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Enantioselective Synthesis of Planar-Chiral Phosphaferrocenes by Molybdenum-Catalyzed Asymmetric Interannular Ring-Closing Metathesis

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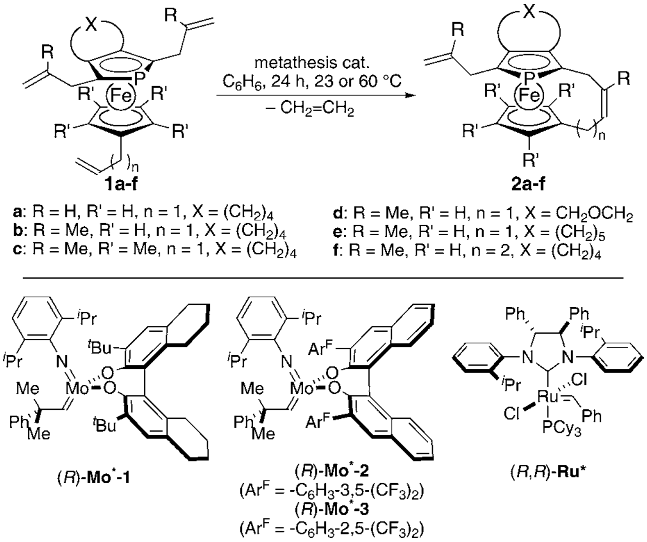
Planar-chiral ferrocenes[1] are important chiral scaffolds and have been utilized in various asymmetric reactions as ligands[2] or catalysts[3] with fair success. Recent entries to this class of compounds are heterometallocenes such as azaferrocenes and phosphaferrocenes, and these Lewis basic organometallics have proven their usefulness in asymmetric synthesis.[2f,g,3b,c] Standard methods of obtaining nonracemic planar-chiral ferrocenes are based either on resolution of racemates or on diastereoselective metalation using chiral directing groups[4] or external chiral bases.[5] Their catalytic enantioselective synthesis is extremely rare,[5d,6,7] and further breakthroughs have been clearly awaited. Recently, we and others reported the preparation of various bridged metallocenes by interannular ring-closing metathesis,[8] which have enabled us to modulate metallocenes by transition metal catalysis. And thus, we are interested in controlling metallocene-based planar chirality using chiral metathesis catalysts. In spite of recent advances in asymmetric ring-closing metathesis (ARCM),[9] the method has been solely applied to the preparation of compounds with C-[9] or P-stereogenic[10] centers. After successful application of ARCM to the kinetic resolution of racemic planar-chiral ferrocenes,[7a,b] we report herewith catalytic enantioselective desymmetrization of planar-prochiral phosphaferrocenes. The asymmetric reactions of the Lewis basic substrates proceed very efficiently in the presence of an appropriate chiral Mo-catalyst, and planar-chiral phosphaferrocenes are obtained in high yields (vs 50% in kinetic resolutions) in up to 99% ee. This is the first application of ARCM to the induction of metallocene-based planar chirality. Indeed, this is the first example of asymmetric synthesis of chiral molecules devoid of stereogenic centers[11] by ARCM.

The substrates for this study are C_s-symmetric phosphaferrocenes **1**, where the two allylic substituents at the 2- and 5-positions in the η^5-phospholide are enantiotopic to each other (Scheme 1).

Scheme 1



1a-f **2a-f**

a: R = H, R' = H, n = 1, X = $(CH_2)_4$
b: R = Me, R' = H, n = 1, X = $(CH_2)_4$
c: R = Me, R' = Me, n = 1, X = $(CH_2)_4$
d: R = Me, R' = H, n = 1, X = CH_2OCH_2
e: R = Me, R' = H, n = 1, X = $(CH_2)_5$
f: R = Me, R' = H, n = 2, X = $(CH_2)_4$

(*R*)-**Mo*-1**

(*R*)-**Mo*-2**
(Ar^F = $-C_6H_3$-3,5-$(CF_3)_2$)
(*R*)-**Mo*-3**
(Ar^F = $-C_6H_3$-2,5-$(CF_3)_2$)

