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Asymmetric Ion-Pairing Catalysis of the Reversible Cyclization of 2′-Hydroxychalcone to Flavanone: Asymmetric Catalysis of an Equilibrating Reaction[‡]

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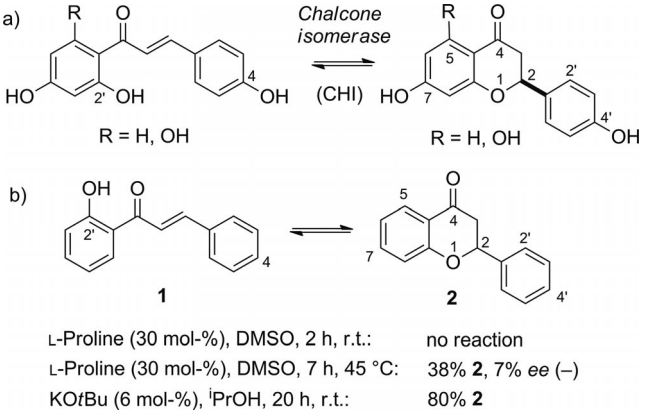
The asymmetric catalytic cyclization of the simple 2′-hydroxychalcone (**1**) to flavanone (**2**), a model for the chalcone isomerase reaction, has been realized as a catalytic asymmetric ion-pairing process with chiral quaternary ammonium salts (e.g., 9-anthracenylmethlycinchoninium chloride; 9-Am-CN-Cl) and NaH as small-molecule co-catalyst. In toluene/$CHCl_3$ solution, the process reaches an intrinsic enantioselectivity of up to S = 14.4 (er = 93.5:6.5). The reversible reaction proceeds in two steps: A fast initial reaction approaches a quasi-equilibrium with $K_{R/S}$ = 4.5, followed by a second, slow racemization phase approaching K_{rac} = 9. A simple mechanistic model featuring a living ion-pairing catalysis with full reversibility is proposed. Deuterium transfer from co-solvent $CDCl_3$ to product **2** and isolation of a Michael conjugate formed from **2** and **1** demonstrate the intermediacy of flavanone enolate ion pairs. A kinetic model shows good agreement with the experimentally observed, peculiar, time-dependent evolution of the species concentrations and the enantiomeric excess of **2**. The reaction is a chemical model of the chalcone isomerase enzymatic reaction. Furthermore, it is an ideal model for studying the characteristic behavior of reversible asymmetric catalyses close to their equilibria.

Introduction

The reversible cyclization of 2′-hydroxychalcones to flavanones is an early step in flavonoid biosynthesis, which is catalyzed by the enzyme chalcone isomerase (Scheme 1, a).[2] Catalysis is effected by folding the chalconate anion into a chiral conformation in the enzyme active site.[3] Additional general acid and base interactions with amino acid side-chains provide accurate structural organization of the transition state of the intramolecular asymmetric conjugate addition of phenolate (oxa-Michael reaction),[3,4] ensuring high enantioselectivity ($S \approx 100000$).[5] In spite of the reversibility of the reaction, (2*S*)-flavanones are thus formed almost exclusively. Such high enantioselectivity cannot be achieved with small-molecule catalysts (organocatalysts), which have only recently been used successfully in asymmetric oxa-Michael-type reactions[6,7] but not yet with any success in the simple model reaction **1**→**2**. We have previously studied asymmetric catalytic cyclization reactions of hydroxychalcones with cinchona alkaloid catalysts[8] and were able to cyclize specifically activated starting materials but not the simple substrate **1**. Scheidt and co-workers demonstrated that the introduction of an activating 2-alkoxycarbonyl group at C-2 of the chalcone substrate facilitates asymmetric ring closure with chiral thiourea catalysts.[9] The same model reaction has since been catalyzed by others using chiral Lewis acids,[10] other bifunctional organocatalysts,[11] or chiral Brønsted acids,[12] providing indirect solutions to the asymmetric synthesis of flavanones.[6a] The direct asymmetric catalytic cyclization **1**→**2** has been attempted without success in the past.[8,12–14] Several authors have acknowledged the difficulty of realizing such a process,



Scheme 1. a) Enzymatic cyclization of hydroxylated chalcones to flavanones. b) Attempted asymmetric catalytic cyclization of 2′-hydroxychalcones to flavanones.

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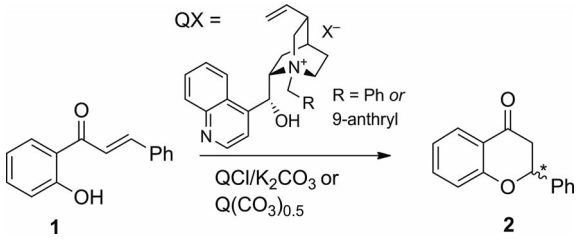
ascribing it to its reversibility or the low reactivity of **1**.[6a,7,9,12,14–16] The topic of asymmetric catalysis of reactions with a low thermodynamic driving force close to their equilibrium is a problem of general interest that has been little studied.[17] We now present a novel asymmetric ion-pairing catalysis that achieves the difficult asymmetric cyclization of **1** to **2** in a manner that is mechanistically comparable to the enzymatic reaction (Scheme 1, a). The reversibility of the reaction has specific consequences for the kinetic evolution of the reaction mixture composition and the enantiomeric excess of flavanone (**2**). A mechanistic and kinetic model is presented that rationalizes the experimentally determined reaction characteristics.

Results and Discussion

Our earlier study indicated that the difficulty of catalyzing the reaction **1**→**2** asymmetrically is connected to its low driving force and reversibility ($K \approx 4$ in *n*BuOH at 120 °C),[8] which creates the inherent risk of racemization under the reaction conditions. The screening of a variety of metal complexes and bifunctional organocatalysts, including cinchona alkaloids, was not very successful (see Table S1 in the Supporting Information for details);[18] only (L)-proline displayed some activity with low enantioselectivity in the cyclization of **1** to **2** (Scheme 1, b) and amino acid decarboxylation was a notable side-reaction.[19] On the other hand, strongly basic catalysts like KO*t*Bu readily induced cyclization at ambient temperature. This led to the idea of combining the successful chiral architecture of cinchona alkaloids[20] with the potentially higher basicity of inorganic bases in a two-component catalyst. When a solution of hydroxychalcone **1** in toluene was stirred with solid K_2CO_3 and the chiral phase-transfer catalyst *N*-benzylcinchonidinium chloride,[21] an asymmetric catalytic cyclization was indeed observed (Table 1, entry 1).

Alternatively, the catalyst components were combined to a quaternary ammonium carbonate salt, which was obtained from the chloride salt and silver carbonate, and used as homogeneous catalysts (Table 1, entries 2 and 3). In dichloromethane, the catalytic cyclization was faster but less stereoselective (entry 3; see Table S2 in the Supporting Information for more solvents). The superiority of *N*-(9-anthracenyl)methyl- over *N*-benzyl-quaternized cinchona alkaloids as chiral catalysts[22] was confirmed in this reaction (entries 4–6). In view of the reversibility of the reaction,[23] a catalytic experiment with 9-Am-CD-CO_3 (Table 1, entry 5) was followed over time by removing samples for chiral HPLC analysis (Figure 1). Both conversion (38%) and *ee* (49%) values stabilized after 80 h. This reaction course is not plausibly explained by thermodynamic or kinetic arguments, but must be due to catalyst deactivation in air, a conclusion justified by later experiments. The most convenient catalyst system that emerged from the initial screening was a combination of the quaternary salt QCl with co-catalytic sodium hydride as base (entry 6); this resulted in a more active catalyst than the ill-defined carbonate salts. The

Table 1. Screening for asymmetric catalysts for the cyclization of **1** to **2**.[a]



Entry	Catalyst[b] (loading [mol-%])	*t* [h]	**2** [%][c]	*ee* [%][c]
1	Bn-CD-Cl/K_2CO_3 (10)	28	65	19 (*S*)
2	Bn-CD-CO_3 (10)	28	41	21 (*S*)
3	Bn-CD-CO_3 (10)[d]	6.5	54	6 (*S*)
4	9-Am-CD-Cl/K_2CO_3 (10/20)	52	28	53 (*S*)
5	9-Am-CD-CO_3 (10)	9	14	55 (*S*)
6	9-Am-CD-Cl/NaH (10)	80	63[e]	47 (*S*)

[a] Conditions: **1** (0.3 mmol), toluene (2 mL), catalyst loading (10 mol-%, as Q^+), ambient temperature. [b] 9-Am = 9-anthrylmethyl; Bn = benzyl. CD = cinchonidine/cinchonidinium. [c] Yield and *ee* of **2** determined by HPLC analysis. [d] Reaction in CH_2Cl_2. [e] Isolated yield of **2**. In addition, **1** (26%) and **3** (12%) were also obtained.

catalysis mixtures displayed the characteristic dark-orange-red color of the chalconate anion (for a photograph, see Figure S2), which points to the presence of an ion pair [Q^+/ChO^-] (ChOH = **1**) as the resting state of the catalysis. This lipophilic ion pair is produced according to Equations (1) and (2), the latter being an ion-exchange reaction driven forward by the precipitation of the stable NaCl(s).

