DOI: 10.1002/ejoc.200700682

Asymmetric Cyclization of 2′-Hydroxychalcones to Flavanones: Catalysis by Chiral Brønsted Acids and Bases

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Keywords: Asymmetric catalysis / Chiral Brønsted acid / Cyclization / Flavanones / Oxygen heterocycles

The asymmetric cyclization of 2′-hydroxychalcones to flavanones is a basic, enzyme-catalyzed step in the biosynthesis of flavonoid natural products, but poses a long-standing problem for asymmetric catalysis with small molecule catalysts. Earlier claims concerning the realization of an asymmetric flavanone synthesis by means of camphorsulfonic acid as chiral Brønsted acid catalysts were reinvestigated using accurate HPLC methods for quantification of enantiomer ratios. The previous claims of asymmetric induction were thus shown to be untenable. On the other hand, cinchona alkaloids serve as chiral Brønsted base mediators for the asymmetric cyclization of either 6′-substituted 2′-hydroxychalcones or 2′,6′-dihydroxychalcones. 2′,6′-Dihydroxy-4,4′-dimethoxychalcone, for instance, cyclized to give the naturally occurring naringenin-4′,7-dimethyl ether in up to 64 % *ee* at 81 % conversion. The catalysis shows a marked dependency of the enantiomeric excess of the product on the catalyst, solvent and reactant concentration. Based on these successful examples of asymmetric cyclizations of 2′-hydroxychalcones to flavanones, requirements for more active asymmetric catalysts can be defined.

1. Introduction

The cyclization of 2′-hydroxychalcones to flavanones (Figure 1) is both a simple model for the addition of an oxygen nucleophile to an alkene and a fundamental step in the biosynthesis of flavonoids.[1] The reaction produces the chromane core that is characteristic of many flavonoids, which are, inter alia, responsible for the colorful appearance of many flowers (as floral pigments), the bitter taste of grapefruit, the color of red wine, and serve for UV and antimicrobial protection of plants.[2] In plants and also in fungi, molds and bacteria,[3] the reaction is catalyzed by the enzyme chalcone isomerase (CHI; EC 5.5.1.6),[4,5] which generates 2*S*-flavanones[4] with an astonishing enantioselectivity estimated of *S*/*R* = 100′000 (*ee* = 99.998 %) from kinetic measurements (Figure 1, b).[4d]

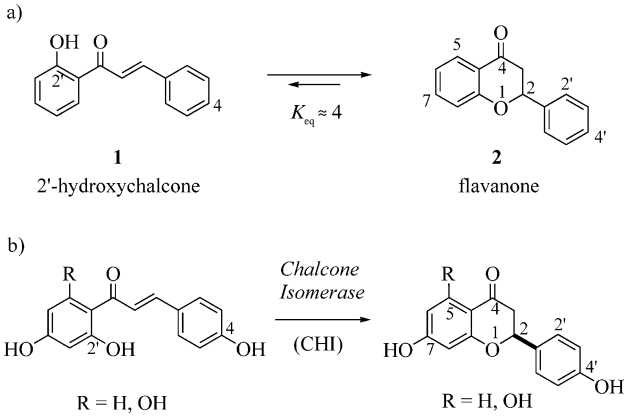

Figure 1. Cyclization of 2′-hydroxychalcones to flavanones. a) Most simple model reaction. b) Flavonoid biosynthesis.

This oxa-Michael type cyclization takes place spontaneously in solution to give an equilibrium mixture of chalcone and flavanone, but the process is typically slow under ambient and neutral conditions, especially for the nonsubstituted 2′-hydroxychalcone **1**.[6] Kostanecki realized the transformation **1**→**2** (Figure 1, a) for the first time in 1904 with a mineral acid catalyst.[7] In the meantime, a wide range of catalytic reagents and conditions have been found to induce the cyclization, including: aqueous buffers at variable pH,[6,8] mineral acids,[7,9] acidic ion-exchange resin,[10] acetic acid,[11] alkali metal hydroxide[6,8b,12] (sometimes combined with phase-transfer catalysts),[13,14] sodium acetate,[8m,15] potassium fluoride,[16] amine bases,[14,17,18] amino acids,[14] photoirradiation,[19] thermal reaction at 60 °C in the solid state[20] or in the melt at 230 °C,[21] catalysis by Co^{III}-salen complexes,[22] Lewis acids,[11a,23] SiO_2,[24] or under electrochemical conditions.[25] All of these methods have in common that they give racemic flavanone (**2**). There is *no example of an asymmetric cyclization*. Indeed, asymmetric syntheses of flavanones[26,27] require multistep-sequences involving chiral auxiliaries and protecting groups, which is in stark contrast to the waste-free, simple and elegant one-step enzymatic asymmetric synthesis mediated by CHI! Scheidt

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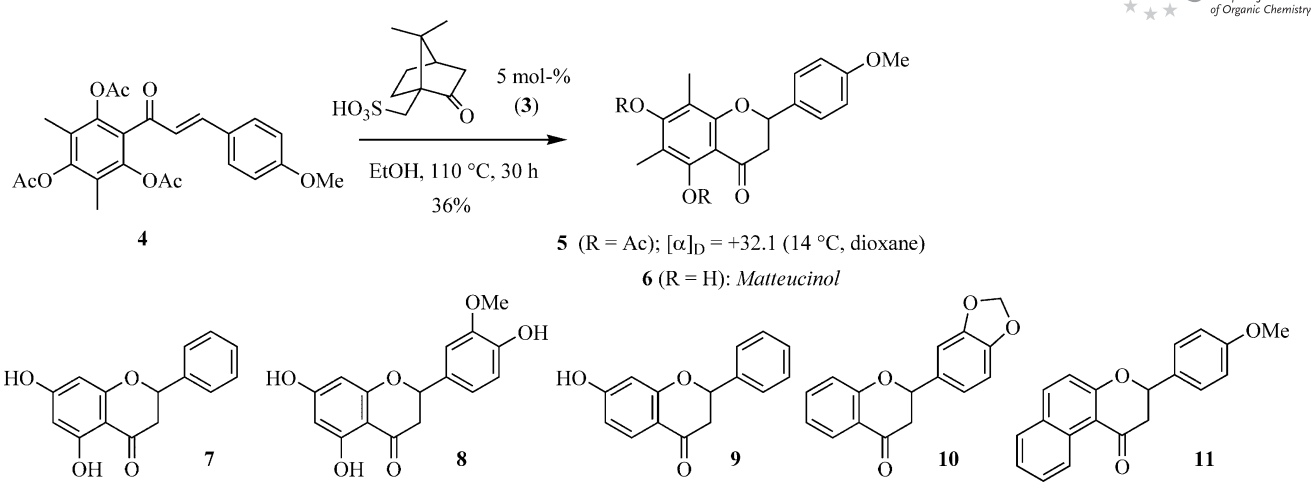


Figure 2. Experiments of Fujise et al. concerning the asymmetric cyclization of chalcones to flavanones. Chalcone precursors of **7** and **8** were the respective chalcone triacetates.

and co-workers have recently shown that a catalytic asymmetric cyclization of hydroxychalcones can be achieved *indirectly* by introducing an activating ester group at C-2 of the substrate; asymmetric cyclization is then mediated by a cinchona-alkaloid-derived catalyst containing urea/tertiary amine functional groups; the flavanone-3-carboxylic esters were decarboxylated in acidic medium to flavanones, which were obtained in up to 94% *ee*.[28] Still, this interesting protocol requires additional synthetic steps for substrate activation and product deprotection. In that sense, the fundamental problem of performing a direct asymmetric cyclization of 2′-hydroxychalcones to the desired flavanones is circumvented, and this reaction remains one of those enzyme-catalyzed processes that proceedes with high enantioselectivity but yet cannot be imitated with a *small-molecule asymmetric catalyst*. Attempts towards finding such a catalyst have been undertaken repeatedly over the years: i. L-Proline is a catalyst for the synthesis of flavanones from hydroxyacetophenones and aryl-substituted aldehydes, where 2′-hydroxychalcones are intermediates.[29] No optical induction was observed. ii. Enantiopure amino acids were tested as catalysts for the cyclization of 2′-hydroxychalcones to flavanones in a solid-liquid interphase reaction in water, with no reported induction.[14] iii. The microwave-assisted cyclization of 2′-hydroxychalcones was performed in the presence of chiral additives such as tartaric acid or *N*-benzyl-1-phenylethylamine, with no observed enantioselectivity.[18] iv. Chiral cobalt-salen complexes were found to catalyze the cyclization of a range of substituted 2′-hydroxychalcones, giving equilibirum mixtures of chalcones and flavanones, with no reported induction.[22] However, in two cases, asymmetric catalytic variants of the direct chalcone/flavanone cyclization have apparently been realized: A series of papers by Fujise et al. report that camphorsulfonic acid (CSA, **3**) catalyzes the ring closure of a handful of 2′-hydroxychalcones to the corresponding flavanones, which were found to be optically active (Figure 2). For several reasons, these results appeared to contradict current expectations regarding catalysis with chiral Brønsted acids, and a reinvestigation was deemed necessary. A second study with apparent success concerns the cinchona-catalyzed cyclization of *ortho*-tigloylphenols to 2,3-dimethylchroman-4-ones that has been shown to proceed with up to 98% *ee* for the *cis* isomer, at a diastereomeric excess of 52% (vide infra, Scheme 4).[30,31] This method has not yet been applied to substrates bearing an aryl group at C-3 of the alkenone unit (i.e., *chalcones*); therefore, it is not clear if an asymmetric synthesis of flavanones is possible by this approach. The object of the present study was therefore to investigate the fundamental viability of an asymmetric cyclizations of 2′-hydroxychalcones to flavanones by i. reinvestigating the reported CSA-catalyzed reactions (as examples of chiral Brønsted acid catalysis) and ii. investigating the catalytic action of chiral Brønsted bases, exemplified by the cinchona alkaloids. Along these lines, we will now show that the CSA-catalyzed cyclization of 2′-hydroxychalcones does not lead to enantiomerically enriched flavanones within the limits of detection of HPLC method (<1% *ee*), and that while the alkaloid-catalyzed asymmetric cyclization of *ortho*-tigloylphenols cannot be generally transferred to 2′-hydroxychalcones, a number of substrates have been found to undergo asymmetric cyclizations with notable levels of induction. Thus we present here the first cases of catalytic asymmetric cyclizations of 2′-hydroxychalcones to flavanones by a nonenzymatic method with small-molecule catalysts, opening the door to the solution of a problem in asymmetric catalysis that had already been explicitly defined in 1938.[32]

