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Organocatalyzed Enantioselective Protonation of Silyl Enol Ethers: Scope, Limitations, and Application to the Preparation of Enantioenriched Homoisoflavones

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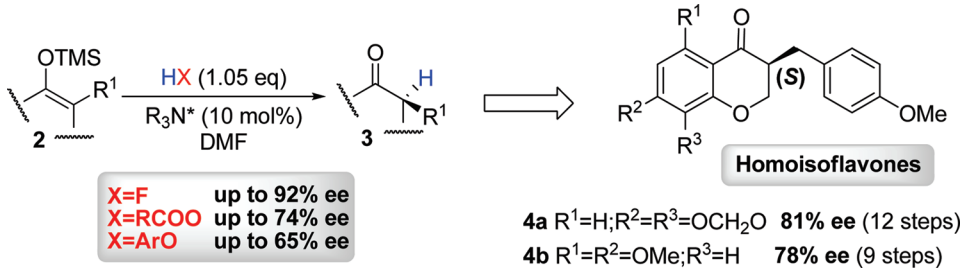

In the present work, enantioselective protonation of silyl enol ethers is reported by means of a variety of chiral nitrogen bases as catalysts, mainly derived from cinchona alkaloids, in the presence of various protic nucleophiles as proton source. A detailed study of the most relevant reaction parameters is disclosed allowing high enantioselectivities of up to 92% ee with excellent yields to be achieved under mild and eco-friendly conditions. The synthetic utility of this organocatalytic protonation was demonstrated during the preparation of two homoisoflavones **4a** and **4b**, isolated from *Chlorophytum Inornatum* and *Scilla Nervosa*, which were obtained with 81% and 78% ee, respectively.

Introduction

A significant amount of research has been devoted to the development of efficient strategies, based on enantioselective protonation of enolates, for accessing enantiomerically enriched α-monosubstituted carbonyl compounds.[1] From a synthetic viewpoint, enantioselective protonation emerges as a good alternative to asymmetric alkylation of enolates which suffer from dialkylation side reactions. In addition, more fundamental aspects related to asymmetric transfer of the smallest element of the periodic table make enantioselective protonation a challenging stereoselective process.

Since the first report of Duhamel and Plaquevent in 1976[2] dealing with the protonation of enolates, a wide range of approaches have been developed including decarboxylative protonation of keto-esters,[3] protonation of photoenols,[4] addition of protic nucleophiles to unsaturated carbonyl compounds[5] and ketenes,[6] as well as biocatalyzed protonation of enol acetates using enzymes[7] and antibodies.[8] Among all these

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(1) For reviews, see: (a) Fehr, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2566–2587. (b) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2010**, *12*, 1–24. (c) Duhamel, L.; Duhamel, P.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653–3691. (d) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359–369.

(2) (a) Duhamel, L. *C. R. Acad. Sci.* **1976**, *282*, 125–127. (b) Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1977**, *18*, 2285–2288. (c) Duhamel, L.; Plaquevent, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 7415–7416.

(3) (a) Blanchet, J.; Baudoux, J.; Amere, M.; Lasne M.-C.; Rouden, J. *Eur. J. Org. Chem.* **2008**, 5493−5506 and references cited therein. (b) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349.

(4) (a) Piva, O.; Mortezaei, R.; Henin, F.; Muzart, J.; Pete, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 9263–9272. (b) Piva, O.; Pete, J. P. *Tetrahedron Lett.* **1990**, *31*, 5157–5160. (c) Henin, F.; Létinois, S.; Muzart, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2037–2044. (d) Henin, F.; Muzart, J.; Pete, J. P.; M'Boungou-M'Passi, A.; Rau, H. *Angew. Chem., Int. Ed.* **1991**, *30*, 416–418. (e) Henin, F.; M'Boungou-M'Passi, A.; Muzart, J.; Pete, J. P. *Tetrahedron* **1994**, *50*, 2849–2864.

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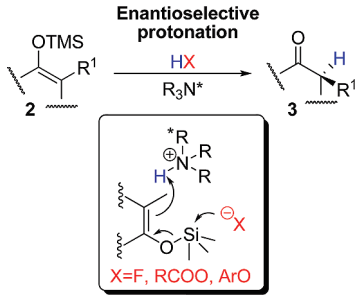
strategies, enantioselective protonation of metal-enolates has largely dominated the literature in this field, providing efficient stoichiometric processes mainly developed by the group of Fehr,[9] Yamamoto,[10] Koga,[11] and Vedejs.[12] The search of catalytic processes has long remained the foremost challenge in this field, until this important milestone was overcome by Fehr, who reported the first catalytic enantioselective protonation of ketenes.[13] This initial report was followed soon after by a series of papers covering either the catalytic protonation of lithium enolates[14] or the catalytic protonation of silyl enolates in the presence of Lewis acid catalysts.[15]

Since then, the challenge faced by synthetic chemists has been to develop catalytic processes under metal-free and environmentally benign conditions. The development of organocatalytic processes is still an important challenge in the field of asymmetric protonation. In this environmental context, because silicon is considered an eco-friendly element due to its abundance and low toxicity, silyl enolates may be regarded as the substrate of choice to address this challenge.

SCHEME 1. Proposed Activation Mode of Silyl Enolate 2 by Means of a Tertiary Ammonium Ion Pair 1-HX (X = F, RCO_2, ArO)



Organocatalytic protonation of silyl enolates has emerged only recently as a useful synthetic tool.[16] We previously reported the first successful organocatalytic protonation of silyl enolates by utilizing various protic nucleophiles as the proton source in the presence of cinchona alkaloids as chiral Brønsted bases.[16a,b] Herein, we present a full account of our investigations into the scope and limitations of this organocatalytic strategy. Shortly afterward, Yamamoto reported another elegant organocatalytic strategy making use of *N*-triflyl thio- or selenophosphoramides as chiral Brønsted acid catalysts in the presence of phenol.[16c] Surprisingly, one should note that only a few synthetic applications involving a catalytic enantioselective protonation have so far been reported in the literature.[9,13] To fill this gap, the efficiency of this organocatalytic process will be demonstrated in the stereoselective synthesis of two natural homoisoflavones.

Results and Discussion

Rational Design of the Enantioselective Organocatalytic Process. It is well-known that Lewis bases such as fluoride[17] and oxanions[18] activate silyl enolates through the formation of either a "naked" enolate anion or hypervalent silicate intermediates.[19] This strong affinity of silicon for such Lewis bases was the starting point in the design of a new organocatalytic process. We postulated that protonation of a chiral tertiary amine by hydrogen fluoride, carboxylic acid, or phenol derivatives would generate a "chiral ion pair" as the active catalytic species wherein the anion (i.e., fluoride, phenoxide, or carboxylate ion) would activate the silyl enolate **2** so as to further facilitate the asymmetric transfer of the proton from the chiral tertiary ammonium counterion in proximity (Scheme 1).

(5) (a) Pracejus, H.; Wilcke, F. W.; Hanemann, K. *J. Prakt. Chem.* **1977**, *319*, 219–229. (b) Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. *J. Chem. Soc., Chem. Commun.* **1991**, 485–486. (c) Li, B. J.; Jiang, L.; Liu, M.; Chen Y. C.; Ding L. S.; Wu, Y. *Synlett* **2005**, 603−606. (d) Leow, D.; Tan, C. H. *Chem. Asian J.* **2009**, *4*, 488–507. (e) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641–5645.

(6) (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22. (b) Pracejus, H.; Maetje, H. *J. Prakt. Chem.* **1964**, *24*, 195–205. (c) Pracejus, H.; Kohl, G. *Justus Liebigs Ann. Chem.* **1969**, *722*, 1–11. (d) Blake, A. J.; Friend, C. L.; Outram, R. J.; Simpkins, N. S.; Whitehead, A. J. *Tetrahedron Lett.* **2001**, *42*, 2877–2881. (e) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637–2638. (f) Hodous, B.-L.; Fu, G.-C. *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007. (g) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176–6177. (h) Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606–4608. (i) Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 4367–4369. (j) Wang, X. N.; Lv, H.; Huang, X. L.; Ye, S. *Org. Biomol. Chem.* **2009**, *7*, 346–350.

(7) (a) Matsumoto, K.; Tsutsumi, S.; Ihori, T.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 9614–9619. (b) Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1063–1066. (c) Sakai, T.; Matsuda, A.; Tanaka, Y.; Korenaga, T.; Ema, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1929–1932.

(8) (a) Fuji, I.; Lerner, R. A.; Janda, K. *J. Am. Chem. Soc.* **1991**, *113*, 8528–8529. (b) Reymond, J. L.; Janda, K.; Lerner, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 2257–2258. (c) Reymond, J. L.; Janda, K.; Lerner, R. A. *Angew. Chem., Int. Ed.* **1994**, *33*, 475–477.

(9) Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *109*, 6910–6911.

(10) (a) Yanagisawa, A.; Kuribayash, T.; Kikuchi, T.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 107–109. (b) Ishihara, K.; Kaneeda, M.; Asakawa, K.; Yamamoto., H. *J. Am. Chem. Soc.* **1994**, *116*, 11179–11180. (c) Yanagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253–10264. (d) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24–25.

(11) Yasukata, T.; Koga, K. *Tetrahedron: Asymmetry* **1993**, *4*, 35–38.

(12) (a) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483–5485. (b) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891–900.

(13) (a) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed.* **1993**, *32*, 1042–1044. (b) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1888–1889.

(14) For catalytic protonation of lithium enolates, see: (a) Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372–374. (b) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 792–2793. (c) Rivière, P.; Koga, K. *Tetrahedron lett.* **1997**, *53*, 7589–7592. (d) Yamashita, Y.; Emura, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **2000**, *41*, 209–213. (e) Mitsuhashi, K.; Ito, R.; Arai, T.; Yanagisawa, A. *Org. Lett.* **2006**, *8*, 1721–1724.

(15) For catalytic protonation of silyl enolates by means of chiral Lewis acids, see: (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854–12855. (b) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2366–2368. (c) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120–8130. (d) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1546–1548. (e) Yanagisawa, A.; Touge, T.; Arai, T. *Pure Appl. Chem.* **2006**, *78*, 519–523. (f) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858–3859.

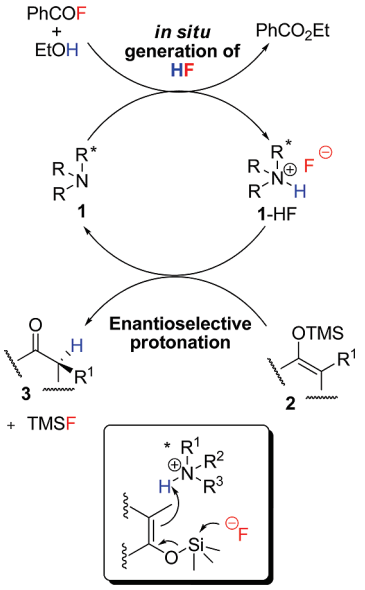
(16) For exhaustive examples of organocatalytic enantioselective protonation of silyl enolates, see: (a) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090–7093. (b) Poisson, T.; Oudeyer, S.; Dalla, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, 2447–2450. (c) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 6246–9247.

