaction is a commonly used synthetic tool for the preparation of tetrahydroisoquinoline and β-carboline alkaloids (Figure 1).[9] This reaction is typically promoted by stoichiometric amounts of strong Brønsted acids, which can have obvious functional group compatibility issues and typically exhibit poor regiochemical control. Therefore, recent investigations of Pictet−Spengler reactions have

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(2) Crimmin, M. R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2009**, *131*, 9670–9685.

(3) (a) Crimmin, M. R.; Barrett, A. G. M.; Hill, M. S.; Hitchcock, P. B.; Procopiou, P. A. *Organometallics* **2007**, *26*, 2953. (b) Crimmin, M. R.; Barrett, A. G. M.; Hill, M. S.; Hitchcock, P. B.; Procopiou, P. A. *Organometallics* **2008**, *27*, 497.

(4) Chisholm, M. H.; Galluchi, J.; Phomphrai, K. *Inorg. Chem.* **2004**, *43*, 6717–6725.

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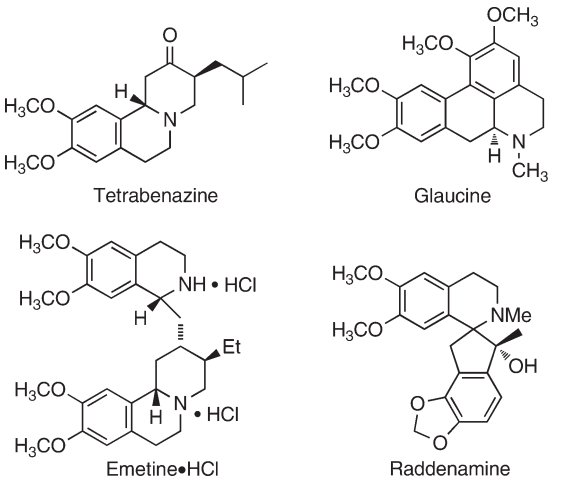


FIGURE 2. Some naturally occurring tetrahydroisoquinolines.

focused on employing Lewis acid catalysts to affect this transformation.[10]

Previously, we reported that 1-substituted 1,2,3,4-tetrahydroisoquinolines can be prepared regioselectively in excellent yields by the reaction of a 1:1 mixture of 3-hydroxyphenthylamine and various aldehydes using a catalytic amount of calcium 1,1,1,3,3,3-hexafluoroisopropoxide ($Ca(HFIP)_2$, **1**).[11] These reactions were conducted at ambient temperature and required 24 h or less to proceed to completion, making this a mild procedure for synthesizing such compounds. The reaction was tolerant of many functional groups and allowed for the installation of alkyl, aryl and alkenyl groups about the 1-position of the tetrahydroisoquinoline molecule. Herein, we report an expanded scope of calcium-catalyzed Pictet-Spengler reactions along with possible mechanistic details for the reaction.

Results and Discussion

In an effort to further expand the substrate scope of the calcium-catalyzed reactions, a series of reactions were carried out using 3-hydroxy-4-methoxyphenethylamine (**2**) and various aldehydes, to provide tetrahydrosioquinolines that contain the oxygen substitution pattern that mimics some naturally occurring tetrahydroisoquinolines (Figure 2). The lack of reactivity of calcium using this type of substrate may be caused by the potential chelating ability of the 1,2-OH/OCH_3 groups. The ability of the amine substrate (**2**) to reversibly coordinate to the calcium complex through the hydroxy and methoxy functionalities likely causes the catalyst to be bound to this area of the molecule, making less calcium catalyst available in the reaction mixture to coordinate to the imine and promote the cyclization (Scheme 1). The product also contains this *ortho* relationship and can therefore coordinate to calcium to deactivate the catalyst.

To overcome this problem, we increased the catalyst loading of (**1**) to 20 mol %, which then allowed the formation of a variety of THIQ from amine **2** and various aldehydes

SCHEME 1

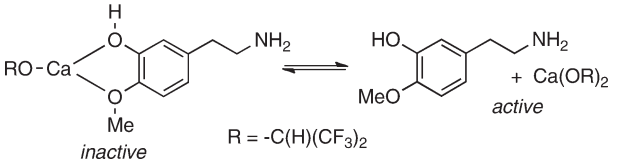
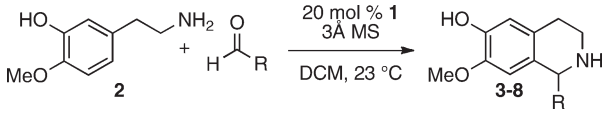
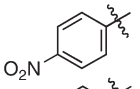
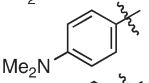
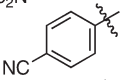
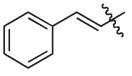
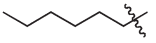


TABLE 1. Pictet−Spengler Reaction of Phenethylamine (2) and Aldehydes[a]



entry	compd	R	time (h)	yield (%)
1	**3**		22	86
2	**4**		24	83
3	**5**		24	91
4	**6**		48	82
5	**7**		24	81
6	**8**		24	79

[a]Yields are an average of two one mmol scale reactions.

(Table 1). All reactions gave the corresponding tetrahydroisoquinoline products in 79−91% yield at 23 °C in less than 24 h. The only outlier was 4-formylbenzonitrile, which required 48 h (entry 4) for the reaction to proceed to completion.

Although the Pictet−Spengler reaction proceeds smoothly with aldehydes, there are few reported methods that employ ketones to prepare 1,1′-disubstituted tetrahydroisoquinolines.[12] Typical ketones employed in the majority of these reactions are activated β-ketoacids or esters. Low-yielding reactions with unactivated ketones are likely caused by slow imine formation, as well as a cyclization step that is inhibited by steric issues encountered during formation of the tetrasubstituted center. To avoid these issues, Pictet−Spengler reactions of ketones are usually separated into multiple steps that involve the synthesis and activation of the imine, followed by a cyclization step after purification. For example, Horiguchi and co-workers reported that the Pictet−Spengler reaction to form 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines required two steps: titanium isopropoxide mediated imine formation following by trifluoroacetic acid mediated cyclization of the resulting imine.[13] One of

(10) (a) Manabe, K.; Nobutou, D.; Kobayashi, S. *Bioorg. Med. Chem.* **2005**, *13*, 5154. (b) Srinivasan, N.; Ganesan, A. *Chem. Commun.* **2003**, 916. (c) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. *Chem. Lett.* **2002**, 428. (d) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348. (e) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521.