$$NaH + ChOH \rightleftharpoons ChONa + H_2(g) \quad (1)$$

$$QCl + ChONa \rightleftharpoons Q^+/ChO^- + NaCl(s) \quad (2)$$

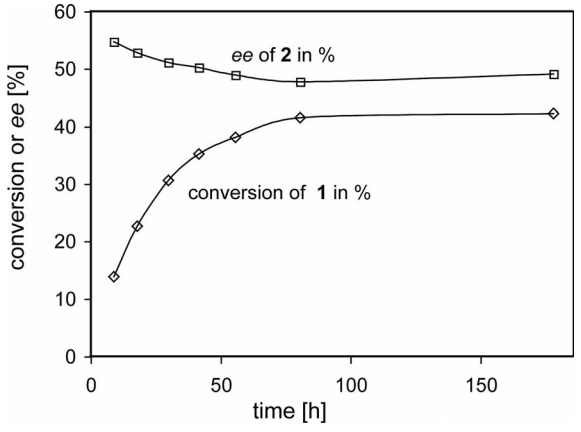


Figure 1. Conversion of **1** and *ee* of **2** vs. time in the cyclization of **1** to **2** with 9-Am-CD-CO_3 as catalyst (Table 1, entry 5); see Table 1 for conditions.

The practical and robust catalyst system composed of 2–10 mol-% (typically 5 mol-%) of 9-anthrylmethylcinchonidinium chloride (9-Am-CD-Cl) and co-catalytic NaH (5–20 mol-%) was preferred in further studies. The base NaH

can be used in slight excess over QCl because the sodium salt NaOCh is not soluble in the reaction medium and induces no background reaction. Catalytic reactions were performed under argon because this increased the catalyst lifetime. A fairly rapid cyclization of **1** to **2** ensued at 45 °C; HPLC analysis of the reaction course revealed the characteristic time-dependency of the conversion (Figure 2, a) and the enantiomeric excess of the product (Figure 2, b).

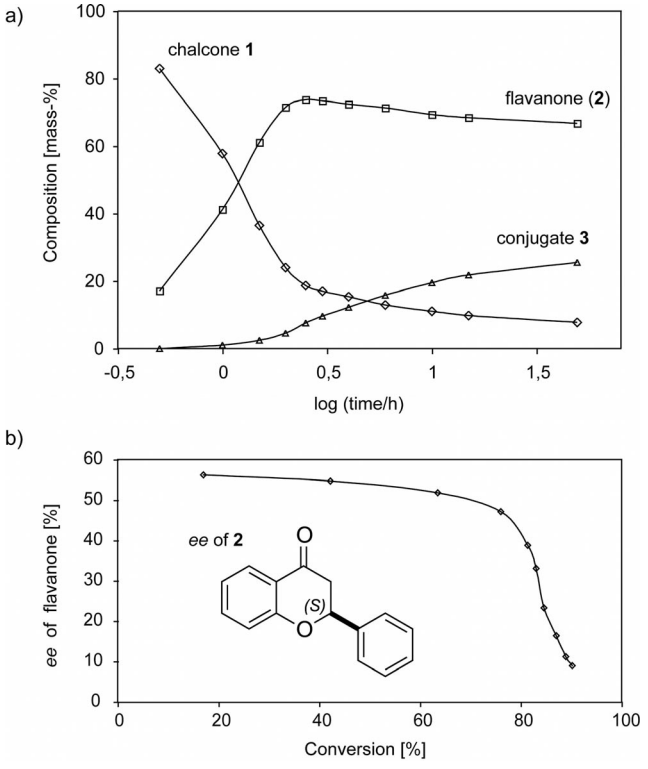
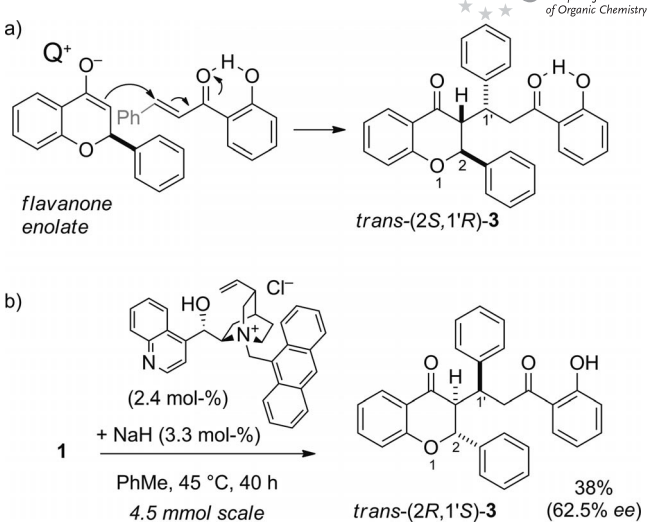


Figure 2. Course of the catalytic reaction **1**→**2** at 45 °C. Conditions: catalyst 9-Am-CD-Cl/NaH (10%), toluene (11 mL/mmol). Curves are interpolated to the measured values. a) Time-dependent composition of the reaction mixture. The data for **2** and **3** represent the sum of both enantiomers. Note the logarithmic timescale. b) Evolution of the enantiomeric excess of flavanone (**2**) as a function of the conversion of **1**.

The reaction was fast in the initial phase and reached a quasi-equilibrium situation with $K_{eq} \approx 4$ (80% of **2**, 20% of **1**). The enantiomeric excess of product **2** remained relatively stable up to this point, but then decreased in a slower racemization phase, and eventually was reduced to less than 10%. In this second phase, a side-product **3** was also formed in considerable amounts; compound **3** is a conjugate of **1** and **2** and must result from the conjugate addition (Michael reaction) of flavanone enolate to substrate **1** (Scheme 2, a).

The structural assignment of **3**, a single diastereomer, was particularly simple as it had earlier been obtained in the base-induced dimerization of **1** under microwave heating and had been fully characterized (NMR, X-ray).[14] In our catalysis reaction, **3** was enantiomerically enriched. The direct asymmetric catalytic synthesis from **1** was improved by using a higher substrate concentration and a more selective catalyst. The kinetic progress of the reaction with the catalyst 9-Am-CN-Cl/NaH (9 mol-%) at 45 °C is shown in Figure 3.



Scheme 2. a) Generation of flavanone–chalcone conjugate **3** as a side-product in the base-catalyzed condensation of **1**. b) Asymmetric catalytic synthesis of **3** from **1**. The assignment of the absolute configuration of **3** is based on that of **2** in the same reaction.

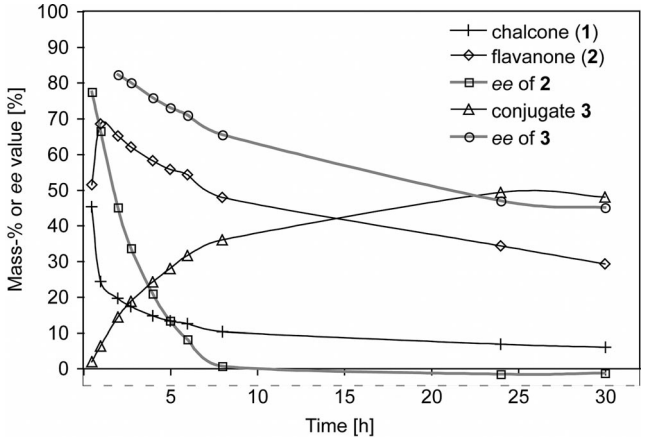


Figure 3. Kinetics and time-dependent enantioselectivity of chalcone/flavanone dimer **3** generation from 2-hydroxychalcone (**1**). Catalysis conditions: 9-Am-CN-Cl (9 mol-%), NaH (10 mol-%), toluene (4.5 mL/mmol), 45 °C. Internal standard for HPLC: 1,6-dibromo-2-isopropoxynaphthalene. Flavanone ([**2**] = [(*S*)-**2**] + [(*R*)-**2**]) was completely racemized after 8 h. The inverted *ee* ($S > R$) of **2** after 10 h might be due to a kinetic resolution or a systematic integration error.

The initial fast cyclization of chalcone to flavanone quickly reached quasi-equilibrium (≈70 mass-% **2**). In the second phase of the reaction, **2** was consumed at the expense of conjugate **3** and the remaining **2** had racemized after 7 h. Maximal conversion to **3** (50 mass-%) was reached after 1 d. A preparative run was performed with only 2.4 mol-% of 9-Am-CN-Cl at a higher substrate concentration (1.6 mL/mmol). After 40 h at 45 °C, conversion to **3** had reached 49% (*ee* = 67%) and (–)-**3** was isolated in 38% yield with 62.5% *ee* (Scheme 2, b).