(17) Takashi, O.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526–533.

(18) For non exhaustive examples on the use of oxanions as Lewis base see: (a) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051. (b) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604–5607. (c) Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chem.—Eur. J.* **2006**, *12*, 5082–5093. (d) Poisson, T.; Gembus, V.; Oudeyer, S.; Marsais, F.; Levacher, V. *J. Org. Chem.* **2009**, *74*, 3516–3519. (e) Gembus, V.; Poisson, T.; Oudeyer, S.; Marsais, F.; Levacher, V. *Synlett* **2009**, 2437–2440.

(19) For recent authoritative reviews on this topic, see: (a) Oestreich, M.; Rendler, S. *Synthesis* **2005**, 1727–1747. (b) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391–1401.

SCHEME 2. Postulated Catalytic Cycle for Enantioselective Protonation of Silyl Enolate 2 by 1-HF Formed in Situ from Benzoyl Fluoride and Ethanol

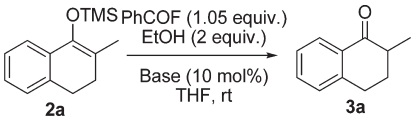


To implement this scenario, we anticipated that hydrogen fluoride salts **1**-HF derived from a chiral amine **1** would be very active chiral sources of protons. Quite surprisingly, such a strategy has been completely ignored so far, probably due to the difficulties regarding the preparation and the storage of dry hydrogen fluoride salts **1**-HF. To thwart the tricky preparation and storage of hydrogen fluoride salts **1**-HF, we planned to use a stoichiometric mixture of acyl fluoride and alcohol as a latent source of HF which, in the presence of a catalytic amount of chiral tertiary amine would deliver "at will" the required hydrogen fluoride salt **1**-HF (Scheme 2).

Preliminary experiments were performed with the silyl enolate **2a** in the presence of benzoyl fluoride, ethanol, and a catalytic amount of various Brønsted bases in THF (Table 1). Quinuclidine and DMAP proved to be the best catalyst candidates providing the desired 2-methyl tetralone **3a** within 3−4 h at room temperature (Table 1, entries 1−3), while both *N*-methylpyrrolidine and triethylamine displayed much lower reactivity (Table 1, entries 4 and 5). Interestingly, when the reaction was carried out without nitrogen base (Table 1, entry 6), only traces of tetralone **3a** were detected after 20 h. This suggests a good control over background reactivity while pointing out the catalytic function of the nitrogen base and giving strong support to the mechanism depicted in Scheme 2. An additional labeling experiment was accomplished with [^{1}D]-ethanol furnishing the corresponding [^{1}D]-tetralone **3a** with a complete deuterium incorporation and full conversion according to the ^{1}H NMR analysis (Table 1, entry 2).

At this point, we turned our attention to the search of chiral nitrogen bases, favoring those having a pyridine or quinuclidine scaffold (Table 2). When the reaction was carried out with several chiral pyridine catalyst derivatives such as Fu's DMAP,[20] Birman's catalyst,[21] or nicotine

TABLE 1. Brønsted Base Screening



entry	Brønsted base	conversion (%)[a]	time (h)
1	quinuclidine	100	3
2		100[b,c]	3
3	DMAP	100	4
4	*N*-methylpyrrolidine	100	20
5	triethylamine	87	20
6	none	3	20

[a]Determined by GC analysis. [b]EtOD was used instead of EtOH. [c]A deuterium incorporation (>95%) was determined by ^{1}H NMR.

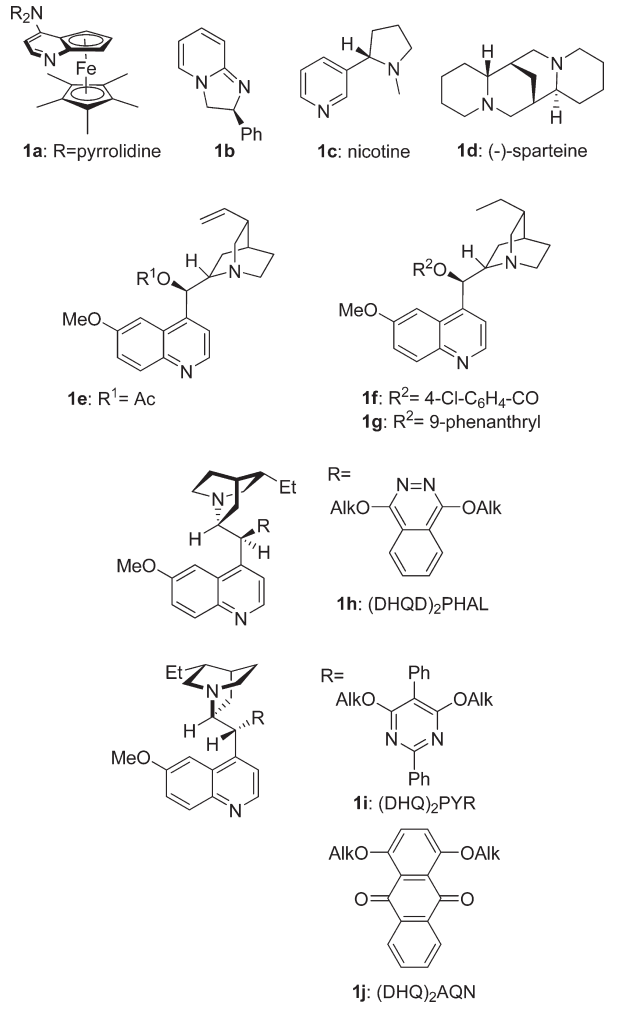
(Table 2, entries 1−3), no significant enantioselectivities were observed despite a full conversion in all cases after 12 h. Although sparteine has been found to be highly efficient in numerous asymmetric processes, its use afforded a modest enantiomeric excess of 9% (Table 2, entry 4).

After an extensive screening of commercially or readily available cinchona alkaloids (Table 2, entries 5−10), dimeric cinchona alkaloids, previously developed by Sharpless,[22] showed promising results (Table 2, entries 8−10), whereas monomeric cinchona alkaloids furnished only modest selectivities (Table 2, entries 5−7). The best result was obtained with $(DHQ)_2AQN$, providing the corresponding 2-methyl tetralone **3a** in 42% ee (Table 2, entry 10). With $(DHQ)_2$-AQN selected as the best catalyst, we first paid attention to the solvent, which proved to be a crucial parameter to obtain an acceptable level of enantioselectivity (Table 2, entries 10−20).

A comparable selectivity as that obtained in THF was reproduced in dioxane (Table 2, entry 11), while the reaction conducted in diethyl ether, chloroform, or toluene has resulted in all cases in lower enantioselectivities (Table 2, entries 12−14). One should notice that polar protic solvents were detrimental to the enantioselectivity affording tetralone **3a** with 20% ee in *tert*-amyl alcohol and as a racemic mixture in methanol (Table 2, entries 15 and 16). The lack of selectivity is likely due to the poor stability of silyl enolates in alcohols, the background protonation prevailing over the catalyzed pathway in those solvents. Finally, we were pleased to find out that aprotic polar solvents have a beneficial effect on the stereochemical outcome of the reaction. The use of acetonitrile, DMF, NMP, and DMSO has provided a significant increase of the enantioselectivity in all cases (Table 2, entries 18−20 respectively). It is well-known that acetonitrile and DMF are commonly used in organic silicon chemistry. Such solvents can be viewed as neutral Lewis bases which can coordinate to silicon resulting in further activation of the silyl enolate. Although DMSO furnished the higher enantiomeric excess values, its use was severely hampered by the formation of a side product resulting from *O*-benzoylation of **2a** with benzoyl fluoride.[23] As a result, DMF offers the best balance between good enantioselectivity and clean conversion into the desired tetralone **3a**.

(20) Ruble, G.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230–7231.
(21) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227.
(22) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448–451.
(23) Poisson, T.; Dalla, V.; Papamicaël, C.; Dupas, G.; Marsais, F.; Levacher, V. *Synlett* **2007**, 381–386.

TABLE 2. Chiral Catalyst and Solvent Screening in Enantioselective Protonation of Silyl Enol Ether 2a[a]

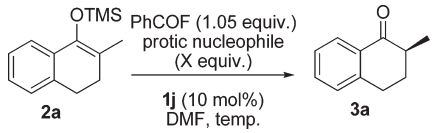


entry	catalyst	solvent	ee[b] (%)	abs conf[c]
1	**1a**	THF	0	
2	**1b**		0	
3	**1c**		0	
4	**1d**		9	*S*
5	**1e**		24	*S*
6	**1f**		20	*S*
7	**1g**		27	*S*
8	**1h**		36	*R*
9	**1i**		39	*S*
10	**1j**		42	*S*
11		dioxane	45	*S*
12		diethyl ether	30	*S*
13		toluene	26	*S*
14		chloroform	19	*S*
15		*tert*-amyl alcohol	20	*S*
16		methanol	0	-
17		acetonitrile	67	*S*
18		DMF	78	*S*
19		NMP	79	*S*
20		DMSO	84	*S*

[a]The reaction was carried out at room temperature with silyl enol ether **2a** (1 equiv), EtOH (2 equiv), PhCOF (1.05 equiv), and chiral catalyst (10 mol %). [b]Determined by HPLC using chiral column after complete conversion (see the Supporting Information). [c]Determined by comparison with literature data.

Allowing for the fact that protic solvents exhibited a detrimental effect on the stereochemical outcome of the reaction, we deemed that the proton source might also be an important variable in the optimization of this organocatalytic process (Table 3, entries 1 and 6−8). Although initial experiments accomplished with ethanol as proton source afforded tetralone **3a** in 78% ee (Table 3, entry 1), a meaningful drop of the selectivity was recorded with methanol providing tetralone **3a** in 67% ee (Table 3, entry 6). This is likely due to a partial alcoholysis of the silyl enolate **2a** occurring more rapidly with methanol than with ethanol. The more sterically hindered isopropanol gave similar results to those obtained with ethanol, however at the expense of the reaction time and along with the formation of a significant amount of a side product arising from the competitive *O*-benzoylation with benzoyl fluoride[23] (Table 3, entry 7). Finally, ethanol was revealed to be the best candidate as proton source. A good compromise between an acceptable reaction time (12 h) and an optimal level of enantioselectivity (81% ee) could be reached by conducting the reaction at room temperature in the presence of 1.05 equiv of ethanol (Table 3, entries 1−5). These reaction conditions are of particular interest with respect to previous catalytic enantioselective protonation reports, which usually required much lower temperatures to reach an optimum of selectivity.