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(12) Bois-Choussy, M.; Cadet, S.; De Paolis, M.; Zhu, J. P. *Tetrahedron Lett.* **2001**, *42*, 4503. Hegedus, A.; Hell, Z. *Tetrahedron Lett.* **2004**, *45*, 8553. Horiguchi, Y.; Kodama, H.; Nakamura, M.; Yoshimura, T.; Hanezi, K.; Hamada, H.; Saitoh, T.; Sano, T. *Chem. Pharm. Bull.* **2002**, *50*, 253. Hudlicky, T.; Kutchan, T. M.; Shen, G.; Sutliff, V. E.; Coscia, C. J. *J. Org. Chem.* **1981**, *46*, 1738. Kawai, M.; Deng, Y. L.; Kimura, I.; Yamamura, H.; Araki, S.; Naoi, M. *Tetrahedron-Asymmetry* **1997**, *8*, 1487. Venkov, A. P.; Angelov, P. A. *Synth. Commun.* **2003**, *33*, 3025.

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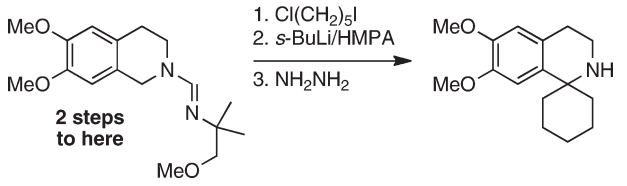
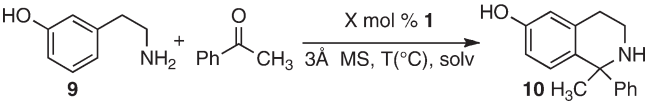
SCHEME 2



the most effective approaches for the synthesis of tetrahydroisoquinolines containing a quaternary center was developed by Meyers (Scheme 2).[14] However, this method is a lengthy multistep sequence of reactions producing spirocyclic tetrahydroisoquinolines. Because of our previous success in catalyzing Pictet−Spengler reactions of aldehydes using catalyst (**1**) and the fact that a Lewis acid catalyst for Pictet−Spengler reactions of ketones does not exist, a thorough examination of ketones was undertaken.

During our previous study of Pictet−Spengler reactions of aldehydes at ambient temperature reactions with ketones failed,[11] although a rigorous study was not undertaken. A number of solvents were tested in the reaction of 3-hydroxyphenethylamine (**9**) with acetophenone in the presence of catalytic $Ca(HFIP)_2$ (**1**). Reacting 10 mol % of (**1**) with 1 equiv of amine (**9**) and acetophenone in dichloromethane at room temperature confirmed that prior standard conditions were not sufficient to promote cyclization to the 1,1′-disubstituted tetrahydroisoquinoline (**10**) (Table 2, entry 1). Imine formation was slow and large amounts of starting ketone and amine were observed in the ^{1}H NMR spectrum of the crude residue. To promote formation of the imine, higher boiling solvents were screened. 1,2-Dimethoxyethane, 1,2-dichloroethane, and 2-methyltetrahydrofuran (entries 2−4) gave inferior results, while toluene (entry 5) proved to be the best solvent. The reaction of acetophenone and amine (**9**) gave 71% yield of the corresponding 1,1′-disubstituted tetrahydroisoquinoline after 24 h at 100 °C with 10 mol % $Ca(HFIP)_2$. In the absence of catalyst, the reaction proceeded sluggishly, giving 29% yield after 24 h at 100 °C (entry 7). Increasing the catalyst loading to 20 mol % provided quantitative conversion to product after 24 h (entry 8−9). After screening lower loadings and reaction times (entry 10−11), 20 mol % of $Ca(HFIP)_2$ (**1**) in toluene at 100 °C proved to be the most general reaction conditions.

TABLE 2. Initial Screening for Pictet−Spengler Reactions of Acetophenone



entry	catalyst (mol %)	solvent	*T* (°C)	time (h)	yield (%)[a]
1	10	DCM	23	24	0
2	10	DCE	85	24	11
3	10	DME	85	24	0
4	10	2-MeTHF	80	24	14
5	10	toluene	100	24	71
6	10	toluene	23	24	11
7	0	toluene	100	24	29
8	20	toluene	100	18	87
9	20	toluene	100	24	98
10	1	toluene	100	96	73
11	10	toluene	100	96	99

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

With these new reaction conditions in hand, a series of ketones were screened (Table 3). The initial test substrate using acetophenone (entry 1) only provided 65% yield of the corresponding product. This THIQ (**10**) suffers from severe solubility issues in common organic solvents, including DMSO, making workup and isolation problematic even though the reaction shows high conversions. Simple ketones work well (entry 2−3) as do ketones that give 1,1′-spiroalkane products (entry 4−6). Substituted acetophenone derivatives also provide the desired products (entry 7−8). Ethyl pyruvate was converted to the corresponding tetrahydroisoquinoline in good yield, but was difficult to purify by column chromatography (entry 9).[15] Ketones bearing a tertiary amine gave a mixture of regioisomers most likely because of the compound's ability to serve as a ligand (vide infra) for the calcium catalyst (entry 10). Bulky ketones, such as benzophenone, were too sterically congested to give any product and the reactions with these ketones showed minimal imine formation by ^{1}H NMR spectroscopy.

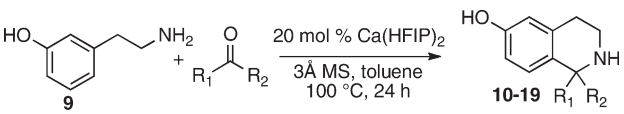
The formation of 1,2,3,4-tetrahydroisoquinolines with ketones employing amine (**2**) would provide products that mimic more naturally occurring tetrahydroisoquinolines because of the guaiacol motif. Good yields were obtained when employing acetone or related ketones (Table 4, entry 1−4). In these entries, the reaction could be conducted at 23 °C. However, the reaction of these ketones with amine **9** required higher temperatures, which may be caused by poorer solubility of the intermediates in these reactions. Unfortunately, acetophenones were not converted to the corresponding tetrahydroisoquinolines in similarly high yields (entry 5−6).