Reaction Analysis

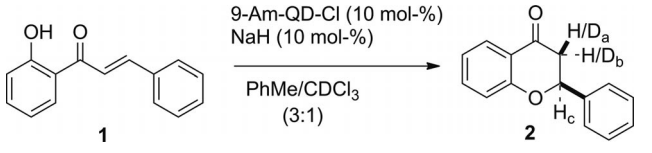
The composition of the catalytic reaction mixture was analyzed by normal-phase chiral HPLC.[24] Chromatograms are shown in the Supporting Information (Figure S1). The signals for chalcone **1** and flavanone enantiomers (*R*)-**2** and (*S*)-**2** are clearly separated, as are those of the enantiomers of conjugate **3**, the broadened peaks of which are better visible in the later stages of the reaction. The concentrations of all reacting species could be determined from a single chromatogram. Quantification was either performed by the summation of absorption-corrected peak areas[18] and normalization to 100% or, for more accurate work, by the use of an internal standard.

Suppression of Side-Product 3 in Mixed Solvent Systems

The initial screening of solvents with the 9-Am-CD-Cl/NaH precatalyst had used a single-point conversion and *ee* analysis after 24 h. The results were not overly informative because the *ee* depends on total conversion as much as on the solvent used. Nevertheless, the screening showed that the generation of side-product **3** also depends on the solvent. Arenes produced as much as 10% of **3** after 24 h, but the C–H acidic solvents chloroform or propionitrile suppressed its generation to only 0.1 or 1%, respectively, in spite of higher overall conversions (see Table S3 in the Supporting Information). This observation provoked a closer inspection of the time-dependent reaction course in selected solvents. The catalysis in toluene (Figure 4, a) reached maximum conversion to flavanone in 9 h. The *ee* of flavanone (**2**) was stable at 58% over the first 6 h, but then decreased after the reaction had reached quasi-equilibrium (Figure 4, a). Steady generation of side-product **3** occurred throughout the reaction. The time-dependent analysis of the reaction in chloroform (Figure 4, b) showed distinct differences: Although the initial level of enantioselectivity was lower (39% *ee*), generation of side-product **3** was almost completely suppressed in this solvent (<0.5%; curves omitted from Figure 4, b). When the catalytic reaction was performed in a 3:1 mixture (v/v) of toluene and chloroform (Figure 4, c), the initial enantioselectivity reached *S*/*R* = 5.0 (66.5% *ee*), which is higher than in either toluene (*S*/*R* = 3.9; *ee* = 59%) or $CHCl_3$ (*S*/*R* = 2.3; *ee* = 39%) alone. The reaction also proceeded faster in the mixed solvent than in either of the pure solvents.

Generation of the side-product **3**, although problematic at high conversions, is suppressed to 2–3% at the onset of the quasi-equilibrium after 4 h (conversion ≈80%). Flavanone enolates as fairly basic species (pK_a = 17)[25,26] are presumed reaction intermediates; the suppression of **3** in chloroform could be due to the acidity of the solvent (pK_a = 13.6).[27] To test this hypothesis, an additional experiment was performed in toluene/$CDCl_3$ (3:1; Table 2). Samples were removed and quenched after certain intervals of time, and the incorporation of deuterium into the flavanone product was analyzed by differential integration of ^1H NMR signals (accuracy: ±2%). Table 2 shows that deuterium is indeed transferred from $CDCl_3$ to flavanone (**2**), and that this process becomes more important in the later stages of the reaction, after the quasi-equilibrium has been

Table 2. Incorporation of deuterium from co-solvent $CDCl_3$ into flavanone.[a]



Entry	Time [h]	**2** [%][b]	*ee* [%][b]	D_a [%][c]	D_b [%][c]
1	1	44	77 (*R*)	1	1
2	4	82	64 (*R*)	32	32
3	6.5	83	50 (*R*)	49	49

[a] Reaction conditions: **1** (100 mg), 9-Am-QD-Cl (10 mol-%), NaH (10 mol-%), toluene (3 mL), $CDCl_3$ (1 mL), room temp. [b] Mol-% of **2**, determined by HPLC. [c] Deuterium incorporation determined by ^1H NMR spectroscopy.

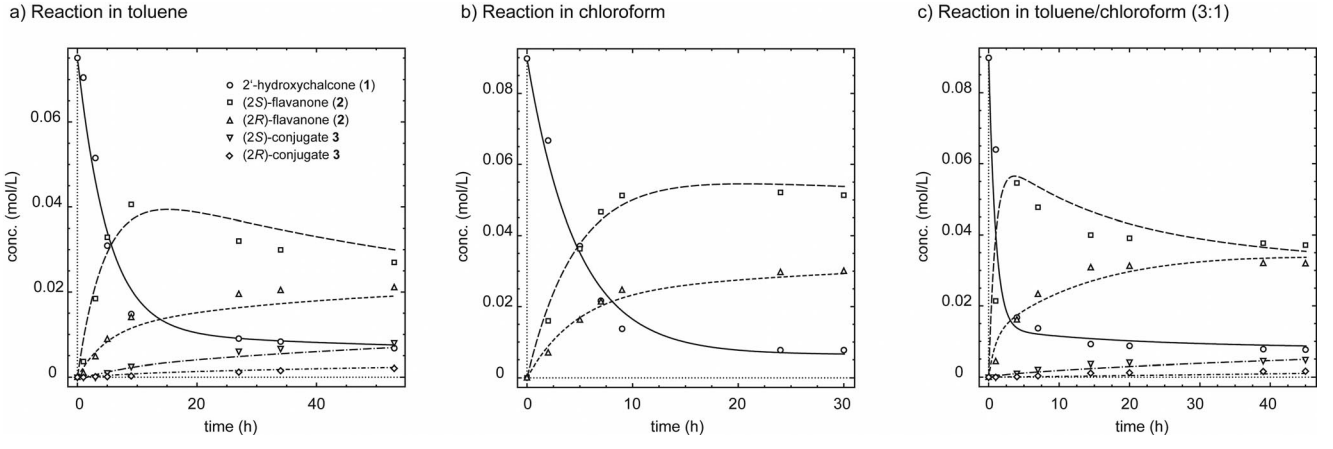
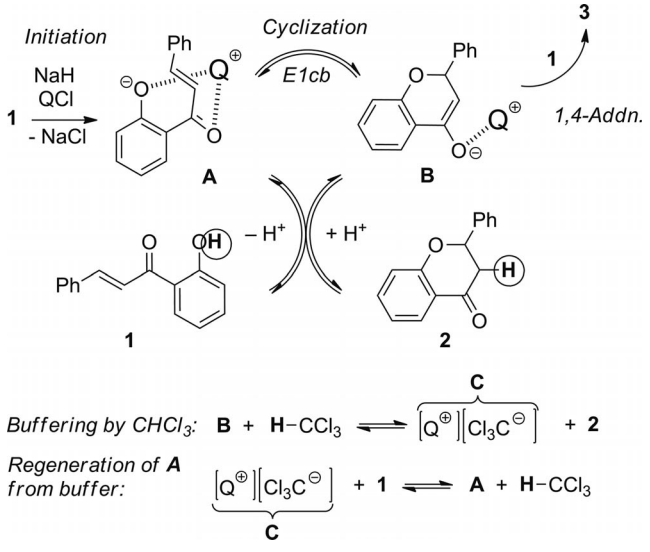


Figure 4. Evolution of species in the catalytic cyclization of **1** to **2** in various solvents. General conditions: **1** (100 mg, 0.45 mmol), 9-Am-CD-Cl/NaH (10%), room temp. a) Reaction performed in toluene (6 mL). b) Reaction performed in chloroform (5 mL). c) Reaction performed in toluene/$CHCl_3$ (3:1; 5 mL). See Tables S4–S6 in the Supporting Information for numerical values. Kinetic curves are fitted to a model discussed later in the text and are intended as guidelines; high accuracy cannot be expected under the conditions used.

reached and the concentration of the acidic starting material **1** ($pK_a \approx 9.6$)[28] has reached low levels. There was no site preference (H_a vs. H_b) for the deuteriation. This is in line with the diastereoselectivity of deuterium incorporation observed in base-catalyzed cyclizations of **1** to **2** via flavanone enolates in protic, deuteriated solvents.[29]

Mechanistic Interpretation

The experimental data acquired so far give some hints about the reaction mechanism of the catalytic cyclization of 2′-hydroxychalcone (**1**) to flavanone (**2**) with the QCl/NaH precatalyst (Scheme 3). The acidic substrate **1** ($pK_a = 9.6$)[28] is deprotonated by NaH to give insoluble ChONa and hydrogen [Equation (1)]; ion exchange with Q^+/Cl^- [Equation (2)] gives the dissolved dark-orange ion pair **A** (for a photograph of the reaction mixture, see Figure S2 in the Supporting Information). The chalconate anion undergoes intramolecular conjugate addition (oxa-Michael cyclization) in the presence of the chiral counter-cation Q^+, the latter inducing stereoselectivity in the attack of the phenolate oxygen to the diastereotopic faces of the alkenone double bond. In the resulting ion pair **B**, cation Q^+ is combined with a strongly basic flavanone enolate ($pK_a = 17$), which can deprotonate another molecule of **1** with regeneration of ion pair **A** and release of product **2**. Alternatively, **B** is protonated to product **2** by the acidic co-solvent chloroform ($pK_a = 13.6$),[27] creating the ion pair Q^+/CCl_3^- (**C**); if $CDCl_3$ is the co-solvent, this process introduces deuterium at C-3 of **2** (see Table 2).



