Organocatalysis

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# Organocatalytic Enantioselective Protonation of Silyl Enolates Mediated by Cinchona Alkaloids and a Latent Source of HF**

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The enantioselective protonation of enolates, as pioneered by Duhamel and Plaquevent,[1] and then intensively pursued by several other research groups,[2] is arguably one of the simplest and most straightforward way to access a wide range of optically active α-substituted carbonyl compounds. Of the existing strategies towards effecting this deracemization process, only a few proceed catalytically,[3] which seriously limits the synthetic utility of this methodology in modern organic synthesis. The rare examples of catalytic processes broadly fall into two main categories. The first one is based on the protonation of lithium enolates in the presence of a substoichiometric chiral source of protons and an excess of an achiral source of protons.[3a–f] A second strategy involves the catalytic protonation of silyl enolates by making use of a chiral Lewis acid catalyst to activate the proton source.[3g–l] Despite the great advances in this field, further development remains to be accomplished, in particular with regard to the design of new organocatalytic processes capable of promoting high enantioselective protonation under mild and more environmentally benign conditions. In this context, we demonstrate herein the first organocatalytic enantioselective protonation of silyl enolates by means of hydrogen fluoride salts of tertiary amines derived from cinchona alkaloids.[4]

Quaternary cinchonium fluoride and hydrogen difluoride salts were previously reported to be catalysts for a variety of asymmetric addition reactions of silicon-based nucleophiles.[5–8] Accordingly, the use of the hydrogen fluoride salts (**1**-HF) of cinchona alkaloids seems to be a very simple and attractive chiral source of protons for the enantioselective protonation of silyl enolates. By taking advantage of the high affinity of silicon for the fluoride anion, we anticipated that such salts would be very active chiral sources of protons, with the resultant specific enolate-activation mode being expected to confine the proton source and C-protonation site of the silyl enolate **2** in proximity. According to this ideal scenario, the asymmetric transfer of a proton should be facilitated through both entropic and enthalpic activations (Figure 1).

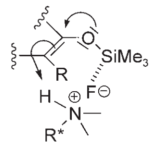
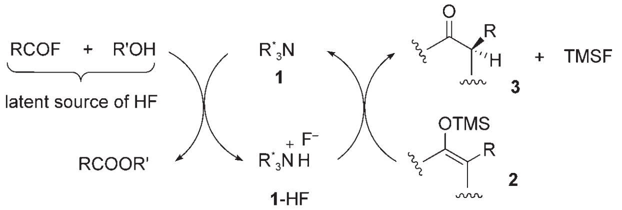


***Figure 1.*** Specific activation of silyl enolates **2** by means of a hydrogen fluoride salt of a tertiary amine (**1**-HF).

Quite surprisingly, such an event has so far been completely ignored, most likely because of the difficulties in preparing and storing dry hydrogen fluoride salts (**1**-HF). Our organocatalytic approach, which is depicted in Scheme 1, overrides this practical limitation. In the presence of a chiral tertiary amine catalyst, a latent source of HF resulting from the unusual combination of an acid fluoride and an alcohol delivers "at will" a catalytic amount of the key hydrogen fluoride salt **1**-HF. Besides providing an elegant solution to thwart the tricky preparation and storage of hydrogen fluoride salts **1**-HF, this approach offers a unique opportunity to design the first organocatalytic enantioselective protonation of silyl enolates.



***Scheme 1.*** Enantioselective protonation of silyl enolates **2** catalyzed by hydrogen fluoride salts of a chiral amine (**1**-HF) generated from a latent source of HF. TMS = trimethylsilyl.

Initial experiments were conducted in the presence of 10 mol% quinuclidine in THF at room temperature using a combination of benzoyl fluoride and ethanol as the latent source of HF, as well as silyl enolate **2a** as a standard substrate (Scheme 2). The protonation proceeded very smoothly, and afforded tetralone **3a** in quantitative yields within 3 h. A labeling experiment conducted in the presence of $[D_1]$ethanol provided tetralone $[D_1]$-**3a** with a high level of deuterium incorporation, thus illustrating that ethanol is the sole proton source responsible for the protonation of silyl enol ether **2a**. In the absence of the tertiary amine, no reaction took place, even after prolonged reaction times, thus demonstrating the full compatibility between the silyl enolate **2a** and the latent

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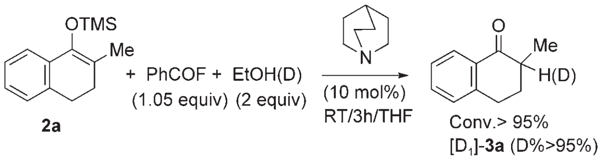
Supporting information for this article (including full experimental details) is available on the WWW under http://www.angewandte.org or from the author.