2. Results

2.1. Reinvestigation of CSA-Catalyzed Asymmetric Cyclizations of 2′-Hydroxychalcones

In a series of papers between 1938 and 1951, Fujise and coworkers had reported several examples of the cyclization of substituted 2′-hydroxychalcones (or acetylated derivatives) in the presence of (+)-10-camphorsulfonic acid (CSA,

3) in substoichiometric amounts in alcoholic solution, in which the resulting flavanones were found to be optically active (Figure 2).[32–35] In the first reported example, matteucinol-chalcone triacetate **4** was heated in EtOH under pressure to give diacetyl-matteucinol **5** in moderated yield with an optical activity close to that of "optically pure" matteucinol diacetate ($[a]_D$ = +32.8), prepared from plant-derived (–)-matteucinol (2*S*-**6**).[36]

Later, Tatsuta applied the protocol to the synthesis of flavanones **7**–**9** in optically active form. Strangely, in these experiments, fully de-acetylated flavanones were obtained from the fully acetylated chalcones.[33] The optical inductions were variable. Nevertheless, 7-hydroxyflavanone (**9**) was formed with $[a]_D$ = +29.3, which implies an optical purity of around 35%.[37] In later experiments, Fujise similarly obtained flavanones **10** and **11** with rather small optical rotations.[34,35] In spite of its simplicity, this method has not found any applications, and has in fact hardly been recognized.[38,39] The topic of asymmetric catalysis with chiral Brønsted acids has remained little explored for a long time,[40] though the situation has dramatically changed in recent years[41] with the successful application of binaphthol-derived phosphoric acids.[42] Camphorsulfonic acid **3**, a readily available chiral acid, has not been reported to give high inductions in catalysis,[40] which is probably related to its conformational flexibility and a limited abililty for participating in secondary interactions with substrates. The success of CSA (**3**) as catalyst of the chalcone-flavanone cyclization is therefore surprising, especially because the reactions were performed in ethanol, whereas modern examples of asymmetric Brønsted acid catalysis almost invariably require apolar solvents which will not rupture weak hydrogen bonding interactions between catalyst and substrate.[41,42] We therefore deemed a reinvestigation of the reaction necessary, applying current knowledge and modern methods for enantiomer analysis. Chalcone **1** was heated to 120 °C in the presence of 20 mol-% of **3** in *n*-butanol. These conditions are intended to simulate those from the early experiments (EtOH, 115–120 °C, pressure tube), but make sampling for analysis easier. The course of the reaction was followed by chiral HPLC and progress curves were fitted to a pseudo first order rate law for the forward and backward reactions ($d[\mathbf{1}]/dt = -k[\mathbf{1}] + k'[\mathbf{2}]$; $K_{eq} = k/k'$). As is evident from Figure 3, the reaction progress was consistent with this rate law.[43] From the kinetic analysis, an equilibrium constant of $K_{eq} = 3.82 \pm 0.07$ is deduced, corresponding to an equilibrium composition of 21% of hydroxychalcone (**1**) and 79% of flavanone (**2**).[44] Over the whole range of the reaction, no significant (≥ 0.7%) enantiomeric excess was detected (see part a of Figure 4 for a typical HPLC trace of the reaction mixture). A blank reaction in the absence of CSA was also performed. Surprisingly, it turns out that the CSA-catalyzed reaction was only faster by a factor of 1.6 (based on pseudo first-order rate constants); consequently, the amount of flavanone formed by CSA catalysis is small (0.6/1.6 ≈ 38%) relative to the product formed by the "non-catalyzed" pathway. Any potential induction due to asymmetric catalysis will be small from the start.

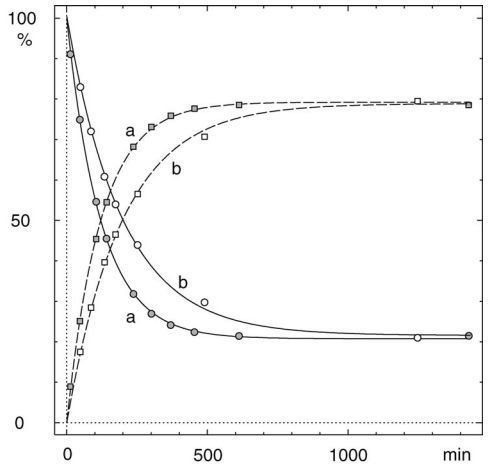


Figure 3. Reaction progress curves for cyclization of **1** to **2** in *n*BuOH at 120 °C. Solid lines: amount of **1** (%), dashed lines: conversion to **2** (%). a) Filled symbols: reaction in the presence of 20 mol-% of CSA. b) Open symbols: reaction without added catalyst (background reaction).

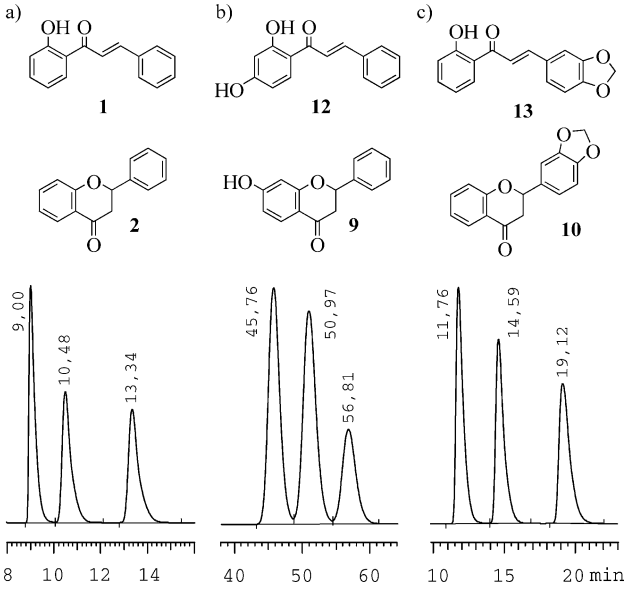


Figure 4. HPLC traces of reaction mixtures from CSA-catalyzed cyclizations of 2′-hydroxychalcones to flavanones. a) Cyclization of **1** to **2**. *Chiralcel OD*, *n*-heptane/*i*PrOH, 97:3, 1 mL/min, λ = 254 nm. Peaks for **1** (integral 36.29%), **2** (integral 31.86%), *ent*-**2** (integral 31.85%). b) Cyclization of **12** to **9**. *Chiralcel OJ*, *n*-heptane/EtOH, 95:5, 1.2 mL/min, λ = 277 nm; peaks for **9** (integral 40.24%), *ent*-**9** (integral 40.62%), **12** (integral 19.13%). c) Cyclization of **13** to **10**. *Chiralcel OD*, *n*-heptane/*i*PrOH = 95:5, 1 mL/min, λ = 254 nm, peaks for **13** (integral 36.03%), **10** (integral 31.93%), *ent*-**10** (integral 32.04%).

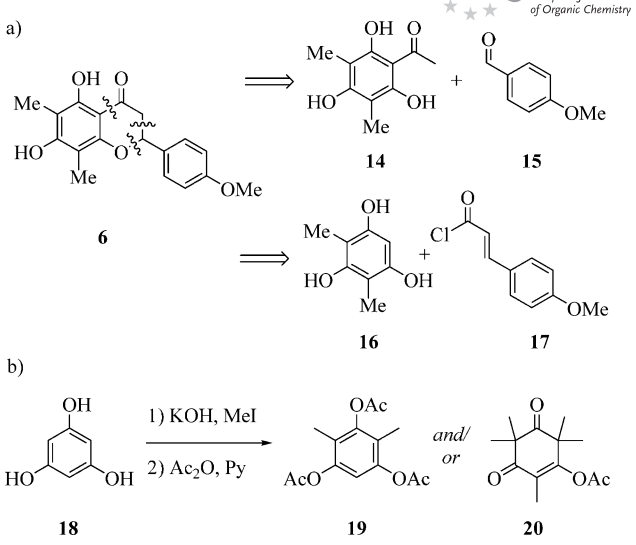
Next, the reaction solution was left standing for about two hours at 4 °C. Flavanone **2** crystallized directly from the reaction solution, but neither crystals nor the remaining material in the mother liquor displayed an enantiomeric excess. In another experiment, pure racemic flavanone was heated to 120 °C in *n*BuOH in the presence of CSA, and, after formation of a significant amount of 2′-hydroxychalcone **1**, the reaction mixture was analyzed by HPLC and

the remaining flavanone **2** found to be racemic. These experiments imply that there is no induction in the CSA-catalyzed cyclization of **1** to **2**, and that neither preferential crystallization nor kinetic resolution in the presence of CSA lead to an enantiomeric excess. We now turned our attention to 2′,4′-dihydroxychalcone (**12**), whose cyclization to flavanone **9** had been described as being accompanied by a significant optical induction (see above).[33] The experiment was performed according to the literature directions by heating chalcone **12** with (+)-CSA in EtOH for 60 h at 115–120 °C in a pressure tube. A sample from the resulting solution was analyzed by HPLC and gave the trace shown in Figure 4 (b). Even though the peaks are not completely baseline separated, the method is sufficiently accurate to exclude an *ee* of >2%.