Scheme 3. Mechanism of the QCl/NaH-catalyzed cyclization of hydroxychalcones to flavanones: An asymmetric ion-pairing catalysis.

Because ion pair **C** is stable towards the elimination of Cl^- in apolar media (no follow-up products from CCl_2 have been observed in our study), it must be the resting state of the catalyst that reinitiates the reaction by deprotonating **1** to recreate ion pair **A** and $CHCl_3$. In pure toluene as solvent, the quenching of **B** by acidic substrate **1** by proton transfer competes with intermolecular conjugate addition of **B** to either **1** or **A** to give **3**. This irreversible side-reaction is suppressed in buffered solvent containing $CHCl_3$, in which the catalyst resting state is Q^+/CCl_3^- (**C**) and the concentrations of **A** and **B** remain low. The catalytic principle operating in the cyclization of **1** to **2** may be defined as living[30] anionic catalysis. Each cyclization event **A**→**B** generates a strong base (enolate; $pK_a = 17$) from a weak base (phenolate; $pK_a = 9.6$); hence the acidic substrate **1** is not deprotonated by a chiral base catalyst, but by the conjugate base of the reaction product, and the chirality is associated with the counter-cation, just as in asymmetric phase-transfer catalysis (APTC). In contrast to APTC, the current reaction proceeds in homogeneous solution, and in contrast to most APTCs, a stoichiometric quantity of base is not required, only a co-catalytic amount.

Kinetic Modeling of the Reversible Asymmetric Catalysis

The mechanistic model developed in the preceding section can be translated into a kinetic reaction scheme. As a test of the accuracy of the scheme and the underlying postulated mechanism, it remains to be shown if such a kinetic scheme will correctly reproduce the peculiar time-dependency of the reactant and product concentrations and of the enantiomeric excess of the product (compare Figure 2). The simplified kinetic model is based on Equations (3) and (4), in which k_R and k_S are the pseudo-first-order rate constants of the forward reactions and include the catalyst concentration, and k_{-R} and k_{-S} are the pseudo-first-order rate constants of the backward reactions.

$$\mathbf{1} \rightleftharpoons (R)\text{-}\mathbf{2};\ K_{eq} = K_R = k_R/k_{-R} \quad (3)$$

$$\mathbf{1} \rightleftharpoons (S)\text{-}\mathbf{2};\ K_{eq} = K_S = k_S/k_{-S} \quad (4)$$

The enantiomers of **2** have equal free energy in a largely achiral environment, translating to the additional restraint shown in Equation (5).

$$K_R = K_S \quad (5)$$

There are two separate equilibria between the starting material **1** and either enantiomer of **2**, with equal equilibrium constants but different equilibration kinetics in the case of asymmetric catalysis. For the kinetic fit, we performed a catalytic reaction with 4.3 mol-% of the 9-AmCN-Cl/NaH catalyst in toluene/$CHCl_3$ (3:1) at room temperature. The reaction proceeded reversibly over a reasonably long timescale, and all the reaction components could be quantified by a single chiral HPLC measurement against an internal standard. The experimental values and fitted curves are shown in Figure 5. The kinetic model correctly reproduces the time-dependent evolution of the reaction mixture (Figure 5) and the *ee* (Figure 6) of product **2**. Some simplifications of the kinetic model need to be pointed out, namely, concentrations of catalyst resting states (**A**, **B**, or **C** in Scheme 3) are not accounted for and a steady catalyst

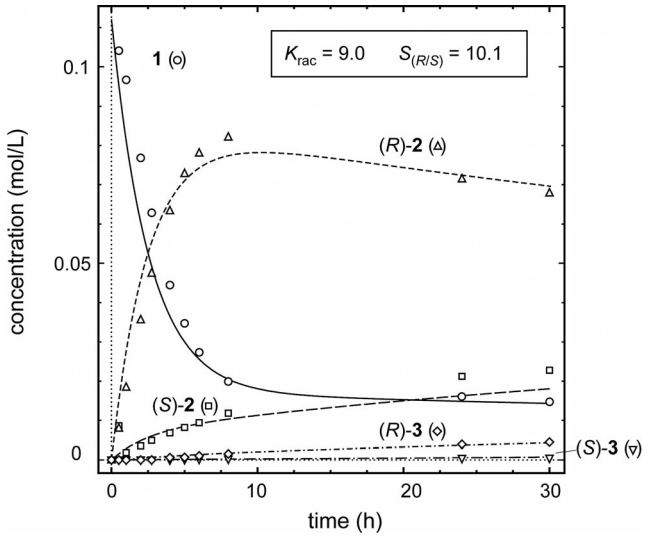


Figure 5. Asymmetric catalytic cyclization of **1** to **2** showing experimental datapoints and fitted curves. Conditions: **1** (2.23 mmol), 9-AmCN-Cl/NaH (4.3/4.9 mol-%), solvent mixture toluene/$CHCl_3$ (3:1; 20 mL), internal standard 1,6-dibromo-2-isopropoxynaphthalene (300 mg), ambient temperature (295 K). $K_R = K_S = 4.5$; $K_{rac} = 9.0$; $S = 10.1$; $k_{tot} = k_R + k_S = 0.33\ h^{-1}$; $k_{R3} = k_{S3} = 0.10\ L\,mol^{-1}h^{-1}$.

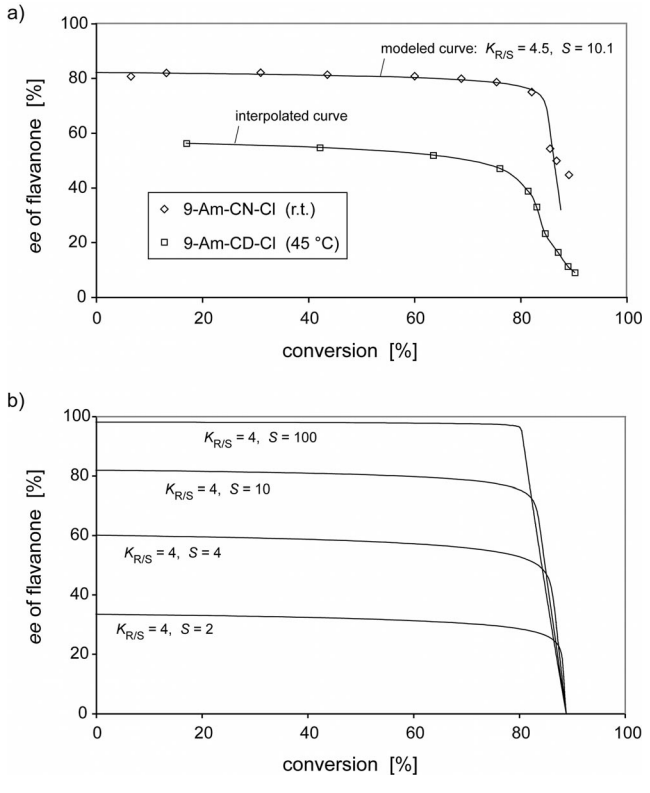


Figure 6. Conversion dependency of product *ee* in reversible asymmetric catalysis. a) Datapoints for catalysis with 9-Am-CN-Cl/NaH (see Figure 5) are compared with a modeled curve using a simplified kinetic model that neglects the generation of **3**. The data for 9-Am-CD-Cl from Figure 2 are included for comparison. b) Calculated *ee* vs. conversion profiles for the reversible asymmetric catalysis **1** = (*S*)-**2**/(*R*)-**2** with $K_{R/S} = 4$ ($K_{rac} = 8$) at different levels of catalyst enantioselectivity *S*.

decomposition that eventually stops the reaction is not included in the model.

A perfect fit of both the early and late reaction phase with the same parameters cannot be expected. In view of this, the good agreement of experimental datapoints and modeled curves for **1**, (*R*)-**2**, and (*S*)-**2** with only three independent parameters is satisfactory and supports the proposed mechanism. Within the simplified kinetic model, the irreversible side-reaction leading to **3** is satisfactorily described by two additional kinetic parameters, Equations (6) and (7).

$$\mathbf{1} + (R)\text{-}\mathbf{2} \rightarrow (R)\text{-}\mathbf{3};\ k_{R3} \quad (6)$$

$$\mathbf{1} + (S)\text{-}\mathbf{2} \rightarrow (S)\text{-}\mathbf{3};\ k_{S3} \quad (7)$$

In conclusion, three parameters are sufficient to characterize this reversible asymmetric catalysis **1**⇌**2**: 1) The intrinsic enantioselectivity $S = k_R/k_S$ of the catalyst, which defines the initial product *ee*, 2) the initial reaction rate, which can be expressed as $-d[\mathbf{1}]/dt = (k_R + k_S)[\mathbf{1}]$ and is also dependent on the catalyst, and 3) the equilibrium constant K_{rac} ($= K_R + K_S = 2K_R$), which is independent of the catalyst.

