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SHORT COMMUNICATION

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Chiral (Cyclopentadienone)iron Complexes for the Catalytic Asymmetric Hydrogenation of Ketones

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Three chiral (cyclopentadienone)iron complexes derived from (*R*)-BINOL (**CK1**–**3**) were synthesized and their structures unambiguously confirmed by X-ray analysis (**CK3**). Under suitable conditions for the in situ conversion into the corresponding (hydroxycyclopentadienyl)iron hydrides (Me_3NO, H_2), the new chiral complexes were tested in the catalytic asymmetric hydrogenation of ketones, showing moderate to good enantioselectivity. In particular, the complex bearing methoxy substituents at the 3,3′-positions of the binaphthyl moiety (**CK2**) proved remarkably more enantioselective than the unsubstituted one (**CK1**) and reached the highest level of enantioselectivity (up to 77 % *ee*) ever obtained with chiral (cyclopentadienone)iron complexes.

Introduction

Asymmetric hydrogenation (AH) is by far the industrially most relevant enantioselective transformation, owing to its operational simplicity and 100% atom economy. During its history of 40 years, thousands of homogeneous catalysts have been developed, allowing the hydrogenation of many substrates with high enantioselectivity.[1] However, most of the AH catalysts rely on very expensive and toxic precious metals (e.g., Ru, Rh, Ir, Pd), which may prevent in some cases their implementation on a large scale.[2] For this reason, developing new catalysts relying on cheap "base metals" (e.g., Fe, Co, Ni, Cu) constitutes the next frontier to unleash the full potential of AH. In particular, Fe appears to be the most appealing base metal due to its abundance (5% of Earth's crust), low cost and scarce toxicity.[3] In spite of these attractive features, the application of Fe in AH is still very limited:[4] a few chiral catalysts have been developed for the hydrogenation of ketones[5] and ketoimines,[5b,6] while no examples were reported with olefins.[7]

In our quest for new chiral Fe catalysts for the AH of ketones, our attention was captured by (cyclopentadienone)- and (hydroxycyclopentadienyl)iron complexes, whose catalytic properties are currently the object of growing interest.[8] Although (cyclopentadienone)iron complexes are known since the 1950s,[9] it was only in 1999 that Knölker and co-workers were able to isolate and characterize the hydroxycyclopentadienyl-activated complex ***act*-K1**, obtained from (cyclopentadienone)iron complex **K1** by Hieber base reaction [Figure 1 (a)].[10] The catalytic potential of complex ***act*-K1** was discovered some years later by Casey and co-workers,[11a] who reported its ability to promote the hydrogenation of carbonyl compounds and proposed a concerted outer-sphere mechanism.[11b] One limitation of ***act*-K1**-type complexes is their sensitivity to air and moisture. However, it has been recently shown that this problem can be circumvented by generating complexes ***act*-K** in situ from their precursors **K** (stable to air, moisture and chromatography) in the presence of Me_3NO,[12] UV light[5c] or K_2CO_3[13] [Figure 1 (b)]. Therefore, unlike most other Fe complexes used in homogeneous hydrogenation,[5b,5e,5f,14] cyclopentadienone complexes **K** are stable pre-catalysts, which do not require an inert or dry atmosphere (e.g., use of a glovebox) to be handled. This attractive feature makes them suitable candidates for practical industrial use. Chiral (cyclopentadienone)iron complexes have been obtained either by replacing one of the CO ligands of a **K** complex with a chiral phosphoramidite,[5c] or by inserting a stereocenter on the ring fused to the cyclopentadienone.[12d] However, despite their theoretical inter-

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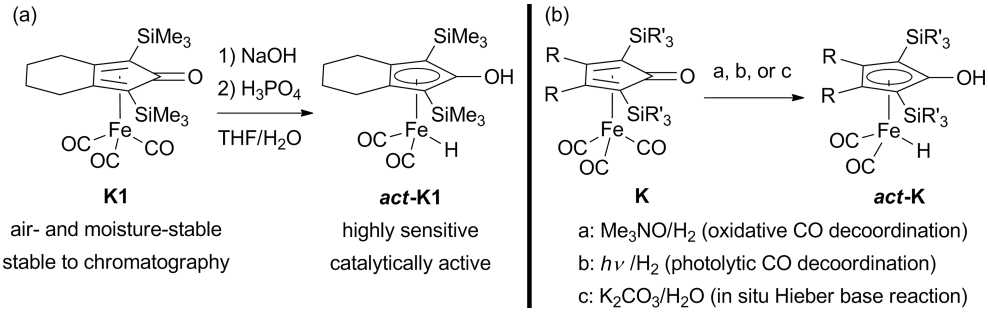