Likewise, chalcone **13** was refluxed for 50 h in EtOH in the presence of 28 mol-% of CSA according to the reported conditions.[34] The HPLC trace of the reaction mixture is shown in part c of Figure 4: it implies again that flavanone **10** was formed with an enantiomer excess below the limits of detection of the analytical method (<1% *ee*). The failure to observe induction in these simple experiments shed doubts on the conclusions reached in the older literature. Nevertheless, we felt that a definite decision as to whether asymmetric cyclizations with CSA are fact or artefact would rely on a reinvestigation of the original example, namely Fujise's 1938 cyclization of the chalcone triacetate **4** to matteucinol-diacetate **5**. It was this original report, on which later experiments were modeled, and the substrate was a quite specific one: matteucinol (**6**; Figure 2), isolated from the fern *Matteuccia orientalis* in 1924,[45] is the first flavanone from plant material which was shown to be optically active.[46] In the absence of plant material, matteucinol is not readily available, but a total synthesis is in reach. Syntheses of **6** have already been reported, but experimental details are not readily available.[47] Favorable retrosynthetic disconnections from **6** lead to dimethyl-trihydroxy-acetophenone (**14**) and anisaldehyde (**15**), or alternatively to dimethyl phloroglucinol (**16**) and *p*-methoxycinnamoyl chloride (**17**) (Scheme 1, a).

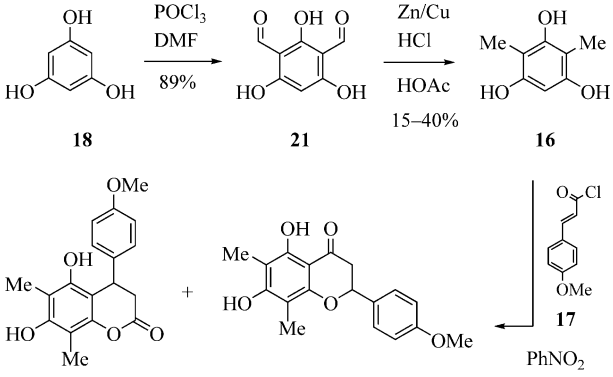
It has been reported that phloroglucinol (**18**) can be methylated under basic conditions to give **19** in 20% yield after acetylative workup (Scheme 1, b), and then converted to **14** by Fries rearrangement.[48] On repeating the methylation/acetylation of **18** we did indeed isolate a nicely crystalline compound in 17% yield, but this turned out to be the cyclohexatrione enolacetate **20**, as evident from spectral analyses and an X-ray crystal structure determination (see the electronic supporting information). We cannot readily explain the discrepancy between our and the literature result for this reaction. Earlier studies on the methylation of resorcinol,[49] phloroglucinol (**18**)[49,50] or trihydroxyacetophenone[51] in basic media with methyl iodide have shown that the nature and yields of products are critically variable with small changes of temperature, reaction time, concentrations and other factors.[50d]

An alternative retrosynthetic disconnection of **6** (Scheme 1, a) leads to dimethyl phloroglucinol (**16**) which



Scheme 1.

may be obtained either via nitration of *meta*-xylene, reduction and hydrolysis,[52] or via selective diformylation of phloroglucinol[53,54] and Clemmensen reduction (Zn/Hg, HCl aq.).[54,53a] We followed the second route (Scheme 2): Reaction of phloroglucinol (**18**) with two equivalents of Vilsmeyer reagent and hydrolysis produced dialdehyde **21** in high yield. The Clemmensen reduction was modified by using a zinc–copper pair instead of toxic zinc amalgam; this approach was partially successful, in that the procedure furnished sufficient material for our synthesis, but the yields of the reaction were variable (Scheme 2).

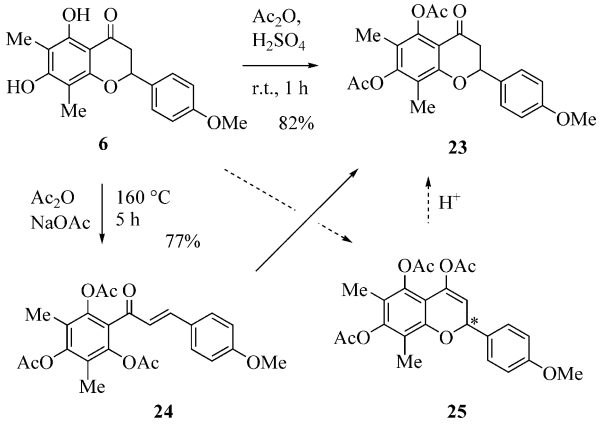


22	6	Conditions:
<5%	22%	$AlCl_3$, 60 °C, 2 h
44%	8%	Montmorillonite, 120 °C, 20 h

Scheme 2. Synthesis of matteucinol.

Friedel–Crafts acylation of **16** with acid chloride **17** gave matteucinol **6** in low, but reproducible yield (Scheme 2). Modified conditions for the Friedel–Crafts reaction on acidic montmorillonite clay[55] returned the isomeric dihydrocoumarine **22** as the major product instead. Racemic

matteucinol forms yellow crystals from acetone. Its identity was secured by literature comparison of melting point, mass spectral and NMR spectroscopic data. Matteucinol (**6**) was derivatized according to Fujise's conditions (Scheme 3): mild acetylation gave diacetate **23** as colorless needles, harsh acetylation by refluxing with Ac_2O/NaOAc, gave chalcone triacetate **24**.[32] The acetate **24** was carefully analyzed in order to exclude that enol ester **25** had been obtained instead. This reaction mode has been observed at least once with a similar flavanone.[56] If Fujise had mistaken enol ester **25** for its isomer **24**, then one could easily understand why refluxing of **25** with CSA in ethanol will give **23** with an intact stereogenic center and optical activity, since all of the starting materials were prepared from optically active **6** (extracted from plants), and the sequence **6**→**25**→**23** (instead of **6**→**24**→**23**) would of course lead to an optically active product. However, our spectroscopic data show that the acetylation product is indeed the achiral chalcone acetate **24**, and had the same melting point as reported by Fujise.



Scheme 3. Derivatization of matteucinol.

Chiral HPLC analysis of **23** was successfully carried out on *Chiralcel-OJ* (Figure 5 a). We were now in a position to repeat the original asymmetric cyclization experiment: **24** was heated in EtOH with 5 mol-% of (+)-CSA in a pressure tube.[32] According to TLC analysis, matteucinol diacetate **23** was formed as the major reaction product, which could be isolated in 40% yield. The results of the HPLC measurements for either the reaction mixture or the purified product show that an enantiomeric excess was not present within the limits of detection of the analytical method (<1% *ee*). In contrast, Fujise et al. had isolated **23** in 36% yield with an optical purity of close to 100% ($[\alpha]_D$ = +32.1 vs. +32.7° for **23**, which had been prepared from natural **6**).[32] According to our results, the claim of an asymmetric synthesis of flavanones by CSA-catalyzed cyclization of hydroxychalcones (or chalcone acetates) cannot be upheld, and the optical activity earlier observed must have been due to reasons other than an enantiomeric excess of the reaction product.

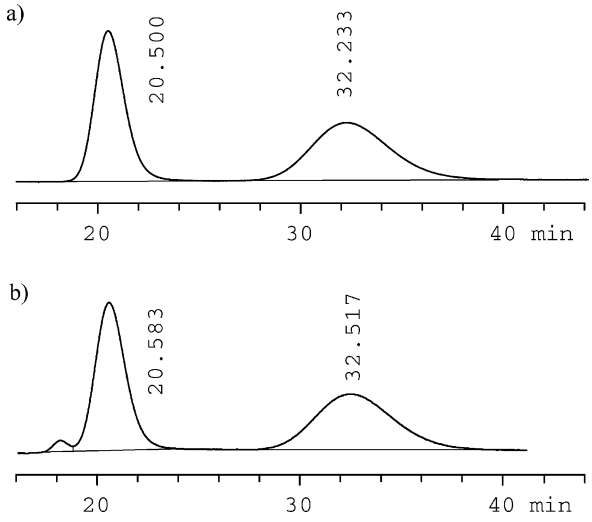
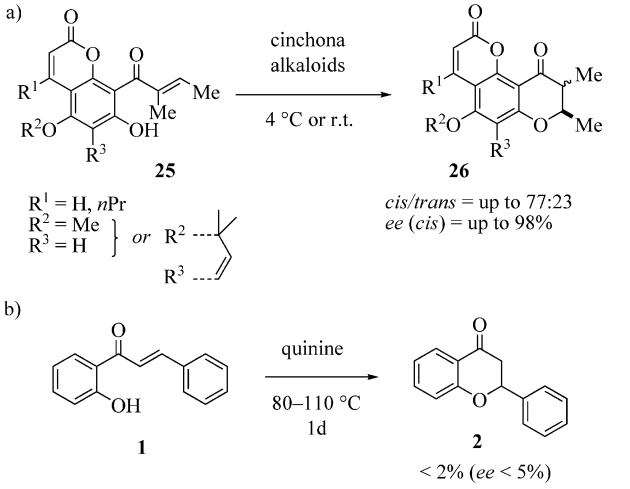


Figure 5. HPLC traces of **23**. a) Racemic reference. HPLC: *Chiralcel-OJ*, EtOH/*n*-heptane, 1:1 (v/v), 0.7 mL/min, λ = 280 nm, α = 1.707, R_S = 2.265; integrals 50.1% and 49.9%. b) Product from the CSA-catalyzed cyclization of **24**; impurity at t_R = 19 min; integrals 49.9% and 48.7%.