(*R*,*R*)-**Ru***

Table 1. Molybdenum-Catalyzed Synthesis of Planar-Chiral Phosphaferrocenes by Enantioselective Desymmetrization[a]

entry	substrate	cat. (mol %)	temp[b]	yields of **2** (%)[c]	%ee of **2**[d]
1	**1a**	(*R*)-**Mo*-1** (20)	23 °C	65 (**2a**)	1
2	**1b**	(*R*)-**Mo*-1** (20)	23 °C	72 (**2b**)	99
3	**1c**	(*R*)-**Mo*-1** (20)	60 °C	7 (**2c**)	98[e]
4	**1d**	(*R*)-**Mo*-1** (20)	60 °C	46 (**2d**)	96 (*S*)
5	**1e**	(*R*)-**Mo*-1** (20)	60 °C	30 (**2e**)	98
6	**1a**	(*R*)-**Mo*-2** (10)	60 °C	83 (**2a**)	8
7	**1b**	(*R*)-**Mo*-2** (10)	60 °C	93 (**2b**)	88
8	**1b**	(*R*)-**Mo*-3** (10)	60 °C	90 (**2b**)	92
9	**1c**	(*R*)-**Mo*-2** (10)	60 °C	83 (**2c**)	99[e]
10	**1d**	(*R*)-**Mo*-3** (10)	60 °C	93 (**2d**)	81 (*S*)
11	**1e**	(*R*)-**Mo*-2** (10)	60 °C	82 (**2e**)	85
12	**1b**	(*R*,*R*)-**Ru*** (10)	60 °C	95 (**2b**)	5
13	**1f**	(*R*)-**Mo*-2** (10)	60 °C	trace	—
14	**1f**	(*R*,*R*)-**Ru*** (10)	60 °C	43 (**2f**)	40

[a] The reaction was carried out in benzene in the presence of an appropriate metathesis catalyst. [b] Bath temperature. [c] Isolated yields of the products **2** by silica gel chromatography. [d] Determined by HPLC analysis with a chiral stationary phase column Daicel Chiralcel OD-H unless otherwise noted. [e] Determined by ^{31}P NMR analysis after converting into the diastereomeric palladacycle complexes (see text).

To initiate our investigations, the desymmetrization reaction was examined using a chiral molybdenum metathesis catalyst (*R*)-**Mo*-1**[12] that was successfully used in the kinetic resolution of the racemic planar-chiral ferrocenes.[7a,b] Enantioselectivity in the desymmetrization of **1** was strongly dependent on the structure of the allylic substituents in the η^5-phospholyl moiety. Treatment of **1a** with (*R*)-**Mo*-1** (20 mol %) for 24 h in benzene at 23 °C resulted in the corresponding bridged monophosphaferrocene **2a** in 65% yield. To our disappointment, however, **2a** was found to be only 1% ee (Table 1, entry 1). The enantioselectivity was dramatically improved by introducing two methallyl groups in place of the allyl substituents in the phospholyl moiety in **1**. And thus, the ARCM reaction of **1b** with (*R*)-**Mo*-1** at 23 °C gave phospha[4]ferrocenophane **2b** with 99% ee in 72% (entry 2). Although (*R*)-**Mo*-1** showed excellent enantioslelectivity in the asymmetric reactions of the other substrates **1c**−**e** to give the corresponding **2c**−**e** in >96% ee, the catalyst was deactivated prior to completion of the reaction, which resulted in lower chemical yields of **2c**−**e** even with relatively higher catalyst loading (entries 3−5). The worst case can be seen in the reaction of **1c**, which gave fully substituted phospha[4]ferrocenophane **2c** with 98% ee in only 7% yield (entry 3). Screening of chiral catalysts was conducted for solving this problem. Various catalytically active Mo-alkylidene species were generated *in situ* as reported by Hoveyda and Schrock[13] and used for the screening experiments. Among 11 Mo complexes examined (see Supporting Information for details), (*R*)-**Mo*-2**[14] and (*R*)-**Mo*-3**,

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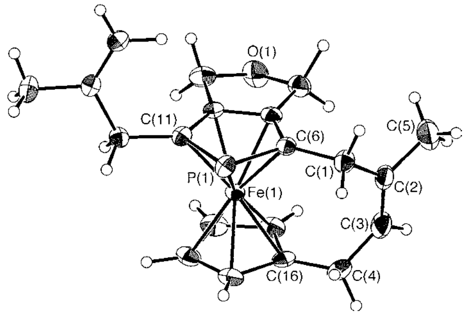

Figure 1. ORTEP drawing of (−)-(*S*)-**2d** with 40% thermal ellipsoids.

