Insertion of Carbenoids into Cp–H Bonds of Ferrocenes: An Enantioselective-Catalytic Entry to Planar-Chiral Ferrocenes**

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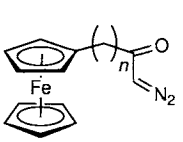
Since the epoch-making discovery of ferrocene in 1951,[1] the chemistry of this organometallic compound has been intensely investigated. Even recently, the ferrocene substructure enjoys a keen scientific interest—especially as a sound construction element for developing new catalysts and materials.[2]

In the course of our work on the preparation and synthetic application of chiral transition metal π complexes,[3] we considered whether cyclization reactions of the type shown in Equation (1) are possible, or, more generally, if ferrocenes can be

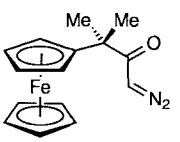
(1)

functionalized (by C–H insertion) upon reaction with carbenes. We assumed that the comparably electron-rich cyclopentadienyl rings of ferrocene could react with electron-poor carbenes (or carbenoids). We report here the success of such reactions and, thus, the first examples of carbene insertion into Cp–H bonds of ferrocene derivatives.[4] Furthermore, we show that this chemistry can be used for the enantioselective-catalytic preparation of planar-chiral ferrocenes.[5]

We employed the metal-catalyzed decomposition of α-diazo carbonyl compounds, since it is a reliable method for generating carbenoid species.[6] The (nonstabilized) electrophilic metal–carbene intermediates show a chemical behavior similar to that of free carbenes, and are well suited for insertions into aryl C–H bonds.[6, 7] As substrates we chose the diazoketones **1**–**3**.



1: $n = 1$
2: $n = 2$



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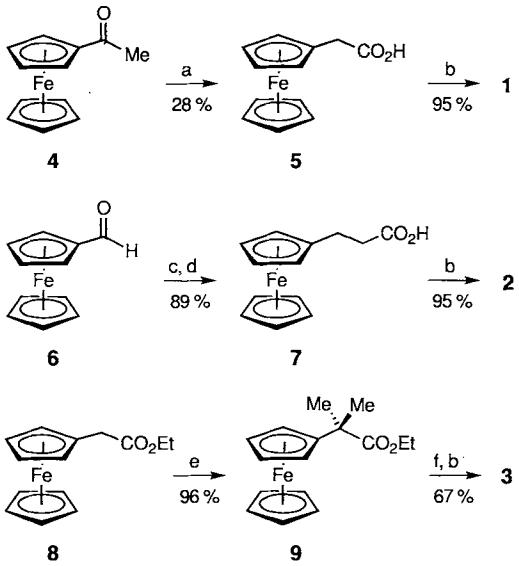
The synthesis of **1** (Scheme 1) started with acetylferrocene (**4**), which was subjected to a Willgerodt reaction to provide ferrocenyl acetic acid (**5**),[8, 9] which in turn was converted into diazoketone **1** in 95% yield by the one-pot procedure described in the Experimental Section.[10] To prepare the homologous substrate **2**, formylferrocene (**6**)[11] was first transformed by decarboxylative Knoevenagel condensation and catalytic hydrogenation into acid **7**,[11, 12] which was further converted into diazoketone **2** in high yield. Substrate **3** was synthesized by esterification of **5** to **8** (MeOH, $SOCl_2$, 83%). Two deprotonation/methylation cycles then afforded the dimethylated compound **9** in almost quantitative yields, from which diazoketone **3** was obtained after hydrolysis by the standard one-pot protocol.[9]



Scheme 1. Preparation of the cyclization precursors **1**–**3**. a) S_8, morpholine, 130 °C, 17 h, then 4N NaOH, reflux, 4 h; b) NaH, C_6H_6, room temperature (RT), then $(COCl)_2$, pyridine, 0 → 55 °C, 2 h, removal of solvent, then CH_2N_2, Et_2O, 0 °C, 30 min; c) $H_2C(CO_2H)_2$, cat. piperidine, pyridine, 100 °C, 2 h; d) H_2, Pd/C, EtOH, RT, 48 h; e) LDA, THF, −60 °C → RT, then aqueous work-up; repetition of the sequence; f) 10% NaOH, MeOH, reflux, 3 h.