2.2. Chiral Base-Catalyzed Approaches to Flavanone Synthesis

Ishikawa and co-workers have recently described that cinchona-catalyzed cyclizations of some *ortho*-tigloylphenols (**25**) to 2,3-dimethylchroman-4-ones (**26**) proceed with very high enantiomeric excess (Scheme 4 a).[30] The reaction is characterized by mild conditions and a marked solvent dependency of enantioselectivity: best results are achieved in nonhydrogen bonding polar aromatic solvents such as chlorobenzene. The products **26** are formed as mixtures of *cis* and *trans* diastereomers, and the diastereoselectivity of the reaction depends critically on the alkaloid catalyst and the solvent, in a way that is difficult to predict. Judging from the published examples (Scheme 4, a) it was not clear whether the reaction had any generality beyond the specific cases of coumarin-derived tigloyl-phenols **25**. Thus we applied the reaction conditions to hydroxychalcone **1**, which was stirred with quinine or cinchonidine at room temp. for two weeks in either EtOAc or CH_2Cl_2, without giving a trace of product **2**. Upon stirring of **1** with 20 mol-% of quinine in chlorobenzene (10 mg/mL) for 1 day at 80 °C, a conversion **1**→**2** of 0.43% (TOF = 0.00083 h^{-1}) was measured by HPLC, with an *ee* of **2** of ≤ 3%. On heating for another 18 h at 110 °C, the conversion rose to 1.9% (TOF = 0.0042 h^{-1}) and the product was essentially racemic (*ee* < 1.3%).[57]

It is now evident that the cinchona-catalyzed reaction is limited in its substrate spectrum and not general with respect to the asymmetric synthesis of flavanones. Nevertheless, it appeared to us that the kinetic barrier in the way of catalysis might be overcome by either using a more active catalysts, or by choosing a more reactive substrate. Both approaches eventually turned out to be successful, and here we present the results of the second approach, where we stuck to cinchona alkaloids as catalysts, but searched for



Scheme 4. Cinchona catalysis of alkenoyl-phenol cyclization. a) Results of Ishikawa and co-workers.[30] b) Unsuccessful extension to 2′-hydroxychalcone.

more active (i.e. *destabilized*) substrates in order to reduce the energy gap between the ground and transition state. From preparative and kinetic investigations, it is known that 2′-hydroxychalcones bearing an additional C-6′ hydroxy group cyclize more readily than those with a hydrogen at C-6′.[8i,8f,58,59] This reactivity difference has usually been explained by assuming a hydrogen-bonding stabilization of the flavanone product[59] or the transition-state (Figure 6, a).[8f,8i] In addition, a range of 2′-hydroxychalcones bearing alkyl or annelated arene substituents at C-6′ also undergo facile cyclization,[20] sometimes during attempted recrystallization.[8k] We have not found explanations for the effect of the 6′-substituent in the literature, but presumably there is a destabilization of the substrate by repulsion between the 6′-substituent and the α-CH bond of the alkenone portion, which disrupts the strong intramolecular hydrogen bond (Figure 6, b).

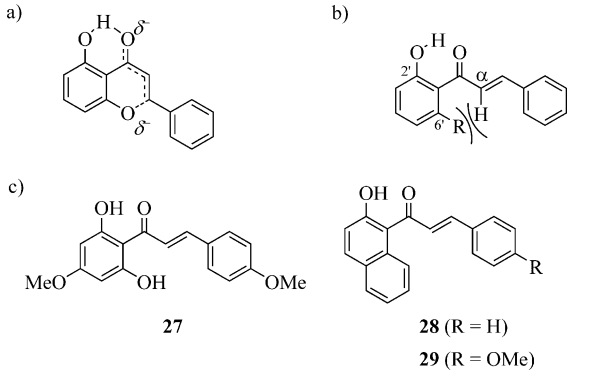
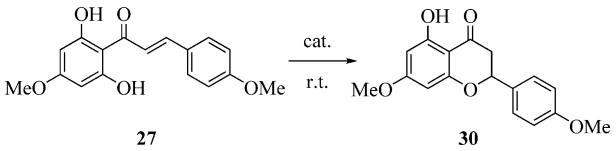


Figure 6. a) Hydrogen-bonding stabilization of the chalcone cyclization transition-state. b) Destabilizing effects of a 6′-substitution. c) Examples of ground-state destabilized chalcones used in this study.

As substrates for our studies, we chose 4,4′-dimethoxy-2′,6′-dihydroxychalcone **27**, which is synthesized from naringenin (5,7,4′-trihydroxyflavanone) in two steps (see experimental),[60] and the chalcones **28** and **29** (Figure 6, c) which are available in one step from commercial precursors.[8k] The high tendency towards cyclization of **27**–**29** means that it is best to first synthesize the corresponding flavanones and perform base-induced ring-opening reactions followed by an acid or TMSCl quench,[58] giving the chalcones.[8k,58,60] Indeed, chalcones **27**–**29** underwent catalytic cyclizations in the presence of cinchona alkaloids (see Tables 1, 2, and 3). The substrates were combined with 0.5 equiv. of alkaloid in a solvent at room temperature, and the reaction progress was followed quantitatively by chiral HPLC analysis. In view of the small scale of the experiments and the slow kinetics, no particular attempt has been undertaken to reduce catalyst loading. Table 1 presents results for the catalytic cyclization of chalcone **27** to naringenin dimethyl ether (**30**). The enantioselectivity of the catalytic asymmetric cyclization was dependent on the nature of the alkaloid catalyst and on the solvent. Dichloromethane as a polar, nonprotic solvent gave relatively fast reactions with low enantioselectivity (entry 1). Reactions in less polar solvents were not successful because of the insolubility of substrate and catalyst, but both *ortho*-dichlorobenzene (*o*-$C_6H_4Cl_2$) and chlorobenzene provide a suitable balance of polarity and solubility. A screening with *o*-$C_6H_4Cl_2$ as solvent with all four cinchona alkaloids (quinine–QN; quinidine–QD; cinchonine–CN; cinchonidine–CD) showed that the pseudo-enantiomeric[61] pair QN/QD bearing methoxy groups gave higher selectivity than CN/CD (entries 2–5). Interestingly, CN produced the same enantiomer in excess as did its "pseudoenantiomer" CD, though with lower absolute selectivity and more slowly, probably due to the low solubility of that alkaloid (entry 4). At extended reaction times, substrate conversions reached >99.8% in either CH_2Cl_2 or *o*-$C_6H_4Cl_2$, which corresponds to $K_{eq} > 500$, considerably higher than for the cyclization of **1** to **2** ($K_{eq} \approx 4$). As a consequence, the reversibility of the reaction is kinetically unimportant and the enantiomer excess does not deteriorate at high conversions (entries 1, 8).

Additional experiments revealed an unusual dependency of enantiomeric excess of the product on the initial concentration of the chalcone substrate, which is strong in *o*-$C_6H_4Cl_2$ as solvent (entries 6–9), but somewhat less pronounced in chlorobenzene (entries 10–13). Because the substrate concentration decreases as the reaction progresses, there is also a conversion dependency of the product enantiomeric excess (entry 8). Since chlorobenzene had turned out to induce higher enantioselectivities in the reaction (entries 10–13), catalyses with all four alkaloids were repeated in that solvent at an optimal substrate concentration of 10 gL^{-1} (entries 12, 14–16). Once again, the pseudo-enantiomers CN and CD show the same absolute sense of induction; after 11 hours of reaction time, the inductions had in fact reached identical levels (entries 15a, 16a), but as the reaction progressed, the value decreased faster for CN (entry 16b). The influence of catalyst concentration was also investigated (entries 17–21) and found to be important at high substrate to catalyst ratios (entry 17), where it led to a lower enantioselectivity. The reason for the substrate-concentration dependency of enantiomeric excess is unclear

Table 1. Asymmetric cyclization of **27** to **30** with cinchona catalysts.



