Practical access to planar chiral 1,2-(α-ketotetramethylene)-ferrocene by non-enzymatic kinetic resolution and conclusive confirmation of its absolute configuration

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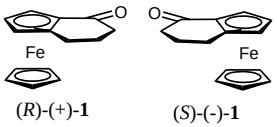
Abstract: The asymmetric transfer hydrogenation (ATH) of racemic 1,2-(α-ketotetramethylene)-ferrocene using Ru(II)/TsDPEN catalysts takes place with a high level of kinetic resolution to deliver the ketone in up to 99% ee. The X-ray crystallographic structure of a derivative of the alcohol co-product serves to confirm conclusively both the absolute configuration of 1,2-(α-ketotetramethylene)-ferrocene and the endo-reduction selectivity.

Ferrocene possesses unique structural and electronic characters, and its derivatives have found a broad range of applications in organic synthesis,[1] materials science,[1b-c,2] and medicinal chemistry.[3] The unique structure of ferrocene allows one to create chiral compounds, especially 1,2-disubstituted derivatives. Planar-chiral 1,2-disubstituted ferrocenyl derivatives have been widely used as the ligands for metal-catalysts[4] and organocatalysts.[5] Planar-chiral 1,2-disubstituted ferrocenes are usually obtained through the resolution of a racemic compound by chiral HPLC[1,5b] diastereoselective directed *ortho* metalation (DoM) induced by various chiral directing groups (in this approach, central chirality in general must be preinstalled),[6] or the enantioselective DoM of ferrocene derivatives with a stoichiometric amount of an external chiral base such as (−)-sparteine.[7] There are also some reports for the catalytic asymmetric synthesis of planar-chiral ferrocenes.[8,9] In most cases, however, the applicability of these catalytic reactions is quite limited, and elaborately designed substrates are required to attain good enantioselectivity. In spite of the recent remarkable progress in the field of asymmetric catalysis, the development of a practical method for synthesizing planar-chiral ferrocenes in a catalytic manner is still a challenging task.

Kinetic resolution (KR) as one of the most powerful tools in asymmetric catalysis has found wide applications in both academia and industry, complementing approaches such as asymmetric synthesis and classical resolution. Transition metal-mediated and more recently organocatalyzed kinetic resolution (KR) have gained popularity within the synthetic community over the last two decades due to the progress made in the development of chiral catalysts for asymmetric reactions. Many catalytic non-enzymatic procedures have been developed providing high enantioselectivity and yield. Indeed, the non-enzymatic KR of racemic compounds based on the use of a chiral catalyst is presently an area of great importance in asymmetric organic synthesis.[10,11]

1,2-(α-Ketotetramethylene)-ferrocene **1** (Figure 1), the first optically active planar-chiral 1,2-disubstituted ferrocenyl derivative,[12] is a key intermediate in the synthesis of chiral auxiliaries and ligands.[13] Enantioenriched **1** has been prepared by classical resolution,[12,13c-e,14] resolution using chiral HPLC,[15] and enzymatic kinetic resolution.[16] In our ongoing project, we need a practical method to obtain optically pure **1**. Herein, we describe a practical access to optically pure **1** by kinetic resolution through the Ru- complexes catalyzed asymmetric transfer hydrogenation.



(*R*)-(+)-**1** (*S*)-(-)-**1**

Figure 1. Structure of planar-chiral 1,2-(α-ketotetramethylene)-ferrocene **1**.

The asymmetric transfer hydrogenation (ATH) using *i*-PrOH or formic acid as hydrogen donors is another well-established method for the reduction of ketones. The [N-(tosyl)-1,2-diphenylethylendiamine]-ruthenium(II) complex, TsDPEN-Ru, developed by Noyori,[17] proved to be an efficient catalyst for the reduction of several arylalkylketones;[18] some examples have also been reported with ferrocenyl substrates.[19,20] We first tested (*S,S*)-TsDPEN-Ru as a catalyst for the KR of (±)-**1**. To our delight, (*S,S*)-TsDPEN-Ru is an efficient catalyst for the KR of (±)-**1** (Scheme 1). Thus, the reaction was carried out in the azeotropic mixture of formic acid and triethylamine (5:2 molar ratio) at 50 °C for 100 h in the presence of 1.0 mol% of (*S,S*)-TsDPEN-Ru to give (*R*)-(+)-**1** in 42% isolated yield with 98% *ee* and *endo*-alcohol (S_{Fc},S_C)-**2** in 55% yield with 79% *ee*. (*R*)-(+)-**1** and (S_{Fc},S_C)-**2** were easily separated by chromatography, and the *ee* values were determined by chiral HPLC using Daicel Chiralpak OD-H column.

