Communications

Kinetic Resolution of Planar-Chiral Ferrocenes by Molybdenum-Catalyzed Enantioselective Metathesis

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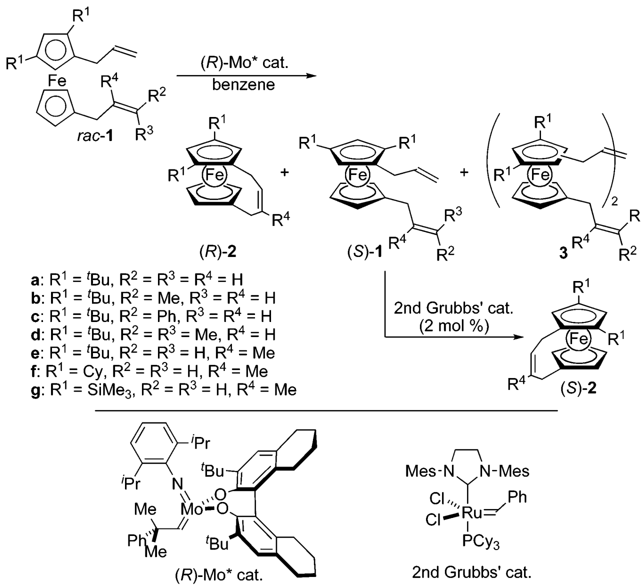
Summary: Kinetic resolution of planar-chiral 1,1′-diallylferrocene derivatives was realized by molybdenum-catalyzed asymmetric ring-closing metathesis with excellent enantioselectivity. This is the first example of highly enantioselective metal-catalyzed methods of preparing optically active planar-chiral metallocenes.

Planar-chiral ferrocenes are important chiral scaffolds in organic and organometallic chemistry.[1] Although such ferrocenes have been used in a variety of asymmetric reactions as ligands[2] or catalysts,[3] 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[4] or by optical resolution of racemic compounds. Enantioselective lithiation of prochiral ferrocenes by a stoichiometric chiral base has also shown fair success.[5] On the other hand, examples of *catalytic* asymmetric synthesis of planar-chiral ferrocene derivatives are extremely rare.[6−8] Apart from several reports on enzymatic resolution of racemic ferrocenes,[6] to the best of our knowledge, only two examples of catalytic induction of ferrocenyl planar chirality was reported so far with modest enantioselectivity.[7,8]

Scheme 1. ARCM Kinetic Resolution of Planar-Chiral Ferrocenes and Metathesis Catalysts.



Richards[9] and we[10] recently reported preparation of [4]-ferrocenophanes by Ru- or Mo-catalyzed metathesis reaction of 1,1′-diallylferrocenes.[11] Here, we report kinetic resolution of planar-chiral 1,1′-diallylferrocene derivatives by Mo-catalyzed asymmetric ring-closing metathesis (ARCM).[12] The reaction

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Table 1. Molybdenum-Catalyzed Asymmetric RCM Kinetic Resolution of Planar-Chiral Ferrocenes[a]

entry	substrate **1** (mol/L)[b]	Mo* cat. (%)	conditions	yields (%)[c] **2**/**1**/**3**	% ee **2**/**1**[d]	k_{rel}[e]
1	**1a** (0.1)	5	23 °C, 15 min	73/26/trace	<1/2	1.03
2	**1b** (0.1)	5	23 °C, 1 h	44/49/trace	12/9	1.4
3	**1c** (0.01)	10	80 °C, 24 h	26/53/16	66/29	6.4
4	**1d** (0.01)	5	70 °C, 24 h	0/54/38	–/7	
5	**1e** (0.1)	5	23 °C, 4 h	23/30/47	>99.5/78	>500
6	**1e** (0.005)	10	50 °C, 24 h	46/47/3	96/95	183
7	**1f** (0.005)	10	50 °C, 24 h	43/41/12	82/83	26
8	**1g** (0.005)	10	50 °C, 24 h	45/52/trace	97/81	165

[a] The reaction was carried out in benzene in the presence of the molybdenum catalyst (*R*)-Mo*. [b]Initial concentration of the substrate. [c]Isolated yields of the products (**2** and **3**) and the recovered substrate (**1**). [d]Enantiomeric excess of the recovered **1** was determined after converting them into **2** by a reaction with the second-generation Grubbs' catalyst. [e]Calculated based on a first-order equation (ref 14).

proceeds very efficiently to afford planar-chiral ferrocenes in high yield with excellent enantiomeric enrichment.