27 **30**

Entry	Catalyst[a]	Solvent	Conc. / g L^{-1}	Time / h	% Conv.[b]	% *ee*[b][c]
1a	CD	CH_2Cl_2	10	24	96	10 (+)
1b				96	>99	9 (+)
2	CD	*o*-$C_6H_4Cl_2$	10	70	79	31 (+)
3	CN	*o*-$C_6H_4Cl_2$	10	70	23	11 (+)
4	QN	*o*-$C_6H_4Cl_2$	10	70	74	52 (+)
5	QD	*o*-$C_6H_4Cl_2$	10	70	69	47 (–)
6	QN	*o*-$C_6H_4Cl_2$	1.6	295	92	23 (+)
7	QN	*o*-$C_6H_4Cl_2$	3.2	170	92	34 (+)
8a	QN (30%)	*o*-$C_6H_4Cl_2$	5	96	66	38 (+)
8b				192	90.2	37 (+)
8c				339	97.4	35 (+)
8d				465	99.0	34 (+)
8e				672	99.7	34 (+)
9	QN	*o*-$C_6H_4Cl_2$	10	70	81	53 (+)
10	QN	PhCl	2.5	90	68	52 (+)
11	QN	PhCl	5	90	82	59 (+)
12	QN	PhCl	10	70	81	64 (+)
13	QN	PhCl	17	90	91	61 (+)
14a	QD	PhCl	10	11	–[d]	57 (–)
14b				70	78	58 (–)
15a	CN	PhCl	10	11	<3	33 (+)
15b				70	10	13 (+)
16a	CD	PhCl	10	11	–[d]	33 (+)
16b				70	70	30 (+)
17	QN (13%)	PhCl	10	44	11	46 (+)
18	QN (30%)	PhCl	10	44	39	58 (+)
19	QN (50%)	PhCl	10	44	72	61 (+)
20	QN (70%)	PhCl	10	44	81	61 (+)
21	QN (100%)	PhCl	10	44	80	59 (+)
22	QN + ROH[e]	PhCl	10	90	85	19 (+)
23	QN + ROH[f]	PhCl	10	90	65	5 (+)

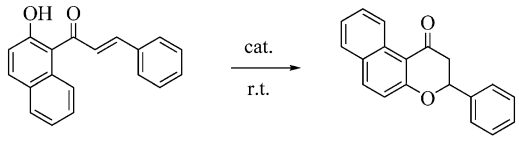
[a] 50 mol-%. [b] Conversion determined by chiral HPLC, see Exp. Sect. [c] Sign of optical rotation of the excess enantiomer (in acetone, λ = 589 nm) given in parentheses; (+)-flavanones usually show 2*R* configuration.[62] [d] Accurate conversions could not be determined due to inhomogeneous reaction mixtures. [e] In the presence of 2 equiv. of 2,6-dihydroxyacetophenone. [f] In the presence of 3.3 equiv. of 2,2,2-trifluoroethanol.

in the absence of mechanistic knowledge, but it is evident that hydrogen-bonding interactions are important: the substrate **27**, the product **30** and the alkaloid catalysts all contain hydrogen-bond donor hydroxy groups. The presence of hydrogen-bond donors lowers the enantioselectivity of the reaction, as is visible from the experiments at high catalyst loadings (enty 21 vs. 20) or high substrate-to-catalyst ratios (entry 17). This was further shown by performing catalytic runs in the presence of the hydrogen-bond donors 2,6-diyhdroxyacetophenone (a substance with a similar hydroxy substitution pattern as the substrate) or trifluoroethanol. In both cases, the enantioselectivity of the reaction dropped (entries 22, 23). The benzo-annelated hydroxychalcones **28** and **29** also underwent asymmetric cyclizations, but slower and with lower selectivities than **27** (see Tables 2 and 3). Both substrates gave very similar results, therefore the following discussion (including Table entry numbers) is valid for either of them. Highest selectivities towards flavanones **31** and **32** were also obtained with quinine (QN) as catalyst. The solvent influence was smaller, with reactions performed in chlorobenzene, *o*-$C_6H_4Cl_2$ or $CDCl_3$ giving similar results. Reactions in CH_2Cl_2 were faster, but less selective (entries 6,7,11). An influence of substrate concentration (and therefore: conversion) on enantioselectivity was essentially absent (entries 8,9). This implies that while noncomplexed OH groups disturb the reaction selectivity, the same is not true for OH groups which are involved in a strong hydrogen bond with a carbonyl group, as is the substrates **28**/**29**.

3. Discussion

The 2′-hydroxychalcone/flavanone cyclization can be considered a model reaction for an olefin hydroalkoxylation reaction. The enzyme chalcone isomerase is capable of catalyzing this particular transformation with astonishing levels of enantioselectivity. Attempts towards achieving this reaction enantioselectively with a small-molecule chiral cata-

Table 2. Asymmetric cyclization of **28** to **31** with cinchona alkaloid catalysts.

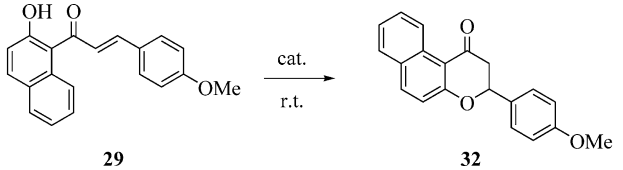


28 **31**

Entry	Catalyst[a]	Solvent[b]	Time / h	% Conv.[c]	% *ee*[c][d]
1	CD	*o*-$C_6H_4Cl_2$	250	59	13 (+)
2	CN	*o*-$C_6H_4Cl_2$	250	32	3 (+)
3	QN	*o*-$C_6H_4Cl_2$	72	36.5	29 (+)
4	QD	*o*-$C_6H_4Cl_2$	72	32	6.2 (–)
5	CD	PhCl	250	58.5	14 (+)
6	CD	CH_2Cl_2	72	57	12 (+)
7	CN	CH_2Cl_2	72	33	1.8 (–)
8a	QN	PhCl	97	58	32 (+)
8b			162	81	33 (+)
9a	QN	PhCl (5 g L^{-1})	97	31	31 (+)
9b			162	48	33 (+)
9c			212	60	33 (+)
10a	QN	$CDCl_3$	27	22	34 (+)
10b			77	61	35 (+)
11a	QN	CH_2Cl_2	27	24	21 (+)
11b			77	82	17 (+)[e]
12a	QD	PhCl	97	60	11 (–)
12b			162	84	12 (–)

[a] 50 mol-%. [b] Substrate concentration c = 10 g L^{-1}. [c] Determined by HPLC. [d] Sign of optical rotation of the excess enantiomer in acetone solution (λ = 589 nm). [e] Increasing concentration in the course of reaction due to solvent evaporation.

Table 3. Asymmetric cyclization of **29** to **32** with cinchona alkaloid catalysts.



29 **32**

Entry	Catalyst[a]	Solvent[b]	Time / h	% Conv.[c]	% *ee*[c][d]
1	CD	*o*-$C_6H_4Cl_2$	250	65	15 (+)
2	CN	*o*-$C_6H_4Cl_2$	70	0	–
3	QN	*o*-$C_6H_4Cl_2$	70	26	25 (+)
4	QD	*o*-$C_6H_4Cl_2$	70	36	8.5 (–)
5	CD	PhCl	240	67	19.4 (+)
6	CD	CH_2Cl_2	70	58	16 (+)
7	CN	CH_2Cl_2	70	33	3.4 (–)
8a	QN	PhCl	108	59	32 (+)
8b			162	78	32 (+)
9a	QN	PhCl (c = 5)	49	17.5	31 (+)
9b			99	34	33 (+)
10a	QD	PhCl	108	73	13 (–)
10b			162	90	13 (–)
11a	QN	CH_2Cl_2	27	39	20 (+)
11b			77	99[e]	16 (+)[e]
12a	QN	$CDCl_3$	27	23	33 (+)
12b			77	62	33 (+)

[a] 50 mol-%. [b] Concentration c = 10 g L^{-1}. [c] Determined by HPLC. [d] Sign of optical rotation of the excess enantiomer in acetone solution (λ = 589 nm). [e] Increasing concentration in the course of reaction due to solvent evaporation.

lysts have been undertaken, but have not been successful, unless additional π-acceptor groups were attached to the olefin moiety.[28] In the present work, we have investigated and analyzed two approaches towards realizing the title reaction, one based on chiral Brønsted acid catalysis, the other on chiral Brønsted base catalysis. Early studies between 1938 and 1951 on the cyclization of several hydroxychalcones (or their acetates) catalyzed by camphorsulfonic acid (CSA) have claimed optical induction and thus a very simple and potentially very useful asymmetric synthesis of flavanones.[32–35] From a current perspective the mechanistic basis for these results is unclear. We have now reinvestigated several CSA-catalyzed cyclizations of hydroxychalcones to flavanones and analyzed the reaction products by means of accurate chiral HPLC methods. Our experiments on the model reaction **1**→**2** reveal that CSA displays only limited catalytic activity in the cyclization reaction of hydroxychalcones, and the background reaction in the absence of an added catalyst leading to racemic product is quite fast. It was also found that the reaction times used in the historical work were too long, such that the reversibility of the chalcone/flavanone equilibrium would have led to a marked erosion of any initial enantiomeric excess. Having established these unfavorable preconditions, we were little surprised to find that the flavanones obtained from CSA-catalyzed reactions were racemic within the limits of accuracy of the HPLC analytical method. We went as far as repeating the original report from 1938, relating to the CSA-catalyzed synthesis of matteucinol chalcone triacetate (**23**) to ascertain whether that specific substrate was critical for the success of the asymmetric reaction. Along these lines, we synthesized matteucinol (**6**) and repeated step by step the original procedures,[32] without observing induction in the CSA-catalyzed reaction. Why the discrepancy with the historical work? We have excluded one potential explanation for the generation of optically active reaction products, namely the intermediacy of enol ester **25** instead of chalcone acetate **23** (see Scheme 3). Now, it can be stated that most of the early work on asymmetric synthesis relied on the determination of optical rotations, sometimes at levels close to the limits of detection. Systematic errors have plagued such measurements, and the reproducibility of some of the early results have later been questioned.[63] In the absence of any plausible explanation, we must therefore assume that the original observation of optical activity in refs.[32–35] was probably due to a systematic error, but certainly not an induction caused by the asymmetric Brønsted acid. On the other hand, the investigation of chiral Brønsted base-catalyzed cyclization of hydroxychalcones has turned out to provide for the first time a solution to the long-standing problem of imitating the asymmetric chalcone isomerase reaction: Taking as a starting point the work of Ishikawa and coworkers on the asymmetric cyclization of *ortho*-tigloylphenols to 2,3-dimethylchroman-4-ones,[30] we find that this reaction is not general, since the cyclization **1**→**2** is not catalyzed to any relevant degree. However, by the use of ground-state destabilized 2′-hydroxychalcone starting materials, the catalytic cyclization of