Figure 1. Knölker's synthesis of CpFe-activated complex ***act*-K1** (a) and reported methods for in situ formation of CpFe-activated complexes ***act*-K** (b).

est, both these approaches met limited success in terms of enantioselectivity (up to 31% *ee* in ketone AH and up to 25% *ee* in ketone asymmetric transfer hydrogenation, respectively).

Results and Discussion

Our approach to the development of chiral **K**-type complexes (**CK**) envisages the use of BINOL-derived chiral cyclopentadienone ligands (Figure 2), whose design was inspired by the chiral Cp ligands recently reported by Cramer et al. for Rh^{III} catalysis.[15]

The synthesis of the 3,3′-unsubstituted complex (*R*)-**CK1** (Scheme 1) was carried out in three steps starting from the commercially available compound (*R*)-**1**.[16]

Dibromide (*R*)-**1** was converted into the more reactive diiodide (*R*)-**2**, which was treated with [(trimethylsilyl)ethynyl]magnesium bromide in the presence of CuI[17] to yield the diyne (*R*)-**3**. The latter compound was then cyclized under the conditions reported by Renaud et al.[12a] [$Fe_2(CO)_9$ in toluene at 90 °C] to yield the complex (*R*)-**CK1**, which proved to be stable in air as expected, and could be purified by chromatography.

Considering the previously reported BINOL-derived catalytic systems[15,18] and the commonly accepted mechanism of the ***act*-K**-catalyzed reductions,[11b] we envisioned that 3,3′-disubstitution on the binaphthyl moiety would be needed to ensure an efficient transfer of stereochemical information from the catalyst's stereoaxis to the substrate. Indeed, in the commonly accepted transition state (TS)[11b]

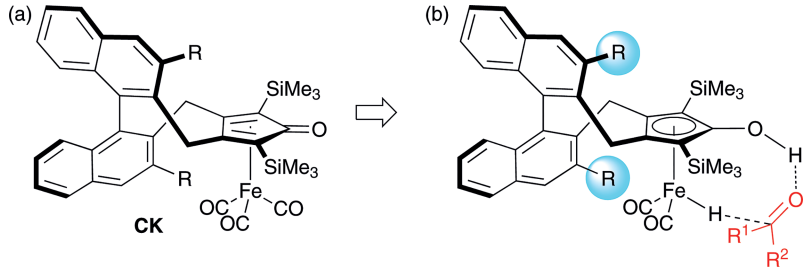
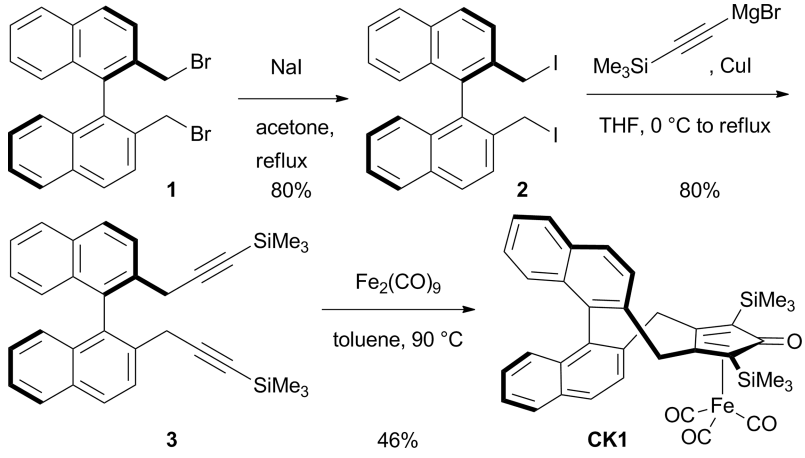
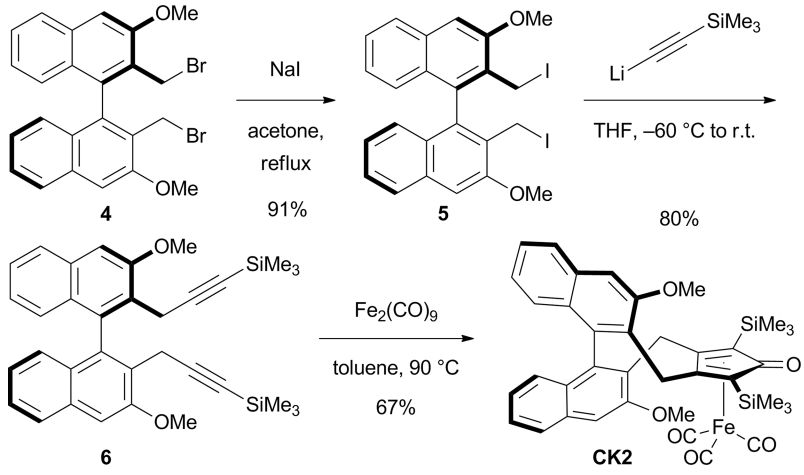


