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Enantioselective organocatalytic Mannich reactions of ferrocenecarbaldehyde

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ABSTRACT

The first examples of highly enantioselective organocatalytic Mannich reactions of ferrocenecarbaldehyde are disclosed. The reaction is catalyzed by simple amino acids and gives access to β-arylamino-β-ferrocenylketones in high yields and with up to 99% ee.

Chiral ferrocene derivatives constitute a firmly established class of ligands for asymmetric catalysis,[1] and are finding increasing application as enantioselective probes and sensors.[2] As a consequence of that, the interest in the development of new methods for the synthesis of enantiopure ferrocenes continues unabated. However, there are still relatively few procedures available for the enantioselective generation of stereogenic centres α to ferrocene that rely on asymmetric catalysis.[3,4] In particular, and to the best of our knowledge, the application of organocatalysis for this purpose has not been described in the literature, in spite of the tremendous current interest in this field.[5]

Asymmetric Mannich reactions are amongst the most powerful carbon-carbon bond forming reactions in organic synthesis, and the resulting β-amino carbonyls are key intermediates in the preparation of biologically relevant chiral amines such as β-lactams and β-amino acids.[6] Since the discovery of enantioselectively organocatalyzed Mannich reactions by List et al. in 2000,[7a] developments in this topic have grown exponentially with the work of Barbas,[8] Córdova,[9] List[7b,10] and many others.[11] Organocatalytic Mannich reactions present a series of advantages such as high yields and enantioselectivities, cheap catalysts (natural amino acids, mainly proline) and environment-friendly conditions, to synthesize chiral amines. With this chemoinformation on mind, we envisioned that an easy, enantioselective entry to β-amino-β-ferrocenylketones (a class of compounds virtually unknown, either in racemic[12] or in scalemic form) could be provided by the organocatalyzed Mannich reaction between imines derived from ferrocenecarbaldehyde and enolizable ketones.

To our delight, we found that simple chiral amino acids **4**–**9** catalyzed the asymmetric Mannich reaction between the *N*-(*p*-methoxyphenyl)imine of ferrocenecarbaldehyde (PMP-ferrocenylimine, **1a**) and acetone (**2a**, used also as a solvent) with up to 99% ee and 93% yield (Table 1). Proline was the most efficient catalyst under our reaction conditions and mediated the formation of **3a** with high chemo- and enantioselectivity (entry 1 of Table 1). When primary amino acids are used as catalysts, the reaction rates decrease and the crotonized product **10** is formed in variable amounts (19–70% yield), probably due to the longer reaction times and to the instability of the initial Mannich adduct **3a** in acidic media.

Moreover, proline catalyzed the asymmetric formation of **3a** in other solvents such as DMF or DMSO. After optimization (Table 2), we found that the best conditions for our reaction involved the use of acetone as a solvent and of proline as a catalyst, at 4 °C. Although the presence of DMSO in the reaction medium accelerated the reaction (entry 4 in Table 2), the enantioselectivity diminished, and the formation of the crotonization product **10** was also favoured (see entry 5).

Building on these initial results, we decided to investigate the proline-catalyzed Mannich reaction between different ferrocenylimines **(1a–f)** and acetone (Table 3). We found that proline catalyzed the asymmetric formation of the corresponding ferrocenyl Mannich bases **3a**–**f** with up to 93% yield and ee values ranging from 57% to 95%.

The Mannich reactions of ferrocenylimines **1a**–**f** were highly chemo- and enantioselective, and the corresponding 4-amino-4-ferrocenylbutanones **3a**–**f** were isolated in high yields and with good to high enantiomeric purities (57–95% ee). Having

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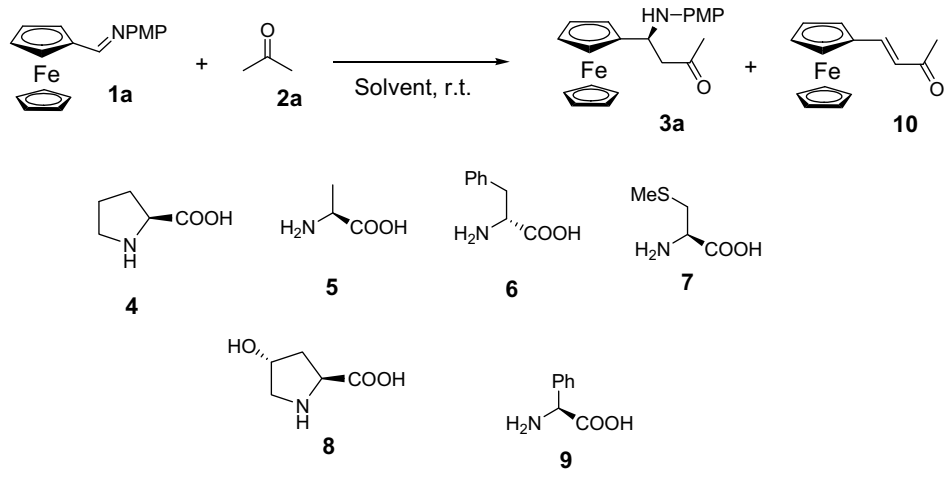
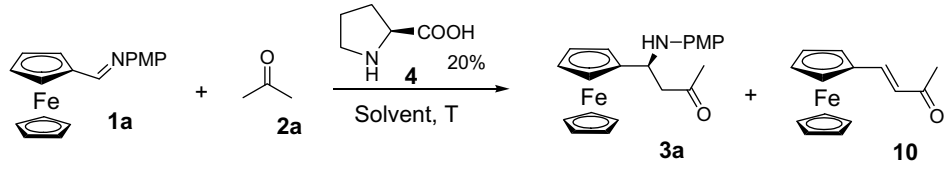
Table 1
Catalyst screening for the reaction between **1a** and **2a**[a]



