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Organocatalytic kinetic resolution of a planar-chiral ferrocenecarbaldehyde

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ABSTRACT

The proline-catalyzed aldol reaction of racemic 2-(2′-pyrimidyl)ferrocenecarbaldehyde with acetone in DMSO at room temperature constitutes as the first example of an organocatalytic kinetic resolution of a planar-chiral compound. The selectivity factor of the kinetic resolution is 9.2, and the stereochemical outcome of the process can be easily rationalized by the standard mechanistic model of the proline-catalyzed aldol reaction.

1. Introduction

Over the past few years, much attention has been paid to the enantioselective preparation of ferrocene derivatives exhibiting planar chirality, given that ligands based on these systems have found widespread use in asymmetric catalysis.[1,2] The classical routes to such compounds rely on the diastereoselective *ortho*-metallation of the cyclopentadiene ring of suitable enantiopure ferrocenes bearing stereogenic atoms at the α-position.[3,4] More recently, the direct enantioselective sparteine-mediated *ortho*-litiation of achiral monosubstituted ferrocenes has been used in some instances to access planar-chiral ferrocenes.[5] Recent research in our laboratory has been focused on the stereocontrolled synthesis of β-ferrocenyl-β-aminoalcohols, a new class of central-chiral ferrocene derivatives, and on the study of their synthetic applications.[6] Over the course of these studies, we have developed an efficient alternative mode of access to planar-chiral ferrocenes, based on the kinetic resolution of racemic 2-substituted vinyl ferrocenes via Sharpless dihydroxylation.[7,8] However, this method presents some drawbacks when applied to systems containing nitrogenated heterocycles as substituents.[9] In an effort to overcome this limitation, we envisaged an organocatalytic kinetic resolution of racemic planar-chiral ferrocenecarbaldehydes.[10]

Since the rediscovery of proline catalysis by List, Lerner, and Barbas,[11] the aldol reaction has become one of the cornerstones of organocatalysis.[12] While the proline-catalyzed aldolization has been used for the dynamic kinetic resolution of atropisomeric amides,[13] of α-formyl-tetrahydrothipyranone derivatives,[14] of β-hydroxy aldehydes,[15] and of 2-oxo-3-arylsuccinates,[16] to the best of our knowledge there are no reports in the literature dealing with its application to the standard kinetic resolution of planar-chiral carbonyls. The proline-catalyzed intermolecular aldol reaction of ketones with aldehydes takes place by an enamine-based mechanism,[17] in which the key, rate-limiting carbon–carbon bond-forming step proceeds through the highly structured transition state shown in Figure 1. The structure of this transition state has been given wide support from both experimental[17b,18] and theoretical studies.[19]

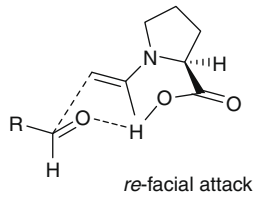

Figure 1. Transition-state model for the L-proline-catalyzed intermolecular aldol reaction.

The application of this model to the L-proline-catalyzed aldol reaction between a ketone and a 2-substituted ferrocenecarbaldehyde leads to four diastereomeric transition states, as depicted in Figure 2. Transition states I and II, with an equatorial ferrocene moiety in the 'chair-like' portion of the nine-membered ring, should in principle be more stable than transition states III and IV. On the other hand, steric interactions between the ferrocene 2-substituent and the enamine moiety should destabilize transition state I with respect to transition state II. Assuming that the priority of the formyl group is higher than that of the 2-substituent, the L-proline-catalyzed aldol reaction of a racemic, 2-substituted ferrocenecarbaldehyde should lead to the preferential reaction of the (*pS*)-enantiomer [affording an (*R*)-aldol by attack of the *re*-face of the aldehyde] and to the starting aldehyde enantioenriched in the (*pR*)-isomer.

