

Asymmetric synthesis of planar–chiral ferrocenes by Mo- or Ru-catalyzed enantioselective metathesis*

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Abstract: Kinetic resolution of planar–chiral 1,1'-diallylferrocene derivatives was realized by Mo- or Ru-catalyzed asymmetric ring-closing metathesis (RCM). The Mo catalyst showed much better performance than the Ru catalyst in the present reactions, and nearly perfect resolution of the racemic ferrocenes was achieved. This is the first example of highly enantioselective metal-catalyzed methods of preparing optically active planar–chiral metallocenes.

Keywords: asymmetric synthesis; planar–chiral; ferrocene; kinetic resolution; metathesis; enantioselective; diastereoselective; molybdenum; ruthenium.

INTRODUCTION

Planar–chiral ferrocenes are important chiral scaffolds in organic and organometallic chemistry [1], however, their preparation in optically active form is still a challenging problem. Most nonracemic planar–chiral ferrocenes were obtained either by diastereoselective metalation utilizing chiral *ortho*-directing groups [2] or by optical resolution of racemic compounds. Enantioselective direct *ortho*-lithiation of planar–prochiral ferrocenes by chirally modified alkyllithium reagents has also showed fair success [3]. To the best of our knowledge, only two examples of nonenzymatic *catalytic* asymmetric induction of ferrocenyl planar chirality were reported so far with modest enantioselectivity [4,5].

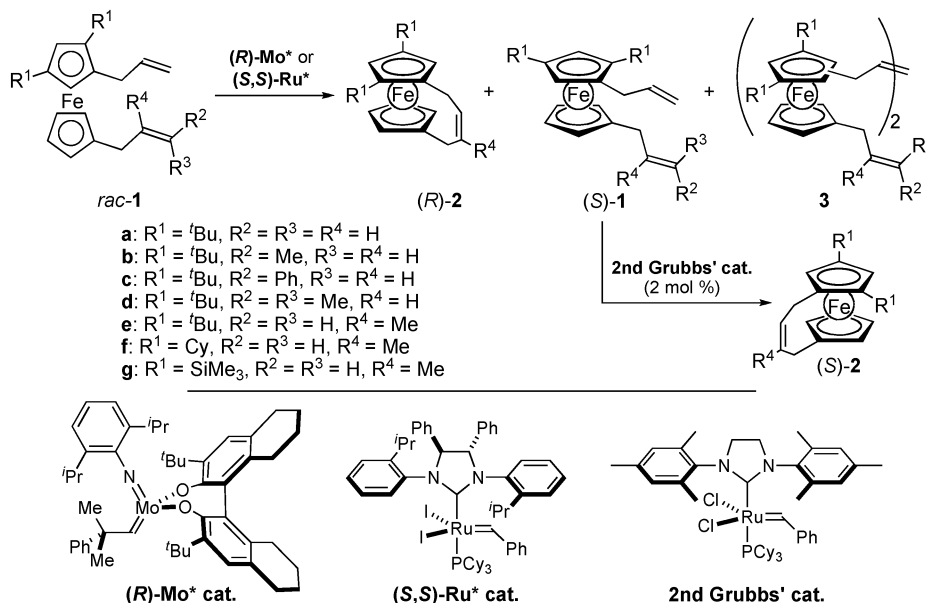
Richards [6] and we [7] recently reported preparation of [4]ferrocenophanes by the Ru- or Mo-catalyzed metathesis reactions of 1,1'-diallylferrocenes. In certain cases, the metathesis reactions proceeded in a diastereoselective fashion and either *meso*- or *dl*-bridged metallocenes could be selectively prepared with a proper choice of reaction conditions and the metathesis catalysts [6,7a]. Now, we have succeeded in developing this protocol into enantioselective kinetic resolution of racemic planar–chiral 1,1'-diallylferrocene derivatives [8]. The reaction proceeds very efficiently by the chiral Mo-metathesis catalyst to afford planar–chiral ferrocenes in high yields with excellent enantiomeric enrichment [9].

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ENANTIOSELECTIVE KINETIC RESOLUTION OF C_1 -SYMMETRIC PLANAR-CHIRAL FERROCENES

Firstly, enantioselective kinetic resolution of C_1 -symmetric planar-chiral ferrocenes was examined. The C_1 -symmetric substrates for this study (*rac*-**1**) possess an unsymmetrically substituted η^5 -(C_5H_2 -1-allyl-2,4- R^1_2) ligand and a monosubstituted η^5 -cyclopentadienyl ligand with an allylic side chain. Readily available chiral metal-carbene species (*R*)-**Mo*** [10] and (*S,S*)-**Ru*** [11] were examined as asymmetric metathesis catalysts (Scheme 1).