Reversibility and Time-Dependent Evolution of the Enantiomeric Excess

The reversibility of the reaction renders enantioselectivity a function of time or conversion. The plot of product *ee* versus conversion has a characteristic shape (Figure 6). In the initial reaction phase, the backward reaction is negligible and the product *ee* reflects the intrinsic selectivity ($S = k_R/k_S$) of the chiral catalyst. Only after the conversion has reached quasi-equilibrium (ca. 80% **2** and 20% **1** for $K_R = 4$), the product *ee* decreases quickly and reaches 0% at the equilibrium conversion value (88.9% for $K_{rac} = 8$). With very selective catalysts it is possible to approach quasi-equilibrium concentrations of the product with little loss of product *ee* (Figure 6, b, curve $S = 100$). The modeling ignores the generation of side-product **3**, which is responsible for the deviations at the higher conversions seen in Figure 6 (a).

Effects of Catalyst and Substrate Structure on Enantioselectivity

A specific catalyst in the chalcone/flavanone cyclization is fully characterized by the initial enantioselectivity and reaction rate. Single-point *ee* determinations of isolated reaction products, as is common analytical practice in irreversible asymmetric catalysis, are not suitable in reversible systems. In practice, three to five samples were removed from a single catalytic run in the initial reaction phase (10–60% conversion) for analysis by chiral HPLC. Use of an internal standard for HPLC was not necessary because side-products were absent in the initial reaction phase. Quantification of **1** and **2** (in mol-%) was possible from the

relative HPLC peak areas corrected for UV absorption factors. The reaction rate is expressed in simplified form as the turnover frequency (TOF [h^{-1}]) and was calculated from early datapoints according to Equation (8).

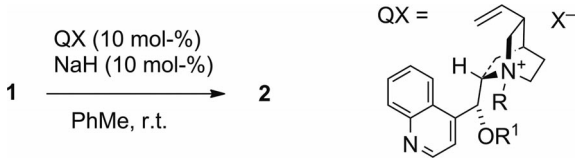
$$\text{TOF } [h^{-1}] = \frac{x_2}{x_{cat.} \cdot t} \qquad \begin{array}{l} x = \text{rel. molar fraction [mol-\%]} \\ t = \text{reaction time [h]} \end{array} \qquad (8)$$

The relative molar fraction of the catalyst corresponds to the loading in mol-%. Because the TOF of a homogeneous catalysis depends on the initial reactant concentration, the latter was kept constant in the catalyst screening experiments.

Influence of the *N*-Alkyl Group in the Quaternized Alkaloid

The effect of the *N*-alkyl group of the quaternized cinchonidine on the catalytic reaction is shown in Table 3. These experiments from an early stage of the project were performed in toluene. Enantioselectivities are somewhat lower than in the optimized solvent systems toluene/$CHCl_3$ or cymene/$CHCl_3$. Starting from *N*-benzylcinchonidinium chloride (Table 3, entry 1), an increase in the size of the *N*-alkyl group to 1-naphthylmethyl and 9-anthracenylmethyl (9-Am) increased both the selectivity and activity of the reaction (entries 2 and 3). However, bulkiness is not the only factor in play because groups like 9-fluorenyl or a silyloxy-substituted benzyl displayed lower selectivity with inversion of induction sense (entries 4 and 5). The extended aromatic π system of the 9-Am substituent might be required for stacking interactions in the deprotonated substrate.

Table 3. Effect of quinuclidine *N*-substitution on catalytic performance.[a]



Entry	Quaternary ammonium salt (QX)			S[b]	*ee*[b] [%]	TOF[b] [h^{-1}]
	R	R^1	X			
1	Bn	H	Cl	1.7	26 (*S*)	0.3
2	1-naphthylmethyl	H	Cl	2.2	37 (*S*)	0.8
3	9-anthracenylmethyl	H	Cl	3.9	59 (*S*)	1.0
4	9-fluorenyl	H	Br	1.6	23 (*R*)	0.06
5	3,5-bis(TBPSO) benzyl	H	Br	1.4	18 (*R*)	0.4
6	Bn	Bn	Br	1.4	16 (*S*)	0.05

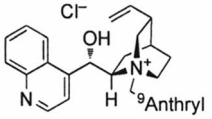
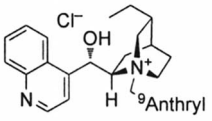
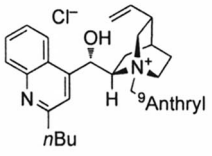
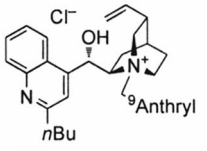
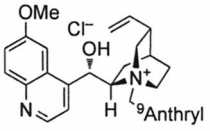
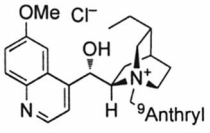
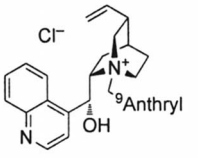
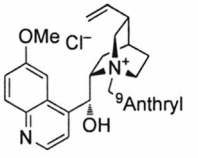
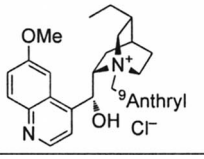
[a] Conditions: cf. scheme, and **1** (0.45 mmol), toluene (3 mL). TBPS = *tert*-butyldiphenylsilyl. [b] Determined by HPLC.

The presence of the alcoholic hydroxy group is also critical for achieving selective catalysis: An experiment with *O*-benzylated *N*-benzylcinchonidinium bromide[31] displayed both low selectivity and activity (entry 6).

Influence of the Alkaloid Structure

The *N*-(9-anthrylmethyl) salts of all major cinchona alkaloids were tested in the reaction (Table 4). Cinchonine

Table 4. Variation of the catalyst in the asymmetric cyclization of **1**→**2**.[a]

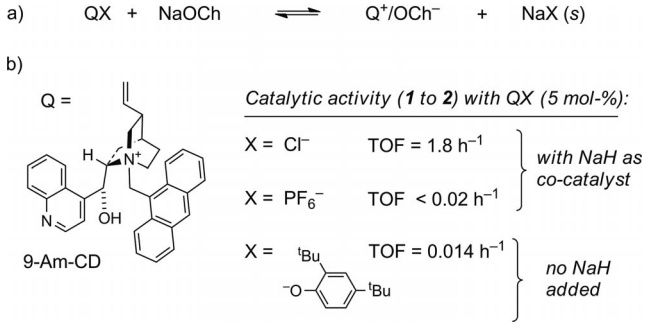
Entry	Catalyst salt QX	Enantioselectivity		TOF
		S	*ee* [%]	[h^{-1}]
1		10	82 (*R*)	3.6
2[b]	"	12.3	85 (*R*)	4.0
3		9	80 (*R*)	2.0
4[b]	"	10	82 (*R*)	2.1
5		10	82 (*R*)	3.0
6[b]	"	13.3	86 (*R*)	3.1
7[b]		12.3	85 (*R*)	3.6
8		7.3	76 (*R*)	2.6
9		4.4	63 (*R*)	2.3
10		4.7	65 (*S*)	1.8
11		1.6	23 (*S*)	1.0
12		1.3	14 (*S*)	1.0

[a] Conditions: **1** (0.45 mmol), QCl (5 mol-%), NaH (6 mol-%), toluene (3 mL), $CHCl_3$ (1 mL). [b] Cymene (3 mL) was used in place of toluene. [c] ^{9}Anthryl = 9-anthracenyl.

(CN) produced the most selective catalyst (entries 1 and 2), which was also more active than the pseudo-enantiomeric cinchonidine (CD) derivative (entries 3 and 4). Variations in the cinchonine structure, such as hydrogenation, isomerization,[32] or 2′-alkylation[33] (entries 3–7) led to modest changes in the catalytic activity with retention of selectivity. The methoxy-substituted alkaloids gave irregular results: Although the quinidine (QD) derivative was only slightly less selective than its non-methoxylated analogue (entry 8 vs. 1), the quinine (QN) derivative was considerably less selective and active than its demethoxylated CD analogue (entry 11 vs. 10). In general, use of cymene instead of toluene as co-solvent led to somewhat higher enantioselectivities.

Catalyst Recuperation and Ion-Pairing Effects

After workup of the catalysis reaction mixtures, the catalyst salt remains in the acidic water phase. Catalyst recuperation was performed for 9-Am-CD-Cl by careful neutralization of the water phase and extraction with CH_2Cl_2 to give the catalyst salt in yields of 50–92%, depending on the reaction scale and solvent volumes. Addition of KPF_6 to the neutralized water phase simplified the extraction of the catalyst, which was then obtained as its more lipophilic 9-Am-CD-PF_6 salt (82% yield). Surprisingly, this salt displayed essentially no catalytic activity in the chalcone/flavanone cyclization reaction; this was confirmed with a pure sample of the independently prepared (from 9-Am-CD-Cl and NH_4PF_6) analytically pure salt. The reduced catalytic activity of 9-Am-CD-PF_6 could be related to the position of the ion-exchange equilibrium between sodium chalconate (ChONa), QX, and the ion pair **A** and NaX [Equation (2), Scheme 4, a]. For small ions like Cl^-, the equilibrium might be on the right due to the high stability of NaCl(s), whereas anions like PF_6^- form lipophilic ion pairs QX that are readily soluble in organic medium and have little tendency to exchange counter-ions with the insoluble NaOCh. The interference of ion-exchange equilibria in the asymmetric catalytic **1**→**2** cyclization reaction is supported by the observation that the salt 9-Am-CD-(2,4-di-*tert*-butylphenolate) is around 100 times less active than the standard 9-Am-CD-Cl/NaH precatalyst (Scheme 4, b). This result was contrary to our expectation: Generation of the ion pair **A** and thus initiation of the catalysis was predicted as 2,4-di-*tert*-butylphenolate (pK_a = 11.6)[34] is sufficiently basic to deprotonate **1** (pK_a = 9.6). Future studies on homogeneous ion-pairing catalysis (and also on APTC) must address the role of the counter-ion in chiral quaternary salts QX more closely.