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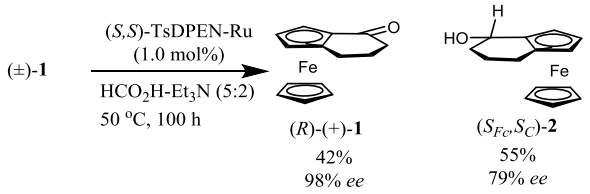
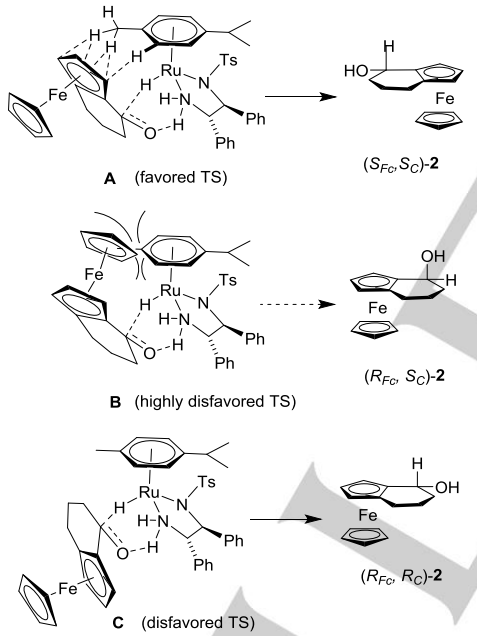
Supporting information for this article is given via a link at the end of the document, and the cif file of (R_C,S_{Fe},S_C)-**5** is available from the CCDC (CCDC 1406081).



Scheme 1. (*S,S*)-TsDPEN-Ru catalyzed KR of (±)-**1** in an azeotropic mixture of formic acid and triethylamine (5:2).

Notably, a possible *exo*-alcohol (R_{Fc},S_C)-**2** (Scheme 2) was not detected in this reaction. The high stereoselectivity of the formation of (S_{Fc},S_C)-**2** can be well explained by the plausible transition state (Scheme 2).[19] In the transition state **B**, the bottom Cp ring of ferrocene and the catalyst repel each other, so that the transition state **B** is extremely disfavored. The formation of (R_{Fc},S_C)-**2** *via* the transition state **B** is highly unlikely. The transition state **C** is also disfavored due to the lack of multiple CH/π interactions. Therefore, the main product of this reaction is (S_{Fc},S_C)-**2**, which selectively forms from (*S*)-**1** *via* the favored transition state **A**, while (*R*)-**1** is recovered unchanged in high *ee*.

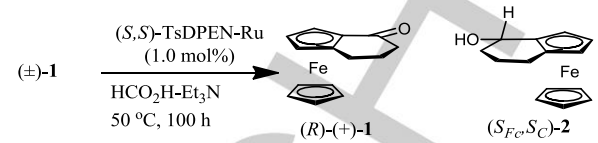


Scheme 2. Plausible transition states in the reduction of (±)-**1** using (*S,S*)-TsDPEN-Ru catalyst.

The formic acid/triethylamine ratio has a significant effect on both the ATH rate and enantioselectivity in the reduction of arylalkylketones.[21] The effects of formic acid/triethylamine molar ratio on the KR of (±)-**1** was investigated (Table 1). Interestingly, the effects of formic acid/triethylamine ratio on catalytic activity and enantioselectivity are not significant in this reaction.