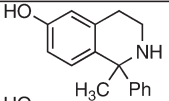
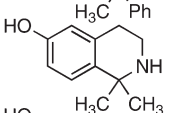
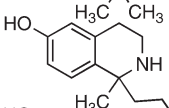
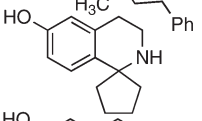
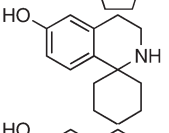
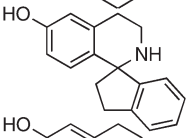
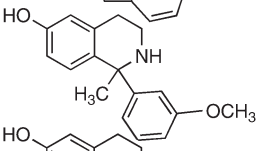
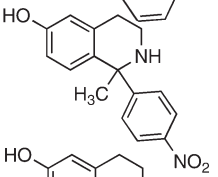
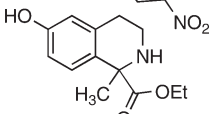
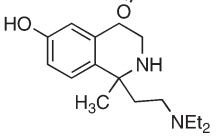
The proposed catalytic cycle for the calcium-catalyzed Pictet−Spengler reaction is shown in Scheme 3. The initial step of the reaction involves the formation of the imine. The calcium complex coordinates to the imine nitrogen, activating the substrate toward attack to create the resonance stabilized carbocation and a covalently bound calcium amido complex. Deprotonation of the acidic hydrogen by the alkoxy ligand followed by hydrolysis of the amido ligand generates the uncomplexed tetrahydroisoquinoline. Currently,

(14) Meyers, A. I.; Du, B.; Gonzalez, M. A. *J. Org. Chem.* **1990**, *55*, 4218.

(15) After working extensively with these THIQ compounds, a comment on their physical properties requires further discussion. Most of these compounds are poorly soluble in organic solvents aside from alcohols and other polar solvents such as DMSO, which may be attributed to the zwitterionic nature of the compounds. IR spectroscopy of the starting phenoxyamines (**2**) and (**9**) as well as the tetrahydrosioquinoline products do not show absorbtions indicative of phenols (3600 cm^{-1}) or amines (3400 cm^{-1}) in the downfield portion of the infrared spectrum. Instead, a very large and very broad peak around 2600 cm^{-1} is observed, which is the characteristic absorbance for ammonium ions and tetrasubstituted amines. By observing this peak, we are presuming that under our reaction conditions the molecules may exist in their zwitterionic form. This form makes for very difficult separation and purification due to the high polarity of the electrostatic interactions within the molecules. In fact, chromatographic separation cannot be achieved without strong eluting conditions as the compounds reside on the baseline. Recrystallization is also an acceptable pathway to obtain the product, but low yields and the compound's ability to retain solvent led us away from this purification method. Therefore, a simple trituration with a low boiling and relatively low polarity solvent such as diethyl ether achieved good yields in most cases, even though this isolation technique is not completely quantitative. Therefore, we observe very high and sometimes even quantitative conversion of starting materials to products, but the chemical properties of these compounds lower the amount of isolated material.

TABLE 3. Pictet−Spengler Reactions of Phenethylamine (9) and Ketones[a]



entry	cmpd	product	% yield
1	**10**		65
2	**11**		86
3	**12**		78
4	**13**		73
5	**14**		78
6	**15**		69
7	**16**		68
8	**17**		84
9	**18**		44(80)[b]
10	**19**		59[c]

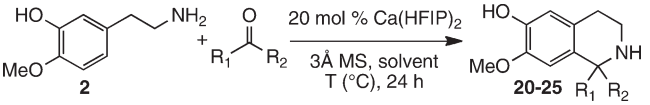
[a]Yields are an average of two one mmol scale reactions. [b]Yield determined by 1H NMR spectroscopy. [c]Yield is a 5:2 mixture of 6-ol and 8-ol regioisomers.

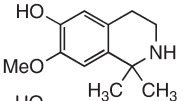
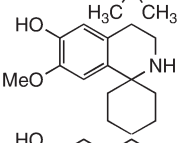
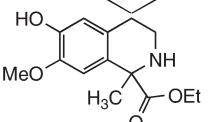
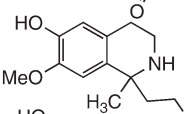
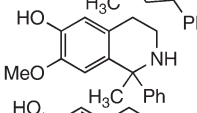
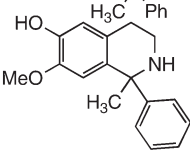
the heterogeneity of this calcium system has prevented exploration of solution phase mechanistic studies.

Literature methods for preparing similar THIQ compounds rely on the use of strong Brønsted acids or Lewis acids to perform this transformation.[10,16] To compare the effectiveness of our calcium-catalyzed Pictet−Spengler reaction with those found in the literature, phenethylamine (**9**) was treated with benzyl acetone to synthesize THIQ (**12**) (Table 5). Using various concentrations of trifluoroacetic acid (entries 1−3) at ambient temperature and at 80 °C gave very poor yields.

(16) Bois-Choussy, M.; Cadet, S.; De Paolis, M.; Zhu, J. P. *Tetrahedron Lett.* **2001**, *42*, 4503.

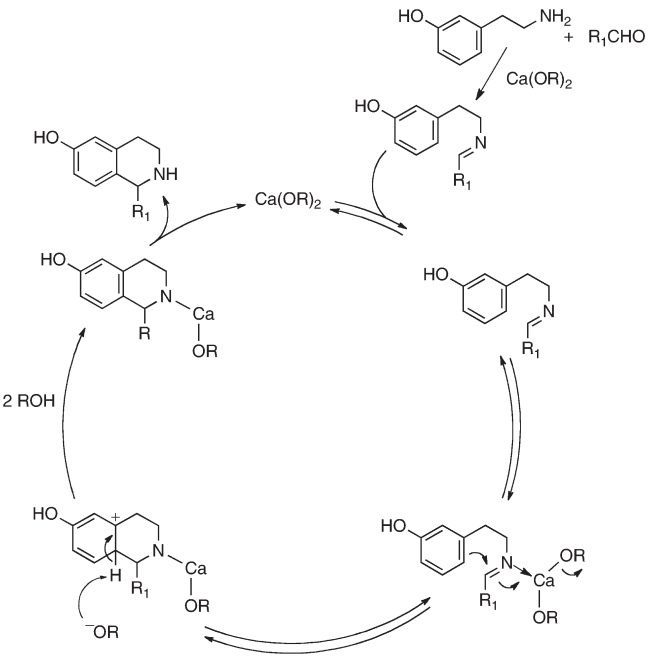
TABLE 4. Pictet−Spengler Reactions of Phenethylamine (2) and Ketones[a]



entry	cmpd	product	solvent	T (°C)	yield(%)
1	**20**		DCM	23 °C	72
2	**21**		DCM	23 °C	86
3	**22**		DCM	23 °C	84[c]
4	**23**		DCM	23 °C	70
5	**24**		toluene	100 °C	39[c]
6	**25**		toluene	100 °C	28[c]

[a]Yields are an average of two one mmol scale reactions. [b]Yield determined by 1H NMR spectroscopy.