Scheme 4. a) The position of the ion-exchange equilibrium producing the catalyst resting state may depend on the nature of the counter-ion X^-. b) The catalytic activity of 9-Am-CD-X salts in the **1**→**2** cyclization varies with the nature of X.

Variation of the Substrate Structure

The asymmetric cyclization of substituted 2′-hydroxychalcones to flavanones was investigated with the catalyst systems 9-Am-CD-Cl/NaH (series I; reaction in toluene/$CHCl_3$) and 9-Am-CN-Cl/NaH (series II; reaction in cymene/$CHCl_3$). Figure 7 gives the intrinsic enantioselectivities of flavanone generation for both catalyst systems. The induction with precatalyst 9-Am-CD-Cl is around 60% *ee* for many flavanones with monosubstitution patterns (Figure 7, a–k). Likewise, catalyst 9-Am-CN-Cl induces consistent but higher selectivities of 80–85% *ee* for these flavanones. In all cases (a–p), the order of elution of the major and minor enantiomer is reversed in the chiral HPLC analysis for the two precatalysts. By analogy to **2**, the flavanones of series I probably display excess of the 2*S* configuration, and those of series II the 2*R* configuration. Deviations from the above induction pattern occur particularly with benzo-annulated flavanones (l–p).

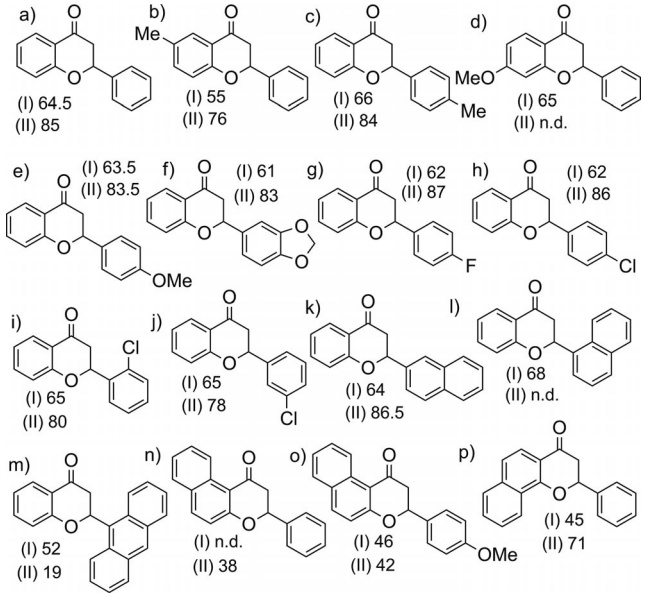
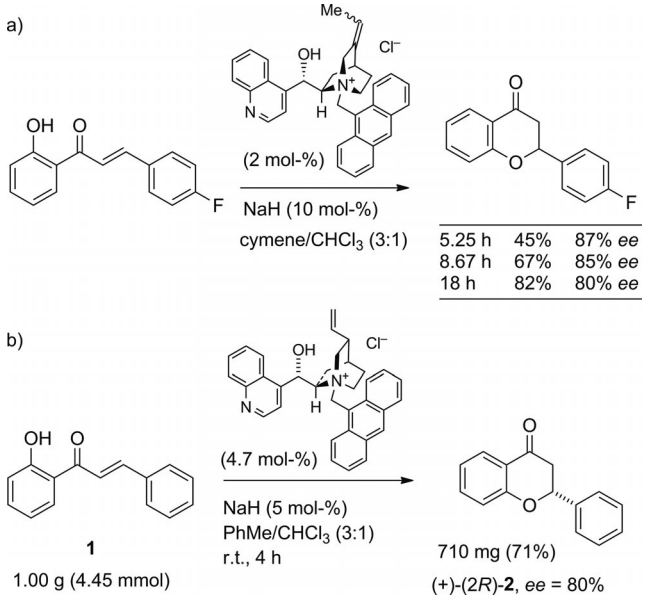


Figure 7. Intrinsic enantioselectivities (% *ee*) for the generation of substituted flavanones with two catalysts. Series I: 9-Am-CD-Cl/NaH (10 mol-%) in toluene/$CHCl_3$ (3:1). Series II: 9-Am-CN-Cl (5 mol-%) in cymene/$CHCl_3$ (3:1). Reaction conditions: hydroxychalcone (0.4 mmol) in solvent (4 mL), room temp. Analysis by chiral HPLC sampling of the reaction mixture; products were not isolated.

Preparative Applications of the Reaction

To date, the asymmetric catalytic chalcone/flavanone cyclization has been studied analytically and mechanistically. By taking into account the peculiarities imposed by the reversibility of the process, it should be possible to develop preparative applications. A careful analysis of the conversion and enantioselectivity as a function of reaction time is required to determine the optimal reaction conditions and times. For example, an analytical run with 4′′-fluoro-2′-hydroxychalcone using only 2 mol-% of 9-Am-CN-Cl/NaH indicated that quenching of the reaction after 9 h gives a decent yield of 4′-fluoroflavanone with 85% *ee*, whereas doubling of the reaction time increased the yield at the cost of a slightly lower enantiomeric excess (Scheme 5, a). The trade-off between yield and enantioselectivity is a characteristic of asymmetric catalyses of reversible processes. A catalytic synthesis of enantioenriched **2** was performed on a gram scale (Scheme 5, b) and showed excellent scalability. HPLC analysis of the reaction mixture indicated a conversion of 75% and a product enantioselectivity of 78% after 4 h (Figure S5 in the Supporting Information). Quenching and isolation of flavanone (*R*)-**2** gave a 71% yield with 80% *ee*. Although this level of enantioselectivity is not satisfactory for synthetic applications,[35] we expect that the reaction can profit from ongoing improvements in asymmetric phase-transfer catalysts.[36] In addition, this new asymmetric catalytic reaction is significant as it is currently the only process known for the direct asymmetric cyclization of 2′-hydroxychalcone (**1**) to flavanone (**2**).



Scheme 5. Establishing optimal conditions for preparative applications of the reversible asymmetric catalytic 2′-hydroxychalcone to flavanone cyclization reaction. a) Analytical testing of a reaction for optimal yield vs. *ee* values by chiral HPLC. b) Preparative run of the reaction with 9-Am-CN-Cl and **1** for obtaining enantioenriched flavanone (+)-(2*R*)-**2**.

Conclusions

We have developed a model for the asymmetric chalcone isomerase reaction that catalyzes the fundamental reaction **1**→**2**, for which no asymmetric process was previously known. Past literature reports have mentioned the difficulty of catalyzing this particular reaction because of its reversibility. Our new process is an asymmetric ion-pairing catalysis in homogeneous solution. The key species is ion pair **A**, formed from the achiral chalconate anion ChO^- and the chiral quaternary ammonium counter-cation Q^+. The cyclization of chalconate within this ion pair produces a strongly basic flavanone enolate ion pair **B** with asymmetric induction. Important structural elements of the chiral cation catalyst are a hydrogen-bond-donating hydroxy group, a positively charged ammonium unit, and an extended aromatic unit (9-anthracenyl) connected to the quaternary nitrogen. We have as yet refrained from drawing a detailed structural model of the transition state. However, it is clear that the above structural elements are responsible for noncovalent interactions within the substrate ion pair, presumably by arene and CH-to-arene stacking, hydrogen bonding, and coulombic attraction. Similar interactions, namely shape complementarity of the binding site[3a] and hydrogen bonding,[3c] have been postulated for the transition state of the enzymatic chalcone isomerase reaction.[3,4] Furthermore, kinetic studies of the chalcone isomerase reaction show that the natural hydroxychalcone substrate is deprotonated at the 2′-hydroxy group in bulk solution prior to binding to the active site.[3b] Therefore, the asymmetric ion-pairing cyclization reported herein has many parallels and can be considered a small-molecule model for the enzymatic process.