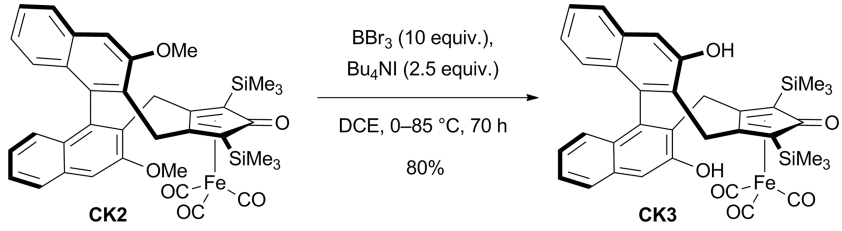
Figure 2. General structure of chiral pre-catalysts **CK** (a) and the expected importance of 3,3′-disubstituted binaphthyls in AH (b).



Scheme 1. Synthesis of the pre-catalyst (*R*)-**CK1**.



Scheme 2. Synthesis of the 3,3′-disubstituted pre-catalyst (*R*)-**CK2**.



Scheme 3. Synthesis of complex (*R*)-**CK3** by demethylation of (*R*)-**CK2**.

[see Figure 2 (b)], the substrate is located at a remarkable distance from the cyclopentadienone-fused ring, where the stereogenic unit of **CK** complexes is located. For this reason, we decided to synthesize a 3,3′-disubstituted complex as shown in Scheme 2.

The bis(bromomethyl) derivative (*R*)-**4**, prepared from (*R*)-BINOL as described by Maruoka et al.,[16] was converted into the corresponding diiodide (*R*)-**5**, which was then treated with [(trimethylsilyl)ethynyl]lithium to yield the diyne (*R*)-**6** in 80% yield.[19] Remarkably, this double alkynylation only proceeded in the presence of methoxy groups in the 3,3′-positions, which prevented us from preparing other 3,3′-disubstituted derivatives. Compound (*R*)-**6** was then cyclized in the presence of $Fe_2(CO)_9$ to yield the 3,3′-dimethoxy-substituted pre-catalyst (*R*)-**CK2**. Attempts to grow crystals of complexes **CK1** and **CK2** failed due to their high solubility in the most common organic solvents. We thus decided to convert **CK2** into the corresponding 3,3′-dihydroxy derivative **CK3** (Scheme 3), as we expected the latter to be easier to crystallize in apolar solvents. Quite harsh reaction conditions (BBr_3 with Bu_4NI as activator at 85 °C[20]) were necessary to achieve full deprotection. Nevertheless, compound (*R*)-**CK3** could be obtained in good yield (80%), which confirmed the remarkable stability of the (cyclopentadienone)iron complex.

To our delight, crystals suitable for X-ray diffraction analysis could be obtained by slow diffusion of hexane into a DCM solution of complex **CK3**[21] (Figure 3).