TABLE 3. Proton Source Screening



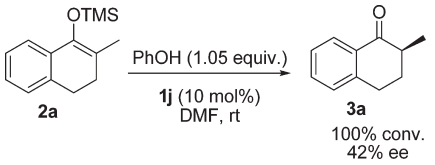
entry	protic nucleophile	*X* (equiv)	temp	ee (%)[a]	time (h)[b]
1	EtOH	2	rt	78	12
2		4	rt	71	12
3		1.05	rt	81	12
4		1.05	0 °C	81	20
5		1.05	−40 °C	−[c]	
6	MeOH	2	rt	67	12
7	*i*-PrOH	2	rt	76	20
8	PhOH	2	rt	57	12

[a]Determined by HPLC analysis using a chiral column (see the Supporting Information). [b]Time after which complete conversion was observed from GC analysis. [c]Less than 5% conversion was observed.

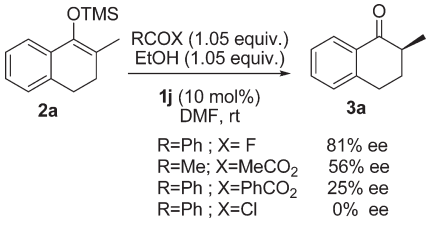
Lastly, and more interestingly from a mechanistic viewpoint, is the experiment performed with phenol as proton source (Table 3, entry 8). Indeed, although the ee values could not be improved, the observed enantioselection may possibly arise from a competitive pathway involving a tertiary ammonium phenoxide as the chiral active source of protons. Previously, quaternary ammonium phenoxide has been reported as Lewis base catalyst in the activation of silyl nucleophile.[18c] To ascertain our hypothesis, the reaction was carried out without benzoyl fluoride, affording 2-methyl tetralone **3a** with 42% ee (Scheme 3). This result indicates that phenols may straightforwardly generate a chiral active proton source by simple protonation of the cinchona alkaloid, paving the way for a substantial simplification of our methodology presented further on.

To gain insight into the role of the ammonium salt anion on the enantioselectivity, benzoyl fluoride was successively replaced by benzoyl chloride or anhydride derivatives. Thus, benzoic or acetic anhydride led to an important decrease of the ee values, however to a lesser extent than with acetic anhydride, whereas benzoyl chloride furnished tetralone **3a**

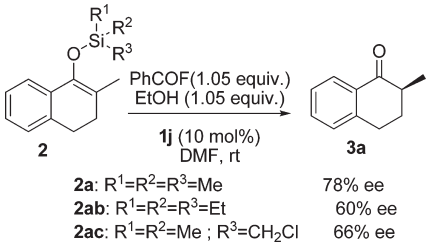
SCHEME 3. Enantioselective Protonation of Silyl Enolate 2a in the Absence of Benzoyl Fluoride



SCHEME 4. Influence of the Ammonium Salt Anion



SCHEME 5. Influence of the Steric Hindrance at the Silicon Atom of the Silyl Enol Ether 2a

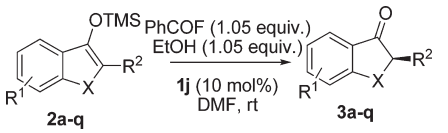


as a racemic mixture. These findings highlight the crucial role of the fluoride anion in the ammonium salt of $(DHQ)_2AQN$ to achieve a high level of enantioinduction (Scheme 4).

We also briefly examined the influence of steric hindrance at the silicon atom on the outcome of the reaction (Scheme 5). It was observed that the enantioselectivity dropped from 78% to 66% when the reaction was carried out with the dimethylchloromethylsilyl enolate **2ac**, whereas the triethylsilyl enolate **2ab** afforded 2-methyl tetralone **3a** in 60% ee. Although the more sterically hindered silyl enolates **2ab** and **2ac** yielded somewhat lower enantiomeric excesses, their greater stability may facilitate their storage for prolonged periods and handling.

Scope and Limitations. With these optimized conditions in hand, we undertook to investigate the scope of the reaction with a variety of cyclic ketones **3a**−**q**. Some general trends regarding the performances of our catalytic system can be emphasized and compared with those of earlier published methods. As depicted in Table 4, the best enantioselectivities could be achieved in the tetralone series reaching 92% ee with silyl enolate **2g** (Table 4, entries 1−7). Nonetheless, one can also notice that substitution at C-6 or C-7 of the tetralone backbone with a methoxy group affected significantly the enantioselection of the protonation, affording tetralones **3h**−**k** in somewhat lower enantiomeric excesses ranging from 35% to 73% (Table 4, entries 8−11). This approach still remains an appealing strategy in indanone series, providing enantiomeric excesses between 62% and 74% (Table 4, entries 12−14). One can see the limitation of this method with benzosuberone **3o** and cyclohexanone **3q**, which are obtained

TABLE 4. Scope and Limitations of the Reaction Using a Latent Source of HF



Entry	X	R^1	R^2	3	Yield(%)	ee(%)[a]	Abs. Conf.[b]
1	$(CH_2)_2$	H	Me	**3a**	88	78	*S*
2		H	Et	**3b**	68	78	*S*
3		H	F	**3c**	83	75	*S*
4		H	Bn	**3d**	84	85	*R*
5		H	3-pyridyl	**3e**	91	74	nd[c]
6		5-MeO	Me	**3f**	98	81	nd
7		5-MeO	Bn	**3g**	86	92	nd
8		6-MeO	Me	**3h**	91	35	nd
9		6-MeO	Bn	**3i**	86	73	nd
10		6-MeO	allyl	**3j**	84	58	nd
11		7-MeO	Bn	**3k**	82	53	nd
12	CH_2	H	Me	**3l**	78	71	*S*
13		H	Et	**3m**	76	74	*S*
14		H	Bn	**3n**	77	62	nd
15	$(CH_2)_3$	H	Me	**3o**	69	25	nd
16	OCH_2	H	Bn	**3p**	87	68	*S*
17	-		-	**3q**	95	58[d]	*S*

[a]Determined by HPLC analysis using a chiral column (see the Supporting Information). [b]Assigned by comparison with literature data. [c]Not determined. [d]Reaction was conducted at −10 °C. A 30% ee was obtained at room temperature.

with 25% and 30% ee, respectively, albeit cyclohexanone **3q** could be isolated with an acceptable level of enantioselectivity of 58% when conducting the reaction at −10 °C (Table 4, entries 15 and 17). Lastly, the performance of our catalytic process was also evaluated in the homoisoflavone series during the protonation of silyl enolate **2p** giving rise to homoisoflavone **3p** with a satisfactory ee of 68% (Table 4, entry 16). It is noteworthy that our strategy is more performing in tetralone and indanone series and complements Yamamoto's[15a,c,16c] and Yanagisawa's[15d,e] catalytic approaches, both of which have proven to be mostly efficient in cycloalkanone series while displaying lower enantioselectivities in tetralone and indanone series.

Simplification of the Catalytic Process. The previous approach required the implementation of a two-component system (PhCOF/EtOH) for the generation of dry HF, which is accompanied by the formation of ethyl benzoate as byproduct. At this stage, we wondered whether our methodology could be made simpler to implement and more effective in terms of atom economy. On the basis of previous results (Table 3, entry 8), we postulated that a more readily handy proton source such as carboxylic acid or phenol derivatives may be employed to develop a simplified organocatalytic process. By protonation of the chiral nitrogen base **1** with RCOOH or ArOH, one can assume a cooperative activation of the silyl enolate **2** by the oxanion in the resulting tertiary ammonium/oxanion ion pair **1**-HX (X = RCOO, ArO) to assist the proton transfer, as the fluoride anion did in our previous approach (Scheme 6).

In a first set of experiments, silyl enolate **2a** was subjected to protonation with various carboxylic acids under the optimized reaction conditions described above, namely with $(DHQ)_2AQN$ **1j** as catalyst in DMF (Table 5). In the presence of acetic or

SCHEME 6. Simplified Organocatalytic Process by Means of Phenol or Carboxylic Derivatives As Proton Sources

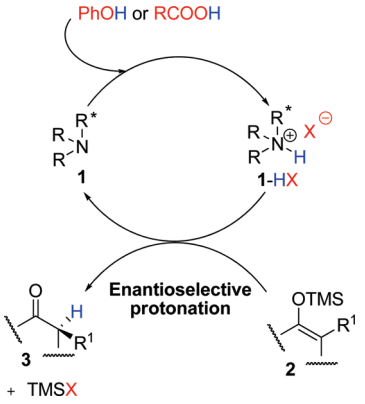
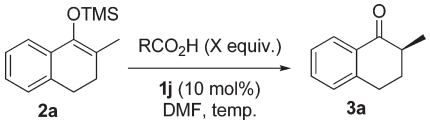


TABLE 5. Carboxylic Acid Screening



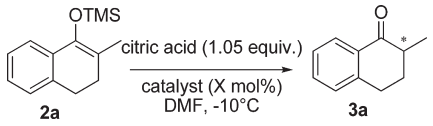
entry	RCO_2H	*X* (equiv)	temp	time (h)[a]	ee (%)[b]
1	$PhCO_2H$	1.05	rt	8	32
2[c]	AcOH	1.05	rt	8	36
3		1.05	0 °C	12	45
4		1.05	−20 °C	120	51
5	citric acid	1.05	rt	8	66
6		1.05	−10 °C	24	71
7		0.35	−10 °C	72	73
8	Boc-L-proline	1.05	rt	8	56
9		1.05	−20 °C	28	68
10	Boc-D-proline	1.05	rt	8	25
11	L-tartric acid	1.05	rt	8	32
12	D-tartric acid	1.05	rt	8	43

[a]Time after which complete conversion was observed from GC analysis. [b]Determined by HPLC analysis using a chiral column (see the Supporting Information). [c]30% of hydrolysis was observed when the reaction was conducted without catalyst at rt.

benzoic acid, full protonation occurred within 8 h with modest enantiomeric excesses of 36% and 32%, respectively (Table 5, entries 1 and 2). When the reaction was carried out at lower temperature, substantial improvements of the ee values were recorded, however at the expense of the reaction time (Table 5, entries 3 and 4). After extensive screening of a wide range of carboxylic acids, citric acid was found to be the best candidate (Table 5, entries 5−7). The use of 1 equiv of citric acid at −10 °C afforded the best compromise between selectivity and reaction time affording tetralone **3a** in 71% ee (Table 5, entry 6). Interestingly, the use of 0.35 equiv of citric acid led to complete conversion and 73% ee, despite an excessive reaction time (Table 5, entry 7). Using enantiopure carboxylic acids (Table 5, entries 8−12), a moderate but significant match/mismatch effect between the chiral ammonium and the chiral carboxylate was observed,[24] without being able to improve the ee value obtained with citric acid. To ensure that no background silyl enolate protonation through a nonselective pathway occurred under the selected conditions

(24) For a selected example of matched/mismatched catalyst ion pair combination, see: Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369.