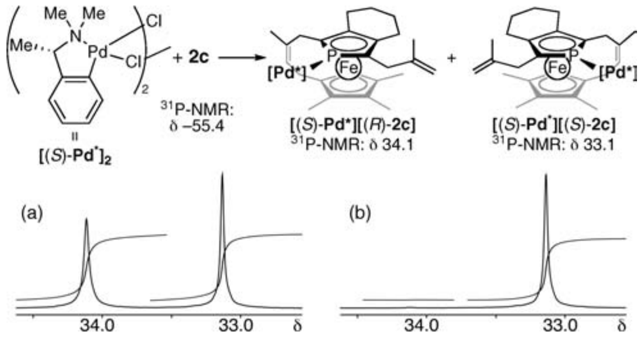

Figure 2. Formation of diastereomeric complexes from **2c** and chiral palladacycle [(*S*)-**Pd***]$_2$ and their ^{31}P{^{1}H}-NMR spectra (162 MHz) in C_6D_6: (a) with racemic **2c**; (b) with (*S*)-**2c** of 99% ee.

which are coordinated with a 3,3′-bis$[C_6H_3(CF_3)_2]$-2,2′-binaphthoxide ligand, showed a high tolerance for the catalyst deactivation without a significant diminution in enantioselectivity. These Mo-catalysts afforded **2b**−**e** in >83% yields in 81−99% ee with 10 mol % catalysts-loading (entries 7−11).[15] Notably, the sterically congested **2c** was obtained in 83% yield in 99% ee using (*R*)-**Mo*-2** (entry 9). While the Mo-catalysts were useful for asymmetric synthesis of the phospha[4]ferrocenophanes, a chiral ruthenium complex (*R*,*R*)-**Ru***[16] showed negligible enantioselectivity in the reaction of **1b** (entry 12). On the contrary, (*R*,*R*)-**Ru*** was a catalyst of choice for the ARCM reaction of **1f** giving the [5]ferrocenophane **2f** in moderate enantioselectivity (40% ee; entry 14). The Mo-catalysts failed to produce the [5]ferrocenophane from **1f** (entry 13).

X-ray crystallography revealed that absolute configuration of the ARCM product **2d** (Table 1, entry 4), which is levorotatory ($[\alpha]^{25}_{D}$ −9.3 (*c* 1.85 in $CHCl_3$)), was (*S*) as shown in Figure 1.

The phosphaferrocenes **2** are capable of coordinating to a transition metal as two-electron donors to create an effective chiral environment around the metal center. This characteristic was utilized for determining the enantiomeric purity of **2c**. Treatment of **2c** with a slight excess of a chiral palladacycle[17] [(*S*)-**Pd***]$_2$ in C_6D_6 afforded a pair of diastereomeric palladacycle-phosphaferrocene complexes at the time of mixing. The ^{31}P{^{1}H}-NMR spectra of the diastereomeric mixtures showed clearly two resolved resonances at δ 33.1 and 34.1, of which integration gave the enantiomeric molar ratios in **2c** (Figure 2). These observations postulate potential uses of the planar-chiral phosphaferrocenes **2** as chiral ligands in transition metal catalysis.

In summary, enantiomerically enriched planar-chiral phosphaferrocenes have been prepared in up to 99% ee through Mo-catalyzed ARCM reactions. This report represents the first application of ARCM to the induction of noncentrochirality and demonstrates the high potential of the ARCM protocol for constructing various chiral molecules. Studies are ongoing in our laboratory to apply these planar-chiral phosphaferrocenes as chiral ligands in asymmetric catalysis.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and crystallographic data of (−)-(*S*)-**2d** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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