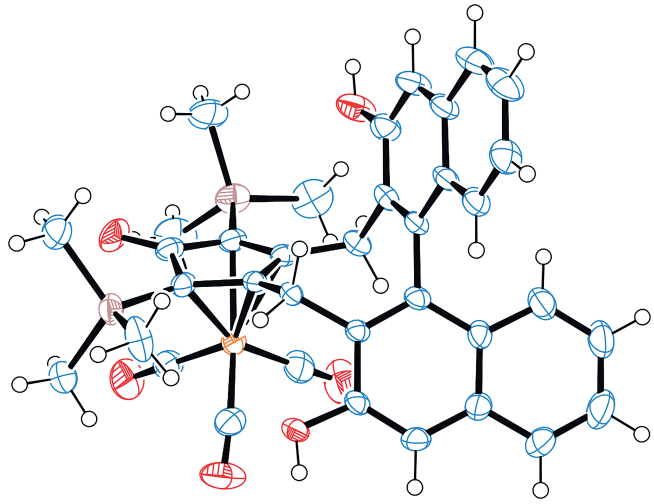
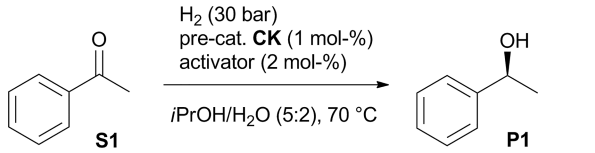


Figure 3. ORTEP diagram of the molecular structure of (*R*)-**CK3** (thermal ellipsoids set at the 50% probability level). Co-crystallized solvent molecules are omitted for clarity.

Pre-catalysts **CK1**, **CK2** and **CK3** were initially tested in the AH of acetophenone **S1** (Table 1, Entry 1–3) under the conditions described by Beller and co-workers,[13] i.e. employing K_2CO_3 as activator to form the corresponding complexes ***act*-CK** in situ [see Figure 1 (b)]. In each of the three experiments a moderate conversion (54–68%) was obtained, along with enantioselectivity in favor of (*S*)-1-phen-

ylethanol (**P1**).[22] Very low conversions (< 5%) were observed in the absence of H_2 suggesting that the hydrogenation pathway is predominant over the transfer hydrogenation from *i*PrOH.[13a,23] In agreement with our expectation, substitution at the 3,3′-positions of the binaphthyl moiety strongly affects the level of enantioselectivity: the observed *ee* follows the same trend of the steric bulk of 3,3′-substituents: H (**CK1**, Entry 1) << OH (**CK3**, Entry 3) < OMe (**CK2**, Entry 2).

Table 1. Test of **CK** pre-catalysts in the AH of acetophenone (**S1**) and screening of different activators.[a]



Entry	CK	Activator	Conversion [%][b]	*ee* [%][b,c]
1	**CK1**	K_2CO_3	62	8
2	**CK2**	K_2CO_3	54	49
3	**CK3**	K_2CO_3	68	47
4	**CK2**	Li_2CO_3	9	52
5	**CK2**	Na_2CO_3	25	53
6	**CK2**	Cs_2CO_3	29	51
7	**CK2**	LiOH	49	51
8	**CK2**	NaOH	35	50
9	**CK2**	KOH	30	52
10	**CK2**	K_3PO_4	23	53
11	**CK2**	Me_3NO	84	50

[a] Reaction conditions: **S1**/**CK**/activator = 100:1:2, P_{H2} = 30 bar, solvent = *i*PrOH/H_2O (5:2), c_0(**S1**) = 1.43 M, T = 70 °C, reaction time 18 h. [b] Determined by GC with a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin). [c] Absolute configuration: *S* in all cases (assigned by comparison of the optical rotation sign with literature data[22]).

Remarkably, the observed stereochemical preference for (*S*)-**P1** is consistent with a pericyclic TS[11b] where **S1** orients its larger substituent (Ph) away from the binaphthyl 3-substituent (OMe) to minimize steric clash (Figure 4). The most enantioselective pre-catalyst **CK2** was selected for further optimization of the reaction parameters. First of all, a series of different activators were screened (Table 1, Entry 4–11): while K_2CO_3 was confirmed to be the most efficient inorganic base in terms of conversion (Entry 2 vs. Entries 4–10), the oxidative CO decomplexation with Me_3NO[12] turned out to be the most efficient activation methodology, leading to high conversion (Entry 11).