The ferrocene substrates for this study (*rac*-**1**, see Scheme 1) possess a trisubstituted η^5-(C_5H_2-1-allyl-2,4-R^1_2) ligand, which constructs a planar-chiral environment in the ferrocenes, and a monosubstituted η^5-cyclopentadienyl ligand with an allylic side chain. A readily available chiral molybdenum species (*R*)-Mo* (Scheme 1)[13] was chosen as an asymmetric metathesis catalyst.

Enantioselectivity in the ARCM kinetic resolution was strongly dependent on the structure of the allylic group in the monosubstituted cyclopentadienyl moiety. Treatment of **1a** with the Mo* catalyst (5 mol %) for 15 min in benzene at 23 °C yielded the corresponding ferrocenophane **2a** in 73%, and the unreacted **1a** was recovered in 26%. To our disappointment, however, the selectivity of the reaction was very low: **2a** was nearly racemic (<1% ee) and the recovered **1a** was only 2% ee (Table 1, entry 1). The RCM reaction of the ferrocene **1b**, which was with η^5-(C_5H_4-crotyl), showed slightly better enantioselectivity and the ferrocenophane **2a** of 12% ee was obtained in 44% yield (entry 2). Introduction of an η^5-(C_5H_4-cinnamyl) ligand in **1c** further improved enantioselectivity of the ARCM, although diluted conditions were required to suppress formation of metathesized homodimer **3** (as a mixture of stereoisomers). A reaction of **1c** at 80 °C (initial concentration of **1c** = 0.01 mol/L) gave **2a** (66% ee, 26% yield) and recovered **1c** (29% ee, 53%). The k_{rel} value ([rate of fast-reacting enantiomer]/[rate of slow-reacting enantiomer]) for this reaction was estimated to be 6.4[14] (entry 3). A reaction of **1d**, which was with η^5-$C_5H_4CH_2CH{=}CMe_2$, produced the dimer **3d** in 38% as a sole metathesis product and **2a** was not detected (entry 4). The recovered **1d** was only 7% ee; that is, kinetic resolution of **1d** at the dimerization was not very efficient.

It was found that the enantioselectivity was dramatically improved by introducing a η^5-(C_5H_4-methallyl) moiety in the ferrocene substrates. The RCM 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 nearly enantiomerically pure form (>99.5% ee) in 23% yield, and unreacted **1e** of 78% ee was recovered in 30% yield. The k_{rel} for this reaction was >500[14] (entry 5). Unfortunately, however, 47% of the substrate was converted to dimer **3e**. The dimer **3e**, which could be converted to the ferrocenophane **2e** by treatment with the second-generation Grubbs catalyst, was only 7% ee; that is, the dimer formation occurred with negligible enantioselectivity. As before, dimerization was minimized in the reaction under diluted conditions. A reaction of **1e** with initial concentration of 0.005 mol/L affords **2e** of 96% ee in 47% yield, and unreacted **1e** of 95% ee was recovered in 46% (entry 6). Although somewhat higher temperature (50 °C) was required to gain a reasonable reaction rate under the high-dilution conditions, enantioselectivity of the reaction was still excellent (k_{rel} = 183) and nearly perfect kinetic resolution of *rac*-**1e** was achieved. As shown in entries 7 and 8, similarly high levels of enantioselectivity and reaction efficiency were observed for kinetic resolution of **1f** (k_{rel} = 26) and **1g** (k_{rel} = 165) also under the optimized conditions.

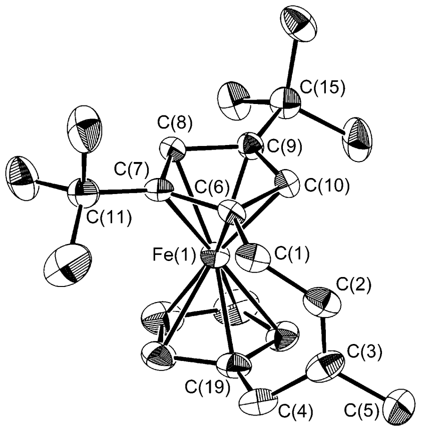

Figure 1. ORTEP drawing of (+)-(*R*)-**2e** with 40% thermal ellipsoids. All hydrogen atoms are omitted for clarity.