SCHEME 3



Heating the reaction mixture in concentrated hydrochloric acid for 24 h surprisingly gave very poor yields as well (entry 4). Heating the starting materials in strong aqueous NaOH

SCHEME 4. Substrate Directing of Regioisomers

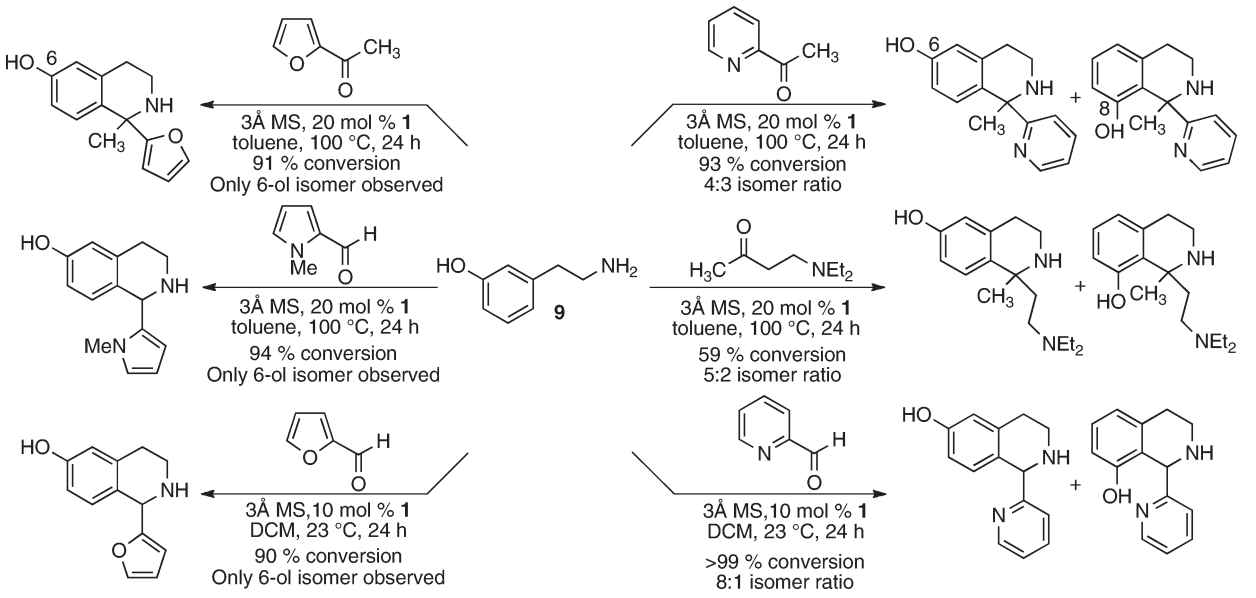
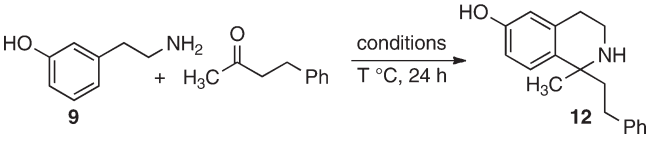


TABLE 5. Acid- or Base-Promoted Pictet–Spengler Reactions[a]



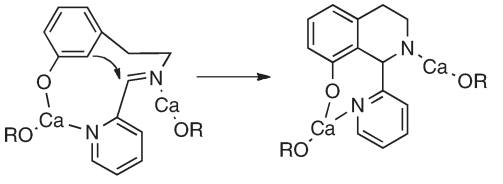
entry	conditions	*T* (°C)	yield (%)
1	2% TFA in DCM	23	< 5
2	1 equiv TFA in DCM	23	< 5
3	2% TFA in CH_3CN	80	< 5
4	Conc. HCl	100	< 5
5	12 M NaOH	100	58
6[b]	cat. $Yb(OTf)_3$/toluene	100	51
7[c]	cat. $Ca(HFIP)_2$/toluene	100	78

[a]Yield determined by ^1H NMR spectroscopy. [b]Refer to ref 10a. [c]Table 3, Entry 3.

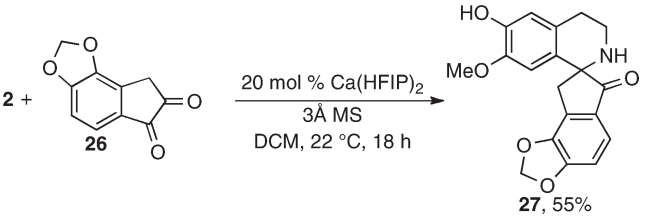
(entry 5) gave the highest result of 58% yield. Employing conditions previously reported by Kobayashi[10] for Pictet–Spengler reactions of aldehydes and phenethylamine **9** gave 51% yield of the desired THIQ. Moreover, this catalyst gave < 30% yield for reactions of phenethylamine **2** with benzyl acetone (see Table 4, entry 4). From these observations, it is unlikely that calcium complex **1** is simply acting as a simple Brønsted acid or base.

During the course of these studies, we observed that Pictet-Spengler reactions promoted by calcium complex (**1**) produced regioselective products in most cases, giving rise to only the 6-ol isomer. However, when a nitrogen functionality is present, the isomeric ratio of products is altered to give mixtures of the favored 6-ol isomer and the disfavored 8-ol regioisomer (Scheme 4). For example, pyridine carboxaldehyde gave an 8:1 mixture of the 6-ol to 8-ol regioisomers (entry 1), while a 4:3 mixture of regioisomers was observed when 2-acetylpyridine was employed (entry 2). The same effect was not observed when fufural, 2-furyl methyl ketone, or *N*-methylpyrrole-2-carboxaldehyde was employed. This observation shows that a nitrogen-bearing substituent can greatly affect the regioselective control of the reaction.

SCHEME 5



SCHEME 6



The observation that the substrate can direct the regiochemistry of the reaction may arise from simultaneous coordination of the calcium to the phenoxide and an additional coordinating group, such as the nitrogen in pyridine (Scheme 5). At this point, attack on the imine will result from most accessible position, *ortho* to the phenoxide, resulting in the 8-ol tetrahydroisoquinoline isomer. This directing effect could be used to control the regiochemistry of the reaction if one desired the less favored isomer.