We then investigated the projected cyclizations with the well-known (achiral) catalysts $[Rh_2(OAc)_4]$ and $[Rh_2(OCOCF_3)_4]$, and found suitable reaction conditions for all three substrates that allowed the preparation of the desired cyclization products (**10**, *rac*-**12**, and *rac*-**14**) in reasonable yields. The most important results are summarized in Table 1; however, here we emphasize some observations explicitly: A bridged ferrocene derivative (**11**) was obtained (as a side product) only in the case of **1**. In all reactions with $[Rh_2(OAc)_4]$ in halogenated solvents (Table 1, entries 1, 3, 6, and 7), ferrocene was isolated as a by-product in considerable amounts (10–20%).[13] Compared to reactions with $[Rh_2(OAc)_4]$, those of **1** and **2** with $[Rh_2(OCOCF_3)_4]$ proceeded much more cleanly (entries 2 and 4), and only 1 mol% of the catalyst was required to provide *rac*-**12** in acceptable yields (47% based on converted starting material). An attempt to carry out the $[Rh_2(OAc)_4]$-catalyzed reaction of **2** in benzene resulted in the formation of significant amounts of the (intermolecular) Buchner product **13**.[14] Preliminary cyclization experiments with **3**, which were carried out in an NMR tube with $[Rh_2(OAc)_4]$ or $[Rh_2(CF_3CO_2)_4]$ in C_6D_6 or

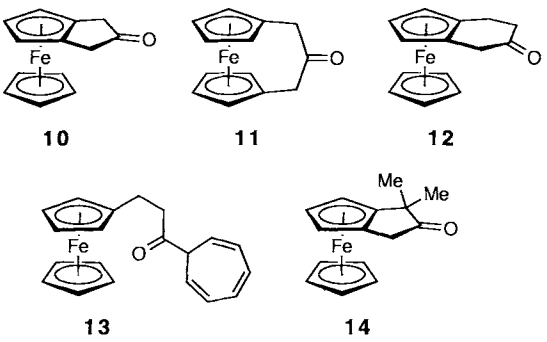


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Table 1. Results of the cyclization experiments carried out with substrates **1**–**3** in the presence of achiral catalysts [a].

Entry	Substrate	Catalyst	Amount [mol%]	Solvent	Products (yield[%][b])
1	**1**	$[Rh_2(OAc)_4]$	13	CH_2Cl_2	**10** (4), **11** (2)
2	**1**	$[Rh_2(CF_3CO_2)_4]$	8	CH_2Cl_2	**10** (35), **11** (4)
3	**2**	$[Rh_2(OAc)_4]$	5	CH_2Cl_2	*rac*-**12** (36)
4	**2**	$[Rh_2(CF_3CO_2)_4]$	1	CH_2Cl_2	*rac*-**12** (35)[c]
5	**2**	$[Rh_2(OAc)_4]$	5	benzene	*rac*-**12** (50), **13** (9)
6	**3**	$[Rh_2(OAc)_4]$	5	C_6H_5F	*rac*-**14** (28)
7	**3**	$[Rh_2(OAc)_4]$	5	$C_6H_5CF_3$	*rac*-**14** (35)
8	**2**	$Cu(hfacac)_2$	5	CH_2Cl_2	*rac*-**12** (38)
9	**3**	$Cu(hfacac)_2$	5	CH_2Cl_2	*rac*-**14** (66)

[a] See Experimental Section. [b] Yields of isolated products after chromatographic separation. [c] In this case, 24% of the starting material **2** was recovered.

$CDCl_3$, showed that the cyclization product *rac*-**14** formed only in traces when the latter was used as the solvent. In contrast, dichloromethane proved to be a more appropriate solvent, and was also better than fluorobenzene and trifluoromethylbenzene.[15] It is known that (in addition to rhodium salts) copper compounds are especially well suited as catalysts for the generation of carbenoids from diazo compounds.[6b] Therefore, we tested the cyclization of substrates **2** and **3** with $Cu(hfacac)_2$ (hfacac = hexafluoroacetylacetonate), which has proven useful for C–H insertions into electron-rich aromatic compounds (e. g. *N*-methyl pyrrol).[16] Indeed, we obtained good results with this catalyst—especially in the case of **3**, which in the presence of $Cu(hfacac)_2$ (5 mol%) afforded *rac*-**14** in 66% yield.