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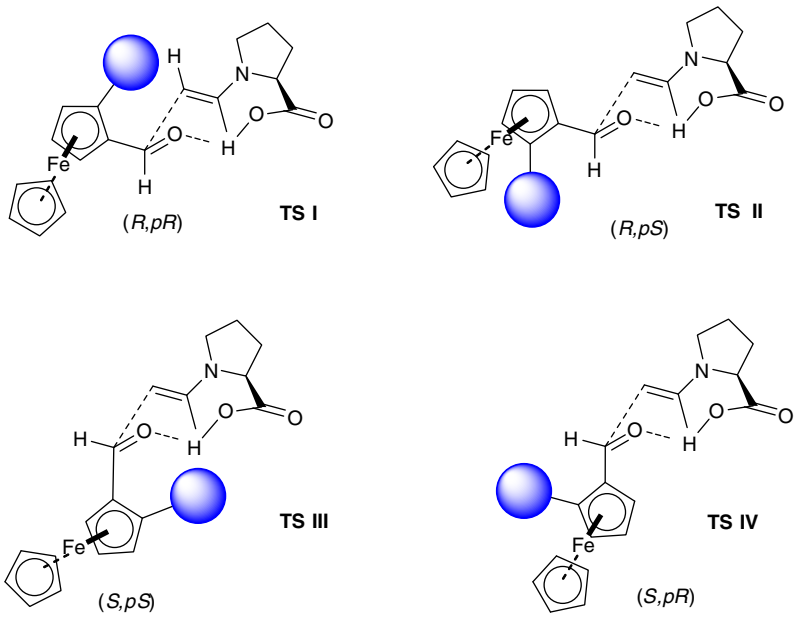
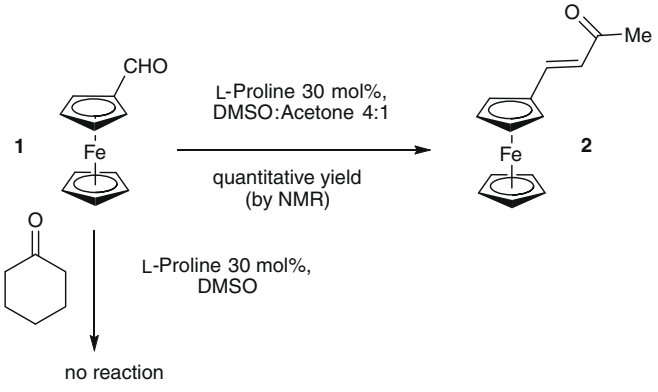


Figure 2. Diastereomeric transition states for the L-proline-catalyzed intermolecular aldol reaction for a 2-substituted ferrocenecarbaldehyde.

2. Results and discussion

In order to test the feasibility of the process, we initially performed the organocatalytic aldol reaction of ferrocenecarbaldehyde **1** by using the standard conditions reported by List et al.[11] As summarized in Scheme 1, the reaction readily took place with acetone, leading to the quantitative formation of 4-ferrocenyl-3-buten-2-one **2**;[20] when a more substituted ketone (cyclohexanone) was used instead of acetone, the starting materials were recovered unchanged after several hours at room temperature. This behavior (i.e., the easy crotonization of the initially formed aldol adduct and the sensitivity of the process to steric hindrance in the ketone component) was not surprising in the light of our previous results in the proline-catalyzed Mannich reaction of ferrocenecarbaldehyde.[21]



Scheme 1. Proline-catayzed intermolecular aldol reaction of ferrocenecarbaldehyde.

We next proceeded with the study of the enantioselective organocatalytic aldol reaction of a planar-chiral ferrocenecarbaldehyde. For this purpose, we selected 2-(2′-pyrimidyl)ferrocenecarbaldehyde **3** as a suitable substrate. This choice satisfied several requisites: (a) the steric bulk of the substituent was reasonably high, being liable to produce a significant discrimination between the diasteromeric transition states; (b) the electron-withdrawing character of the pyrimidyne moiety ensured a good reactivity of the substrate; (c) the aldehyde **3** is easily synthesized both in racemic and in enantioenriched form, its absolute configuration being readily ascertained both by polarimetry and by chiral HPLC.[22]

When the racemic aldehyde **3** was reacted with acetone in DMSO as a solvent and L-proline as a catalyst, we obtained, after 2 h at room temperature, enantioenriched starting material, together with two different optically active reaction products: the crotonized adduct **4** and aldol **5**, as shown in Scheme 2. Interestingly enough, aldol **5** was obtained in a highly diastereopure fashion, according to the NMR (^{1}H and ^{13}C) and HPLC. The enantiomeric excess, as well as the absolute configuration, of the recovered aldehyde **3** was determined after reduction to the corresponding alcohol with sodium borohydride, by HPLC analysis (Chiralcel® OD column).[22] We found (*pR*)-stereochemistry for this material by comparison with an authentic sample,[22] in accordance with the mechanistic model in Figure 2.

We then performed the reaction at different conversions, monitored by ^{1}H NMR, and after chromatographic purification of the reaction mixture we determined the yields and the enantiomeric purities of the products (Table 1).

