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A novel class of fluorinated cinchona alkaloids as surface modifiers for the enantioselective heterogeneous hydrogenation of α-ketoesters

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ABSTRACT

Novel C-9 fluorinated cinchona alkaloid derivatives were investigated as chiral surface modifiers for the platinum-catalyzed asymmetric heterogeneous hydrogenation of α-ketoesters. Enantioselectivities approaching those observed with the parent alkaloids were obtained, and direct comparison with conformationally labile deoxycinchonidine confirmed that the C-9 fluorine atom is important for performance. In this study, the 9-fluoro derivative of cinchonidine was shown to effect the reduction of ketopantolactone to (*R*)-pantolactone in quantitative yield with good levels of enantioinduction (57% *ee*) providing preliminary validation for this novel class of surface modifiers.

1. Introduction

Cinchona alkaloid derivatives constitute a privileged class of ligands for asymmetric catalysis owing to their versatility and remarkable performance in a range of enantioselective transformations [1]; an excellent example being the catalytic hydrogenation of activated ketones on a modified platinum surface. Since its conception in the early 1970s the Orito Reaction [2] has retained its dominant position in both academic and industrial heterogeneous catalysis research [3]. This hydrogen transfer process, like countless other fundamental processes in the physical and life sciences, centres upon one unifying phenomenon: surface-based molecular recognition [4]. In the case of the Orito Reaction, the quinoline fragment of the cinchona alkaloid modifier serves as a surface anchor thus creating a chiral quinuclidine "pocket" for the subsequent hydrogen transfer step [5]. Hence, expression of chirality on a metal surface can be used to transfer molecular information, in this case by the efficient discrimination of two enantiotopic faces of a planar carbonyl group. However, despite rigorous and continued efforts from the catalysis community to broaden its generality, this transformation continues to suffer from a relatively narrow substrate scope and a strong dependence on quinine-based alkaloid modifiers [3(a–c)]. Major changes in the composition of the modifier structure have severe ramifications on catalysis, yet subtle modifications are tolerated and can be employed to induce spectacular changes in reactivity [3(a–c), 6]. Motivated by these observations, we initiated a systematic study of the catalytic performance of cinchona alkaloid derivatives in which the C-9 hydroxyl functionality had been substituted by fluorine. Recently, this laboratory reported that protonated 9-fluoro-cinchona alkaloid derivatives show a strong preference to adopt a *syn-clinal* (NCCF torsion angle) conformation in the solid state [7]; an observation that can be rationalised by invoking an $F^{\delta-}$–N^{+} electrostatic interaction (Fig. 1) [8]. We therefore sought to emulate this concept in a dynamic sense and apply it in the realm of heterogeneous catalysis.

It was envisaged that under standard hydrogenation conditions (H_2, Pt/Al_2O_3) the quinuclidine nitrogen of surface-bound β-fluoroamines (2) would be protonated, thus triggering a conformational change as a consequence of a charge-dipole effect (Fig. 2). Consequently, a rigid chiral pocket would be created that may potentially discriminate between the two planar, enantiotopic faces. Ultimately, this would generate a series of conformationally restricted surface modifiers with minimal disruption to the alkaloid core. Moreover, the low Van der Waals radius of fluorine coupled with the chemically inert nature of the C–F bond rendered such structures attractive as modifiers [9]. To the best of our knowledge only one study exists in the literature where a cin-

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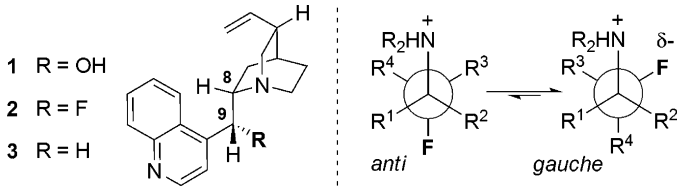


Fig. 1. Cinchonidine derivatives and the *gauche* effect of protonated β-fluoroamines.