Single-crystal X-ray crystallography revealed that absolute configuration of the ARCM product **2e** (Table 1, entry 5; >99.5% ee), which was dextrorotatory ($[\alpha]^{30}_D$ +22 (*c* 0.50 in $CHCl_3$)), was *R*, as shown in Figure 1. The configurations of other ARCM products were assigned by analogy.

For highly enantioselective kinetic resolution of *rac*-**1**, an allyl group in a trisubstituted cyclopentadienyl needs to be more reactive than an allylic substituent in a monosubstituted cyclopentadienyl. When the (*R*)-Mo* species approaches *rac*-**1a**, initial metathesis occurs with the less crowded C_5H_4-allyl moiety preferentially to form a diastereomeric mixture of (R_a,R_p)- and (R_a,S_p)-**4** ("R_a" represents absolute configuration of the axially chiral biaryl moiety in Mo*) and formation of **5** is unfavorable (Scheme 2, top). Whereas the allyl group in C_5H_4-allyl is remote from the planar-chiral η^5-$C_5H_2{}^tBu_2$(allyl) moiety, initial me-

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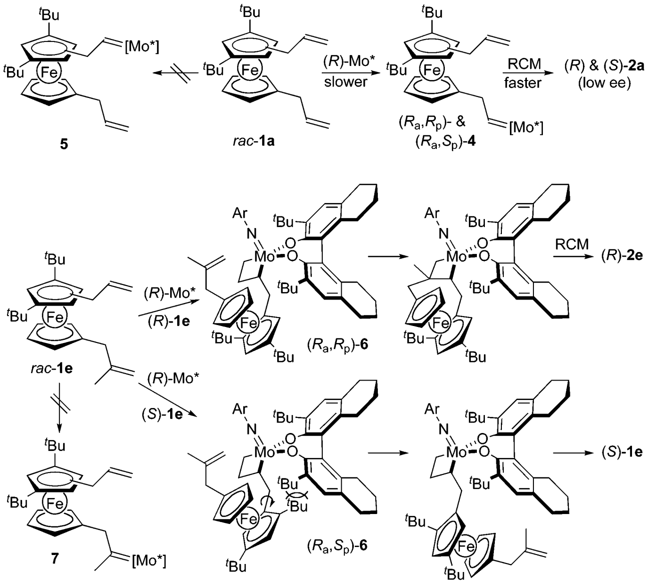
Scheme 2. Plausible Stereochemical Pathways of the Mo-Catalyzed ARCM Kinetic Resolution of 1



tathesis with (*R*)-Mo* takes place with negligible stereoselectivity. Following the RCM step in **4** is an intramolecular process, and thus both (R_a,R_p)- and (R_a,S_p)-**4** can be smoothly transformed into the corresponding ferrocenoephanes to give **2a** in nearly racemic form. On the other hand, with a less reactive methallyl group in a monosubstituted Cp in place of the allyl group, the reaction between (*R*)-Mo* and *rac*-**1e** takes place at the allyl group in the planar-chiral trisubstituted Cp preferentially and formation of **7** is minor. While (R_a,R_p)-**6** is transformed into (*R*)-**2e** smoothly via RCM, the epimeric (R_a,S_p)-**6** is forced to take an unfavorable conformation due to the steric repulsion between a ^{t}Bu group in η^5-$C_5H_2{}^tBu_2$(allyl) and a ^{t}Bu group in the chiral biaryl ligand in (*R*)-Mo* to liberate (*S*)-**1e** (Scheme 2, bottom).

In summary, we have developed an effective method for kinetic resolution of racemic planar-chiral ferrocene derivatives via molybdenum-catalyzed asymmetric ring-closing metathesis. This is the first example of highly enantioselective metal-catalyzed induction of planar chirality in metallocene substrates.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and crystallographic data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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