2′-hydroxychalcones **27**–**29** to the corresponding flavanones **30**–**32** has been achieved in variable selectivities up to 64% enantiomeric excess. Incidentally, (2*S*)-naringenin 4′,7-dimethyl ether (**30**) is a naturally occurring substance which has been isolated many times from plants,[64] and the results in Table 3 represent the first asymmetric syntheses of that material. The ground-state properties which affect the ease of cyclization of 2′-hydroxyalkenones **A** to chromanones **B** (Figure 7) can now be summarized as follows: i. Aryl substituents at C-3 (R^3) stabilize the ground state by conjugation, decreasing K_{eq} = [**B**]/[**A**] and slowing down cyclization. For a series of chalcones, π- and σ-accepting substituents $R^{Ar'}$ increase the acceptor strength, translating into a higher K_{eq} according to a Hammett correlation.[65] ii. The presence of a substituent $R^{6'}$-C-6′ destabilizes the chalcone starting material by repulsion with R^2 (including R^2 = H), increasing K_{eq}. The repulsion between R6′ and the carbonyl group in **B** is less severe, because the carbonyl group tilts out of the aromatic plane, away from R6′. iii. If both C-2 and C-3 in **A** are substituted, steric repulsion will destabilize **A** and increase K_{eq}. If any of these substituents is an acceptor, the chalcone is electronically destabilized, increasing K_{eq}. iv. The presence of a 6′-hydroxy group facilitates cyclization (see discussion above). In addition to the traditional explanations (flavanone stabilization/intramolecular acid catalysis by the hydrogen bond), we propose that the accelerating effect of the 6′-OH may also be due to ground-state destabilization, as discussed more generally for 6′-substituted chalcones above.

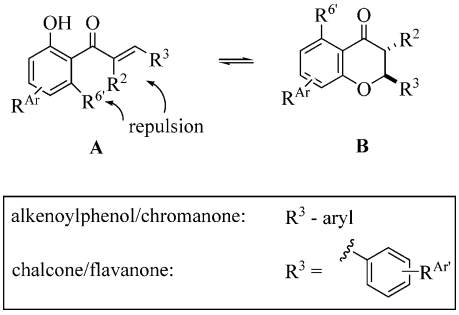


Figure 7. Structural factors in cyclization equilibriums leading to chromanones/flavanones.

Based on these generalizations, an analysis of published experimental data is possible: The *ortho*-tigloylphenol substrates used by Ishikawa and co-workers profit from the presence of repelling substituents R^2 and R^3 in the substrate, the presence of a substituent $R^{6'}$, and the absence of an aryl group R^3, which explains the high reactivity of the substrates towards catalytic cyclization. Likewise, the success in the recent report on asymmetric catalytic cyclizations of 2-substituted-chalcones by Scheidt and co-workers relies not only on the electronic activation provided by an ester group in R^2 (CO_2tBu), but also the repulsion (in **A**) between groups R^2 and R^3. None of the above mentioned facilitating factors apply to the most simple transformation **1**→**2**, for which catalysis by the weakly basic cinchona alkaloids is not feasible, and no other asymmetric catalyst is currently in sight. However, the enzyme *chalcone isomerase* (CHI) is capable of catalyzing cyclizations of similarly nonactivated substrates (part b of Figure 1, R = H). In this context, it is interesting to analyze the decisive mechanistic factors of the enzymatic reaction, which have recently been deduced from X-ray structure data and kinetic analyses.[5] It has been found that the hydroxychalcone enters the enzyme active site as the chalconate monoanion, where it binds to the active site through interactions with several amino acid residues. This forces upon the achiral anion a chiral conformation, from which cyclization occurs to an enzyme-bound flavanone enolate, which is intercepted by protonation to release (2*S*)-flavanone. *A critical factor for acceleration of the cyclization is the deprotonation of the substrate prior to binding to the enzyme*: the deprotonation removes the hydrogen bridge, which stabilizes the ground state, thereby increasing both conformational freedom and nucleophilicity of the phenolate anion.[5] If these observations are translated into requirements for a small-molecule catalyst for the asymmetric cyclization of nonactivated hydroxychyclones, it follows that we need a catalyst that is sufficiently basic to fully deprotonate the substrate, and which folds the achiral chalconate anion into a chiral conformation by providing multi-point noncovalent interactions, such as hydrogen bonding, arene π-stacking, and ion pairing. This line of reasoning has indeed led to the discovery of an asymmetric catalyst for the conversion **1**→**2**, and progress along these lines will be reported in due course.

4. Conclusion

In conclusion, the asymmetric catalytic cyclization of 2′-hydroxychalcones to flavanones using chiral Brønsted acids and -bases has been investigated. Earlier reports on a camphor sulfonic acid catalyzed asymmetric cyclizations of hydroxychalcones in alcoholic solvent have been disproved. Ground-state-destabilized hydroxychalcones with a low kinetic barrier towards cyclization were found to undergo asymmetric catalytic cyclizations (*ee* up to 64%) to flavanones in the presence of cinchona alkaloids, providing for the first time an example of the direct catalytic asymmetric 2′-hydroxychalcone to flavanone transformation with a small-molecule catalyst.

Experimental Section

Reagent grade solvents were used for reactions and distilled technical grade solvents for column chromatography on SiO_2. Melting points were measured in open capillaries on a metal heating block with a digital thermometer. The following substances were obtained from commercial sources: **1** (Fluka), **2** (Acros), (+)-CSA (**3**) (Fluka), *rac*-naringenin (Acros). *p*-Methoxycinnamoyl chloride (**17**) was prepared by a literature procedure.[66] The chalcones and flavanones in this work are known substances which were prepared according to literature references and/or identified by comparison of NMR spectra and melting points to literature data: 2′,4′-dihydroxychalcone,[67] 7-hydroxyflavanone (**9**),[8j] 3,4-methylenedioxy-2′-hydroxychalcone,[68] 3′,4′-methylenedioxyflavanone (**10**),[34,9b,69]

5′,6′-benzo-2′-hydroxychalcone (**28**) and 5,6-benzoflavanone **31**,[8k] 4-methoxy-5′,6′-benzochalcone (**29**) and 4′-methoxy-5,6-benzoflavanone **32**,[70] naringenin 4′,7-dimethyl ether chalcone (**27**)[8i] and naringenin 4′,7-dimethyl ether (**30**).[60,71]

General Procedure for the Cinchona-Catalyzed Cyclization of 2′-Hydroxychalcones to Flavanones: The 2′-hydroxychalcone (5 mg, ca 0.017 mmol) and the alkaloid (2.5 mg for CN and CD; 2.7 mg for QN and QD; 0.0085 mmol, 50 mol-%) are stirred in the solvent (0.5 or 1 mL; filtered through neutral Al_2O_3) at room temperature. Conversions and *ee* were determined by HPLC (see the Supporting Information for conditions) and through comparison with test-mixtures containing known quantities of chalcone and flavanone. The reaction was quenched by addition of a drop of HOAc, evaporated in vacuo and the residue separated by column chromatography (SiO_2, EtOAc/hexanes or toluene). Products were identified by comparison of their NMR spectroscopic data to literature values.

NMR Spectroscopic Data not Reported in the Literature

Compound 29: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OMe), 6.93 (d, J = 8.8 Hz, 2 H Arl), 7.18 (d, J = 9.8 Hz, 1 H), 7.36–7.43 (m, 1 H), 7.37 (d, J = 16.2 Hz, 1 H), 7.49–7.61 (m, 3 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.69–7.93 (m, 2 H), 8.07 (d, J = 9.4 Hz, 1 H), 12.57 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5 (CH_3), 114.5 (CH), 116.0 (C), 119.4 (CH), 123.8 (CH), 124.7 (CH), 125.1 (CH), 127.5 (C), 127.7 (CH), 128.6 (C), 129.2 (CH), 130.5 (CH), 131.5 (C), 136.4 (CH), 143.0 (CH), 161.8 (C), 162.4 (C), 194.4 (C) ppm.

Compound 31: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (dd, J = 16.5, 3.1 Hz, 1 H), 3.22 (dd, J = 16.5, 13.8 Hz, 1 H), 5.59 (dd, J = 13.8, 3.0 Hz, 1 H), 7.17 (d, J = 9.0 Hz, 1 H), 7.36–7.53 (m, 6 H), 7.65 (ddd, J = 8.7, 6.9, 1.4 Hz, 1 H), 7.76 (br. d, J = 8.1 Hz, 1 H), 7.94 (d, J = 8.9 Hz, 1 H), 9.49 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.8 (CH_2), 79.7 (CH), 112.6 (C), 118.8 (CH), 124.9 (CH), 125.9 (CH), 126.2 (CH), 128.4 (CH), 128.8 (CH), 128.8 (CH), 129.2 (C), 129.7 (CH), 131.4 (C), 137.6 (CH), 138.5 (C), 163.6 (C), 192.9 (C) ppm.