TABLE 6. Chiral Catalyst Screening



entry	catalyst	*X* (mol %)	time (h)[a]	ee (%)[b,c]
1	**1j**	10	10	66
2		5	14	60
3		2	17	57
4	**1i**	10	12	55
5	**1h**	10	12	32[d]
6	**1e**	10	12	40
7	**1g**	10	12	45
8	quinine **1k**	10	12	25
9	**1a**	10	12	5

[a]Time after which complete conversion was observed from GC analysis. [b]Determined by HPLC using chiral column (see the Supporting Information). [c]unless otherwise mentioned, *S* absolute configuration was assigned by comparison with literature data. [d]*R* absolute configuration was assigned by comparison with literature data.

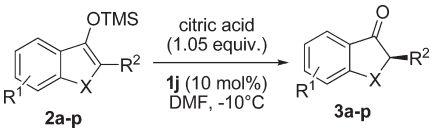
(1.05 equiv of citric acid, DMF, −10 °C, 24 h), the reaction was carried out without catalyst **1j**. In these control experiment conditions, less than 10% of racemic tetralone **3a** was obtained providing strong evidence in favor of the postulated activation of the silyl enolate by the carboxylate anion. However, it is worthwhile to note that reaction temperature was found to be a key variable in controlling the background protonation, showing that a higher percentage of hydrolysis was obtained at room temperature (i.e., 30% within 24 h).

A rapid screening of solvents revealed that DMF and DMSO were suitable for this reaction, an enantiomeric excess of 66% being obtained in both cases at room temperature in the presence of **1j** (10 mol %) and 1.05 equiv of citric acid. All other solvents, namely CH_2Cl_2, CH_3CN, THF, and dioxane, were found to be inefficient due to the solubility issue of citric acid. Finally, DMF was preferred over DMSO for its cryogenic properties.

We then surveyed the performances of numerous chiral catalysts **1** under these new simplified conditions (Table 6). During this catalyst screening, the same trend as that pointed out in Table 2 was observed, i.e., dimeric cinchona alkaloids exhibited higher selectivities than their monomeric counterparts (Table 6, entries 1−5 vs 6−8). Among them, $(DHQ)_2$-AQN **1j**, already previously selected as the best candidate, emerged once again as the most effective catalyst, providing the higher selectivities even with a catalyst loading as low as 2 mol % (Table 6, entries 1−3). The substitution of the hydroxyl group at the C-9 position appeared to be essential to ensure a satisfactory selectivity (Table 6, entries 6−7 vs 8). Finally, the chiral ferrocenyl DMAP **1a** was also assessed as catalyst; although a full conversion was observed, tetralone **3a** was obtained as a quasi-racemic mixture (Table 6, entry 9).

After having optimized the reaction conditions, we next evaluated the generality of this simplified approach by using various silyl enolates **3** and by comparing its enantioselective performances with that making use of a latent source of HF (Table 7). In all cases, cyclic ketones **3a**−**i**,**k**,***l***,**n**,**p** were obtained in excellent yields and enantioselectivities ranging from 27% to 74% ee. As already observed with the two-component process involving PhCOF/EtOH (Table 4), silyl enolates of tetralone derivatives were found to afford the

TABLE 7. Scope of the Reaction Using Citric Acid As Proton Source



entry	X	R^1	R^2	3	yield (%)	ee (%)[a]	abs conf[b]
1	$(CH_2)_2$	H	Me	**3a**	95	70	*S*
2		H	Et	**3b**	93	58	*S*
3		H	F	**3c**	91	34	*S*
4		H	Bn	**3d**	97	60	*R*
5		5-MeO	Me	**3f**	98	75	nd[c]
6		5-MeO	Bn	**3g**	92	74	nd
7		6-MeO	Me	**3h**	91	27	nd
8		6-MeO	Bn	**3i**	98	43	nd
9		7-MeO	Bn	**3k**	94	53	nd
10	CH_2	H	Me	***3l***	97	43	*S*
11		H	Bn	**3n**	94	45	nd
12	OCH_2	H	Bn	**3p**	95	68	*S*

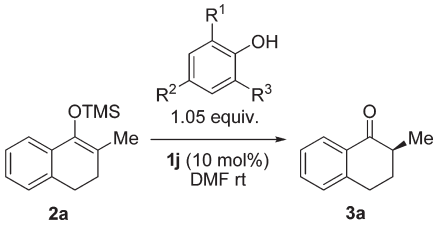
[a]Determined by HPLC using chiral column (see the Supporting Information). [b]Assigned by comparison with literature data. [c]Not determinated.

highest enantioselectivities, with the exception of 2-fluoro tetralone **2c**, which was obtained with 34% ee (Table 7, entries 1−8). One can observe that both catalytic procedures follow the same tendencies regarding the influence of the substitution pattern of the tetralone skeleton on their enantioselective performances. In particular, *C*-5-methoxy-substituted silyl enolates **2f**,**g** gave the highest selectivity (Table 7, entries 5 and 6), while *C*-6 and *C*-7-methoxy-substituted silyl enol ethers **2h**,**i**,**k** led to markedly lower asymmetric inductions (Table 7, entries 7−9). Similarly, indanones were isolated with rather modest enantioselectivities not exceeding 45% ee (Table 7, entries 10 and 11) whereas chromanone silyl enolate **2p** afforded the corresponding ketone **3p** with an acceptable 68% ee (Table 8, entry 12).

In a last attempt to improve the enantioselective performances of this simplified approach by seeking to thwart the background protonation observed with citric acid at room temperature, we focused our attention on using phenols as proton source (Table 8). As mentioned in Scheme 3, we were pleased to observe that the reaction could proceed very smoothly in the sole presence of phenol and $(DHQ)_2AQN$ **1j** in DMF without PhCOF, affording tetralone **3a** in quantitative conversion within 2 days and a promising ee of 42%. Furthermore, a control experiment carried out in the absence of the catalyst clearly showed that, in contrast to citric acid, the catalytic process is not plagued by a competitive uncatalyzed background protonation at room temperature. This encouraging result prompted us to screen different phenol derivatives in the presence of $(DHQ)_2$-AQN **1j** as catalyst in DMF at room temperature.

When using 2-hydroxyphenol (pyrocatechol), the reaction proceeded to completion within 12 h, however to the detriment of the enantioselectivity which dropped to 9% (Table 8, entries 1 and 2). The influence of the substitution pattern of the phenol on the enantioselectivity follows a general trend of improving the enantiomeric excess with the presence of electrodonating groups (Table 8, entries 3−8), with a optimal level of enantioselection of 65% ee attained after 4 days with 4-methoxyphenol (guaiacol) (Table 8, entry 8). Although the reaction time could be advantageously reduced to 3 days by increasing the amount of catalyst **1j** to 20 mol %, no improvement of the asymmetric induction

TABLE 8. Phenol Derivatives Screening



entry	R^1	R^2	R^3	ee (%)[a]	time (h)
1	H	H	H	42	48
2	H	H	OH	9	12
3	H	CN	H	9	10
4	H	Me	H	32	55
5	H	OMe	H	46	60
6	H	H	CN	20	10
7	H	H	Me	57	72
8	H	H	OMe	65	96
9				67[b]	72
10	H	H	OEt	53	84
11	H	H	O*i*-Pr	38	84
12	OMe	H	OMe	-[c]	

[a]Determined by HPLC using chiral column (see the Supporting Information). [b]20 mol % of $(DHQ)_2AQN$ was used. [c]No conversion was observed by GC analysis

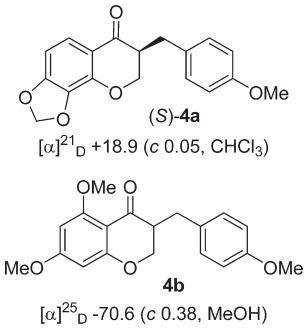


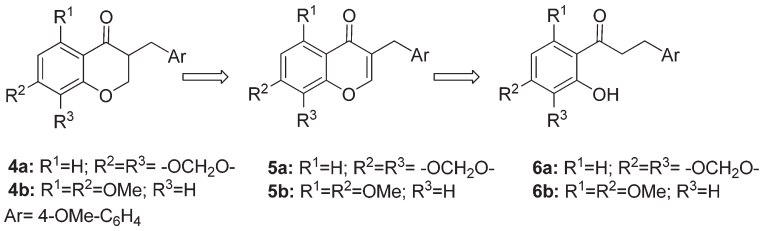
FIGURE 1. Structure of homoisoflavones **4a** and **4b** isolated from *Chlorophytum Inornatum* and *Scilla Nervosa*, respectively.

was observed (Table 8, entries 8 and 9). Finally, the use of bulkier 2-alkoxyphenols (Table 8, entries 10 and 11) or 2,2′-dimethoxyphenol (Table 8, entry 12) has a dramatic effect on both the enantiomeric excesses and the reaction rate. Although the use of carboxylic acid or phenol derivatives as proton sources gives rise to more atom economic and operationally simpler catalytic procedures than the initial strategy involving a hydrogen fluoride salt **1**-HF, the later remains more attractive with respect to both enantioselectivities and reaction rates.

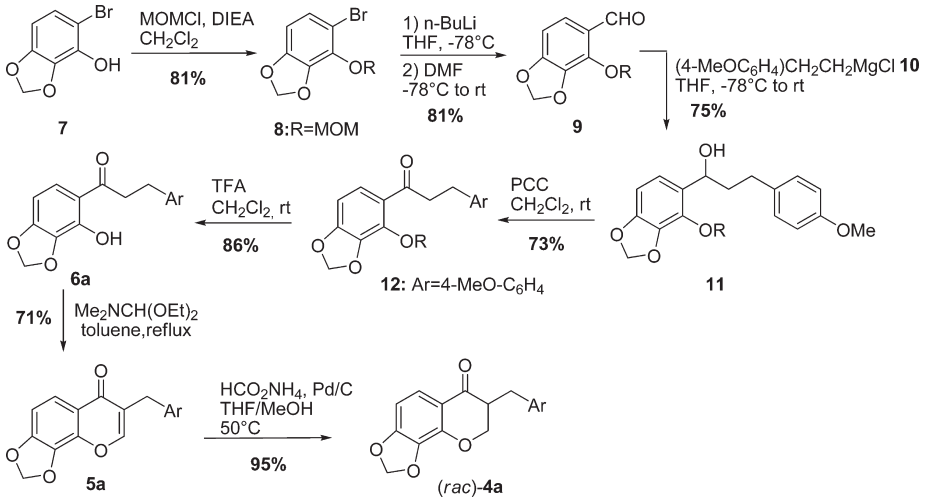
Application to the Deracemization of Two Natural Homoisoflavones. To illustrate the synthetic potential of this new organocatalytic enantioselective protonation of silyl enolates, we then turned our attention to the deracemization of two natural homosioflavones **4a** and **4b** extracted from *Chlorophytum Inornatum* and *Scilla Nervosa*, respectively (Figure 1). Homoisoflavones belong to Flavonoids which are an important class of natural product displaying various biological properties.[25] Homoisoflavone **4a** first isolated by

(25) For selected examples of biological activities of homoisoflavones, see: Siddaiah, V.; Rao, C. V.; Venkateswarlu, S.; Krishnaraju, A. V.; Subbaraju, G. V. *Bioorg. Med. Chem.* **2006**, *14*, 2545−2551 and references cited therein.