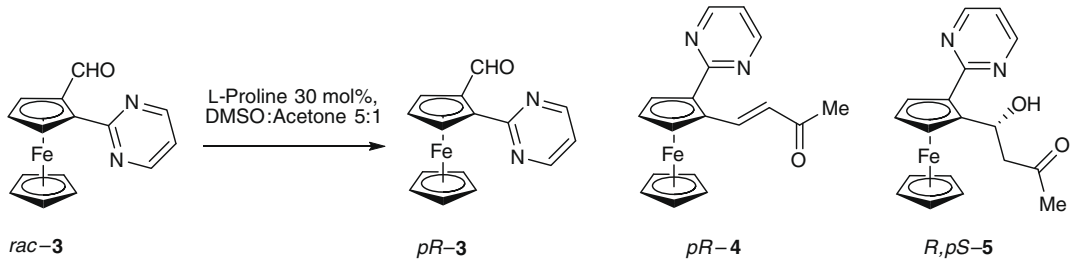
Table 1
L-Proline-catalyzed aldol reaction of racemic aldehyde **3** with acetone (Scheme 2) at different conversions

Entry	% Conversion	**3** (% Yield[a], % ee[b])	**4** (% Yield[a], % ee[b])	**5** (% Yield[a], % ee[b])
1	30	70, 33	15, 62	15, 57
2	35	65, 42	13, 55	22, 52
3	45	55, 53	24, 50	21, 48
4	56	44, 73	30, 40	26, 38
5	63	37, 78	41, 34	21, 36
6	95	5, nd[c]	65, 2	31, 8

[a] Yield of isolated product after chromatographic purification.
[b] By HPLC (Chiralcel® OD column).
[c] Not determined.

A plot of the enantiomeric excess of the recovered aldehyde **3** versus the reaction conversion allowed us to establish, without doubt, the existence of a kinetic resolution process, for which an (*S*)-selectivity factor[23] of 9.2 was calculated.

In order to confirm that aldol products **4** and **5** were mostly arising from the (*pS*)-enantiomer of **3**, an enantioenriched sample



Scheme 2. Kinetic resolution of planar–chiral ferrocenecarbaldehyde **3** by asymmetric organocatalytic aldol reaction with acetone.

of (*pR*)-**3** (85% ee, prepared independently,[22] was reacted with acetone in the presence of racemic proline as the catalyst (Scheme 3). After 17 h at room temperature, (*pS*)-**4** and (*S,pR*)-**5** were isolated in 35% and in 47% yields, respectively. Please note the change in the relative priority of the ferrocene substituents between **3** and **4** and between **4** and **5**.

The stereochemical assignment of the products arising from the kinetic resolution process was completed thanks to an X-ray diffraction analysis of **5**,[24] which unambiguously established an (R^*,pS^*) relative configuration for this compound (Fig. 3). The aldol adduct **5** thus arises from a reaction path going through the transition state II of Figure 2.

In the initial stages of the kinetic resolution, the crotonized compound **4** appears to originate from the initially formed (*S,pS*)-diastereomer of **5**. It can be seen from the data in Table 1 that both the products are obtained with a very similar enantiomeric purity and, for conversions lower than 60%, with comparable yields (entries 1–4). Only for more prolonged reaction times is the yield of **4** much higher than that of **5**, suggesting that some of the product **4** in entries 5 and 6 of Table 1 arises from the dehydration of the (*R,pS*)-isomer of **5**. These observations seem to indicate that transition states II and III in Figure 2 have comparable energies in the case of aldehyde **3**, and that the kinetic resolution is dominated by the relatively higher energies of the transition states I and IV. We hypothesize that hydrogen bonding between one of the pyrimidyne nitrogens and the carboxylic acid group can stabilize transition state III, that leads to the (*S,pS*)-aldol product (Fig. 4).

The easy dehydration of the (*S,pS*)-diastereomer could also be tentatively explained by the presence of a hydrogen bond of the protonated hydroxyl with a pyrimidine nitrogen. The formation of this hydrogen bond would be much less favorable for the (*R,pS*)-diastereomer, because it would lead to repulsive steric interactions between the acetone and the ferrocene moieties (Fig. 5).