Compound 32: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (dd, J = 16.5, 3.0 Hz, 1 H), 3.23 (dd, J = 16.5, 13.8 Hz, 1 H), 3.83 (s, 3 H, OMe), 5.52 (dd, J = 13.8, 3.0 Hz, 1 H), 6.94–7.00 (m, 2 H Arl), 7.14 (d, J = 9.0 Hz, 1 H Arl), 7.39–7.49 (m, 3 H Arl), 7.64 (ddd, J = 8.7, 7.0, 1.5 Hz, 1 H Arl), 7.73–7.78 (m, 1 H Arl), 7.92 (d, J = 8.9 Hz, 1 H Arl), 9.48 (d, J = 8.6 Hz, 1 H Arl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.6 (CH_2), 55.5 (CH_3), 79.4 (CH), 112.5 (C), 114.2 (CH), 118.9 (CH), 124.8 (CH), 125.8 (CH), 127.8 (CH), 128.3 (CH), 129.2 (C), 129.6 (CH), 130.5 (C), 131.4 (C), 137.5 (C), 159.9 (C), 163.7 (C), 193.1 (C) ppm.

New Synthesis of 1-(2,6-Dihydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl}prop-2-en-1-one (27): The procedure cited in ref.[8i] gave mixtures of flavanone and chalcone, with low yields of chalcone. The TMSCl quenching method[58] was advantageous: To **30** (1.06 g, 3.53 mmol) in CH_2Cl_2 (10 mL) and chlorotrimethylsilane (5.0 mL, 39.6 mmol) was added dropwise with stirring and cooling in a room temp. water bath DBN (3.5 mL, 28.3 mmol) over 30 min. The homogeneous solution was stirred for 3 days (not optimized), poured onto EtOAc (50 mL) and 2.4 M aq. HCl (50 mL) and the mixture shaken for 10 minutes. The organic phase was washed with 2.4 M aq. HCl (1×) and water (4×), then evaporated to dryness. The orange residue was suspended in toluene/CH_2Cl_2 (1:1, 15 mL). The suspension was reduced to a volume of ca 5 mL by rotatory evaporation and overlayered with hexanes (10 mL). After standing (5 h), the product was filtered and washed with hexanes to give an orange crystalline powder (729 mg, 69%). Spectral data corresponded to literature values.[8i]

5-Acetoxy-2,2,4,4,6-pentamethylcyclohex-5-en-1,3-dione (20); Attempted Synthesis of Dimethylphloroglucine (16): Dry phloroglucinol (22.74 g, 0.16 mol) was dissolved in degassed MeOH (150 mL). A solution of KOH (19.13 g, 85%, 0.29 mol) in a minimum of water (15 mL, *CAUTION, dissolves with heating!*) was added. After cooling to room temp., MeI (25 mL, 0.40 mol) was added in small portions over 2 h. The mixture was stirred for 1 d at room temp. Another addition of solid KOH (20.7 g, 0.31 mol, *CAUTION, see above*) in small portions and of MeI (30 mL, 0.48 mol) in small portions was followed by dilution with MeOH to a volume of 500 mL and stirring for 2 d at room temp. The reaction was quenched by addition of NEt_3 (10 mL; *destroys excess toxic MeI before workup*) and the solvents evaporated to dryness (60 °C/15 mbar). Azeotropic drying of the residue with toluene (3 × 50 mL) and *t*BuOMe (3 × 50 mL) with evaporation after each addition was followed by addition of *t*BuOMe (100 mL), pyridine (60 mL) and acetic anhydride (60 mL). The resulting suspension was stirred overnight at room temp. and another day at 60 °C. The mixture was diluted with EtOAc (400 mL) and Water (400 mL), the aqueous phase extracted with EtOAc (3 × 100 mL) and the combined organic phases washed with 2 M HCl aq. (4 × 100 mL), water (2 × 100 mL) and $NaHCO_3$ aq. (4 × 200 mL). The organic phase was dried with Na_2SO_4, evaporated, and the residue submitted to column chromatography (*t*BuOMe/hexanes, 1:5–1:3) to give the least polar and main product **20** as colorless crystals (6.30 g, 17%). X-ray quality crystals were obtained from hexane. R_f = 0.4 (SiO_2; *t*BuOMe/hexanes, 1:5); m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 1.38 (s, 6 H), 1.73 (s, 3 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7 (CH_3), 20.7 (CH_3), 24.1 (CH_3), 24.9 (CH_3), 48.5 (C), 56.8 (C), 83.3 (C), 122.8 (C), 163.4 (C), 166.5 (C), 199.3 (C), 211.3 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2995 (m), 2942 (m), 2878 (w), 1765 (s), 1724 (m), 1674 (m), 1468 (m), 1376 (m), 1331 (m), 1184 (s), 1099 (s), 1007 (m), 876 (m), 581 (m) cm^{-1}. MS (EI): m/z (%) = 238 (30) $[M]^+$, 196 (31), 178 (25), 168 (22), 126 (100). $C_{13}H_{18}O_4$ (238.28): calcd. C 65.53, H 7.61; found C 65.53, H 7.82.

X-ray Crystal Structure of 20: $C_{13}H_{18}O_4$, M_r = 238.28, monoclinic, space group $P2_1/n$ (14), $D_{calcd.}$ = 1.238 g/cm^3, Z = 4, a = 8.3494(18) Å, b = 10.392(4) Å, c = 14.746(4) Å, β = 92.441(11)°, V_{cell} = 1278.3(7) Å^3. Enraf–Nonius CAD4, Cu-K_α radiation, λ = 1.54179 Å, T = 298 K. Approximate crystal dimensions = 0.3 × 0.3 × 0.3 mm^3. Numbers of measured, independent and observed reflections: 5121, 2310, 1797. R_{int} = 0.056. Final R = 0.072, R_w = 0.080 for 154 parameters and 1775 reflections with $I > 2\sigma(I)$ and Θ_{max} = 67.81°.

CCDC-652790 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.au.uk/data_request/cif.

Phloroglucinoldicarbaldehyde (21):[54] a) Vilsmeyer reagent: $POCl_3$ (85 mL, 0.93 mol) was added dropwise with strong stirring to *N*,*N*-dimethylformamide (72 mL, 0.93 mol) at 20–35 °C with occasional cooling (ice/water bath). After complete addition and 30 min of stirring at room temp., the resulting yellow viscous liquid was transferred into a dropping funnel. b) Phloroglucinol dihydrate was dried to constant weight in an open beaker at 150 °C (20 h). Anhydrous phloroglucinol (**18**; 56.5 g, 0.448 mol) was dissolved in dioxane (185 mL; distilled from KOH/$FeSO_4$) with heating, then cooled to room temp. The Vilsmeyer reagent was slowly added to the phloroglucinol/dioxane solution with stirring and occasional cool-

ing at a reaction temperature below 30 °C. After complete addition, the mixture was set aside overnight, after which it had crystallized to a yellow solid. This material was transferred into a 2 L Erlenmeyer with plenty of ice and little water, adjusting the total volume of the mixture to 1.8 L by addition of more ice. The mixture was slowly warmed to room temp. with stirring. From the initially formed yellow solution, a yellow solid precipitated. After stirring for 3 h at room temp., the mixture was filtered and the solid washed with water. The solid was suspended in water (300 mL) and heated to boiling, followed by cooling in an ice bath with stirring. Filtration and washing with little water gave an orange-yellow solid which was dried in an oven at 90 °C to constant weight (**21**; 72.7 g, 89%). The material may be purified by recrystallization from hot EtOAc in the presence of some added water for increasing solubility (!), even though on cooling, crystals of the anhydrous substance separate from the solution. R_f = 0.75 (SiO_2; CH_2Cl_2/MeOH, 6:1); m.p. above 220 °C (dec.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.90 (s, 1 H Arl), 10.00 (s, 2 H, CHO), 12.50 (br. s, 2 H, OH), 13.58 (br. s, 1 H, OH) ppm. ^{13}C NMR (76 MHz, [D$_6$]DMSO): δ = 94.6 (CH), 104.2 (C), 169.5 (C), 169.9 (C), 191.8 (CH) ppm. IR (KBr): $\tilde{\nu}$ = 1618 s (br), 1442 (m), 1396 (m), 1273 (m), 1181 (m), 808 (m), 611 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 182 (100) [M]$^+$, 154 (52), 153 (63), 108 (5). $C_8H_6O_5$ (182.13): calcd. C 52.76, H 3.32; found C 52.76, H 3.16.