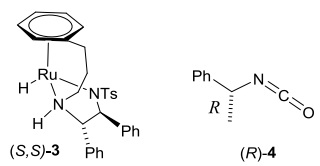
The KR of (±)-**1** has been scaled up to 10 grams using 1.0 mol% of (*S,S*)-TsDPEN-Ru as catalyst and azeotropic mixture of formic acid and triethylamine (5:2) as hydrogen donor to give (*R*)-(+)-**1** in 40% isolated yield with 99% ee and (S_{Fc},S_C)-**2** in 53% yield with 81% ee.

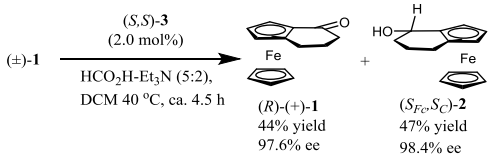
Table 1. The effects of formic acid/triethylamine ratio on the KR of (±)-**1**.



entry	HCO_2H/Et_3N	Conversion (%)	*ee* (%)	
			(*R*)-(+)-**1**	(S_{Fc},S_C)-**2**
1	5:2	57	98	79
2	4:1	56	97	79
3	3:1	55	95	81
4	2:1	59	97	75
5	1:1	58	99	77

Using the 'tethered' catalyst (*S,S*)-**3**, a derivative of (*S,S*)-TsDPEN-Ru, developed by Wills et al,[22] high activity and enantioselectivity were also observed, and almost perfect results were achieved in the KR of (±)-**1**. Thus, in the presence of 2.0 mol% of (*S,S*)-**3**, substrate (±)-**1** was reduced with a high degree of selectivity to give the ketone (*R*)-**1** in 98% *ee* and (S_{Fc},S_C)-**2** in 97% *ee* at ca. 50% conversion, after a reaction at 40 °C in an azeotropic mixture of formic acid and triethylamine (5:2) for 20h. The (*S,S*) enantiomer of catalyst **3** selectively reduced the S_{Fe} enantiomer of substrate in agreement with the results for the untethered (*S,S*)-TsDPEN-Ru. The addition of a small amount of DCM to help rapidly dissolve the ketone reduced the reaction time to ca. 4.5 h. to achieve ca 50% conversion (2.0 mol% of (*S,S*)-**3**, 40 °C). This reduced reaction time reflects the higher reactivity of catalyst **3** relative to the untethered form.[22] From this reaction, ketone (*R*)-(+)-**1** was isolated in 44% yield (i.e. 88% of theoretical) and 97.6% ee whilst alcohol (S_{Fc},S_C)-**2** was isolated in 47% yield and 98.4% ee (Scheme 3). Full details of this reaction and the chromatographic separation on silica gel are given in the supporting information. The reduction of (±)-**1** with (*R,R*)-**3** in this reaction was followed over time (Figure 2) revealing a rapid reduction of one substrate enantiomer followed by a much slower second phase of reduction as the reaction approached ca. 50% conversion, as would be predicted for a highly selective kinetic resolution of this type. In this reaction, the ee of the alcohol would be expected to decrease with extended reaction time, however the ee of the remaining ketone would be predicted to remain high. Hence following the reaction permitted the conversion to be halted at the ideal time for optimised formation of both product and remaining starting material.





Scheme 3. (*S,S*)-**3** catalyzed KR of (±)-**1** in an azeotropic mixture of formic acid and triethylamine (5:2) with added DCM.

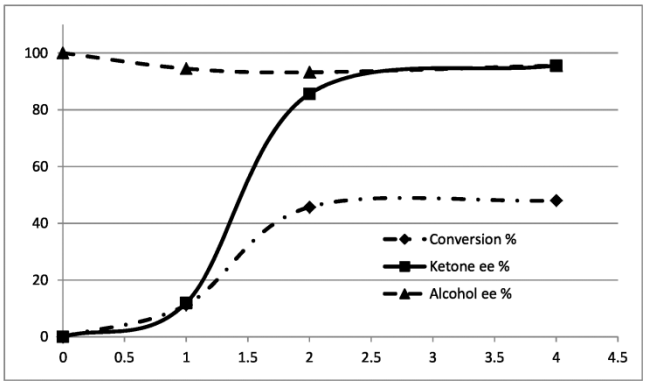
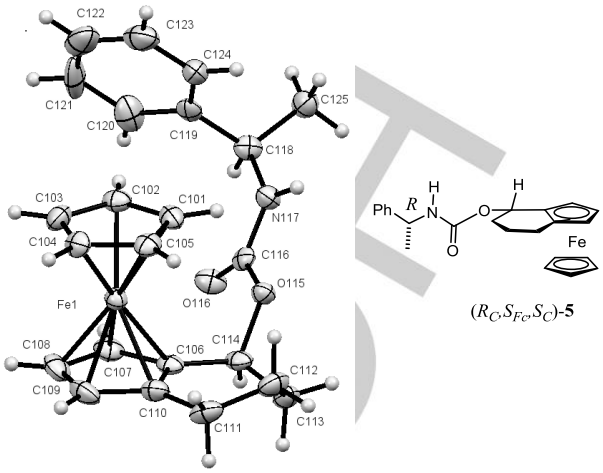