The optimization was continued by assessing the effect of changing H_2 pressure, temperature and solvent (Table 2). We found that neither increasing pressure (Entry 2) nor temperature (Entry 3) led to full conversion, which instead could be obtained by increasing the catalyst loading to 2 mol-% (Entry 5; isolated yield 94%). Lowering the temperature to 50 °C increased the *ee* to 55%, but at the cost of conversion (Entry 4). We next screened several different solvents (Entries 7–15), but all of them gave lower conversions compared to the *i*PrOH/H_2O (5:2) mixture. In particular, the presence of water turned out to be beneficial for the conversion (cf. Entries 1 and 7).

Having established the optimal reaction conditions for the ***act*-CK2**-catalyzed AH, we assessed the scope of the reaction (Table 3).

As expected, electron-poor acetophenone derivatives (**S2** and **S4**) were more reactive than electron-rich 4′-methoxyacetophenone (**S3**) (Table 3, Entry 2 vs. Entries 1 and 3). As a general trend for the methyl ketones (Table 3, Entries 1–6 and 11–13), *S*-selectivity was always observed, and the *ee* increased along with the steric bulk of the other C=O substituent (*t*Bu > 1-Np > Cy > 2-Np ≈ Ph ≈ Py ≈ *p*-XC_6H_4 >> *i*Bu). Unfortunately, the most hindered substrates also gave lower conversions (e.g., Table 3, Entries 4 and 13). The hydrogenation of 3-acetylpyridine (**S7**) also proved to be sluggish (Table 3, Entry 6), possibly due to its ability to coordinate Fe. A similar trend was observed for cyclic ketones, with 1-tetralone (**S9**) giving a much higher *ee* (77%) and a lower conversion than 2-tetralone (**S10**) (Table 3, Entry 8 vs. 9). Surprisingly, the reduction of **S10** and **S11** showed opposite stereochemical preference (*R*- instead of *S*-prod-

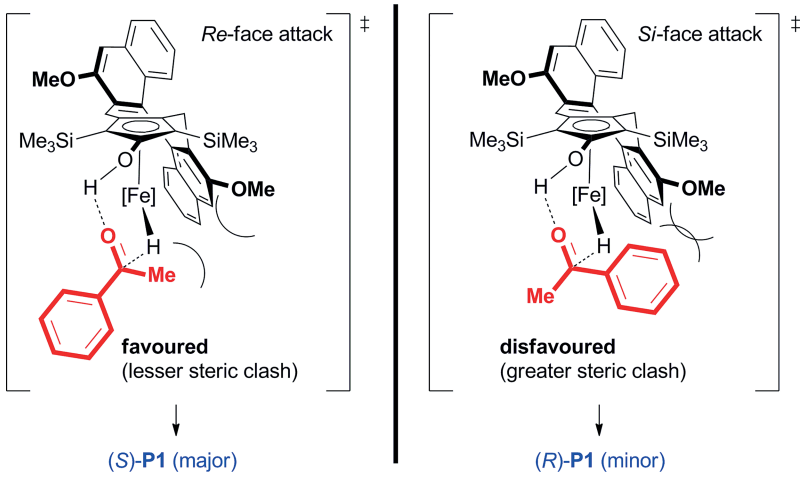
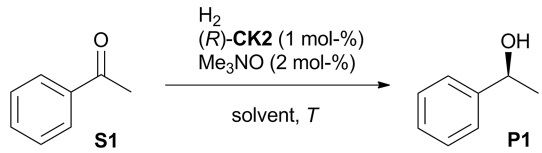


Figure 4. Stereoselection model based on the commonly accepted TS of ***act*-K**-catalyzed AH.[11b]

Table 2. Optimization of reaction parameters of the AH of acetophenone (**S1**) promoted by pre-catalyst **CK2**.[a]