This work has also shed light on issues of asymmetric catalysis of reversible reactions close to equilibrium. Few such examples have been described in the literature, and the practical consequences of their reversibility are not widely appreciated.[17] The simplistic assumption that a reversible catalysis cannot be catalyzed asymmetrically because of the inherent danger of racemization of the reaction product must be rejected. It is necessary to perform time-dependent analyses of conversion and enantiomeric excess in asymmetric catalyses in order to recognize reversible processes. Single-point *ee* determinations of reaction products after workup may conceal the true efficiency of an asymmetric catalyst. The characteristic course of a reversible asymmetric catalysis involves an initial quasi-equilibration of the substrate and major enantiomer (characterized by $K_{R/S}$) followed by a slower equilibration of the substrate with racemic product (characterized by $K_{rac} = 2K_{R/S}$). This racemization is necessarily accompanied by a further increase of conversion. We have been able to reproduce the kinetic course of the asymmetric catalytic reaction **1**→**2**, including its characteristic *ee* versus conversion plot, by means of a simple model using only the initial reaction rate, the equilibrium constant K_{rac}, and the intrinsic enantioselectivity S of the catalyst as variables. The structurally simple cyclization of 2′-hydroxychalcone (**1**) to flavanone (**2**) has proven to be

an interesting model reaction of general interest for asymmetric catalysis.

Experimental Section

General: 9-Am-CD-Cl, Bn-CD-Cl, and Bn-QN-Cl were obtained commercially. The following salts were prepared according to literature procedures: 9-Am-QN-Cl[37] and other 9-Am salts,[38,39] 1-Npm-CD-Cl,[40] and *N*,*O*-dibenzylcinchonidinium bromide.[31] The 2′-hydroxychalcones were obtained by known methods, of which aldol condensation of 2-hydroxyacetophenones with aryl aldehydes and finely powdered $Ba(OH)_2 \cdot 8H_2O$ in EtOH proved to be the most general;[41] see the Supporting Information for detailed procedures. CC is flash column chromatography. Kinetic fits were performed by using the Dynafit program (BioKin).[42]

General Procedure for the Quaternization of Cinchona Alkaloids (GP1):[22c] A mixture of the alkaloid (1 equiv.) and alkylating agent (1 equiv.) was heated at reflux for 3 h in toluene (5 mL/mmol). After cooling to room temp., the mixture was diluted with 10 times its volume of diethyl ether. The precipitated salt was filtered, washed with diethyl ether, and dried in high vacuum. This general procedure gave satisfactory results, but the reaction products contained variable amounts of the alkaloid hydrochloride (or hydrobromide). Suitable recrystallization procedures must be found for each individual case. Because alkaloid hydrohalides do not interfere with the catalytic cyclization of **1** to **2**, crude products can in principle be used when screening new quaternary salts for catalysis.

***N*-(9-Anthracenylmethyl)cinchoninium Chloride (9-Am-CN-Cl):** This procedure includes a purification protocol and gives crystalline product. Cinchonine (2.94 g, 10.0 mmol; dried in an oven at 100 °C) and 9-chloromethylanthracene (2.30 g, 10.1 mmol) in toluene (30 mL) were heated at reflux (oil-bath 130 °C) with stirring using a large magnetic stirring bar. After 1 h, the resulting thick yellow suspension was diluted with more toluene (20 mL) and heated at reflux for another 2 h with efficient magnetic stirring. The reaction mixture was diluted with *t*BuOMe (50 mL), filtered, and the solids washed with *t*BuOMe. After drying at 100 °C, 4.049 g (85%) of a yellow powder was obtained, which consisted (according to ^{1}H NMR) of a 3.75:1 ratio of 9-Am-CN-Cl and CN·HCl. Purification: The solid was suspended in EtOAc (20 mL) and dissolved by the addition of sufficient $CHCl_3$ (ca. 50 mL). The organic phase was extracted twice with water (50 mL) containing aq. HCl (0.5 mL of a 2.4 M solution; 2× 1.2 mmol) and once with water (30 mL), dried with $MgSO_4$, and evaporated to a small volume. The remaining viscous liquid was diluted with toluene (50 mL) and set aside for crystallization. [If crystallization started during the evaporation, the resulting suspension was alternatively diluted with toluene (50 mL) and slowly evaporated to a small volume prior to filtration.] Filtration and washing with toluene gave yellow crystals which were dried in an oven at 100 °C to give the product as a toluene solvate QCl·1.3C_7H_8 (4.015 g, 63%). Notes: This salt is markedly less soluble in CH_2Cl_2 than in $CHCl_3$. The washing sequence with dilute aq. HCl extracts CN·HCl into the water phase (as the highly soluble CN·2HCl). The amount of aq. HCl needed for this selective extraction is estimated from the mass and composition (by ^{1}H NMR) of the crude product. Use of excess acid will lead to loss of 9-Am-CN-Cl and the formation of a yellow precipitate (probably 9-Am-CN-Cl·HCl) in the aqueous phase. Commercial cinchonine may contain several % of dihydrocinchonine; this is also quaternized and the resulting 9-Am-DHCN-Cl can be recognized by a peak at δ_H = 0.46 (t, *J* = 7.3 Hz, 3 H) ppm.

***N*-[3,5-Bis(di-*tert*-butylphenylsilyloxy)phenyl]methylcinchonidinium Bromide:** Synthesis according to the general procedure GP1 from cinchonidine and 3,5-bis(*tert*-butyldiphenylsilyloxy)benzyl bromide, yyield 60%. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.05 (s, 18 H), 1.10–1.23 (m, 2 H), 1.38–1.54 (m, 1 H), 1.79–1.93 (m, 2 H), 2.00–2.15 (m, 2 H), 2.24–2.37 (m, 1 H), 2.51–2.82 (m, 3 H), 3.34–3.46 (m, 1 H), 4.40 (d, *J* = 12.2 Hz, 1 H), 4.40–4.51 (m, 1 H), 4.90–5.03 (m, 2 H), 5.24–5.39 (m, 1 H), 5.66 (d, *J* = 12.2 Hz, 1 H), 6.44 (t, *J* = 2.1 Hz, 1 H), 6.51–6.61 (m, 2 H), 6.63 (d, *J* = 2.1 Hz, 2 H), 7.23–7.63 (m, 20 H), 7.75–7.82 (m, 2 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 8.87 (d, *J* = 4.5 Hz, 1 H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 19.4 (C), 21.6 (CH_2), 24.9 (CH_2), 26.6 (CH_3), 38.0 (CH), 51.1 (CH_2), 61.4 (CH_2), 63.6 (CH), 64.2 (CH_2), 69.4 (CH), 114.3 (CH), 117.9 (CH_2), 118.3 (CH), 120.5 (CH), 122.4 (CH), 124.6 (C), 127.4 (CH), 127.9 (CH), 129.1 (CH), 130.0 (CH), 130.1 (CH), 130.6 (CH), 132.3 (C), 135.6 (CH), 136.5 (CH), 144.8 (C), 148.0 (C), 150.2 (CH), 156.9 (C) ppm; 1 signal (C) not detected. $C_{58}H_{65}BrN_2O_3Si_2 \cdot 3H_2O$ (1028.29): calcd. C 67.75, H 6.96, N 2.72; found C 67.80, H 6.70, N 2.53.

9-Anthracenylmethylcinchonidinium Hexafluorophosphate (9-Am-CD-PF_6): *N*-(9-Anthracenylmethyl)cinchonidinium chloride (178.6 mg, 90% purity, 0.308 mmol) was dissolved in CH_2Cl_2 (10 mL) and shaken for several minutes with a solution of NH_4PF_6 (500 mg) in water (20 mL). The aqueous phase was re-extracted with CH_2Cl_2 (5 mL). This procedure (aq. NH_4PF_6, then re-extraction) was repeated twice. The organic phase was dried with $MgSO_4$, filtered, and the solvents evaporated. The residue was dissolved in CH_2Cl_2 (2 mL) and overlayed with Et_2O (6 mL) and set aside for crystallization at 4 °C. Filtration and washing with pentane gave a bright-yellow powder (149 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (m, 1 H), 1.72–2.89 (several m, 7 H), 3.44–3.48 (m, 1 H), 4.06–4.21 (m, 1 H), 4.48–4.64 (m, 1 H), 4.84–4.97 (m, 2 H), 5.19–5.34 (m, 2 H), 5.37–5.52 (m, 1 H), 5.97 (d, *J* = 13.6 Hz, 1 H), 6.71 (s, 1 H), 7.22–7.32 (m, 1 H), 7.43 (dd, *J* = 8.4, 6.7 Hz, 1 H), 7.52–7.73 (m, 4 H), 7.79 (d, *J* = 7.9 Hz, 1 H), 7.83 (d, *J* = 4.5 Hz, 1 H), 7.89 (d, *J* = 7.9 Hz, 1 H), 8.02 (dd, *J* = 8.4, 1.0 Hz, 1 H), 8.13 (d, *J* = 8.3 Hz, 1 H), 8.21 (d, *J* = 9.1 Hz, 1 H), 8.28 (s, 1 H), 8.32 (d, *J* = 9.0 Hz, 1 H), 8.86 (d, *J* = 4.5 Hz, 1 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –144 (J_{PF} = 715 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –68.4 (J_{PF} = 715 Hz) ppm. $C_{34}H_{33}F_6N_2OP \cdot 0.3H_2O$: calcd. C 64.21, H 5.32, N 4.40; found C 64.24, H 5.44, N 4.21.