SCHEME 7. Retrosynthetic Route for the Preparation of Homoisoflavones 4a and 4b



SCHEME 8. Synthesis of Homoisoflavone (*rac*)-4a



Gibbons et al. in 2006 from *Chlorophytum Inornatum* has shown significant antibacterial activity.[26] An *S* absolute configuration was postulated by the authors by comparison of the specific optical rotation of **4a** with similar known homoisoflavones. To the best of our knowledge, only one racemic synthesis has been reported in 2008 by Zhang et al.[27] Homoisoflavone **4b** was isolated from *Scilla Nervosa* simultaneously and independently by Mulholland et al.[28] and Abegaz et al.[29] in 1999. No information about the absolute configuration of homoisoflavone **4b** has been mentioned so far in the literature. In contrast to **4a**, several racemic syntheses have already been described;[30] the synthetic racemic compound **4b** was reported to exhibit antiviral properties.[31]

Both racemic homoisoflovones **4a** and **4b** were prepared according to a reaction sequence partially reported for the preparation of **4b**.[30h] Key steps of this reaction sequence include the reduction of the double bond of 3-benzylchromones **5a** and **5b**, respectively, obtained by cyclization of 2′-hydroxy-dihydrochalcones **6a** and **6b** when treated with *N*,*N*-dimethylformamide diethyl acetal (Scheme 7).

We first embarked on the synthesis of homoisoflovane (*rac*)-**4a**, which commences with the preparation of the *o*-bromophenol **7**, obtained in 63% overall yield according to a three-step reaction sequence described by Rigby et al.[32] After protection of the phenol moiety as a MOM ether, compound **8** was subjected to halogen−metal exchange conditions to furnish the lithiated species, which was subsequently trapped with DMF to afford aldehyde **9** in 66% yield from **7**. The freshly prepared Grignard reagent **10** was smoothly added to aldehyde **9** producing alcohol **11** in 75% yield, which undergoes oxidation in the presence of PCC to afford ketone **12** in 73% yield. Acidic cleavage of the MOM ether furnished 2′-hydroxy-dihydrochalcone **6a** (86%), which was subjected to cyclization by treatment with *N*,*N*-dimethylformamide diethyl acetal under the conditions reported by Gomis et al.[30h] The resulting chromone **5a**, obtained in 71% yield, was subsequently hydrogenated over Pd/C with ammonium formate to provide the desired racemic chromanone (*rac*)-**4a** in 95% yield (Scheme 8).

Homoisoflavone **4b** was obtained following a similar pathway as that described above from the commercially available salicylaldehyde **13**, which was first protected as TBDMS ether followed by addition of the Grignard reagent

(26) O'Donnell, G.; Bucar, F.; Gibbons, S. *Phytochemistry* **2006**, *67*, 178–182.

(27) Zhang, L.; Zhang, W.-G.; Kang, J.; Bao, K.; Da, Y.; Yao, X.-S. *J. Asian Nat. Prod. Res.* **2008**, *10*, 909–913.

(28) Bangani, V.; Crouch, N. R.; Mullholland, D. A. *Phytochemistry* **1999**, *51*, 947–951.

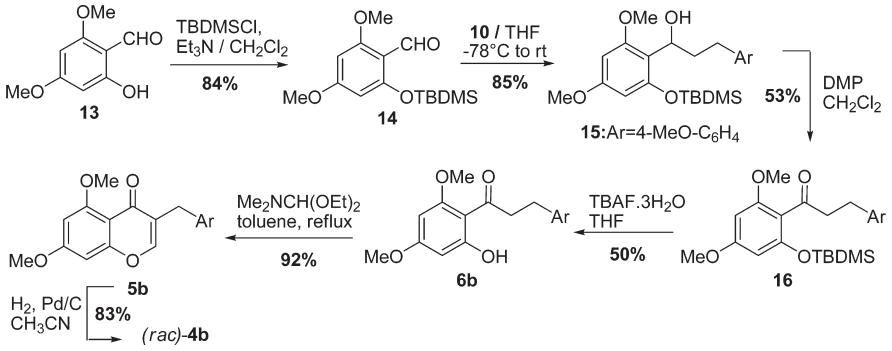
(29) Silayo, A.; Ngadjui, B. T.; Abegaz, B. M. *Phytochemistry* **1999**, *52*, 947–955.

(30) (a) Jaspal, S.; Grover, S. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43*, 1782–1783. (b) Davis, F. A.; Chen, B. C. *Tetrahedron Lett.* **1990**, *31*, 6823–6826. (c) Pinkey, J. P. K.; Grover, S. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1986**, *25*, 365–367. (d) Makrandi, J. K.; Grover., S. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1980**, *19*, 739–743. (e) Chatterjea, J. N.; Shaw, S. C.; Lal, P. K.; Singh, R. P. *J. Indian Chem. Soc.* **1979**, *56*, 1006–1009. (f) Heller, W.; Andermatt, P.; Schaad, W. A.; Tamm, C. *Helv. Chim. Acta* **1976**, *59*, 2048–2058. (g) Farkas, L.; Gottsegen, A.; Nogradi, M.; Strelisky, J. *Tetrahedron* **1971**, 5049–5054. (h) Kirkiacharian, B. S.; Gomis, M. *Synth. Commun.* **2005**, *35*, 563–569.

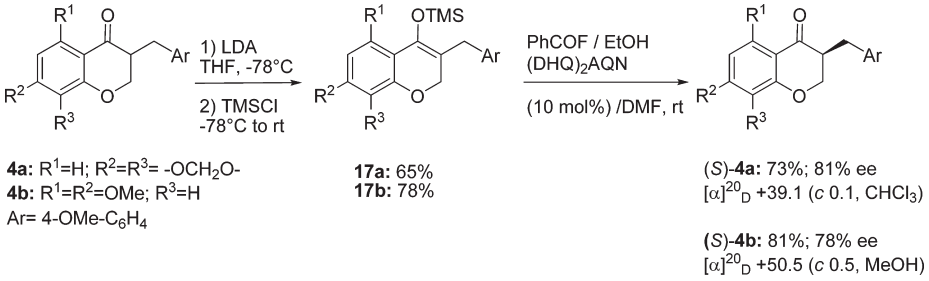
(31) (a) Desideri, N.; Olivieri, S.; Stein, M. L.; Sgro, R.; Orsi, N.; Conti., C. *Antiviral Chem. Chemother.* **1997**, *8*, 545–555. (b) Tait, S.; Salvati, A. L.; Desideri, N.; Fiore, L. *Antiviral Res.* **2006**, *72*, 252–255.

(32) (a) Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655–12656. (b) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624–6628.

SCHEME 9. Synthesis of Homoisoflavone (*rac*)-4b



SCHEME 10. Deracemization of Homoisoflavones 4a and 4b by a Sequence of Silyl Enolate Formation/Enantioselective Protonation



10 to give the corresponding alcohol **15** in 74% over the two steps. All attempts to oxidize alcohol **15** into ketone **16** using classical methods (i.e., PCC, $KMnO_4$, TEMPO/NaOCl, IBX, Swern conditions) resulted in a complete degradation of the starting material. Finally, we were pleased to find that Dess-Martin periodinane (DMP) can be used as an effective oxidizing agent to afford ketone **16** in a moderate yield of 53%, which after deprotection of TBDMS ether with TBAF afforded the cyclization precursor **6b**. Lastly, the desired homoisoflavone (*rac*)-**4b** was obtained in 76% yield from **6b** according to a two-step sequence (cyclization and reduction) previously reported in the literature (Scheme 9).[30h]

Both homoisoflavones (*rac*)-**4a** and (*rac*)-**4b** were then subjected to a deracemization process via enantioselective protonation of their corresponding silyl enolates **17a** and **17b** by implementing the most efficient process using in situ generation of HF in the presence of $(DHQ)_2AQN$ (Scheme 10). We were pleased to obtain the enantiomerically enriched homoisoflavone **4a** in 73% yield and 81% ee, while its analogue **4b** was isolated in comparable yield and enantioselectivity. According to our previous observations regarding the sense of the asymmetric induction of the protonation in the chromanone series (Table 4, entry 16), (*S*)-absolute configuration was assigned in the major enantiomer. A comparison of the optical rotations with those of the natural products previously reported in the literature,[26,29] corroborates the (*S*)-configuration in the natural homoisoflavone **4a** previously postulated,[26] and leads us to suggest a (*R*)-absolute configuration in the natural homoisoflavone **4b**.

Conclusion

In summary, we have reported a full account of our investigation focusing on the development of an organocatalytic enantioselective protonation by using readily available cinchona alkaloid catalysts and various protic nucleophiles such as HF (generated in situ from benzoyl fluoride and ethanol), carboxylic acid, or phenol derivatives. The resulting tertiary ammonium ion pairs **1**-HX (X = F, RCO_2, ArO) were revealed to be very powerful chiral protonating agents. The nature of the anion, which is assumed to activate the silyl group to facilitate proton delivery from the ammonium cation, proved to be a key element in the design of this catalytic approach. Thus, high levels of asymmetric induction (up to 92% ee) were obtained under mild and metal-free conditions, using in situ generated HF as a proton source. Then, a simplification of this process was developed using carboxylic acid or phenol derivatives as proton source. Although the resulting chiral ammonium carboxylate **1**-RCO_2H or phenoxide **1**-ArOH led to lower enantiomeric excesses, this approach provides an important gain in terms of atom economy and practical simplicity. An investigation of the scope and limitations of our methodology clearly showed higher performances in tetralone and indalone series. Then, the most effective catalytic process (i.e., HF formed in situ by reaction of PhCOF with EtOH) was successfully applied in the enantioselective synthesis of two homoisoflavones **4a** and **4b** isolated from *Chlorophytum Inornatum* and *Scilla Nervosa*. Both homoisoflavones **4a** and **4b** were obtained with good enantiomeric excesses of 81% (7% overall yield over 12 steps) and 78% (9% overall yield over 9 steps), respectively, highlighting the synthetic potential of this organocatalytic strategy in a deracemization process of bioactive α-substituted ketones.