Figure 2. Conversion of (±)-**1** over time (hours) using 2 mol% (*S,S*)-**3** catalyst.

1,2-(α-Ketotetramethylene)ferrocene **1** occupies a key position in the determination of the absolute configurations of ferrocene derivatives.[23] The relative and absolute configurations of **1** and reduction product **2** had been elegantly established by Schlögl using chemical method, Horeau's method, IR methods, Optical Rotatory Dispersion and Circular Dichroism, *etc*.[23] In order to prove conclusively the absolute and relative configuration of the reduction product in this reaction, the alcohol (S_{Fc},S_C)-**2** formed by reduction of ketone (±)-**1** using 2 mol% catalyst (*S,S*)-**3** in the earlier reaction was isolated and treated with the isocyanate derivatising agent (*R*)-**4**.[24] X-ray crystallographic analysis of the adduct (R_C,S_{Fe},S_C)-**5** (Figure 3) confirmed the endo configuration of the precursor alcohol and that the alcohol **2** was of *S*-configuration at the sp^3 centre and *S* configuration at the chiral plane, as predicted. As far as we are aware this represents the first conclusive crystallographic evidence of the relative and absolute reduction selectivity of ferrocenyl ketone (±)-**1**.



(R_C,S_{Fe},S_C)-**5**

Figure 3. Solid state structure with atom labeling of one of the crystallographically independent molecules in the asymmetric unit of (R_C,S_{Fe},S_C)-**5** (CCDC 1406081). Thermal ellipsoids are drawn at 50% probability.

Experimental Section

An oven-dried Schlenk tube was charged with (±)-**1** (0.5 g, 1.97 mmol) and (*S,S*)-TsDPEN-RuCl(*p*-cymene) (12.5 mg,19.7 umol) under argon. A degassed mixture of triethylamine and formic acid with desired ratio (10 ml, corresponding to Table 1) was then added. The mixture was stirred at 50 ° C, and a degassed mixture of triethylamine and formic acid with desired ratio (5 mL, corresponding to Table 1) was added in intervals of 24 h. After 100 h, the mixture was transferred to a separating funnel and partitioned with iced water and CH_2Cl_2. The organic phase was separated, washed with water, and dried over anhydrous Na_2SO_4. Volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc/PE=1/30) to give (*R*)-(+)-**1** as red crystals and (S_{Fc},S_C)-**2** as a yellow oil. The procedure for reduction using (*S,*S)-**3** and further experimental details are given in the Supporting Information.

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Keywords: Ferrocene • asymmetric • transfer • hydrogenation • TsDPEN • absolute configuration

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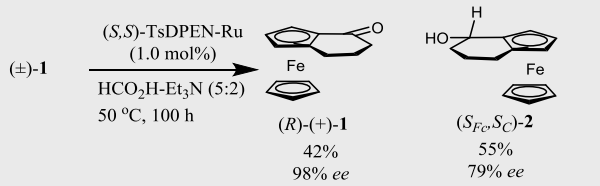

The absolute and relative configuration of the reduction was confirmed by X-ray crystallographic analysis of a derivative of the alcohol.

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Practical access to planar chiral 1,2-(α-ketotetramethylene)-ferrocene by non-enzymic kinetic resolution and conclusive confirmation of its absolute configuration.