Scheme 1 Enantioselective kinetic resolution of planar-chiral ferrocenes by Mo- or Ru-catalyzed ARCM.

The selectivity in the asymmetric ring-closing metathesis (ARCM) kinetic resolution was strongly dependent on the structure of the allylic group in the achiral cyclopentadienyl moiety. When **1a** was treated with the Mo catalyst (5 mol %) for 15 min in benzene at 23 °C, the corresponding ferrocenophane **2a** was obtained in 73 % yield and the unreacted **1a** was recovered in 26 %. However, the selectivity of the reaction was very low: **2a** was nearly racemic, and the recovered **1a** was only 2 % ee (Table 1, entry 1). The ARCM reaction of the ferrocene **1b** showed slightly better enantioselectivity, and the ferrocenophane **2a** of 12 % ee was obtained in 44 % yield (entry 2). A reaction of **1c** with initial concentration of 0.01 mol/L at 80 °C afforded **2a** (66 % ee, 26 % yield) and **1c** (29 % ee, 53 % yield). The k_{rel} value for this reaction was estimated to be 6.4 (entry 3). A reaction of **1d** produced the dimer **3d** in 38 % as a sole metathesis product, and **2a** was not detected (entry 4). The ee of the recovered **1d** was only 7 %.

It was found that the enantioselectivity was dramatically improved by introducing an η^5 -(C_5H_4 -methallyl) moiety in the ferrocene substrates. The ARCM reaction of **1e** at 23 °C (initial concentration of **1e** = 0.1 mol/L) proceeded with excellent enantioselectivity. The bridged-ferrocene **2e** was obtained in a nearly enantiomerically pure form (>99.5 % ee) in 23 % yield and the unreacted **1e** was recovered in 30 % yield with 78 % ee. The k_{rel} value for this reaction was >500 (entry 5). Unfortunately, however, 47 % of the substrate was converted to the dimer **3e**. Dimerization was minimized in the reaction under diluted conditions. A reaction of **1e** at 50 °C with initial concentration of 0.005 mol/L affords **2e** of 96 % ee in 47 % yield, and the unreacted **1e** of 95 % ee was recovered in 46 % ($k_{rel} = 183$;

entry 6). As shown in entries 7 and 8, similarly high levels of enantioselectivity and reaction efficiency were obtained for kinetic resolution of **1f** ($k_{\text{rel}} = 26$) and **1g** ($k_{\text{rel}} = 165$) also under the optimized conditions.

The Ru metathesis catalyst (*S,S*)-**Ru**^{*}, which was generated in situ from the corresponding dichlororuthenium complex and NaI [11], was also effective for the kinetic resolution of **1**, but was less enantioselective than (*R*)-**Mo**^{*} (entries 9–11). As observed in the Mo-catalyzed reactions, almost no enantioselectivity was seen in the Ru-catalyzed reaction of the diallyl-substrate **1a** (entry 9). On the other hand, moderate asymmetric induction was detected in the reactions of the substrates with a methallyl group, and the k_{rel} values for the reactions with **1e** and **1g** were estimated to be 5.9 and 4.1, respectively (entries 10 and 11). The formation of the metathesized dimer **3** was scarcely observed in the Ru-catalyzed reactions, and thus the reactions could be conducted under nondiluted conditions.

Table 1 Mo- or Ru-catalyzed enantioselective kinetic resolution of planar-chiral ferrocenes.^a

Entry	Substrate 1 (mol/L) ^b	Cat. (%)	Conditions	Yields (%) ^c 2/1/3	% ee 2/1 ^d	k_{rel} ^e
1	1a (0.1)	(<i>R</i>)- Mo [*] (5)	23 °C, 15 min	73/26/trace	<1/2	1.03
2	1b (0.1)	(<i>R</i>)- Mo [*] (5)	23 °C, 1 h	44/49/trace	12/9	1.4
3	1c (0.01)	(<i>R</i>)- Mo [*] (10)	80 °C, 24 h	26/53/16	66/29	6.4
4	1d (0.01)	(<i>R</i>)- Mo [*] (5)	70 °C, 24 h	0/54/38	—/7	—
5	1e (0.1)	(<i>R</i>)- Mo [*] (5)	23 °C, 4 h	23/30/47	>99.5/78	>500
6	1e (0.005)	(<i>R</i>)- Mo [*] (10)	50 °C, 24 h	46/47/3	96/95	183
7	1f (0.005)	(<i>R</i>)- Mo [*] (10)	50 °C, 24 h	43/41/12	82/83	26
8	1g (0.005)	(<i>R</i>)- Mo [*] (10)	50 °C, 24 h	45/52/trace	97/81	165
9	1a (0.1)	(<i>S,S</i>)- Ru [*] (5)	23 °C, 20 min	25/70/trace	1/<1	<1.01
10	1e (0.1)	(<i>S,S</i>)- Ru [*] (5)	23 °C, 2 h	10/79/trace	68/12	5.9
11	1g (0.1)	(<i>S,S</i>)- Ru [*] (5)	23 °C, 2 h	8/85/trace	58/9	4.1