In an effort to exploit this new Pictet–Spengler methodology we decided to target spirobenzylisoquinoline alkaloids. Spirobenzylisoquinoline alkaloids (SBA) are components of plants that are employed in Eastern medicine[17] and have been shown to exhibit antiviral activity.[18] Tetrahydroisoquinoline (**27**) is a common intermediate to several of these compounds. To examine (**1**) as a catalyst to prepare intermediate (**27**), amine (**2**) and dione (**26**) were exposed to the optimized reaction conditions (Scheme 6). The spiroisoquinoline

(17) Kim, D. K.; Shin, T. Y. *Arch. Pharm.* **2000**, *23*, 459.
(18) Orhan, I.; Ozcelik, B.; Karaoglu, T.; Sener, B. *Z. Naturforsch. C: Biosci.* **2007**, *62*, 19.

product was isolated in 55% yield (average of two runs). This result proves more effective than similar reactions that required 96 h to obtain 44% yield of **27** using HCl as a promoter.[19]

In conclusion, we have demonstrated an efficient calcium-catalyzed synthesis of various 1,2,3,4-tetrahydrosioquiolines. Remarkably, the $Ca(HFIP)_2$ complex also promotes the Pictet-Spengler reaction of ketones with amines to produce 1,1′-disubstituted 1,2,3,4-tetrahydrosioquinolines in a single step. Further studies are ongoing in our laboratory to develop an asymmetric calcium-catalyzed Pictet−Spengler reaction.

Experimental Section

General Procedure for Calcium-Catalyzed Pictet−Spengler Reactions: Procedure A. 1-Phenyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (3). In a drybox, an oven-dried 50 mL RBF with stir bar is charged with calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.2 mg, 0.201 mmol, 19.9 mol %), 3-hydroxy-4-methoxyphenethylamine (168 mg, 1.01 mmol) and 3 Å MS (400 mg). The flask is sealed and removed from the drybox where dry DCM (10 mL) and benzaldehyde (112 mg, 1.06 mmol) are added via syringe, respectively. The reaction is allowed to stir for 22 h at ambient temperature. The reaction suspension was added to a separatory funnel containing H_2O (5 mL) and brine (10 mL). The organic layer is removed and the aqueous layer is extracted (EtOAc, 2 × 10 mL) and the organic layers combined, dried (Na_2SO_4), filtered through Celite and concentrated. The crude residue is triturated with small amounts of Et_2O to give the product **3** (222 mg, 0.868 mmol, 86%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ 2.52−2.59 (m, 1H), 2.68−2.75 (m, 1H), 2.79−2.85 (m, 1H), 2.96−3.01 (m, 1H), 3.49 (s, 3H), 4.89 (s, 1H), 6.14 (s, 1H), 6.53 (s, 1H), 7.22−7.32 (m, 5H), 8.74 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 28.5, 41.2, 55.6, 60.5, 111.7, 115.4, 126.7, 127.9, 128.7, 128.7, 144.9, 145.5, 145.6; IR (KBr): 3283, 3034, 2934, 2911, 2836, 2706, 2536, 1601, 1522, 1458, 1433, 1412, 1361, 1254, 1207, 1112, 1098, 1020, 804, 700. HRMS (ESI): calcd for $C_{16}H_{17}NO_2$ $[M + H]^+$ 256.1332, found 256.1326.

General Procedure for Calcium-Catalyzed Pictet−Spengler Reactions: Procedure B. 1-(*p*-Nitrophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (4). In a drybox, an oven-dried 50 mL RBF with stir bar is charged with calcium 1,1,1,3,3,3-hexafluoroisopropoxide (76.7 mg, 0.205 mmol, 20.5 mol %), 3-hydroxy-4-methoxyphenethylamine (168 mg, 1.00 mmol), *p*-nitrobenzaldehyde (155 mg, 1.03 mmol) and 3 Å MS (400 mg). The flask is sealed and removed from the drybox where dry DCM (10 mL) is added via syringe. The reaction is allowed to stir for 22 h at ambient temperature. The reaction suspension was added to a separatory funnel containing H_2O (5 mL) and brine (10 mL). The organic layer is removed and the aqueous layer is extracted (EtOAc, 2 × 10 mL) and the organic layers combined, dried (Na_2SO_4), filtered through Celite and concentrated. The crude residue is triturated with small amounts of Et_2O to give the product **4** (249 mg, 0.829 mmol, 83%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO): δ 2.54−2.60 (m, 1H), 2.67−2.74 (m, 1H), 2.80−2.95 (m, 2H+1H), 3.51 (s, 3H), 5.04 (s, 1H), 6.16 (s, 1H), 6.56 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 8.82 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): 28.3, 40.8, 55.7, 59.5, 111.6, 115.6, 123.1, 127.4, 127.9, 129.9, 145.2, 145.7, 146.3, 153.7; IR (KBr): 3262, 3074, 3020, 2944, 2874, 1593, 1516, 1436, 1350, 1278, 1239, 1213, 1118, 1090, 1024, 855, 814, 747, 701. HRMS (ESI): calcd for $C_{16}H_{16}N_2O_4$ $[M + H]^+$ 301.1183, found 301.1170.

1-(*p*-Dimethylaminophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5). The compound is prepared using general procedure B. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.0 mg, 0.200 mmol, 20.0 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (168 mg, 1.00 mmol) and *p*-(dimethylamino)-benzaldehyde (153 mg, 1.02 mmol) in DCM for 22 h at ambient temperature to give the product **5** (272 mg, 0.912 mmol, 91%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ 2.50−2.58 (m, 1H), 2.65−2.72 (m, 1H), 2.75−2.82 (m, 1H), 2.86 (s, 6H), 2.95−3.01 (m, 1H), 3.50 (s, 3H), 4.76 (s, 1H), 6.17 (s, 1H), 6.50 (s, 1H), 6.65 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 8.68 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): 28.6, 40.2, 41.3, 55.7, 60.1, 111.8, 112.0, 115.4, 127.8, 129.2, 129.7, 133.3, 144.8, 145.4, 149.4; IR (KBr): 3270, 3010, 2972, 2950, 2892, 2559, 1616, 1523, 1444, 1352, 1328, 1271, 1255, 1215, 1164, 797. HRMS (ESI): calcd for $C_{18}H_{21}N_2O_2$ $[M + H]^+$ 299.1754, found 299.1744.

1-(*p*-Cyanophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (6). The compound is prepared using general procedure B. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (74.3 mg, 0.201 mmol, 20.0 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (167 mg, 1.00 mmol) and *p*-cyanobenzaldehyde (132 mg, 1.01 mmol) in DCM (10 mL) for 48 h at ambient temperature to give the product **6** (231 mg, 0.824 mmol, 82%) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 2.53−2.59 (m, 1H), 2.66−2.73 (m, 1H), 2.78−2.84 (m, 1H+1H), 2.88−2.94 (m, 1H), 3.51 (s, 3H), 4.98 (s, 1H), 6.15 (s, 1H), 6.54 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 8.81 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): 28.3, 40.8, 55.7, 59.8, 109.5, 111.6, 115.6, 119.0, 127.5, 128.0, 129.7, 131.9, 145.2, 145.7, 151.5; IR (KBr): 3270, 3044, 2999, 2916, 2840, 2559, 2226, 1607, 1508, 1449, 1281, 1203, 1096, 1018, 830, 813, 763, 564. HRMS (ESI): calcd for $C_{17}H_{16}N_2O_2$ $[M + H]^+$ 281.1285, found 281.1290.