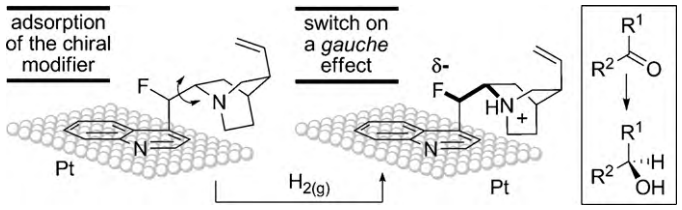


Fig. 2. Postulated model for the asymmetric hydrogenation reaction.

chona alkaloid fluorinated at the stereogenic center C-9 has been used in the platinum-catalyzed hydrogenation of ethyl pyruvate. 9-Fluoro-10,11-dihydrocinchonidine afforded rather low *ee*s in different solvents [10% *ee* (AcOH), 13% *ee* (EtOH) and 30% *ee* ($PhCH_3$)] [6e].

Herein we report a comparative study of the platinum-catalyzed asymmetric hydrogenation reactions of α-ketoesters mediated by 9-fluoro cinchona alkaloid derivatives and compare the competence of these surface modifiers with cinchonidine **1** and its conformationally labile deoxygenated analogue **3**. In order to test our hypothesis, the asymmetric hydrogenation of the industrially important feedstock ketopantolactone (KPL) 4 and the model substrate ethylpyruvate (EP) **6** were investigated on a Pt/Al_2O_3 surface varying solvent and modifier structure.

2. Experimental

2.1. Materials

In general, analytical grade reagents and solvents were used. Toluene (Fluka, >99.7%) was dried over activated molecular sieves 4 Å; acetic acid (Acros organics, 99.8%), and CD (Fluka, >98% alkaloid) were used as received. The 5 wt% Pt/Al_2O_3 catalyst was purchased from Engelhard (Engelhard 4759). The catalyst was pretreated in flowing H_2 at 400 °C for 90 min prior to use, resulting in a Pt dispersion of 0.2 as determined by TEM [10].

The synthesis and selected solid state analysis of compounds **8** and **9**, and **11**–**13** have been described in Ref. [7]. Synthesis of **10**: To a mixture of cinchonidine (589 mg, 2.0 mmol, 1.0 equiv.) in THF (4 mL) at −20 °C under an atmosphere of Ar was added diethylaminosulfur trifluoride (DAST) (367 μL, 3.0 mmol, 1.5 equiv.) dropwise. The reaction mixture was kept at −20 °C for 14 h. The resulting solution was then quenched with saturated $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH 10:1) afforded a mixture of compounds from which **10** [R_f 0.45 (CH_2Cl_2/MeOH, 10:1)] was isolated by column chromatography. The free base was independently treated with HCl in MeOH (1.25 M) until pH 1 was reached and the solvents were removed *in vacuo* to give **10** as a white powder (25 mg, 3%); m.p. 154–155 °C; $[\alpha]^{25}_D$ = +25.8 (*c* 0.21 in MeOH); ^{1}H NMR (400 MHz, MeOD) δ = 9.37 (d, *J* = 5.6 Hz, 1H; H-C2'), 8.80 (d, *J* = 8.6 Hz, 1H; H-C5'), 8.42 (d, *J* = 5.6 Hz, 1H; H-C3'), 8.39 (d, *J* = 8.6 Hz, 1H; H-C8'), 8.28 (ddd, *J* = 8.4, 7.1, 1.0 Hz, 1H; H-C7'), 8.14 (ddd, *J* = 8.4, 7.0, 0.9 Hz, 1H; H-C6'), 6.92 (dd, ^2J(H,F) = 47.5 Hz and *J* = 9.7 Hz, 1H; H-C9), 5.92 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H; H-C10), 5.25 (d, *J* = 17.2 Hz, 1H; H-C11), 5.17 (d, *J* = 10.4 Hz, 1H; H-C11), 4.45–4.58 (m, 1H; H-C8), 3.96–4.07 (m, 1H; H-C6), 3.77 (dd, *J* = 13.1, 10.7 Hz, 1H; H-C2), 3.38–3.55 (m, 2H; H-C2 and H-C6), 2.88–2.98 (m, 1H; H-C3), 2.20–2.31 (m, 1H; H-C5), 2.08–2.20 (m, 2H; H-C4 and H-