Table 2. Selected spectroscopic data for **1**–**3**, **10**, **11**, *rac*-**12**, and *rac*-**14**. IR (CCl_4); ^1H NMR (400 MHz, $CDCl_3$); ^{13}C NMR (67.7 or 100.64 MHz, $CDCl_3$, additional DEPT).

1: IR: $\tilde{\nu}$ = 3057, 3047, 2099, 1645, 1631, 1362, 1297, 1105, 1077, 822 cm^{-1}; ^1H NMR: δ = 3.34 (s, 2H), 4.12 (s, 5H), 4.14 (s, 4H), 5.14 (s, 1H); ^{13}C NMR: δ = 42.3 (CH_2), 64.0 (CH), 68.3 (CH), 68.7 (CH), 69.1 (CH), 80.8, 193.1; HR-MS: calcd for $C_{13}H_{12}FeN_2O$: 268.0299, found: 268.0297.

2: IR: $\tilde{\nu}$ = 3093, 2958, 2102, 1639, 1371, 1371, 1362 cm^{-1}; ^1H NMR: δ = 2.46–2.58 (m, 2H), 2.64–2.72 (pseudo t, 2H), 4.06 (s, 4H), 4.12 (s, 5H), 5.22 (s, 1H); ^{13}C NMR: δ = 24.9 (CH_2), 42.4 (CH_2), 54.5 (CH), 67.3 (CH), 68.0 (CH), 68.5 (CH), 87.4, 194.2; HR-MS: calcd for $C_{14}H_{14}FeN_2O$: 282.0455, found: 282.0463.

3: IR: $\tilde{\nu}$ = 3096, 2975, 2097, 1626, 1333, 819 cm^{-1}; ^1H NMR: δ = 1.56 (s, 6H), 4.15 (pseudo t, 2H), 4.2 (s, 5H), 4.22 (m, 2H), 5.02 (s, 1H); ^{13}C NMR: δ = 25.6 (CH_3), 45.5, 52.3 (CH), 66.6 (CH), 68.0 (CH), 68.6 (CH), 95.2, 199.2; HR-MS: calcd for $C_{15}H_{16}FeN_2O$: 296.0612, found: 296.0617.

10: IR: $\tilde{\nu}$ = 3095, 2887, 1858, 1760, 1408, 1401, 1241, 1169, 1154, 1104, 832, 805 cm^{-1}; ^1H NMR: δ = 3.14 (dd, J = 21, 1.5 Hz, 2H), 3.32 (dd, J = 21, 1.5 Hz, 2H), 4.03 (s, 5H), 4.13 (t, J = 2 Hz, 1H), 4.27 (d, J = 2 Hz, 2H); ^{13}C NMR: δ = 41.0 (CH_2), 62.7 (CH), 67.5 (CH), 69.8 (CH), 87.2, 215.3; HR-MS: calcd for $C_{13}H_{12}FeO$: 240.0238, found: 240.0249.

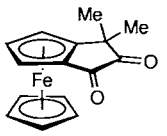
11: IR: $\tilde{\nu}$ = 3089, 2920, 1746, 1695, 1666, 1194, 809 cm^{-1}; ^1H NMR: δ = 3.04 (s, 4H), 4.04 (s, 4H), 4.17 (s, 4H); ^{13}C NMR: δ = 38.6 (CH_2), 70.0 (CH), 70.4 (CH), 76.4, 216.7; HR-MS: calcd for $C_{13}H_{12}FeO$: 240.0238, found: 240.0248.

rac-**12**: IR: $\tilde{\nu}$ = 3090, 2931, 2851, 1709, 1410, 1338, 1296, 1105, 1000, 822 cm^{-1}; ^1H NMR: δ = 2.6–2.84 (m, 3H), 2.88–3.0 (m, 1H), 3.18 (d, J = 20 Hz, 1H), 3.38 (d, J = 20 Hz, 1H), 4.07 (m, 1H), 4.08 (s, 5H), 4.11 (t, J = 2.5 Hz, 1H), 4.18 (m, 1H); ^{13}C NMR: δ = 22.5 (CH_2), 39.5 (CH_2), 40.1 (CH_2), 65.3 (CH), 65.7 (CH), 66.6 (CH), 69.2 (CH), 81.1, 84.1, 209.8; HR-MS: calcd for $C_{14}H_{14}FeO$: 254.0394, found: 254.0397.