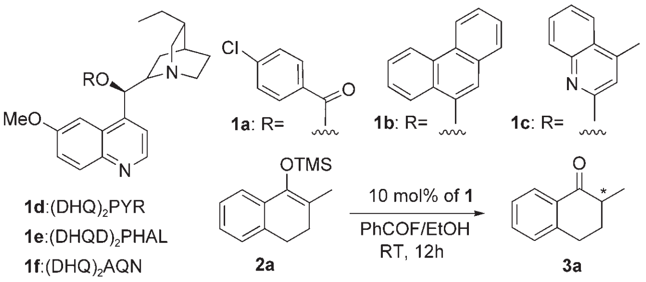


***Scheme 2.*** Organocatalytic protonation of silyl enol ether **2a** mediated by PhCOF and EtOH as a latent source of HF in the presence of quinuclidine as a catalyst.

source of HF while providing strong evidence for the proposed organocatalytic mechanism illustrated in Scheme 1.

The good catalytic performance exhibited by quinuclidine prompted us to select commercially available cinchona alkaloids **1a–f** as appealing candidates to tackle the challenging task of controlling the stereoselectivity of this organocatalytic proton transfer (Table 1). A first set of experiments were performed with 10 mol% of the cinchona alkaloids in THF at room temperature for 12 h. All the cinchona alkaloids (**1a–f**) provided tetralone **3a** in 100% conversion, but with moderate *ee* values that ranged from 20 to 42%, with the best results being obtained with biscinchona alkaloids **1d–f** (Table 1, entries 4–6). It is interesting to note that cinchona alkaloid **1c** gave rise to tetralone **3a** with opposite enantioselectivity, and indicates that the quinoline moiety is responsible for this enantio-inversion (Table 1, entry 3). On the basis of these results, $(DHQ)_2AQN$ (**1f**) was finally selected as the best candidate for further optimization of the reaction conditions.

***Table 1:*** Cinchona alkaloids screening: Enantioselective protonation of silyl enol ether **2a**.[a]

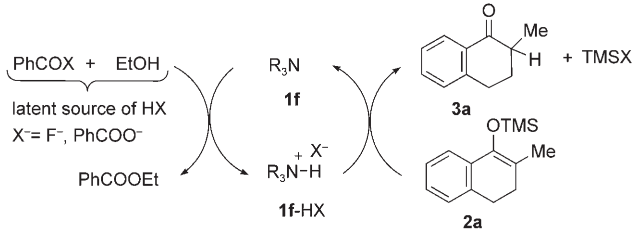


| Entry | Cinchona alkaloid **1** | Solvent | Conv. [%][b] | *ee* [%][c] | Abs. conf.[d] |
|---|---|---|---|---|---|
| 1 | **1a** | THF | 100 | 20 | *S* |
| 2 | **1b** | THF | 100 | 26 | *S* |
| 3 | **1c** | THF | 100 | 21 | *R* |
| 4 | **1d** | THF | 100 | 39 | *S* |
| 5 | **1e** | THF | 100 | 36 | *S* |
| 6 | **1f** | THF | 100 | 42 | *S* |

[a] Unless otherwise noted, the reaction was carried out in anhydrous THF (2 mL) at room temperature with silyl enol ether **2a** (1 mmol), EtOH (2.0 mmol), PhCOF (1.05 mmol), and **1** (10 mol%). [b] Determined by GC/MS. [c] Determined by HPLC, see the Supporting Information. [d] Assigned by comparison of the sign of the optical rotation with literature data. $(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2PHAL$ = hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether.