Entry	Catalyst	Solvent	Time (d)	Yield **3a**[b] (%)	Yield **10**[b] (%)	ee[c] (%)
1	**4**	Acetone	2	93	0	84
2	**5**	Acetone	30	18	70	59
3	**6**	Acetone	60	19	65	−84
4	**7**	Acetone	18	65	19	62
5	**8**	Acetone	60	44	44	68
6	**9**	Acetone	21	28	50	99

[a] Experimental conditions: A mixture of **1a** (0.25 mmol) and catalyst (20 mol %) in acetone (1.0 mL) was stirred at the temperature and conditions indicated in the table.
[b] Isolated yield after column chromatography.
[c] Determined by chiral-phase HPLC analyses.

Table 2
Optimization of the Mannich reaction[a]



Entry	Temperature	Solvent	Time (d)	Yield **3**[b] (%)	Yield **10**[b] (%)	ee[c] (%)
1	rt	Acetone	2	93	0	84
2	4 °C	Acetone	3	88	0	87
3	−20 °C	Acetone	7	Traces	0	90
4	rt	Acetone/DMSO 5:1	1	88	5	77
5	rt	Acetone/DMSO 1:5	1	0	100	–
6	4 °C	Acetone/DMF 5:1	2	84	0	88
7	4 °C	Acetone/DMF 1:5	2	78	0	88

[a] Experimental conditions: A mixture of **1a** (0.25 mmol) and catalyst (20 mol %) in 1.0 mL of the solvent described in table was stirred at the temperature and conditions displayed in the table.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analyses.

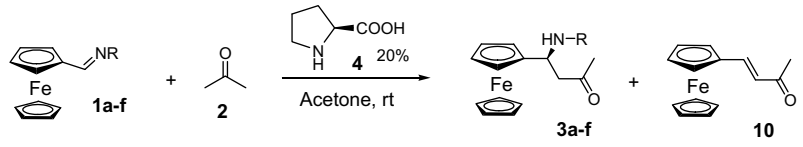
demonstrated the effectiveness of our Mannich process, we turned our attention towards the use of different ketones (Table 4).

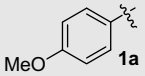
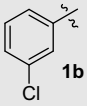
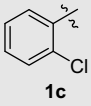
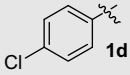
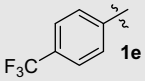
Notably, the reaction between butanone and **2b** ferrocenylimines **1a** and **1b** affords the Mannich adducts in good yields (75–79%) and regioselectivities (4:1 to 5:1), and with moderate enantioselectivities (55–78% ee). However, the process requires long reaction times and when bulkier ketones (cyclohexanone, protected dihydroxyketones, etc.) were used no reaction was observed. It appears that the steric requirements of the reaction with ferrocenylimines, due to the tridimensional nature of the ferrocenyl moiety, dictate that bulky ketones remain unreacted. This also explains the high regioselectivity favouring the product arising from the less substituted enamine intermediate observed when butanone was used (up to 5:1); in contrast, when PMP-phenylimine is reacted with butanone, a 1:1.2 regioisomeric mixture, slightly favouring the adduct arising from the most substituted enamine intermediate, is obtained.[13]

Next, we studied the possible presence of nonlinear effects in our system (Fig. 1).

As shown in Figure 1, the reaction between PMP-ferrocenylimine **1a** and acetone (at rt and with a total 0.05 M proline concentration in acetone) exhibits nonlinear effects very similar to those described by Blackmond and co-workers in the proline-catalyzed aldol reaction between acetone and *o*-chlorobenzaldehyde in DMSO solution.[14] The characteristic sigmoidal shape of the curve relating the Mannich adduct enantiomeric excess with proline enantiomeric excess indicates the existence of nonlinear effects dictated by the equilibrium solid-liquid phase behaviour of proline