(*E*)-1-Styryl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7). The compound is prepared using general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.2 mg, 0.201 mmol, 20.0 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (167 mg, 1.00 mmol) and *trans*-cinnamaldehyde (136 mg, 1.06 mmol) in DCM (10 mL) for 20 h at ambient temperature. Purification was achieved by adsorbing the crude reaction mixture onto silica gel, loading the silica onto a short column and flushing the column (25% EtOAc in hexanes) to remove impurities. The remaining silica was washed with MeOH and filtered. The filtrate was concentrated to dryness to give the product **7** (227 mg, 0.81 mmol, 81%) as a red crystalline solid. ^{1}H NMR (400 MHz, DMSO): δ 2.53−2.64 (m, 2H), 2.81−2.87 (m, 1H), 3.04−3.09 (m, 1H), 3.65 (s, 3H), 4.45 (d, J = 7.2 Hz, 1H), 6.33−6.39 (m, 1H), 6.51−6.58 (m, 3H), 7.20−7.25 (m, 1H), 7.27−7.33 (m, 2H), 7.38−7.45 (m, 2H), 8.77 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 28.5, 40.8, 55.8, 58.1, 111.2, 115.7, 126.2, 127.2, 127.5, 127.8, 128.6, 129.9, 133.4, 137.0, 145.0, 145.7; IR (KBr): 3282, 3059, 3021, 2932, 2835, 2582, 1598, 1509, 1448, 1328, 1274, 1209, 1128, 1022, 967, 692. HRMS (ESI): calcd for $C_{18}H_{19}NO_2$ $[M + H]^+$ 282.1489, found 282.1489.

1-Hexyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (8). The compound is prepared using general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.3 mg, 0.201 mmol, 20.1 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (168 mg, 1.00 mmol) and heptanal (122 mg, 1.07 mmol) in DCM (10 mL) for 24 h at ambient temperature. Purification was achieved by adsorbing the crude reaction mixture onto silica gel, loading the silica onto a short column and flushing the column (25% EtOAc in hexanes) to remove impurities. The remaining silica was washed with MeOH and filtered. The filtrate was concentrated to dryness to give the product **8** (210 mg, 0.797 mmol, 79%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85−0.91 (m, 3H), 1.29−1.48 (m, 8H), 1.65−1.83 (m, 2H), 2.58−2.74 (m, 2H), 2.91−2.98 (m, 1H), 3.18−3.24 (m, 1H), 3.84 (s, 3H), 3.88−3.91 (m, 1H), 4.17 (bs, 1H), 6.58 (s, 1H), 6.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 26.3, 29.4, 29.7, 32.1, 36.8, 41.2, 55.7, 56.2, 10.8, 115.0, 128.0, 131.1, 144.2,

(19) McLean, S.; Lin, M.-S.; Whelan, J. *Can. J. Chem.* **1970**, *48*, 948.

145.3; IR (KBr): 3292, 3267, 3066, 3006, 2925, 2851, 2716, 1606, 1514, 1466, 1273, 1214, 1110, 1028, 846, 806. HRMS (ESI): calcd for $C_{16}H_{25}NO_2$ $[M + H]^+$ 264.1958, found 264.1959.

1-Methyl-1-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (10). The compound is prepared using general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.0 mg, 0.200 mmol) was reacted with 3-hydroxyphenethylamine (137 mg, 1.00 mmol) and acetophenone (129 mg, 1.07 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **10** (156 mg, 0.650 mmol, 65%) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 1.65 (s, 3H), 2.54−2.60 (m, 2H), 2.68−2.76 (m, 1H), 2.80−2.85 (m, 1H), 6.50 (s, 1H), 6.56 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.11−7.14 (m, 1H), 7.19−7.22 (m, 4H), 9.13 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 29.7, 30.4, 38.4, 58.1, 112.8, 114.9, 125.8, 127.0, 127.5, 128.4, 132.7, 136.3, 149.7, 155.1; IR (KBr): 3294, 3231, 3055, 3023, 2990, 2964, 2931, 2583, 1605, 1579, 1500, 1444, 1373, 1351, 1295, 1245, 1186, 1162, 1138, 1084, 1028, 977, 868, 843, 822, 769, 706. HRMS (ESI): calcd for $C_{16}H_{17}NO$ $[M + H]^+$ 240.1383, found 240.1372.

1,1-Dimethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (11). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (74.7 mg, 0.200 mmol, 20.0 mol %) was reacted with 3-hydroxyphenethylamine (137 mg, 0.997 mmol) and acetone (61.8 mg, 1.06 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **11** (152 mg, 0.857 mmol, 86%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ 1.28 (s, 6H), 2.56 (t, J = 5.6 Hz, 2H), 2.90 (t, J = 5.6 Hz, 2H), 6.398 (s, 1H), 6.52 (d, J = 1.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 30.4, 31.1, 38.4, 51.9, 113.2, 114.7, 126.6, 134.9, 135.4, 154.73; IR (KBr): 3415, 3261, 3038, 3016, 2972, 2951, 3797, 2694, 2610, 1618, 1582, 1498, 1367, 1264, 1256, 1242, 1158, 1127, 1088, 1061, 991, 868, 812. HRMS (ESI): calcd for $C_{11}H_{15}NO$ $[M + H]^+$ 178.1226, found 178.1221.

1-Methyl-1-phenethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (12). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.8 mg, 0.203 mmol, 20.3 mol %) was reacted with 3-hydroxyphenethylamine (137 mg, 1.00 mmol) and benzylacetone (148 mg, 1.00 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **12** (210 mg, 0.784 mmol, 78%) as an off-white crystalline solid. ^{1}H NMR (400 MHz, DMSO): δ 1.31 (s, 3H), 1.76 (td, J = 12.8 Hz, 4.8 Hz, 1H), 2.00 (td, J = 13.6 Hz, 4.4 Hz, 1H), 2.30 (td, J = 12.6 Hz, 4.0 Hz, 1H), 2.50−2.52 (m, 1H), 2.53−2.68 (m, 2H), 2.94 (t, J = 5.2 Hz, 2H), 6.44 (d, J = 2.8 Hz, 1H), 6.58 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.11 (dd, J = 9.2 Hz, 6.8 Hz, 3H), 7.20−7.24 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ 29.2, 30.0, 30.5, 38.4, 45.0, 54.5, 113.3, 114.7, 125.3, 126.6, 128.1, 133.9, 136.2, 143.1, 154.6; IR (KBr) 3274, 3232, 3022, 2946, 2681, 2580, 1602, 1577, 1496, 1453, 1379, 1350, 1296, 1250, 1159, 1114, 881, 855, 817, 754, 702. HRMS (ESI): calcd for $C_{18}H_{21}NO$ $[M + H]^+$ 268.1696, found 268.1682.