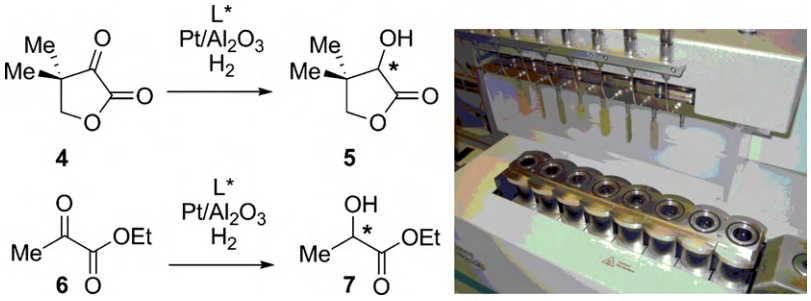


Fig. 3. Reactions investigated and the Endeavor® parallel reactor system.

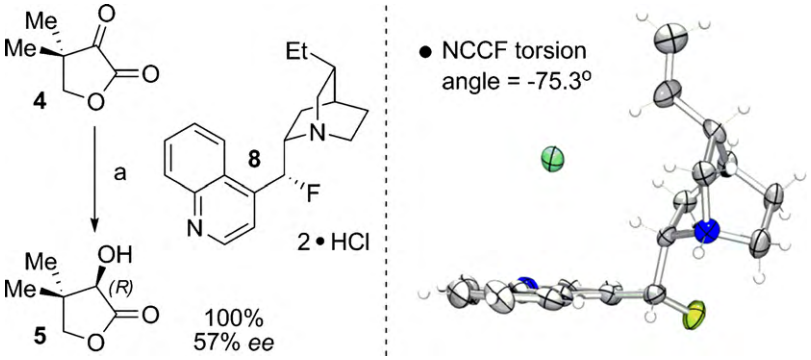
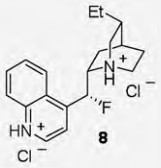
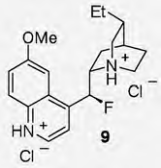
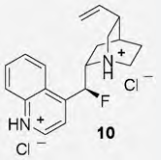
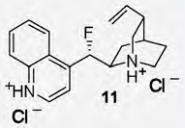
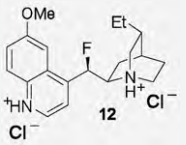
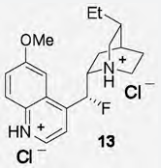


Fig. 4. Asymmetric hydrogenation of ketopantolactone using chiral modifier 8 (left); a) 42 mg Pt/Al_2O_3, 1.84 mmol ketopantolactone (KPL), 6.5 μmol modifier (HCl salt), 5 mL toluene, 20 bar H_2, 2 h, 1000 rpm. The crystal structure of **2** (right) shows the $F^{\delta-}$–N^+ *gauche* effect; one chloride anion has been omitted for clarity [7].

Table 1
Enantioselective hydrogenation of ketopantolactone on Pt/Al_2O_3 with fluorinated cinchona alkaloid modifiers[a].

Entry	Modifier	Conv. (%)	*ee*[b] (%) AcOH	*ee*[b] (%) toluene	Δ*ee* (%)
1	 **8**	100	17 (*R*)	57 (*R*)	40
2	 **9**	100	12 (*R*)	54 (*R*)	42
3	 **10**	100	8 (*R*)	52 (*R*)	44
4	 **11**	100	12 (*S*)	40 (*S*)	28
5	 **12**	100	8 (*S*)	28 (*S*)	20
6	 **13**	100	14 (*R*)	27 (*R*)	13

[a] Conditions: 42 mg Pt/Al_2O_3, 1.84 mmol ketopantolactone, 6.5 μmol modifier, 5 mL solvent, 20 bar H_2, 2 h, 1000 rpm. Modifier **8** [(3R,4S,8S,9R)-9-Fluoro-10,11-dihydrocinchonane dihydrochloride salt], **9** [(3R,4S,8S,9S)-9-Fluoro-6′-methoxy-10,11-dihydrocinchonane dihydrochloride salt], **10** [(3R,4S,8S,9S)-9-Fluoro-10,11-dihydrocinchonane dihydrochloride salt], **11** [(3R,4S,8R,9S)-9-Fluorocinchonane dihydrochloride salt], **12** [(3R,4S,8R,9R)-9-Fluoro-6′-methoxy-10,11-dihydrocinchonane dihydrochloride salt], **13** [(3R,4S,8S,9R)-9-fluoro-6′-methoxy-10,11-dihydrocinchonane dihydrochloride salt].
[b] Determined by chiral GC analysis.