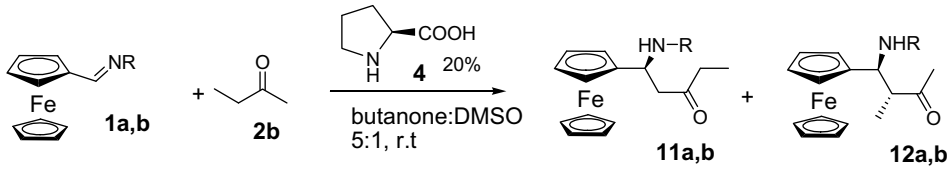
Table 3
Scope of the Mannich reaction of ferrocenylimines[a]

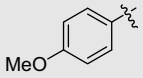
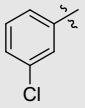


Entry	R	Product	Time (h)	Yield **3**[b] (%)	Yield **10**[b] (%)	ee[c] (%)
1		**3a**	48	93	0	84
2		**3b**	72	74	8	95
3		**3c**	72	54	7	57
4		**3d**	72	55	14	91
5		**3e**	72	38	58	87
6		**3f**	312	65	16	91

[a] Experimental conditions: A mixture of **1** (0.25 mmol) and catalyst (20 mol %) in 1.0 mL of acetone was stirred at the temperature and conditions displayed in the Table. The crude products **3a**–**f** were purified by column chromatography.
[b] Isolated yields of pure products **3a**–**f** after silica gel column chromatography.
[c] Determined by chiral-phase HPLC analyses.

Table 4
Mannich reaction with butanone **2b**[a]



Entry	R	Time	Yield **11** + **12** (%)	**11**:**12**[b]	ee[c] (%)
1		7d	75	5:1	**11a** 67% **12a**[d] n.d.
2		7d	79	4:1	**11b** 55% **12b**[d] 78%

[a] Experimental conditions: A mixture of **1a** (0.25 mmol) and catalyst (20 mol %) in 1.0 mL of a 5:1 butanone/DMSO mixture was stirred at the temperature and conditions displayed in the Table. The crude products **11** and **12** were purified by column chromatography.
[b] Regioisomer ratio determined by ^{1}H NMR of the reaction.
[c] Determined by chiral-phase HPLC analyses.
[d] Diastereomer ratio >10:1.

(i.e., preferential solubility of the enantiopure conglomerate vs the racemic form).

We have assigned an absolute (*S*) configuration to the major enantiomers obtained under L-proline catalysis in accordance with the observed stereochemical outcome of amino acid catalyzed Mannich reactions that can be rationalized with the mechanistic model proposed by List in 2002[7b,15] (see Scheme 1). This mechanistic model has been given a firm theoretical support through the studies made by Bahmanyar and Houk.[16] Although it is known that imines may undergo (*E*)/(*Z*) isomerization,[17] the (*Z*)-isomers are only present in very low equilibrium concentrations. Accordingly, in the Mannich reaction transition state, it is assumed that (*E*) configuration is adopted by imine. The *si* face of the imine is selectively attacked by the enamine to allow for protonation of its lone pair, leading to an (*S*) configuration for the newly created stereocentre. Attack by the *re* face of the imine, leading to the (*R*) enantiomer,

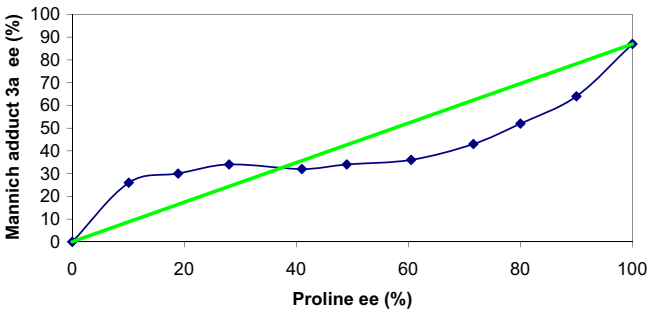
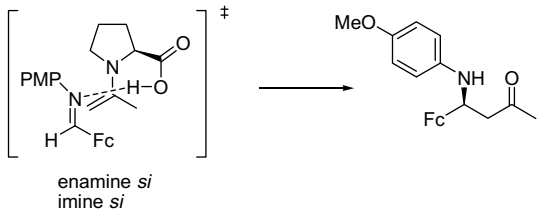


Figure 1. Nonlinear effects in the Mannich reaction between ferrocenylimine **1a** and acetone.



Scheme 1. Stereoselectivity of proline catalysis in Mannich reactions of ferrocenylimines **1a**.

would result in unfavourable steric interactions between the pyrrolidine and the ferrocenyl moieties.[18]

In summary, we report herein the first examples of a highly chemo- and enantioselective organocatalytic Mannich reaction of ferrocenylimines. The reaction is efficiently catalyzed by simple chiral amino acids, affording for the first time the corresponding β-amino-β-ferrocenylketone derivatives in high yields and enantioselectivities. Mechanistic studies and synthetic applications of this transformation, as well as the development of other enantioselective synthesis of ferrocenes based on this concept, are ongoing in our laboratory.

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18. Experimental evidence in support of this assignment has been recently obtained in our laboratory in connection with another project and will be reported in due course: Balaguer, A.-N.; Gómez-Sal, P.; Moyano, A.; Rios, R., in preparation.