rac-**14**: IR: $\tilde{\nu}$ = 3094, 2965, 2928, 1745, 1106, 820 cm^{-1}; ^1H NMR: δ = 1.12 (s, 3H), 1.56 (s, 3H), 3.18 (d, J = 20 Hz, 1H), 3.26 (d, J = 20 Hz, 1H), 4.04 (s, 5H), 4.16 (t, J = 2 Hz, 1H), 4.22 (d, J = 2 Hz, 1H), 4.3 (d, J = 2 Hz, 1H); ^{13}C NMR: δ = 23.0 (CH_3), 27.9 (CH_3), 38.5 (CH_2), 46.9, 59.9 (CH), 62.2 (CH), 67.0 (CH), 83.0, 100.3, 218.6; HR-MS: calcd for $C_{15}H_{16}FeO$: 268.0551, found: 268.0553.

rac-**15**: IR: $\tilde{\nu}$ = 3102, 2966, 2931, 2863, 1751, 1699, 1480, 1455 cm^{-1}; ^1H NMR: δ = 1.23 (s, 3H), 1.63 (s, 3H), 4.27 (s, 5H), 4.70 (pseudo d, J = 2.5 Hz, 1H), 5.03 (pseudo t, 1H, J = 2.5 Hz), 5.15 (d, J = 2.5 Hz, 1H); ^{13}C NMR: δ = 23.1 (CH_3), 30.1 (CH_3), 42.7, 65.0 (CH), 67.8 (CH), 76.0 (CH), 76.1 (CH), 77.2, 79.8, 175.9, 204.8; HR-MS: calcd for $C_{15}H_{14}FeO_2$: 282.0343, found: 282.0347

The cyclization products **10**, *rac*-**12**, and *rac*-**14** (spectroscopic data are given in Table 2) are surprisingly sensitive towards oxidation; they decompose upon exposure to air under formation of polar, intensely colored by-products. For instance, violet 1,2-diketone *rac*-**15** was isolated from a solution of *rac*-**14** with a catalytic amount of $Cu(hfacac)_2$ in dichloromethane that was exposed to the air for several hours. Furthermore, aerobic workup of the reaction mixture from the treatment of **1** with $Cu(hfacac)_2$ in dichloromethane provided a product of constitution **16**[17] in 19% yield as a 1:1 mixture of diastereomers. This was apparently formed by oxidative dimerization of **10**.



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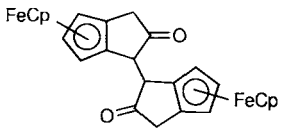

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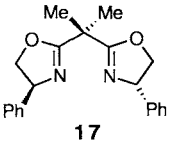
Because the cyclizations **2** → *rac*-**12** and **3** → *rac*-**14** represent chirogenic reactions[18] that can in general be conducted enantioselectively, it was straightforward to test these reactions with chiral catalysts.[19] Our first attempt with the prominent mepy-rhodium(II) complex[20] furnished disappointing results.[21] In contrast, cyclization experiments with the catalyst (5 mol%) prepared in situ from copper(I) triflate and **17**[22] in dichloromethane at reflux were successful. In the case of **2**, we obtained the cylization product **12**[23] in 72% yield with an enantiomeric excess of 78% *ee* (Scheme 2). Cyclization of **3**, performed under the same



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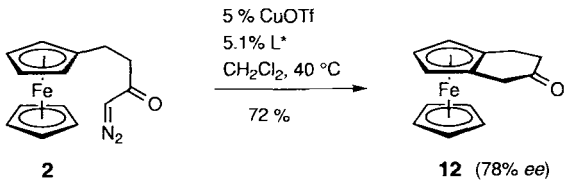
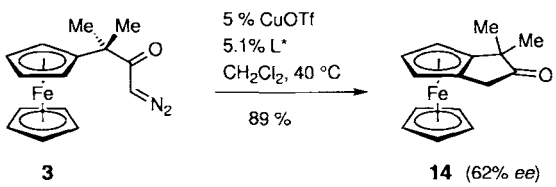


2 **12** (78% *ee*)

Scheme 2. Enantioselective cyclization of **2**. Tf = trifluoromethanesulfonyl, L* = chiral ligand.

conditions, also furnished an optically active product (**14**)[24] in good yield (89%) with an enantiomeric purity of 62% *ee* (Scheme 3). It is remarkable that these reactions not only proceeded with significant enantioselectivity but also gave higher chemical yields than those with the achiral catalysts. Further investigations must now show if the enantioselectivity can be increased by varying the catalyst systems.