A selection of the most representative results is summarized in Table 2. We first examined the influence of the solvent on the stereochemical outcome of the reaction. While less polar solvents proved to be less effective (Table 2, entries 1–3), we were pleased to notice a considerable improvement of the enantioselectivity in more polar solvents, with values of 78% *ee* being reached in DMF and *N*-methylpyrrolidone (NMP; Table 2, entries 6 and 7). At lower temperature, the reaction rate is considerably reduced, but without any improvement in the enantioselectivity (Table 2, entry 6). This result is of particular interest with respect to the few existing catalytic processes which usually need to be conducted at −78°C to reach optimum enantioselectivity.[3] Although DMSO furnished somewhat higher *ee* values, its use was severely hampered by the formation of a side product resulting from O-benzoylation of **2a** with benzoyl fluoride (Table 2, entry 8).[9] The conclusions drawn from this set of experiments resulted in DMF being the solvent of choice for obtaining the best balance between good enantioselectivity and clean conversion into the desired tetralone **3a**. Attempts to reduce the amount of catalyst resulted in a drop in the enantioselectivity, although without any noticeable lowering of the reaction rate (Table 2, entries 9 and 10). The influence of the EtOH/PhCOF ratio was then examined: this study showed that both the reaction rate and stereochemical outcome of the protonation remained unaffected by changing this ratio from 2:1 to 1:1 (Table 2, entries 6 and 11). Some

***Table 2:*** Optimization of the reaction conditions: Enantioselective organocatalytic protonation of silyl enol ether **2a** by means of $(DHQ)_2AQN$ (**1f**).[a]



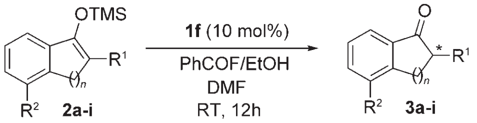
| Entry | Solvent | **1f** [%] | EtOH [equiv] | PhCOX [1.05 equiv] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | THF | 10 | 2 | PhCOF | 42 |
| 2 | toluene | 10 | 2 | PhCOF | 26 |
| 3 | $CHCl_3$ | 10 | 2 | PhCOF | 19 |
| 4 | dioxane | 10 | 2 | PhCOF | 45 |
| 5 | $CH_3CN$ | 10 | 2 | PhCOF | 68 |
| 6 | DMF | 10 | 2 | PhCOF | 78<br>78[d] |
| 7 | NMP | 10 | 2 | PhCOF | 78 |
| 8 | DMSO[c] | 10 | 2 | PhCOF | 84 |
| 9 | DMF | 5 | 2 | PhCOF | 50 |
| 10 | DMF | 2 | 2 | PhCOF | 30 |
| 11 | DMF | 10 | 1 | PhCOF | 81 |
| 12 | DMF | 10 | 4 | PhCOF | 71 |
| 13 | DMF | 10 | 2 | $(PhCO)_2O$ | 45 |

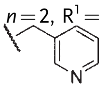
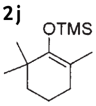
[a] Unless otherwise noted, the reaction was carried out at room temperature with silyl enol ether **2a** (1 mmol), EtOH (2 mmol), PhCOX (1.05 mmol), and **1f** (10 mol%). [b] Determined by HPLC; see the Supporting Information. [c] Some *O*-benzoylation of silyl enolate **2a** was observed, see Ref. [9]. [d] Reaction performed at −20°C.

erosion of the enantioselectivity was, however, observed when this ratio was increased to 4:1 (Table 2, entry 12).[10] Interestingly, whereas benzoyl fluoride afforded tetralone **3a** in 78 % *ee*, a serious diminution of the enantioselectivity was evident with benzoic anhydride, which furnished tetralone **3a** with only 45 % *ee* (Table 2, entries 6 and 13). The superiority of benzoyl fluoride over benzoic anhydride in regard to chiral induction illustrated that the nature of the counteranion in the catalytic active species **1f**-HX ($X^- = F^-$, $PhCOO^-$) is an important parameter in this organocatalytic approach.