Experimental Section

General Experimental Information. CH_2Cl_2, CH_3CN, DMF, DMSO, toluene, chlorotrimethylsilane, $(i\text{-}Pr)_2NH$, and diisopropylamine (DIPA) were distilled from CaH_2. THF, Et_2O, and dioxane were distilled from Na/benzophenone. *n*-BuLi (2.5 M in hexanes) was titrated with menthol and phenantroline as

indicator prior to use. PCC was freshly prepared according to the literature prior to use.[33] Grignard reagent were prepare according to the Gillman procedure.[34] The following compounds were prepared according to published procedures: silyl enol ethers **2a**,**b**,**d**,**e**,**f**,**g**,***l***,**m**,**n**,**q**,[16a] **2c**,**p**,[16b] **2h**,**o**,[35] ketones **3a**,**b**,**d**,**e**,**f**,**g**,***l***,**m**,**n**,**q**[16a] and **3c**,**p**,[16b] and bromo phenol **7**.[32b] All these compounds gave satisfactory ^{1}H and ^{13}C NMR analyses. All reagents were used as received unless otherwise indicated. The NMR spectra were recorded at 300 (^{1}H) and 75 MHz (^{13}C) with $CDCl_3$ as solvent and the residual solvent (δ 7.26, ^{1}H; δ 77.16, ^{13}C) as internal standard unless otherwise indicated. Melting points are uncorrected, analytical thin layer chromatographies (TLC) were performed on a QF-254 precoated silica on aluminum and visualized by UV fluorescence quenching, vanilin, $KMnO_4$, or PMA staining. Flash chromatographies were performed with silica gel (70−230 μm) unless otherwise indicated. HPLC analyses were performed with chiral columns (4.6 mm ×25 cm) in heptane/isopropanol solvent mixtures with visualization at 254 nm (UV 1000 detector) unless otherwise stated. Gas chromatographies were performed with a DB-5 columm (30 m × 0.25 mm ×25 μm). All experiments were conducted under nitrogen atmosphere in oven-dried glassware with magnetic stirring, using standard Schlenk techniques.

Synthesis of Silyl Enol Ethers 2ab, 2ac, 2h,i,j,k,o (Procedure A). To a solution of (*i*-Pr)$_2$NH (1.19 mL, 8.4 mmol) at 0 °C in dry THF (50 mL) was added *n*-BuLi (2.5 M solution in hexane, 3.22 mL, 8.05 mmol), then the whole was stirred for 15 min at this temperature, after which the ketone **3** (7 mmol) was slowly added at −78 °C. After 1 h at this temperature, freshly distilled TMSCl (1 mL, 7.7 mmol) was added and the solution was allowed to reach room temperature before being stirred for 2 h. A solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvents were removed under vacumm and the residue was purified by flash chromatography affording the pure silyl enol ethers **2**.

2-Methyl-1-triethylsilyloxytetral-1-ene, 2ab. The titled compound was prepared according to procedure A from ketone **3a** (1.05 mL, 7 mmol) and TESCl (1.29 mL, 7.7 mmol) affording the desired silyl enol ether **2ab** (1.56 g, 81% yield). Colorless oil. R_f (silica gel, 5% Et_2O in cyclohexane) 0.80. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (q, 6H, J = 7.0 Hz), 0.97 (t, 9H, J = 7.0 Hz), 1.83 (s, 3H), 2.22 (t, 2H, J = 7.9 Hz), 2.71 (t, 2H, J = 7.9 Hz), 7.05−7.19 (m, 3H), 7.33−7.36 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.5, 7.0, 17.3, 28.3, 29.3, 116.7, 121.4, 126.0, 126.2, 126.7, 134.6, 136.6, 142.8. HRMS (EI) calcd for $C_{17}H_{26}OSi$ (M^+) 274.1753, found 274.1762.

2-Methyl-1-((chloromethyldimethyl)silyloxy)tetral-1-ene, 2ac. The titled compound was prepared according to procedure A from ketone **3a** (1.06 mL, 7 mmol) and $ClCH_2SiMe_2Cl$ (1 mL, 7.7 mmol) affording the desired silyl enol ether **2ac** (1.40 g, 75% yield). Colorless oil. R_f (silica gel, 5% Et_2O in cyclohexane) 0.63. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 1.60 (s, 3H), 2.03 (t, 2H, J = 6.8 Hz), 2.51 (t, 2H, J = 6.8 Hz), 2.64 (s, 2H), 6.87−7.02 (m, 3H), 7.04−7.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.5, 17.5, 28.4, 29.3, 30.1, 117.8, 121.4, 126.5, 126.8, 127.2, 134.1, 136.2, 142.2. HRMS (EI) calcd for $C_{14}H_{19}ClOSi$ (M^+) 266.0894, found 266.0889.

2-Methyl-6-methoxy-1-trimethylsilyloxytetral-1-ene, 2h. The titled compound was prepared according to procedure A from ketone **3h** (1.33 g, 7 mmol) and TMSCl (1 mL, 7.7 mmol) affording the desired silyl enol ether **2h** (1.47 g, 80% yield). Colorless oil. R_f (silica gel, 5% Et_2O in cyclohexane) 0.65. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.59 (s, 3H), 2.04 (t, 2H, J = 7.7 Hz), 2.52 (t, 2H, J = 7.7 Hz), 3.60 (s, 3H), 6.46−6.52 (m, 2H), 7.02−7.06 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.7, 17.2, 28.8, 29.2, 55.3, 110.6, 113.2, 114.3, 122.8, 127.6, 137.9, 142.2, 158.2.

2-Benzyl-6-methoxy-1-trimethylsilyloxytetral-1-ene, 2i. The titled compound was prepared according to procedure A from ketone **3i** (1.86 g, 7 mmol) and TMSCl (1 mL, 7.7 mmol) affording the desired silyl enol ether **2i** (1.75 g, 74% yield). Green oil. R_f (silica gel, 15% Et_2O in cyclohexane) 0.75. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 9H), 2.09 (t, 2H, J = 7.9 Hz), 2.68 (t, 2H, J = 7.5 Hz), 3.61 (s, 2H), 3.79 (s, 3H), 6.66 (d, 1H, J = 2.4 Hz), 6.71−6.74 (dd, 1H, J = 8.3 Hz, J = 2.4 Hz), 7.14−7.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.0, 26.9, 29.1, 36.9, 55.6, 110.9, 113.4, 116.8, 123.7, 126.1, 127.7, 128.6, 129.1, 138.5, 140.7, 143.6, 158.8. HRMS (API^+) calcd for $C_{21}H_{27}O_2Si$ ($M + H^+$) 339.1780, found 339.1765.

2-Allyl-6-methoxy-1-trimethylsilyloxytetral-1-ene, 2j. The titled compound was prepared according to procedure A from ketone **3j** (1.51 g, 7 mmol) and TMSCl (1 mL, 7.7 mmol) affording the desired silyl enol ether **2j** (1.78 g, 88% yield). Colorless oil. R_f (silica gel, 5% Et_2O in cyclohexane) 0.88. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 2.20 (t, 2H, J = 7.9 Hz), 2.69 (t, 2H, J = 7.5 Hz), 2.99 (d, 2H, J = 6.3 Hz), 3.79 (s, 3H), 5.02−5.13 (m, 2H), 5.72−5.85 (m, 1H), 6.66−6.72 (m, 2H), 7.23−7.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.7, 26.4, 28.9, 35.0, 55.3, 110.7, 113.2, 115.8, 123.3, 127.5, 136.5, 138.3, 142.9, 158.5. HRMS (API^+) calcd for $C_{17}H_{25}O_2Si$ ($M + H^+$) 289.1624, found 289.1616.

2-Benzyl-7-methoxy-1-trimethylsilyloxy-tetral-1-ene, 2k. The titled compound was prepared according to procedure A from ketone **3k** (1.86 g, 7 mmol) and TMSCl (1 mL, 7.7 mmol) affording the desired silyl enol ether **2k** (1.75 g, 74% yield). Colorless oil. R_f (silica gel, 10% Et_2O in cyclohexane) 0.65. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 9H), 2.09 (t, 2H, J = 8.0 Hz), 2.64 (t, 2H, J = 7.5 Hz), 3.63 (s, 2H), 3.81 (s, 3H), 6.67 (dd, 1H, J = 8.0 Hz, J = 2.5 Hz), 6.97−7.00 (m, 2H), 7.15−7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0, 26.2, 26.4, 36.1, 54.6, 107.2, 111.3, 119.1, 125.2, 126.8, 127.6, 127.8, 128.1, 134.7, 139.4, 142.7, 157.6. HRMS (API^+) calcd for $C_{21}H_{27}O_2Si$ ($M + H^+$) 339.1780, found 339.1794.

8-Methyl-9-trimethylsilyloxy-6,7-dihydro-[5*H*]-benzocycloheptene, 2o. The titled compound was prepared according to procedure A from ketone **3o** (1.22 g, 7 mmol) and TMSCl (1 mL, 7.7 mmol) affording the desired silyl enol ether **2o** (1.50 g, 87% yield). Colorless oil. R_f (silica gel, 5% Et_2O in cyclohexane) 0.65. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 1.81 (t, 2H, J = 7.1 Hz), 1.89 (s, 3H), 2.09 (q, 2H, J = 7.1 Hz), 2.56 (t, 2H, J = 7.0 Hz), 7.14 (m, 2H), 7.17−7.23 (m, 1H), 7.39 (d, 1H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.8, 18.0, 30.0, 32.9, 34.0, 118.1, 126.0, 127.1, 127.2, 128.8, 140.1, 140.3, 143.2.

Organocatalytic Enantioselective Protonation. Organocatalytic Enantioselective Protonation Mediated by PhCOF/EtOH (Procedure B). To a solution of silyl enol ether **2** (0.5 mmol) in dry DMF (0.5 mL) was added $(DHQ)_2AQN$ **1j** (10 mol %, 43 mg, 0.05 mmol) at rt as a solution in DMF (0.5 mL) followed by EtOH (1.05 equiv, 30 μL, 0.525 mmol) and benzoyl fluoride (1.05 equiv, 57 μL, 0.525 mmol). The solution was stirred at this temperature until complete disappearance of the starting material (monitored by GC/MS). The solution was diluted with Et_2O and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), then the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (3 × 25 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash chromatography affording the pure ketone **3**, which was analyzed by chiral HPLC.

Organocatalytic Enantioselective Protonation Mediated by Citric Acid (Procedure C). To a solution of silyl enol ether **2** (0.5 mmol) and $(DHQ)_2AQN$ **1j** (10 mol %, 43 mg, 0.05 mmol)

(33) Corey., E. J.; Suggs., J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
(34) Gilman, H.; Kirby., R. H. *Org. Synth.* **1925**, *5*, 75–77.
(35) Eames, J.; Weerasooriya, N.; Coumbarides, G. S. *Eur. J. Org. Chem.* **2002**, 181–187.

in DMF (0.5 mL) was added citric acid (1.05 equiv, 100 mg, 0.525 mmol) at −10 °C as a solution in DMF (0.5 mL). The reaction was stirred at −10 °C until complete disappearance of the starting material (monitored by gas chromatography). The solution was diluted with Et_2O (10 mL), washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (3 × 10 mL), dried over $MgSO_4$, and concentrated. The residue was filtered through a short pad of silica gel (Et_2O as eluent) to give the pure ketone **3**, which was analyzed by chiral HPLC.