C5), 1.90–2.02 (m, 1H; H-C7), 1.46–1.56 ppm (m, 1H; H-C7); ^{13}C NMR (100 MHz, MeOD) δ = 150.7 (d, ^2J(C,F) = 17.9 Hz, C4‘), 146.7 (C2‘), 140.4 (C8a‘), 138.6 (C10), 136.4 (C7‘), 132.4 (C6‘), 128.3 (d, ^3J(C,F) = 2.2 Hz, C4a‘), 126.5 (d, ^4J(C,F) = 2.5 Hz, C5‘), 123.4 (C8‘), 122.9 (d, ^3J(C,F) = 7.7 Hz, C3‘), 118.0 (C11), 89.4 (d, ^1J(C,F) = 181.2 Hz, C9), 61.1 (d, ^2J(C,F) = 19.4 Hz, C8), 54.7 (C2), 43.3 (C6), 38.1 (C3), 27.4 (C4), 24.9 (C5), 22.5 ppm (d, ^3J(C,F) = 4.3 Hz, C7); ^{19}F NMR (376 MHz, MeOD) δ = −177.9 ppm (dd, ^2J(F,H) = 47.5 Hz and ^3J(F,H) = 9.1 Hz); IR (neat): $\tilde{\nu}$ = 3358, 2929, 2465, 2052, 1985, 1663, 1604, 1546, 1498, 1464, 1381, 1234, 1110, 995, 915, 833, 765, 658, 631, 608 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{22}FN_2$ $[M-HCl_2]^+$: 297.1762; found 297.1751.

2.2. Catalytic tests

Hydrogenation of ketopantolactone (KPL) was carried out in an Endeavor® parallel pressure reactor system (Argonaut Technologies). This multiple-reactor system (Fig. 3) contains eight mechanically stirred, 15 mL stainless steel pressure, glass-lined reactors. Under standard conditions, 42 mg of catalyst, 1.84 mmol of substrate, 6.5 μmol of modifier, and 5 mL of solvent were stirred (at 1000 rpm) at room temperature and 20 bar overpressure of H_2 for 2 h. The conversions and *ee* values were determined by gas chromatography analysis of the reaction mixture, using a HP 6890 gas chromatograph and a Chirasil-DEX CB (Chrompack 7502; 25 m × 0.25 mm × 0.25 μm) capillary column. The enantiomeric excesses were calculated according to the equation *ee* % = (([*R*] − [*S*])/([*R*] + [*S*])) × 100. The reproducibility of the results has been ensured by repeating the hydrogenation reaction in the presence of each type of modifier three times under the same conditions. The error of the measurements has been calculated as the standard deviation of the hydrogen consumption experimental points collected throughout three repetitions of the hydrogenation test (0.9% in average). For some selected modifiers, corresponding batch reactor tests in a Baskerville autoclave have been performed under identical experimental conditions and the very good agreement of the data confirmed the reliability of the high-throughput methodology.

Table 2
Enantioselective hydrogenation of ketopantolactone and ethyl pyruvate on Pt/Al_2O_3 with cinchona alkaloid modifiers 1, 2 and 3[a].

Entry	Ketone	Modifier	Conv. (%)[b] AcOH	*ee*[b] (%) AcOH	Conv. (%)[b] PhMe	*ee*[b] (%) PhMe
1	KPL	1	100	67 (*R*)	100	66 (*R*)
2	EP	1	100	90 (*R*)	100	82 (*R*)
3	KPL	2	100	16 (*R*)	100	54 (*R*)
4	EP	2	100	42 (*R*)	100	60 (*R*)
5	KPL	3	100	9 (*R*)	100	45 (*R*)
6	EP	3	100	25 (*R*)	100	20 (*R*)

[a] Conditions: 42 mg Pt/Al_2O_3, 1.84 mmol substrate (ketopantolactone KPL, ethyl pyruvate EP), 6.5 μmol modifier (HCl salt), 5 mL solvent, 20 bar H_2, 2 h, 1000 rpm.
[b] Determined by chiral GC analysis.