3′,4′-Dihydro-2′H-spiro[cyclopentane-1,1′-isoquinolin]-6′-ol (13). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.8 mg, 0.207 mmol, 20.5 mol %) was reacted with 3-hydroxyphenethylamine (139 mg, 1.01 mmol) and cyclopentanone (93.5 mg, 1.11 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **13** (150 mg, 0.740 mmol, 73%) as a tan solid. ^{1}H NMR (400 MHz, DMSO): δ 1.69−1.77 (m, 8H), 2.55 (t, J = 5.6 Hz, 2H), 2.83 (t, J = 5.6 Hz, 2H), 6.37 (s, 1H), 6.53 (dd, J = 2.4 Hz, 8.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 9.08 (bs, 1H); ^{13}C NMR (100 MHz, DMSO, relaxation time = 10 s): δ 24.5, 30.3, 39.4, 42.4, 63.6, 113.4, 114.4, 126.6, 134.1, 136.4, 154.5; IR (KBr): 3260, 3021, 2949, 2872, 2790, 2701, 2611, 1618, 1581, 1498, 1117, 853, 807. HRMS (ESI): calcd for $C_{13}H_{17}NO$ $[M + H]^+$ 204.1383, found 204.1391.

3′,4′-Dihydro-2′H-spiro[cyclohexane-1,1′-isoquinolin]-6′-ol (14). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.0 mg, 0.200 mmol, 20.0 mol %) was reacted with 3-hydroxyphenethylamine (138 mg, 1.01 mmol) and cyclohexanone (99.4 mg, 1.01 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **14** (170 mg, 0.781 mmol, 78%) as an off-white crystalline solid. ^{1}H NMR (400 MHz, DMSO): δ 1.17−1.25 (m, 1H), 1.40 (d, J = 12.4 Hz, 2H), 1.52−1.70 (m, 7H), 1.80 (bs, 1H), 2.53 (t, J = 5.6 Hz, 2H), 2.83 (t, J = 6.0 Hz, 2H), 6.39 (d, J = 2.0 Hz, 1H), 6.54 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 9.10 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 21.3, 25.5, 30.5, 37.6, 37.8, 53.3, 113.1, 114.7, 126.5, 135.7, 136.1, 154.6; IR (KBr): 3305, 3049, 3028, 2925, 2861, 2532, 1606, 1502, 1456, 1257, 1242, 1232, 1145, 1123, 1066, 1034, 972, 944, 863, 850, 826, 808. HRMS (ESI): calcd for $C_{14}H_{19}NO$ $[M + H]^+$ 218.1539, found 218.1533.

2,3,3′,4′-Tetrahydro-2′H-spiro[indene-1,1′-isoquinolin]-6′-ol (15). The compound is prepared according to general procedure B. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (76.1 mg, 0.203 mmol, 20.2 mol %) was reacted with 3-hydroxyphenethylamine (138 mg, 1.01 mmol) and 1-indanone (151 mg, 1.14 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **15** (175 mg, 0.696 mmol, 69%) as a gray solid. ^{1}H NMR (400 MHz, DMSO): δ 2.21−2.33 (m, 3H), 2.61−2.66 (m, 1H), 2.77−3.08 (m, 5H), 6.42−6.48 (m, 3H), 6.79 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 7.17 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 9.08 (bs, 1H); ^{13}C NMR (125 MHz, DMSO, relaxation time = 5 s): δ 29.5, 29.8, 39.5, 42.4, 67.6, 113.3, 114.4, 124.3, 124.3, 126.1, 127.0, 128.1, 132.7, 136.6, 143.5, 150.8, 155.0; IR (KBr): 3386, 3265, 3066, 3018, 2939, 2855, 2588, 1607, 1456, 1360, 1304, 1252, 1156, 765. HRMS (ESI): calcd for $C_{17}H_{17}NO$ $[M + H]^+$ 252.1383, found 252.1394.

1-Methyl-1-(3-methoxyphenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (16). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (76.0 mg, 0.203 mmol, 20.0 mol %) was reacted with 3-hydroxyphenethylamine (141 mg, 1.03 mmol) and 3′-methoxyacetophenone (156 mg, 1.04 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **16** (189 mg, 0.701 mmol, 68%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ 1.62 (s, 3H), 2.53−2.59 (m, 2H), 2.68−2.73 (m, 1H), 2.80−2.82 (m, 1H), 3.68 (s, 3H), 6.49 (s, 1H), 6.55 (dd, J = 2.8 Hz, 8.4 Hz, 1H), 6.71−6.73 (m, 1H), 6.77 (s, 2H), 6.90 (d, J = 8.4 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 9.15 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 29.6, 30.4, 38.4, 54.8, 58.1, 110.5, 112.7, 113.5, 114.8, 119.4, 128.3, 128.4, 132.6, 136.2, 151.5, 155.1, 158.7; IR (KBr): 3276, 3245, 3000, 2961, 2931, 2588, 1606, 1582, 1486, 1451, 1430, 1293, 1254, 1163, 1040, 858, 826, 786, 705. HRMS (ESI): calcd for $C_{17}H_{19}NO_2$ $[M + H]^+$ 270.1489, found 270.1485.

1-Methyl-1-(4-nitrophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (17). The compound is prepared according to general procedure B. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.9 mg, 0.203 mmol, 20.0 mol %) was reacted with 3-hydroxyphenethylamine (141 mg, 1.02 mmol) and 4′-nitroacetophenone (182 mg, 1.10 mmol) in toluene (10 mL) for 24 h at 100 °C to give the product **17** (246 mg, 0.865 mmol, 84%) as a brown-red solid. ^{1}H NMR (400 MHz, DMSO): δ 1.67 (s, 3H), 2.48−2.53 (m, 1H), 2.66−2.73 (m, 2H), 2.83−2.86 (m, 1H), 6.50 (s, 1H), 6.55 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H), 9.19 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 29.5, 29.9, 38.5, 58.3, 113.1, 115.1, 122.7, 128.3, 131.6, 136.4, 145.7, 155.5, 157.8; IR (KBr): 3265, 3252, 3109, 3054, 2979, 2939, 2695, 1604, 1579, 1517, 1500, 1464, 1351, 1296, 1250, 1111, 1068, 855, 818, 789, 755, 699. HRMS (ESI): calcd for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 285.1234, found 285.1226.