3. Conclusions

In conclusion, we have reported the first example of an organocatalytic kinetic resolution of a planar-chiral compound, that takes place with moderate selectivity. The observed stereochemical outcome of the resolution fits reasonably well within the mechanistic model commonly accepted for proline-catalyzed aldol reactions. Mechanistic studies, synthetic applications of this transformation, and the development of other kinetic resolutions based on this concept are currently being pursued in our laboratory.[25]

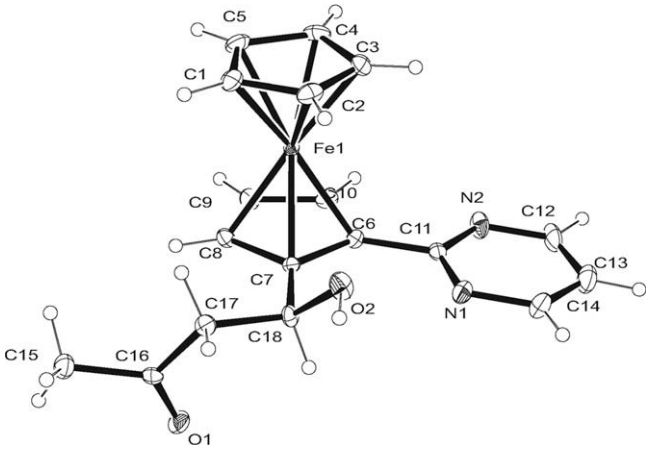
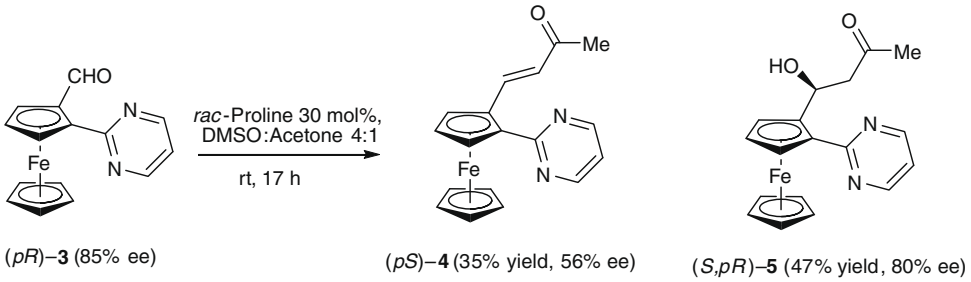


Figure 3. X-ray crystal structure of the aldol adduct **5**, showing a (R^*,pS^*) relative configuration for this compound.

4. Experimental

4.1. General experimental procedure for the organocatalyzed aldol reactions of 3[11,26]

In a small glass vial, a solution of proline (3.0 mg, 0.026 mmol), 2-(2'-pyrimidyl)ferrocenecarbaldehyde **3**[22] (25 mg, 0.086 mmol), and acetone (0.17 mL, 2.3 mmol) in DMSO (0.68 mL) was stirred at room temperature and monitored by ^{1}H NMR. Once the desired conversion was achieved, the reaction mixture was poured over brine (5 mL) and diluted with water (5 mL). The resulting solution was extracted with ethyl acetate (3 × 15 mL), and the combined organic phases were dried over anhydrous sodium sulfate. Elimina-



Scheme 3. Aldol reaction of ferrocenecarbaldehyde *pR*-**3** with acetone catalyzed by racemic proline.

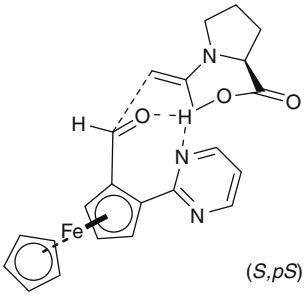


Figure 4. Proposed transition state for the formation of aldol (*S,pS*)-**5**.

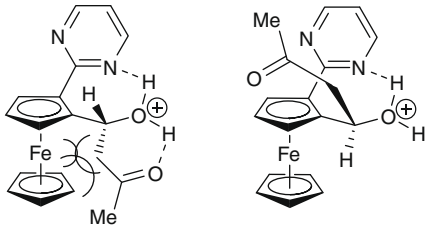


Figure 5. Mechanistic hypothesis for the preferred dehydration of aldol (*S,pS*)-**5**.

tion of the solvents under reduced pressure afforded the crude reaction mixture that was purified by column chromatography on silicagel, using hexanes–ethyl acetate mixtures of increasing polarity (from 5% to 50% ethyl acetate) led to the isolation of unreacted aldehyde **3**, of the crotonized product **4** and of the aldol adduct **5**.