Reduction of 21 to Dimethylphloroglucin (16): The literature procedure is recommended.[53a,54]

Acylation of 16 with *p*-Methoxycinnamoyl Chloride (17) and Montmorillonite to 6,8-Dimethyl-5,7-dihydroxy-4-(*p*-methoxyphenyl)chroman-2-one (22): Dimethylphloroglucine (**16**; 100 mg, 0.65 mmol), **17** (140 mg, 0.7 mmol) and montmorillonite KSF (300 mg) were stirred in $PhNO_2$ (2 mL) at 110 °C for 20 h. Dilution with EtOAc, followed by filtration and washing of the organic phase with water and evaporation gave a residue that was purified by column chromatography (EtOAc/hexanes, 1:3–1:1) to give matteucinol (**6**; 17.0 mg, 8%) and a beige solid (**22**; 90 mg, 44%). An analytical sample was recrystallized from CH_2Cl_2/hexanes. Data for **22**: R_f = 0.24 (SiO_2; EtOAc/hexanes, 1:2); m.p. 187–188 °C. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 2.16 (s, 3 H, Me), 2.17 (s, 3 H, Me), 2.92 (dd, *J* = 15.7, 1.9 Hz, 1 3-H), 3.08 (dd, *J* = 15.7, 6.8 Hz, 1 3-H), 3.74 (s, 3 H, OMe), 4.64 (d, *J* = 6.5, 1.6 Hz, 1 4-H), 6.80–6.86 (A_2 of A_2B_2, 2 H Arl), 7.02–7.08 (B_2 of A_2B_2, 2 H Arl), 7.49 (s, 1 H, OH), 7.51 (s, 1 H, OH) ppm. ^{13}C NMR (76 MHz, [D$_6$]acetone): δ = 8.7 (CH_3), 9.3 (CH_3), 35.1 (CH), 38.1 (CH_2), 55.4 (CH_3), 105.0 (C), 106.2 (C), 108.5 (C), 114.7 (CH), 128.9 (CH), 134.9 (C), 149.6 (C), 150.8 (C), 154.1 (C), 159.5 (C), 168.4 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3467 s (br), 2924 (w), 1758 (s), 1620 (m), 1470 (m), 1115 (s), 833 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 314 (80) M$^+$, 271 (55), 241 (23), 206 (100), 178 (17). $C_{18}H_{18}O_5$ (314.33): calcd. for $C_{18}H_{18}O_5$ + 0.3H_2O: C 67.62, H 5.86; found C 67.53, H 5.95.

Acylation of 16 with *p*-Methoxycinnamoyl Chloride (17) and $AlCl_3$ to Matteucinol (6): Dimethylphloroglucine (**16**; 540 mg, 3.5 mmol) was suspended in $PhNO_2$ (10 mL) and $AlCl_3$ (650 mg, 4.9 mmol) was added in portions. The mixture was heated to 60 °C and a solution/suspension of **17** (690 mg, 3.5 mmol) in $PhNO_2$ (6 mL) was slowly added. The reaction mixture was stirred for 2 h at 60 °C, cooled to room temp. and quenched by addition of water, 2 M aq. HCl and EtOAc. The aqueous phase was extracted with EtOAc (2×) and the collected organic phases washed with 2 M aq. HCl, $NaHCO_3$ aq. (2×) and water (2×). Evaporation and separation of the residue by column chromatography (*t*BuOMe/hexanes, 1:10, then EtOAc/hexanes, 1:3–1:2–1:1) gave matteucinol (**6**; 246 mg, 22%), lactone **22** (180 mg, 16%) and dimethylphloroglucine (**16**; 180 mg, 33%). Data for Matteucinol (**6**): R_f = 0.6 (SiO_2; EtOAc/hexanes, 1:2); m.p. 171.0–172.8 °C (ref.[72] 172.5–173 °C; 172–172.5 °C).[32] ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 2.03 (s, 3 H), 2.04 (s, 3 H), 2.79 (dd, *J* = 17.0, 3.1 Hz, 1 H), 3.12 (dd, *J* = 17.0, 12.6 Hz, 1 H), 3.82 (s, 3 H, OMe), 5.46 (dd, *J* = 12.5, 2.7 Hz, 1 H), 6.99 (d, *J* = 8.7 Hz, 2 H Arl), 7.49 (d, *J* = 8.7 Hz, 2 H Arl), 8.45 (br. s, 1 H, OH), 12.42 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 7.5 (CH_3), 8.2 (CH_3), 43.5 (CH_2), 55.5 (CH_3), 79.2 (CH), 103.0 (C), 103.2 (C), 104.1 (C), 114.6 (CH), 128.5 (CH), 132.1 (C), 158.5 (C), 159.9 (C), 160.6 (C), 162.8 (C), 197.4 (C) ppm. Analytical data were in accord with literature values.[73]

Matteucinolchalcone Triacetate (24): Matteucinol (**6**; 79.5 mg, 0.253 mmol), NaOAc (1.10 g, 13.4 mmol) and Ac_2O (5 mL) were heated to 160–170 °C (oilbath) and refluxed for 5 h. After cooling, the mixture was transferred to a separatory funnel with EtOAc (50 mL) and water. The organic phase was washed with water (2×) and $NaHCO_3$ aq. (2×). Evaporation and purification by column chromatography (EtOAc/hexanes, 1:3–1:2) gave product-fractions, which were evaporated and crystallized from CH_2Cl_2/hexanes by overlayering and standing at 4 °C to give faint yellow crystals that were washed with hexanes (85.7 mg, 77%). R_f = 0.11 (SiO_2; EtOAc/hexanes, 1:3); m.p. 152–153 °C (ref.[32] 152–153 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97 (s, 6 H, 2 Me), 2.14 (s, 6 H, 2 Me), 2.38 (s, 3 H, Me), 3.84 (s, 3 H, OMe), 6.79 (d, *J* = 16.1 Hz, 1 H), 6.88–6.92 (m, 2 H Arl), 7.41 (d, *J* = 16.1 Hz, 1 H), 7.48–7.52 (m, 2 H Arl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.5, 20.4, 20.5, 55.4, 114.5, 123.0, 124.1, 125.4, 126.8, 130.5, 144.9, 147.1, 149.6, 162.0, 167.9, 168.2, 191.0 ppm. IR (KBr): $\tilde{\nu}$ = 2942 (w), 1769 (s), 1647 (s), 1604 (s), 1374 (m), 1253 (m), 1190 (s), 1086 (s), 821 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 440 (36) [M]$^+$, 398 (26), 356 (100), 338 (21), 314 (44), 222 (18), 180 (35). $C_{24}H_{24}O_8$ (440.44): calcd. C 65.45, H 5.49; found C 65.36, H 5.37.

Matteucinol Diacetate (23): Matteucinol (**6**; 58.0 mg, 0.185 mmol), Ac_2O (1 mL) and a small drop of concd. H_2SO_4 (ca. 15 mg) were stirred for 45 min at room temp. The mixture was diluted with water and EtOAc, the organic phase washed (2 × $NaHCO_3$ aq., 1 × water), dried ($MgSO_4$) and the solvents evaporated. The residue was dissolved in CH_2Cl_2 (3 mL) and *t*BuOMe (15 mL), followed by slow rotatory evaporation to a volume of 2 mL and overlayering with hexanes (6 mL). The product slowly crystallized at –20 °C. Filtration and washing with hexanes gave colorless needles of **23** (60.3 mg, 82%). R_f = 0.33 (SiO_2; EtOAc/hexanes, 1:3); m.p. 177–178 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.95 (s, 3 H, Me), 2.03 (s, 3 H, Me), 2.37 (s, 3 H, Me), 2.42 (s, 3 H, Me), 2.75 (dd, *J* = 16.7, 2.3 Hz, 1 H), 3.03 (dd, *J* = 16.6, 13.7 Hz, 1 H), 3.83 (s, 3 H, OMe), 5.42 (d, *J* = 13.6 Hz, 1 H), 6.93–6.99 (m, 2 H Arl), 7.35–7.41 (m, 2 H Arl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.2, 9.6, 20.4, 21.0, 45.2, 55.4, 79.0, 111.6 (br), 114.2, 117.8, 118.0 (br), 127.5, 130.6, 146.5 (br), 153.6, 159.1, 159.9, 167.9, 169.4 (br), 190.4 (br) ppm. MS (EI): *m*/*z* (%) = 398 (30) [M]$^+$, 356 (100), 314 (35), 222 (20), 180 (51), 134 (20). IR (KBr): $\tilde{\nu}$ = 2932 (w), 1761 (s), 1684 (m), 1609 (m), 1516 (m), 1450 (m), 1355 (m), 1219 (s) cm^{-1}. $C_{22}H_{22}O_7$ (398.41): calcd. C 66.32, H 5.57; found C 66.19, H 5.36.

CSA-Catalyzed Cyclization of 24 to 23. Repetition of the Fujise Experiment: Chalcone triacetate **24** (38 mg, 0.086 mmol) and (+)-camphorsulfonic acid (1.0 mg, 0.0043 mmol, 5 mol-%) were dissolved in EtOH abs. (3 mL) and heated to 110 °C in an open thick-walled glas pressure tube. When the volume of the reaction solution had reached 2 mL by evaporation of EtOH, the tube was closed and kept for 24 h at 110 °C. After cooling, toluene (3 mL) was added, the mixture partially evaporated to 2 mL and separated by column chromatography (EtOAc/hexanes, 1:4–1:1) to give matteucinol-di-

acetate (**25**; 11.7 mg, 40%). According to the HPLC-analysis (for conditions see the electronic supporting information), the product was racemic within the limits of accuracy of the analysis ($ee < 2\%$).

Supporting Information (see also the footnote on the first page of this article): Conditions for chiral HPLC analysis of flavanones **2**, **9**, **10**, **23**, **30**–**32**, and figures for the X-ray structural analysis of compound **20**.

Acknowledgments

L. H. thanks the Deutsche Forschungsgemeinschaft (DFG) for funding within the *Emmy Noether Programm*, and Prof. Carsten Bolm, RWTH Aachen, for continuing support.

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Received: July 24, 2007
Published Online: October 8, 2007