^aThe reactions were carried out in benzene (with **Mo**^{*}) or in THF (with **Ru**^{*}).

^bInitial concentration of the substrate.

^cIsolated yields of the products (**2** and **3**) and the recovered substrate (**1**).

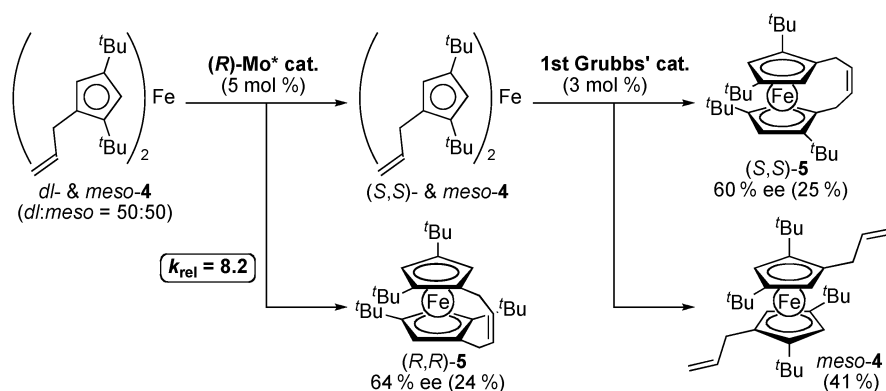
^dEnantiomeric excess of the recovered **1** was determined after converting them into **2** by a reaction with the second-generation Grubbs' catalyst.

^eCalculated based on a first-order equation [12].

ENANTIO- AND DIASTEREOSELECTIVE KINETIC RESOLUTION OF ACHIRAL C₅- AND PLANAR-CHIRAL C₂-SYMMETRIC FERROCENES

In the precedented paper, we described the Ru-catalyzed diastereoselective kinetic resolution of the *meso*- and the *dl*-isomers in bis(η^5 -1-allyl-2,4-di-*tert*-butylcyclopentadienyl)iron(II) (**4**) [7a]. Because of their close similarity, the two isomers in **4** were hardly separable by standard methods, such as chromatography (including HPLC, GPC, or GC with a capillary column), recrystallization, or distillation. In the presence of the first-generation Grubbs' catalyst RuCl₂(=CHPh)(PCy₃)₂, however, only the *dl*-isomer underwent the RCM and the two isomers were *chemically* separated with nearly perfect selectivity.

Extension of the chemical separation method into the enantio- and diastereoselective kinetic resolution of the three stereoisomers in **4**, namely, (*R,R*)-**4**, (*S,S*)-**4**, and (*R,S*)-**4** (*meso*-**4**), was examined and the results are illustrated in Scheme 2. It was found that (*R*)-**Mo**^{*} catalyst (5 mol %) preferentially cyclized (*R,R*)-**4** in benzene at 60 °C, and the bridged ferrocene (*R,R*)-**5** of 64 % ee was obtained in 24 % yield. After the Mo-catalyzed reaction, the cyclized *meso*-isomer (*meso*-**5**) was not detected in the solution. From the reaction mixture, the cyclized (*R,R*)-**5** and the unreacted **4** were easily separated by preparative GPC. The separated isomeric mixture of **4**, which mainly contained (*S,S*)-**4** and *meso*-**4**, was reacted with the first-generation Grubbs' catalyst (3 mol %) under the conditions reported previously [7a], and (*S,S*)-**4** was selectively cyclized to give (*S,S*)-**5** of 60 % ee in 25 % yield and the unreacted



Scheme 2 Enantio- and diastereoselective kinetic resolution of a mixture of *dl*- and *meso*-4.

meso-4 was recovered in 41 % as a single isomer. The k_{rel} value for the first step in Scheme 2 was estimated to be 8.2 [12].

In summary, we have developed an effective method for kinetic resolution of the racemic planar-chiral C_1 - and C_2 -symmetric ferrocene derivatives via Mo- or Ru-catalyzed enantioselective RCM.

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