General Procedure for the Catalytic Cyclization of 2′-Hydroxychalcone (1) to Flavanone (2) (GP2): Solid NaH (60% in oil; 5–10 mol-%; see note a below) was added to a degassed suspension/solution of 2′-hydroxychalcone (100 mg, 0.45 mmol) in toluene (or cymene, 3 mL; see note b below). The mixture was stirred for 5 min to give an orange suspension. The quaternary ammonium salt (2–10 mol-%) was then added in a counter-stream of argon either as a solid (single solvent reaction) or as a solution in $CHCl_3$ (0.7–1.0 mL; see note b below). The reaction mixture was stirred at room temp. for the desired time. Sampling for HPLC analysis: A small quantity of the stirred reaction mixture was removed with a Pasteur pipette (ca. 0.05 mL), diluted with *t*BuOMe (1 mL), and shaken with aq. HCl (2.4 M, 0.5 mL). The organic phase was directly used for HPLC analysis. Workup: The reaction was quenched by addition of aq. HCl (2.4 M, 5 mL) and *t*BuOMe (10 mL). The organic phase was washed with water (3× 20 mL) and dried with $MgSO_4$. After filtration and evaporation, the residue was purified by CC (SiO_2, *t*BuOMe/hexanes, 1:10). Notes: a) This small quantity of NaH is best removed with a spatula from a tared vessel on an analytical balance in a single operation. The spatula is then dipped into the reaction mixture until the NaH is completely washed into the reac-

tion mixture. The quantity of base was adapted as follows: For 5–10 mol-% of QCl, around 1.8 mg of NaH (60% in oil, 0.045 mmol, 10 mol-%) are applied, for 2–5 mol-% of QCl, around 0.8–1 mg of NaH (4–5 mol-%). The presence of a small excess of base is not problematic. b) The reaction solvents were filtered through neutral Al_2O_3 prior to use; this removes acid traces from $CHCl_3$ and peroxide traces from aromatic solvents (particularly for cymene).

Synthesis of Enantioenriched Flavanone (2): In a Schlenk vessel under argon, 2′-hydroxychalcone (**1**; 1.000 g, 4.46 mmol) and NaH (60% in oil; 10.6 mg, 0.265 mmol, 6 mol-%) were stirred in toluene (20 mL, degassed) to give a yellow solution/suspension. A solution of *N*-(9-anthracenylmethyl)cinchoninium chloride (108.3 mg, 0.208 mmol, 4.7 mol-%) in $CHCl_3$ (7 mL; filtered through Al_2O_3) was added and the reaction mixture stirred for 4 h at room temp. (22 °C). The reaction was quenched by the addition of aq. HCl (2.4 M, 4 mL) and the organic phase washed with water. After evaporation, the residue was purified by CC (SiO_2, *t*BuOMe/hexanes = 1:10) to give a colorless solid (709 mg, 71%). $[\alpha]_D = +50.2 \pm 2.0$ (c = 0.75; $CHCl_3$); lit.:[43] $[\alpha]_D = +62.8$ (c = 1 in $CHCl_3$) for a sample of (+)-(2*R*)-**2** with 95% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.90 (dd, J = 16.8, 2.9 Hz, 1 H), 3.10 (dd, J = 16.8, 13.4 Hz, 1 H), 5.50 (dd, J = 13.3, 2.9 Hz, 1 H), 7.04–7.09 (m, 2 H), 7.39–7.55 (m, 6 H), 7.94 (dd, J = 8.1, 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (CH_2), 79.6 (CH), 118.2 (CH), 120.5 (C), 121.6 (CH), 126.2 (CH), 127.1 (CH), 128.8 (CH), 128.9 (CH), 136.2 (CH), 138.8 (C), 162.0 (C), 192.0 (C) ppm. $C_{15}H_{12}O_2$ (224.26): calcd. C 80.34, H 5.39; found C 80.14, H 5.52.

(2*R*,3*S*)-3-[(*S*)-3-(2-Hydroxyphenyl)-3-oxo-1-phenylpropyl]-2-phenylchroman-4-one (Flavanone/Chalcone Conjugate 3): In a Schlenk vessel under argon, 2′-hydroxychalcone (1.003 g, 4.47 mmol) and *N*-(9-anthracenylmethyl)cinchoninium chloride (57 mg, 0.11 mmol, 2.4 mol-%) were stirred in toluene (7 mL, degassed). NaH (60% in oil; 6 mg, 0.15 mmol, 3.3 mol-%) was added to give a yellow solution/suspension. The reaction mixture was stirred for 40 h at 45 °C in an oil-bath. The reaction was quenched by the addition of aq. HCl (2.4 M, 4 mL) and *t*BuOMe (50 mL) and the organic phase was washed with water. After evaporation, the residue was purified by CC (SiO_2, *t*BuOMe/hexanes = 1:5–1:3) to give a colorless solid (378.4 mg, 38%); m.p. 140–142 °C. $[\alpha]_D = -107.8$ (c = 0.5, EtOH). HPLC (Chiralcel-OJ, *n*-heptane/*i*PrOH = 80:20, 0.8 mL/min, λ = 254 nm): 62.5% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (dd, J = 10.7, 2.5 Hz, 1 H), 3.47 (dd, J = 17.6, 4.8 Hz, 1 H), 3.58 (dd, J = 17.6, 8.9 Hz, 1 H), 3.98 (ddd, J = 10.7, 8.9, 4.8 Hz, 1 H), 5.29 (d, J = 2.3 Hz, 1 H), 6.79–7.78 (m, 18 H), 11.89 (s, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.7 (CH), 42.1 (CH_2), 56.0 (CH), 79.0 (CH), 118.1 (CH), 118.4 (CH), 118.8 (CH), 119.3 (C), 120.6 (C), 121.5 (CH), 126.3 (CH), 127.0 (CH), 127.4 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 129.0 (CH), 129.7 (CH), 136.2 (CH), 136.7 (CH), 137.7 (C), 141.1 (C), 159.3 (C), 162.1 (C), 193.4 (C), 203.3 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3451 (s), 3061 (w), 2925 (s), 1682 (s), 1284 (m) cm^{-1}. MS (EI): m/z (%) = 448 (1) $[M]^+$, 312 (16), 224 (66), 223 (100), 147 (16), 121 (64). $C_{30}H_{24}O_4$ (448.51): calcd. C 80.34, H 5.39; found C 80.21, H 5.66. Assignment of the 2*R*,1′*S* predominating configuration is based on the generation of (2*R*)-flavanone with the same catalyst.

Catalyst Recuperation as the Chloride Salt: A catalytic reaction according to GP2 was quenched and worked up as described in the general procedure. The aqueous phases were collected and washed with *t*BuOMe (2× 20 mL) and then neutralized by the addition of satd. $NaHCO_3$. An equal volume of satd. NaCl was added and the aqueous phase extracted with CH_2Cl_2 (3× 20 mL). The organic phase was washed with satd. NaCl and dried with $MgSO_4$. After evaporation, the residue was analyzed by ^{1}H NMR and, if necessary, precipitated from CH_2Cl_2/*t*BuOMe or CH_2Cl_2/pentane. Yields: 50–92%, depending on reaction scale and catalyst loading.

Catalyst Recuperation as the Hexafluorophosphate Salt: A catalytic reaction according to GP2 (2.2 mmol scale, 10 mol-% catalyst) was quenched and worked up as described above. The aqueous phase collected from workup/extraction/washing was washed with *t*BuOMe (2× 20 mL) and neutralized by the addition of satd. $NaHCO_3$. A solution of NH_4PF_6 (200 mg, 1.2 mmol) in H_2O (2 mL) was added and the turbid mixture extracted with CH_2Cl_2 (2× 10 mL). The organic phase was washed with a solution of NH_4PF_6 (200 mg in 5 mL H_2O), dried with $MgSO_4$, filtered, and the solvents evaporated to dryness. The residue was analyzed directly by ^{1}H NMR or after crystallization (precipitation) from CH_2Cl_2/*t*BuOMe; yield 82%.

Supporting Information (see footnote on the first page of this article): Detailed catalyst screening results, analytical data, procedures for chalcone synthesis, and selected NMR spectra of reaction products.

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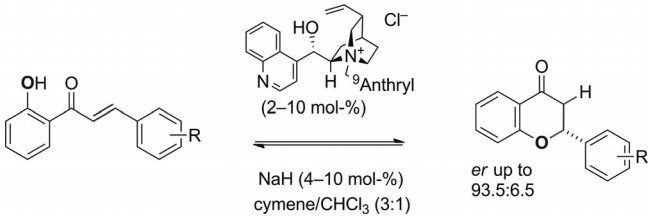

The cyclization of nonactivated 2′-hydroxychalcones to flavanones has been realized for the first time with asymmetric induction. In spite of the reversibility of the reactions, this ion-pairing catalysis reaches intrinsic enantioselectivities of up to S = 14.4 (*er* = 93.5:6.5) and illustrates the characteristic behavior of reversible asymmetric catalyses close to their equilibria.