4.2. Spectral and analytical data for compounds 4 and 5

4.2.1. (*pR,E*)-4-[2-(2′-Pyrimidyl)ferrocenyl]but-3-ene-2-one, 4

Orange gum; $[\alpha]_D^{20} = +648$ (*c* 0.05, $CHCl_3$); IR (NaCl film): 2924, 1700, 1653, 1588, 1506, 1457, 1397, 812, 438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 16. 4 Hz, 1H), 8.62 (d, *J* = 4.8 Hz, 2H), 7.03 (t, *J* = 5.0 Hz, 1H), 6.39 (d, *J* = 16. 4 Hz, 1H), 5.35 (m, 1H), 4.84 (m, 1H), 4.65 (m, 1H), 4.02 (s, 5H), 2.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8 (C), 169.5 (C), 156.7 (2 CH), 146.5 (CH), 126.1 (CH), 117.7 (CH), 82.3 (C), 79.3 (C), 73.6 (CH), 71.9 (CH), 71.4 (5 CH), 68.9 (CH), 29.7 (CH_3) ppm; HRMS (ESI-TOF$^+$): *m/z* calcd for $C_{18}H_{17}FeN_2O$ [M+H$^+$]: 333.0684; found: 333.0676. The enantiomeric excess (ee) was determined to be 56% by HPLC using a Chiralcel OD column (30% *i*-PrOH/hexanes, 0.7 mL/min, 254 nm): Retention time (*pR*, 9.30 min), retention time (*pS*, 26.8 min).

4.2.2. (*R,pS*)-4-[2-(2′-Pyrimidyl)ferrocenyl]4-hydroxy-2-butanone, 5

Orange solid, mp 116–117 °C; $[\alpha]_D^{20} = -28$ (*c* 0.05, $CHCl_3$); IR (KBr): 3853, 2361, 2338, 1734, 1653, 1615, 1569, 1558, 1506, 1479, 1398, 1253, 812, 668, 418, 408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.8 Hz, 2H), 7.09 (t, *J* = 4.8 Hz, 1H), 6.36 (br s, 1H), 5.32 (m, 1H), 5.20 (m, 1H), 4.46 (m, 1H), 4.41 (t, *J* = 2.4 Hz, 1H), 4.19 (s, 5H), 2.96 (m, 2H), 2.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.3 (C), 170.0 (C), 156.7 (2 CH), 117.1 (CH), 94.6 (C), 71.0 (CH), 70.6 (CH), 70.2 (5 CH), 70.2 (C), 68.8 (CH), 64.1 (CH), 50.3 (CH_2), 30.6 (CH_3) ppm; HRMS (ESI-TOF$^+$): *m/z* calcd for $C_{18}H_{19}FeN_2O_2$ [M+H$^+$]: 351.0782; found: 351.0778. The enantiomeric excess (ee) was determined to be 52% by HPLC using a Chiralcel OD column (30% *i*-PrOH/hexanes, 0.7 mL/min, 254 nm): Retention time (*S,pR*, 10.1 min), retention time (*R,pS*, 12.4 min).

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24. *X-ray diffraction analysis of* **5**: A suitable prismatic orange crystal ($0.3 \times 0.2 \times 0.2$ mm) was selected and covered with mineral oil mounted in the N_2 stream of a Bruker-Nonius Kappa CCD diffractometer equipped with Mo Kα radiation ($\lambda = 0.71073$ Å) source. The structure was solved by direct methods, and refined using full-matrix least-squares on F^2. All non hydrogen atoms were refined anisotropically and the H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 time the equivalent temperature factor of the atom to which they are linked. Crystal Data for **5**: $C_{18}H_{18}FeN_2O_2$, $M = 350{,}19$, monoclinic space group $P21/c$, $a = 8.7823(5)$, $b = 18{,}657(2)$, $c = 10.3123(16)$ Å, $\beta = 113.561(6)^\circ$, $V = 1548.8(3)$ Å^3, $Z = 4$, $d_{calcd} = 1.502$ Mg/m^3, μ(Mo Kα) = 0.985 mm^{-1}, $F(0\,0\,0) = 728$, $T = 200.0$ K, 27048 reflections measured, 3555 uniques with $I > 2\sigma(I)$ were used in all calculations. $R_1 = 0.0666$, $wR_2 = 0.1584$. CCDC 728235 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
25. Preliminary results indicate that *N,N*-diethyl-2-formylferrocenecarboxamide also experiences a kinetic resolution when submitted to the proline-catalyzed aldol reaction with acetone, albeit with a poorer selectivity factor ($S = 2.9$).
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