3. Results and discussion

Studies were initiated by evaluating the hydrogenation of ketopantolactone **4** using the fluorocinchonidine derivative **8**: the single crystal X-ray structure of **2** (10,11-dehydro-**8**) had previously been determined (NCCF torsion angle = −75.3°) [7] lending support to our initial supposition. Gratifyingly, the reduction of **4** on a Pt/Al_2O_3 surface (20 bar H_2) furnished the desired (*R*)-configured product **5** in quantitative yield and with reasonable levels of enantioinduction (57% *ee*, Fig. 4).

With this preliminary validation in hand we sought to evaluate the performance of related fluorinated chiral modifiers (**9**–**13**) on the conversion of ketopantolactone **4** to pantolactone **5** (Table 1). Interestingly, the efficacy of the ligand appeared to have little dependence on the configuration at C-9 (entries 1 and 3; **8** and **10**, respectively) with both the degree and sense of enantioinduction being dictated by the C-8 centre (entries 5 and 6; **12** and **13**, respectively). Moreover, the impact of the methoxy group on the enantioselectivity appears to be case dependent. Whereas hydrogenations using the (*R*)-configured derivatives **8** and **13** (entries 1 and 6) lead to notable differences in the optical purity of the product (57% *ee* and 27% *ee* in toluene), the (*S*)-configured modifiers **9** and **10** (entries 2 and 3, respectively) are comparable ($\Delta ee = 2\%$). Yet, in this analysis, the performance of compound **9** rivals that of the lead modifier structure **8** regardless of the obvious structural variances (57% *ee* and 54% *ee* respectively; entries 1 and 2). The discrepancies in enantioinduction are tentatively attributed to subtle differences in the surface bound conformations of these modifiers; an issue that is the subject of much conjecture [5(b),11]. Furthermore, reactions using this ligand class show a clear solvent dependence that manifests itself in the enantiopurity of the product. Acetic acid has a highly detrimental effect on selectivity; an observation that is consistent with the disruption of the postulated $F^{\delta-}$–N^+ electrostatic effect that is central to our working hypothesis [12]. In extreme cases the discrepancy in enantiomeric excess can be as much as 44% (compound **10**, entry 3). However, in toluene the catalytic competence of this class of surface modifiers is encouraging and warrants further investigation.

In order to quantify the results of Table 1 ($ee_{max} = 57\%$) in the general context of heterogeneous catalysis, the hydrogenation of KPL **4** and EP **6** were performed using cinchonidine **1** and its conformationally labile derivative deoxycinchonidine **3** [13] for comparison (Table 2). Irrespective of the substrate, the parent alkaloid 1 furnished the desired products with superior levels of enantioinduction (entries 1 and 2). Removal of the C9 hydroxyl group had an adverse effect on the enantiomeric excess giving the lowest *ee*s of this screen. Gratifyingly however, the fluorinated surrogate of cinchonidine **2** gave respectable enantioselectivities in both the reaction of KPL and EP (entries 3 and 4; 54% *ee* and 60% *ee* respectively) in complete accordance with the preliminary results described in Fig. 4 for the 10,11-dihydro modifier **8** (57% *ee*). Whilst the results of this study do not surpass the limits of the current technology, this preliminary data firmly establishes that C9 fluorinated cinchona alkaloid derivates approach the enantioselectivities observed using the parent systems (66% vs 57% for the hydrogenation of ketopantolactone).

4. Conclusions

In summary, we have reported a novel class of fluorinated surface modifiers for the asymmetric heterogeneous hydrogenation of α-ketoesters. The superior levels of induction observed with the C9 fluorinated analogues, as compared with the 9-deoxy system, is rationalised by invoking a $F^{\delta-}$–N^+ *gauche* effect that is triggered upon protonation of the quinuclidine nitrogen, thus rigidifying the alkaloid scaffold. Efforts to prepare modifiers with enhanced performance based on this principle are currently on-going and will be reported in due course. Particular emphasis will be placed on investigating the surface binding mode of species such as 8 and the ensuing surface bound conformational dynamics.

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