Organocatalytic Enantioselective Protonation Mediated by Guaiacol (Procedure D). To a solution of silyl enol ether **2** (0.5 mmol) and $(DHQ)_2AQN$ **1j** (10 mol %, 43 mg, 0.05 mmol) in DMF (0.5 mL) at rt was added guaiacol (1.05 equiv, 65 mg, 0.525 mmol) as a solution in DMF (0.5 mL). The reaction was stirred at rt until complete disappearance of the starting material (monitored by gas chromatography). The solution was diluted with Et_2O (10 mL), washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (3 × 10 mL), dried over $MgSO_4$, and concentrated. The residue was filtered through a short pad of silica gel (Et_2O as eluent) to give the pure ketone **3**, which was analyzed by chiral HPLC.

Synthesis of Homoisoflavone 4a. 1-Bromo-2-methoxymethyloxy-3,4-methylenedioxybenzene, 8. To a solution of bromo phenol **7** (2.170 g, 10 mmol) in CH_2Cl_2 (50 mL) was added DIEA (3.31 mL, 20 mmol) and MOMCl (0.911 mL, 12 mmol). The solution was stirred for 2 h and quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the pure bromo dioxolane **8** (2.27 g, 87% yield). Colorless oil. R_f (silica gel, 25% Et_2O in petroleum ether) 0.43. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 5.37 (s, 2H), 6.04 (s, 2H), 6.55 (d, 1H, J = 8.4 Hz), 7.09 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.5, 97.2, 102.0, 104.9, 108.1, 125.6, 137.4, 138.8, 148.9. Anal. Calcd for $C_9H_9BrO_4$: C, 41.41; H, 3.47. Found: C, 41.53; H, 3.58.

2-Methoxymethyloxy-3,4-methylenedioxybenzaldehyde, 9. To a solution of bromo dioxolane **8** (0.264 g, 1.01 mmol) in THF (2.5 mL) was added *n*-BuLi (2.5 M in hexane, 0.49 mL, 1.21 mmol) at −78 °C. The solution was stirred for 15 min, then DMF (0.234 mL, 3.03 mmol) was added and the solution was warmed to rt before being stirred for an additional 30 min. The solution was then quenched with NH_4Cl (saturated, 5 mL) and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the corresponding aldehyde **9** (172 mg, 81% yield). Colorless oil. R_f (silica gel, 25% Et_20 in petroleum ether) 0.21. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 3H), 5.33 (s, 2H), 6.01 (s, 2H), 6.60 (d, 1H, J = 8.3 Hz), 7.43 (d, 1H, J = 8.3 Hz), 10.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.5, 97.2, 102.4, 104.3, 123.8, 124.9, 137.0, 142.5, 154.7, 188.1. IR (KBr, cm^{-1}) 925, 1275, 1349, 1473, 1615, 1681. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.34; H, 4.86.

1-(2-Methoxymethyloxy-3,4-methylenedioxyphenyl)-3-(4-methoxyphenyl)propanol, 11. To a solution of *p*-methoxyphenethylmagnesium chloride **10** (0.25 M in THF, 10.69 mmol) was added aldehyde **9** (1.123 g, 5.35 mmol) as a solution in THF (10 mL) at −78 °C. The solution was stirred for 30 min at −78 °C before being warmed to rt and stirred for an additional 30 min at this temperature. After adding a saturated aqueous solution of NH_4Cl (30 mL), the aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to give the corresponding alcohol **11** (1.39 g, 75% yield). Colorless oil. R_f (silica gel, 50% Et_2O in petroleum ether) 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96−2.17 (m, 2H), 2.58−2.76 (m, 2H), 3.45 (s, 3H), 3.78 (s, 3H), 4.87−4.91 (m, 1H), 5.27 (s, 2H), 5.92 (s, 2H), 6.58 (d, 1H, J = 8.1 Hz), 6.81−6.88 (m, 3H), 7.12 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 38.3, 55.3, 57.4, 68.8, 97.2, 101.2, 103.6, 113.8, 119.8, 129.4, 130.0, 130.5, 134.1, 137.7, 148.5, 157.8. IR (KBr, cm^{-1}) 1047, 1247, 1466, 1513, 1611, 2934, 3410. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.96; H, 6.21.

1-(2-Methoxymethyloxy-3,4-methylenedioxyphenyl)-3-(4-methoxyphenyl)propanone, 12. To a solution of alcohol **11** (1.800 g, 5.19 mmol) in CH_2Cl_2 (50 mL) was added PCC (2.67 g, 10.4 mmol) and the resulting solution was stirred for 2 h at rt. The solution was concentrated and the residue was purified by flash chromatography to give the corresponding ketone **12** (1.31 g, 73% yield). Colorless oil. R_f (silica gel, 75% Et_2O in petroleum ether) 0.43. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, 2H, J = 8.0 Hz), 3.25 (t, 2H, J = 7.9 Hz), 3.45 (s, 3H), 3.78 (s, 3H), 5.30 (s, 2H), 6.02 (s, 2H), 6.59 (d, 1H, J = 8.3 Hz), 6.82 (d, 2H, J = 8.6 Hz), 7.15 (d, 2H, J = 8.6 Hz), 7.27 (d, 1H, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 45.4, 55.5, 57.8, 97.6, 102.1, 103.9, 114.1, 125.4, 127.2, 129.6, 133.8, 137.7, 139.7, 152.5, 158.1, 200.4. IR (KBr, cm^{-1}) 1030, 1246, 1464, 1513, 1613, 1674. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.31; H, 5.96.

1-(2-Hydroxy-3,4-methylenedioxyphenyl)-3-(4-methoxyphenyl)-propanone, 6a. To a solution of ketone **12** (1.000 g, 2.9 mmol) in CH_2Cl_2 (30 mL) was added TFA (0.432 mL, 5.8 mmol) and the solution was allowed to stir for 1 h before being quenched with brine. After phase separation, the organic layer was dried over $MgSO_4$ and concentrated to afford keto phenol **6a** (749 mg, 86% yield). White solid. Mp 94−96 °C. R_f (silica gel, 75% Et_2O in petroleum ether) 0.54. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (t, 2H, J = 7.8 Hz), 3.20 (t, 2H, J = 7.8 Hz), 3.78 (s, 3H), 6.04 (s, 2H), 6.43 (d, 1H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.6 Hz), 7.15 (d, 2H, J = 8.6 Hz), 7.37 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.52, 40.46, 55.40, 100.92, 10.78, 114.12, 116.63, 126.01, 129.49, 132.87, 134.66, 147.18, 154.01, 158.24, 204.77. IR (KBr, cm^{-1}) 1064, 1236, 1299, 1450, 1496, 1544, 1611, 1661, 2905. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.85 ; H, 5.46.

3-(4-Methoxybenzyl)-7,8-methylenedioxychromen-4-one, 5a. To a solution of keto phenol **6a** (0.750 g, 2.5 mmol) in toluene (50 mL) was added *N*,*N*-dimethylformamide diethyl acetal (0.641 mL, 3.74 mmol) and the solution was refluxed for 10 h. The solution was diluted with Et_2O (15 mL), washed with brine (15 mL), dried over $MgSO_4$, and concentrated. The residue was purified by recrystallization from dichloromethane/petroleum ether affording chromenone **5a** (551 mg, 71% yield). White solid. Mp 121−123 °C. R_f (silica gel, 25% EtOAc in petroleum ether) 0.29. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 2H), 3.76 (s, 3H), 6.13 (s, 2H), 6.83 (d, 2H, J = 8.5 Hz), 6.89 (d, 1H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5 Hz), 7.49 (s, 1H), 7.77 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.04, 55.47, 103.43, 107.28, 114.22, 120.16, 120.63, 124.62, 130.23, 130.67, 134.62, 141.66, 152.22, 152.30, 158.45, 176.67. IR (KBr, cm^{-1}) 905, 1031, 1174, 1247, 1289, 1500, 1544, 1610, 1632, 1649. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.85; H, 4.47.

3-(4-Methoxyphenyl)-7,8-methylenedioxychroman-4-one, (*rac*)-4a. To a solution of chromenone **5a** (0.350 g, 1.13 mmol) in THF/MeOH (4:1, 30 mL) were added Pd/C (10% w, 175 mg, 0.16 mmol) and $HCOONH_4$ (2.11 g, 33.6 mmol). The resulting solution was placed under hydrogen atmosphere (1 atm) and heated at 50 °C for 3 h. The solution was then cooled to rt, degassed, and filtered through a pad of Celite. The solvents were then removed under vacuum and the residue was purified by flash chromatography to afford the pure ketone (*rac*)-**4a** (335 mg, 95% yield). White solid. Mp 105−106 °C. R_f (silica gel, 60% AcOEt in petroleum ether) 0.73. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67−2.75 (m, 1H), 2.80−2.89 (m, 1H), 3.18 (dd, 1H, J = 4.16 Hz, J = 13.6 Hz), 3.80 (s, 3H), 4.24 (dd, 1H, J = 11.4 Hz, J = 7.05 Hz), 4.41 (dd, 1H, J = 11.4 Hz, J = 4.0 Hz), 6.09 (s, 2H), 6.61 (d, 1H, J = 8.4 Hz), 6.85 (d, 2H, J = 8.5 Hz), 7.16

(d, 2H, J = 8.5 Hz), 7.59 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 48.5, 55.6, 70.3, 103.0, 103.8, 114.4, 117.6, 123.4, 130.3, 130.5, 134.7, 145.8, 154.3, 158.7, 192.5. IR (KBr, cm^{-1}) 1031, 1083, 1241, 1367, 1458, 1512, 1633, 1680, 2918; HRMS (CI$^+$) calcd for $C_{18}H_{17}O_5$ (M + H$^+$) 313.1059, found 313.1059.

3-(4-Methoxybenzyl)-6-trimethylsilyloxy-[8*H*]-[1,3]-dioxolo-[4,5-*H*]chromene, 17a. The titled compound was prepared according to procedure A from ketone (*rac*)-**4a** (156 mg, 0.5 mmol) and TMSCl (70 μL, 0.55 mmol) affording the desired silyl enol ether **17a** (125 mg, 65% yield). Colorless oil. R_f (silica gel, 25% Et_2O in petroleum ether) 0.46. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9H), 3.50 (s, 2H), 3,78 (s, 3H), 4,62 (s, 2H), 5.95 (s, 2H), 6.46 (d, 1H, J = 8.1 Hz), 6.81−6.85 (m, 3H), 7.15 (d, 2H, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.9, 32.8, 55.5, 69.5, 101.3, 101.9, 111.2, 114.2, 116.2, 119.2, 129.7, 130.6, 134.0, 138.7, 141.1, 149.3, 158.4. HRMS (API$^+$) calcd for $C_{21}H_{25}O_5Si$ (M + H$^+$) 385.1471, found 385.1461.