The experiments described here show for the first time that carbene insertions into Cp–H bonds of ferrocene derivatives are possible and can be used (in a preparatively attractive man-



3 **14** (62% *ee*)

Scheme 3. Enantioselective cyclization of **3**.

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ner) for synthesizing interesting new compounds. This extends the chemistry of ferrocene by a basic new variant, and also opens a unique opportunity for the enantioselective-catalytic synthesis of planar-chiral ferrocene derivatives.

Experimental Section

General procedure for preparing the cyclization precursors **1**–**3** from the corresponding ferrocenyl alkanoic acids: To a stirred suspension of the ferrocenyl alkanoic acid (4.1 mmol) in anhydrous benzene (60 mL) was added sodium hydride (4.18 mmol) under an argon atmosphere, and after 10 min pyridine (2.61 mmol). The mixture was cooled to 0 °C, and freshly distilled oxalyl chloride (26.5 mmol) added dropwise. After complete addition stirring was continued for 30 min at 0 °C, for 30 min at room temperature, and finally for 1 h at 55 °C. After filtration of the reaction mixture through a short pad of silica gel, the solvent and excess oxalyl chloride were completely removed in vacuo. The dark brown residue was dissolved in Et_2O (15 mL), and a solution of diazomethane (35 ml, ≈0.6 M in Et_2O) added at 0 °C. After the reaction mixture was stirred for 20 min at 0 °C excess diazomethane and solvent were completely removed in vacuo, and the residue was purified by flash chromatography (hexane/EtOAc).

General procedure for the cyclization experiments summarized in Table 1: To a solution of the catalyst (34 μmol; 5 mol%) in the anhydrous solvent (10 mL) was added dropwise at RT under an atmosphere of argon a solution of the diazoketone (0.68 mmol) in the solvent (5 mL) within about 30 min. Gas evolution (N_2) indicated the decomposition of the diazo compound. After complete addition stirring was continued until complete conversion was reached (usually about one hour). After rapid filtration of the dark brown reaction mixture through a short pad of silica gel under argon, the solvent was completely removed in vacuo. The products were separated and purified by flash chromatography or radial chromatography (using a chromatotron) under an argon atmosphere.

Enantioselective cyclizations: Ligand **17** (17.3 μmol) was added to a solution of $Cu^{I}OTf$ (17 μmol; weighed in a glove box) in CH_2Cl_2 (3 mL) under an argon atmosphere. After the reaction mixture was stirred for 2 h at RT, the green solution of the catalyst was heated to reflux, and a solution of the substrate (**2** or **3**; 0.34 mmol) in CH_2Cl_2 (10 mL) slowly added within 2 h with a syringe pump (all under argon). After complete addition the brownish solution was heated at reflux for 20 min before being subjected to work-up as described above. The enantiomeric excess of the product was determined with HPLC (Daicel, Chiralcel OJ).

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[21] The use of this catalyst resulted in an extremely slow conversion to give a complex mixture containing the desired cyclization product at best in traces.
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[23] $[\alpha]_D^{20} = -107.7$, $c = 0.115$ in $CHCl_3$. The absolute configuration of the cyclization product (**12** or *ent*-**12**) was not established; the enantiomeric excess was determined with HPLC using a Daicel Chiralcel OJ column.
[24] $[\alpha]_D^{20} = -68.8$, $c = 0.08$ in $CHCl_3$. The absolute configuration of the cyclization product (**14** oder *ent*-**14**) was not established; the enantiomeric excess was determined with HPLC using a Daicel Chiralcel OJ column.

Asymmetric Self-Replication of Chiral 1,2-Amino Alcohols by Highly Enantioselective Autoinductive Reduction**

Takanori Shibata, Tomohide Takahashi, Takashi Konishi, and Kenso Soai*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Self-replication, like the chirality of the components, is one of the most characteristic features of living organisms. Therefore, self-replication of a chiral molecule is of much interest. The concept of self-replication, however, has not been applied in asymmetric synthesis; almost all conventional asymmetric syntheses require chiral auxiliaries with structures which differ from

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