With this optimized catalytic process in hand (Table 2, entry 11), the reaction scope was investigated using various silyl enolates **2b–j** (Table 3). We were pleased to find that silyl enolates **2a–j** afforded the corresponding tetralones **3a–j** with satisfactory to good enantioselectivities of up to 92 % *ee* (Table 3, entries 1–6). While still acceptable, somewhat lower enantioselectivities ranging from 64 % to 74 % *ee* were obtained in the indanone series from silyl enolates **2g–i** (Table 3, entries 7–9). The more reactive silyl enolate **2j** afforded the corresponding cyclohexanone **3j** with a rather modest 30 % *ee*, which, however, could be significantly improved by conducting the reaction at −10 °C (Table 3, entry 10). In all cases, ketones **3a–i** were isolated in excellent yields (70–98 %).

***Table 3:*** Reaction scope: Enantioselective organocatalytic protonation of various silyl enol ether **2a–i** by means of $(DHQ)_2AQN$ (**1f**).[a]



| Entry | Silyl enolates **2** | Yield [%][b] | *ee* [%][c] | Configuration[d] |
|---|---|---|---|---|
| 1 | **2a**: $n=2$, $R^1=Me$, $R^2=H$ | 88 | 81 | *S* |
| 2 | **2b**: $n=2$, $R^1=Et$, $R^2=H$ | 70 | 78 | *S* |
| 3 | **2c**: $n=2$, $R^1=Bn$, $R^2=H$ | 84 | 85 | *R* |
| 4 | **2d**: $n=2$, $R^1=$<br>$R^1=$  $R^2 = H$ | 91 | 74 | nd[f] |
| 5 | **2e**: $n=2$, $R^1=Me$,<br>$R^2=OMe$ | 98 | 81 | nd |
| 6 | **2f**: $n=2$, $R^1=Bn$,<br>$R^2=OMe$ | **86** | **92** | nd |
| 7 | **2g**: $n=1$, $R^1=Me$, $R^2=H$ | 78 | 71 | *S* |
| 8 | **2h**: $n=1$, $R^1=Et$, $R^2=H$ | 76 | 74 | *S* |
| 9 | **2i**: $n=1$, $R^1=Bn$, $R^2=H$ | 78 | 64 | nd |
| 10 | **2j**<br> OTMS | 98 | 30 | *S* |
|  |  | 95 | 58[e] |  |

[a] Unless otherwise noted, the reaction was carried out in DMF (2 mL) at room temperature for 12 h with silyl enol ether **2** (1 mmol), EtOH (1.05 mmol), PhCOF (1.05 mmol), and **1f** (10 mol%). [b] Yield of isolated product. [c] Determined by HPLC, see the Supporting Information. [d] Assigned by comparison with literature data. [e] Reaction conducted at −10 °C. [f] nd = not determined.

In summary, we have developed the first organocatalytic enantioselective protonation of silyl enolates by using readily available cinchona alkaloid catalysts and a latent source of HF. High enantioselectivities of up to 92 % were obtained under mild, neutral, and metal-free conditions. The methodology reported in this study adds to the repertoires of asymmetric catalytic protonation, organocatalyzed reactions, and of reactions that can be catalyzed by cinchona alkaloid derivatives, in particular those building on the enantioselective activation of silicon-based nucleophiles by a cinchonium fluoride ion. Further investigations of this innovative organocatalytic approach, including exploration of new chiral tertiary amines, a detailed mechanism, and expanded substrate scope, are underway.

## Experimental Section

Typical procedure for enantioselective protonation of silyl enolate **2a**: A solution of **1f** (73 mg, 0.085 mmol) in DMF (0.5 mL), EtOH (0.05 mL, 0.89 mmol), and benzoyl fluoride (110 mg, 0.89 mmol) were added successively to a solution of silyl enolate **2a** (0.197 g, 0.85 mmol) in dry DMF (1.2 mL). The solution was stirred at room temperature until all the starting material had completely disappeared (monitored by GC/MS). The solution was diluted with $Et_2O$ (10 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous solution was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with saturated brine (3 × 25 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum, the residue was purified by flash chromatography on silica gel ($Et_2O$/cyclohexane 3:97) to afford the pure tetralone **3a**, which was analyzed by chiral HPLC.

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[10] Under identical conditions as those reported in Table 3, entry 6, the use of other alcohols in place of EtOH led to diminished enantioselectivities.