3-(4-Methoxyphenyl)-7,8-methylenedioxychroman-4-one, (*S*)-4a. The titled compound was prepared according to procedure B from the silyl enolate **17a** (108 mg, 0.28 mmol) affording the desired enantioenriched chromanone **4a** (64 mg, 73% yield). $[\alpha]^{20}_D$ +39.1 (c 0.1, $CHCl_3$), 81% ee determined by chiral HPLC (OJ-H, 1 mL·min^{-1}, heptane/*i*-PrOH 8:2 v/v, retention time of both enantiomers: 69.04 min (*S*) major and 98.52 min (*R*) minor).

Synthesis of Homoisoflavone 4b. 2-[(1,1-Dimethylethyl)dimethylsilyloxy]-4,6-dimethoxybenzaldehyde, 14. To a solution of 4,6-dimethoxysalicylaldehyde **13** (0.322 g, 1.76 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.3 mL, 2.11 mmol) and TBDMSCl (0.278 g, 1.85 mmol). The solution was stirred until complete disappearance of the starting material. The solution was concentrated and the residue was purified by flash chromatography to afford the corresponding phenol silyl ether **14** (438 mg, 84% yield). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 6H), 1.00 (s, 9H), 3.82 (s, 3H), 3.87 (s, 3H), 5.98 (d, 1H, J = 3.0 Hz), 6.09 (d, 1H, J = 3.0 Hz), 10.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.1, 18.6, 25.9, 55.9, 56.1, 92.0, 97.9, 111.6, 161.8, 163.3, 165.9, 188.2. IR (KBr, cm^{-1}) 1683. Anal. Calcd for $C_{15}H_{24}O_4Si$: C, 60.78; H, 8.16. Found: C, 60.62 ; H, 8.31.

1-(2-[(*tert*-Butyl)dimethylsilyloxy]-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)propanol, 15. To a solution of *p*-methoxyphenetylmagnesium chloride **10** (0.25 M in THF, 108 μL, 27 mmol) at −78 °C was added aldehyde **14** (3.253 g, 10.9 mmol) as a solution in THF (20 mL). The solution was stirred for 30 min at this temperature then warmed to rt and stirred for 30 min. The reaction mixture was quenched with NH_4Cl (saturated, 30 mL) and diluted with Et_2O (30 mL). After phase separation, the aqueous layer was extracted with Et_2O (3 × 40 mL), then the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to give alcohol **15** (4 g, 85% yield). Orange oil. R_f (silica gel, 20% EtOAc in cyclohexane) 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 6H), 0.90 (s, 9H), 1.85−1.97 (m,1H), 2.11−2.23 (m, 1H), 2.50−2.60 (m, 1H), 2.77−2.86 (m,1H), 3.58 (d, 1H, J = 11.4 Hz), 3.76 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 4.99−5.07 (m, 1H), 6.02 (d, 1H, J = 2.2 Hz), 6.13 (d, 1H, J = 2.2 Hz), 6.80 (d, 2H, J = 8.5 Hz), 7.10 (d, 2H, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.2, −3.7, 18.6, 32.1, 40.0, 55.6 (2), 55.8, 68.3, 92.3, 97.7, 114.0, 115.4, 129.6, 135.0, 154.1, 157.9, 159.5, 159.9. IR (KBr, cm^{-1}) 837, 1109, 1151, 1246, 1512, 1608, 2932, 3561. Anal. Calcd for $C_{24}H_{36}O_5Si$: C, 66.63; H, 8.39. Found: C, 66.78; H, 8.41.

1-(2-[(*tert*-Butyl)dimethylsilyloxy]-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)propanone, 16. To a solution of alcohol **15** (2.188 g, 5.05 mmol) in CH_2Cl_2 (85 mL) was added Dess-Martin periodinane (3.21 g, 7.57 mmol). The solution was stirred for 4 h, then quenched with $NaHCO_3/Na_2S_2O_3$ (saturated, 1:1, 40 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the corresponding ketone **16** (1.15 g, 53% yield). Colorless oil. R_f (silica gel, 10% EtOAc in cyclohexane) 0.20. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.95 (s, 9H), 2.89−3.05 (m, 2H), 3.00−3.05 (m, 2H), 3.73 (s, 3H), 3.77 (s, 6H), 5.98 (d, 1H, J = 1.3 Hz), 6.09 (d, 1H, J = 1.3 Hz), 6.81 (d, 2H, J = 8.4 Hz), 7.10 (d, 2H, J = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.0, 18.4, 25.9, 29.2, 47.1, 55.5, 55.6, 55.9, 91.8, 97.8, 114.0, 116.6, 129.5, 133.8, 154.1, 158.0, 158.4, 161.8, 203.9. IR (KBr, cm^{-1}) 837, 1117, 1154, 1513, 1604, 1703, 2932. Anal. Calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 66.96; H, 8.15.

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-propanone, 6b. To a solution of ketone **16** (1.150 g, 2.67 mmol) in THF (30 mL) was added TBAF·3H_2O (1.685 g, 5.34 mmol) and the solution was stirred for 1 h. The resulting mixture was concentrated, diluted with EtOAc (30 mL), washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford the corresponding keto-phenol **6b** (422 mg, 50% yield). Glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (t, 2H, J = 7.2 Hz), 3.28 (t, 2H, J = 7.2 Hz), 3.78 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 5.92 (d, 1H, J = 2.3 Hz), 6.07 (d, 1H, J = 2.3 Hz), 6.85 (d, 2H, J = 8.6 Hz), 7.17 (d, 2H, J = 8.6 Hz), 14.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6, 46.2, 55.4, 55.7, 55.76, 90.9, 93.8, 105.8, 114.0, 129.5, 133.9, 158.0, 162.9, 166.1, 167.8, 204.8. IR (KBr, cm^{-1}) 823, 1115, 1206, 1219, 1513, 1584, 1619. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.52; H, 6.58.

3-(4-Methoxybenzyl)-5,7-dimethoxychromen-4-one, 5b. To a solution of keto-phenol **6b** (0.411 g, 1.3 mmol) in toluene (20 mL) was added *N*,*N*-dimethylformamide diethyl acetal (0.267 mL, 1.56 mmol) and the solution was refluxed for 10 h. The solution was diluted with Et_2O (20 mL), washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to afford chromenone **5b** (390 mg, 92% yield). White solid. Mp 96−98 °C. R_f (silica gel, 50% EtOAc in cyclohexane) 0.25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 2H), 3.76 (s, 3H), 3,84 (s, 3H), 3.91 (s, 3H), 6.33 (dd, 2H, J = 2.3 Hz, J = 12.3 Hz), 6.82 (d, 2H, J = 8.6 Hz), 7.20 (d, 2H, J = 8.6 Hz), 7.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0, 55.6, 56.0, 56.6, 92.7, 96.2, 109.7, 114.2, 126.3, 130.5, 131.3, 150.8, 158.4, 160.4, 161.4, 164.0, 176.7. IR (KBr, cm^{-1}) 817, 1084, 1510, 1611, 1651. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.06; H, 5.64.

3-(4-Methoxybenzyl)-5,7-dimethoxychroman-4-one, (*rac*)-4b. To a solution of chromenone **5b** (0.310 g, 0.95 mmol) in MeCN (12 mL) was added Pd/C (10% w, 100 mg, 0.095 mmol) and the solution was placed under hydrogen atmosphere (1 atm) for 2 days. The solution was degassed, filtered, and concentrated. The residue was purified by flash chromatography to afford dihydrochromanone (*rac*)-**4b** (259 mg, 83% yield). White solid. Mp 81−82 °C. R_f (silica gel, 50% AcOEt in petroleum ether) 0.48. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58−2.66 (m, 1H), 2.69−2.77 (m, 1H), 3.20 (dd, 1H, J = 3.7 Hz, J = 13.3 Hz), 3.79 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 4.05−4.13 (m, 1H), 4.26 (dd, 1H, J = 3.8 Hz, J = 11.2 Hz), 6.06 (m, 2H), 6.85 (d, 2H, J = 8.6 Hz), 7.15 (d, 2H, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.36, 48.91, 55.61, 55.91, 56.47, 69.20, 93.31, 93.48, 105.73, 114.32, 130.47, 130.93, 158.55, 162.90, 165.26, 166.08, 191.80. IR (KBr, cm^{-1}) 1035, 1226, 1257, 1512, 1619, 1668, 2939. HRMS (EI) calcd for $C_{19}H_{20}O_5$ (M$^+$) 328.1311, found 328.1306.

3-(4-Methoxybenzyl)-4-trimethylsilyloxy-[8*H*]-[1,3]-dioxolo-[4,5-*H*]chromene, 17b. The titled compound was prepared according to procedure A from ketone (*rac*)-**4b** (164 mg, 0.5 mmol) and TMSCl (70 μL, 0.55 mmol) affording the desired

silyl enol ether **17b** (156 mg, 78% yield). Colorless oil. R_f (silica gel, 40% AcOEt in petroleum ether) 0.71. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 9H), 3.56 (s, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 4.32 (s, 2H), 6.09 (s, 2H), 6.81 (d, 2H, J = 8.6 Hz), 7.15 (d, 2H, J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.6, 32.7, 55.5, 55.6 (2), 69.0, 93.3, 93.9, 106.3, 111.2, 114.1, 129.9, 131.3, 141.1, 157.3, 158.3, 158.4, 160.9. HRMS (ESI$^+$) calcd for $C_{22}H_{29}O_5Si$ (M + H$^+$) 401.1784, found 401.1772.

3-(4-Methoxybenzyl)-5,7-dimethoxychroman-4-one, (*S*)-4b. The titled compound was prepared according to procedure B from silyl enol **17b** (112 mg, 0.28 mmol) affording the desired enantioenriched chromanone **4b** (75 mg, 81% yield). $[\alpha]^{20}_D$ +50.5 (*c* 0.5, MeOH), 78% ee determined by chiral HPLC (AD-H, 1 mL·min^{-1}, heptane/*i*-PrOH 8:2 v/v, retention time of both enantiomers: 23.03 min (*S*) major and 41.95 min (*R*) minor).

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Supporting Information Available: General procedures for the synthesis of racemic ketones **3**, copies of ^{1}H and ^{13}C NMR spectra for the compounds silyl enolates **2** and ketones **3h**,**i**,**j**,**k**,**o**, homoisoflavones **4a**,**b** and for their synthetic precursors, and copies of HPLC chromatograms for ketones **3h**,**i**,**j**,**k**,**o** and homoisoflavones **4a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.