1-Methyl-1-(ethylcarboxylate)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (18). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.8 mg, 0.203 mmol, 20.1 mol %) was reacted with 3-hydroxyphenethylamine (138 mg, 1.01 mmol) and ethyl pyruvate (140 mg, 1.20 mmol)

in toluene (10 mL) for 24 h at 100 °C to give the product **18** (104 mg, 0.442 mmol, 44%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO): δ 1.14 (t, J = 7.2 Hz, 3H), 1.47 (s, 3H), 2.52−2.54 (m, 1H), 2.64−2.71 (m, 1H), 2.88−3.00 (m, 2H), 4.06 (q, J = 2.8 Hz, 2H), 6.44−6.44 (m, 1H), 6.55−6.58 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 9.21 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 14.0, 28.0, 29.6, 60.1, 60.4, 113.2, 114.7, 128.0, 128.2, 128.9, 136.3, 155.6, 175.3; IR (KBr): 3299, 3063, 2977, 2929, 2683, 2602, 1724, 1608, 1508, 1458, 1356, 1313, 1246, 1149, 1111, 1014, 843. HRMS (ESI): calcd for $C_{13}H_{17}NO_3$ $[M + H]^+$ 236.1281, found 236.1277.

1,1-Dimethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydrosioquinol-ine (20). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (75.3 mg, 0.201 mmol, 20.1 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (167 mg, 1.00 mmol) and acetone (59.0 mg, 1.02 mmol) in DCM (10 mL) for 24 h at ambient temperature to give the product **20** (149 mg, 0.721 mmol, 72%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ 1.31 (s, 6H), 2.49 (t, J = 5.6 Hz, 2H), 2.89 (t, J = 5.6 Hz, 2H), 3.72 (s, 3H), 6.40 (s, 1H), 6.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 29.3, 30.9, 38.5, 52.2, 55.9, 110.0, 115.3, 126.5, 134.8, 144.4, 145.8; IR (KBr): 3267, 3012, 2962, 2829, 2683, 2588, 1570, 1512, 1442, 1266, 1222, 1208, 1150, 1066, 787; HRMS (ESI): calcd for $C_{12}H_{17}NO_2$ $[M+H]^+$: 208.1332, found 208.1327.

7′-Methoxy-3′,4′-dihydro-2′H-spiro[cyclohexane-1,1′-isoquinolin]-6′-ol (21). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (78.2 mg, 0.209 mmol, 20.4 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (171 mg, 1.02 mmol) and cyclohexanone (103.5 mg, 1.05 mmol) in DCM (10 mL) for 24 h at ambient temperature to give the product **21** (212 mg, 0.856 mmol, 84%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22−1.36 (m, 1H), 1.60−1.80 (m, 9H), 2.66 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 3.88 (s, 3H), 6.60 (s, 1H), 6.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 25.9, 38.3, 38.6, 54.5, 56.3, 108.5, 114.8, 128.2, 136.6, 143.8, 145.1; IR (KBr): 3308, 3010, 2929, 2843, 2591, 1607, 1528, 1450, 1331, 1255, 1216, 1121, 1043, 839, 779. HRMS (ESI): calcd for $C_{15}H_{21}NO_2$ $[M + H]^+$ 248.1645, found 248.1637.

1-Methyl-1-(2-phenylethyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (23). The compound is prepared according to general procedure A. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (74.0 mg, 0.198 mmol, 20.0 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (167.6 mg, 1.01 mmol) and benzylacetone (153.2 mg, 1.03 mmol) in DCM (10 mL) for 24 h at ambient temperature to give the product **23** (210 mg, 0.704 mmol, 70%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): δ 1.33 (s, 3H), 1.79 (td, J = 12.6, 5.2 Hz, 1H), 2.02 (td, J = 13.2, 4.4 Hz, 1H), 2.32 (td, J = 12.8 Hz, 4.4 Hz, 1H), 2.43−2.48 (m, 1H), 2.53−2.67 (m, 2H), 2.92 (t, J = 5.2 Hz, 2H), 3.72 (s, 3H), 6.43 (s, 1H), 6.73 (s, 1H), 7.10−7.15 (m, 3H), 7.22−7.25 (m, 2H), 8.63 (bs, 1H); ^{13}C NMR (100 MHz, DMSO): δ 29.1, 29.6, 30.1, 38.5, 44.9, 54.6, 55.9, 110.0, 115.3, 125.3, 127.4, 128.2, 134.0, 143.2, 144.2, 145.9; IR (KBr): 3265, 3024, 2954, 2836, 2705, 2559, 1508, 1452, 1259, 1208, 789. HRMS (ESI): calcd for $C_{19}H_{23}NO_2$ $[M + H]^+$ 298.1802, found 298.1798.

6′-Hydroxy-7′-methoxy-3′,4′-dihydro-2′H-spiro[indeno[5,4-d]-[1,3]dioxole-7,1′-isoquinolin]-6(8H)-one (27). The compound is prepared according to general procedure B. Calcium 1,1,1,3,3,3-hexafluoroisopropoxide (8.0 mg, 0.020 mmol, 20.4 mol %) was reacted with 3-hydroxy-4-methoxyphenethylamine (17.2 mg, 0.103 mmol) and 4,5-methylenedioxyindane-1,2,-dione[19] **26** (19.0 mg, 0.100 mmol) in DCM (10 mL) for 18 h at ambient temperature. The product was isolated by column chromatography (2% MeOH in DCM) to give the product **27** (17.8 mg, 0.052 mmol, 52%) as an off-white solid. A second run gave the product (19.7 mg, 0.058 mmol) in a 58% yield for a two-run average of 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66−2.72 (m, 1H), 2.79−2.86 (m, 1H), 3.01−3.08 (m, 1H), 3.37 (s, 2H), 3.39−3.45 (m, 1H), 3.65 (s, 3H), 6.09−6.14 (m, 3H), 6.67 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.0, 40.5, 42.0, 56.2, 67.0, 77.4, 102.5, 107.3, 109.5, 115.2, 121.1, 128.9, 129.3, 131.0, 132.2, 144.2, 145.0, 145.7, 153.6, 204.5; IR (KBr): 3281, 3004, 2934, 1719, 1633, 1510, 1472, 1378, 1259, 1049, 1021, 923, 880, 817, 736. HRMS (ESI): calcd for $C_{19}H_{17}NO_5$ $[M + H]^+$ 340.1179, found 340.1162.

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