Entry	Solvent	*P* [bar]	*T* [°C]	Conversion [%][b]	*ee* [%][b,c]
1	*i*PrOH/H_2O (5:2)	30	70	84	50
2	*i*PrOH/H_2O (5:2)	50	70	85	51
3	iPrOH/H_2O (5:2)	30	80	59	50
4	*i*PrOH/H_2O (5:2)	30	50	33	55
5[d]	*i*PrOH/H_2O (5:2)	30	70	100[e]	50
6[f]	*i*PrOH/H_2O (5:2)	30	70	58	51
7	*i*PrOH	30	70	15	54
8	EtOH/H_2O (5:2)	30	70	21	49
9	CF_3CH_2OH/H_2O (5:2)	30	70	74	42
10	DME/H_2O (5:2)	30	70	56	52
11	dioxane/H_2O (5:2)	30	70	56	52
12	CH_3CN/H_2O (5:2)	30	70	3	53
13	DMF/H_2O (5:2)	30	70	26	54
14	DCE/H_2O (5:2)	30	70	34	54
15	toluene/H_2O (5:2)	30	70	8	53

[a] Reaction conditions: **S1**/**CK2**/Me_3NO = 100:1:2, P_{H2} = 30 bar, c_0(**S1**) = 1.43 M. [b] See the footnote of Table 1. [c] See the footnote of Table 1. [d] 2 mol-% **CK2** (4 mol-% Me_3NO) employed. [e] Yield of the isolated product **P1** 94%. [f] c_0(**S1**) = 0.72 M.

uct). Propiophenone (**S8**) (Table 3, Entry 7) gave a similar conversion and a slightly better *ee* than acetophenone (**S1**) (Table 2, Entry 4).

Conclusions

We have developed new BINOL-derived chiral (cyclopentadienone)iron complexes (**CK**), which display high stability to air, moisture and chromatography. The new compounds can be converted in situ into the corresponding hydroxycyclopentadienyl complexes ***act*-CK**, which catalyze the AH of ketones with better enantioselectivities (up to 77% *ee*) than any other reported chiral (cyclopentadienone)iron complex.[5c,12d] As the obtained enantioselectivity increases with the steric bulk of the binaphthyl 3,3′-substituents of **CK**, future work will focus on the synthesis of new complexes with various 3,3′-substituents starting from the 3,3′-dihydroxy-substituted complex **CK3**.

Experimental Section

General Procedure for the Asymmetric Hydrogenation: Hydrogenations were run in a 450 mL Parr autoclave equipped with a removable aluminum block that can accommodate up to fifteen magnetically stirred 7 mL glass vials. The catalyst [0.005 mmol (1 mol-%) or 0.01 mmol (2 mol-%)] was weighed in the glass vials, which were accommodated in the aluminum block after adding magnetic stir bars in each of them. The block was placed in a Schlenk tube, where it was subjected to three vacuum/nitrogen cycles. *i*PrOH (0.25 mL) was added to each vial, and stirring was started. Me_3NO [0.01 mmol (2 mol-%) or 0.02 mmol (4 mol-%)] was added to each vial as an H_2O solution (0.1 mL). After stirring at room temperature under nitrogen for 10 min, the substrate (0.5 mmol) was added to the mixtures. Each vial was capped with a Teflon septum pierced by a needle, the block was transferred into the autoclave, and stirring was started. After purging four times with hydrogen at the selected pressure, heating was started. The reactions were stirred under hydrogen pressure overnight and then analyzed for conversion and *ee* determination.

Acknowledgments

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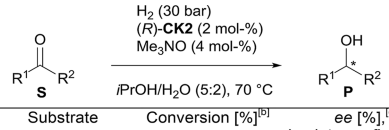
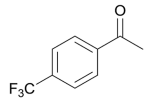
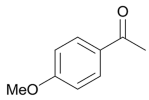
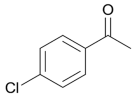
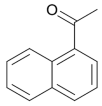
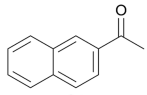
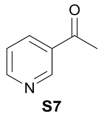
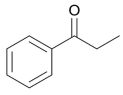
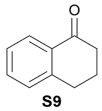
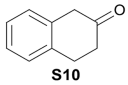
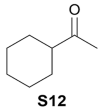
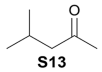
[1] For a comprehensive review of the topic, see: *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**.
[2] a) D. J. Ager, A. H. M. de Vries, J. G. de Vries, *Chem. Soc. Rev.* **2012**, *41*, 3340–3380; b) *Asymmetric Catalysis on Industrial Scale*, 2nd ed. ("Challenges, Approaches, Solutions") (Eds.: H.-U. Blaser, H.-J. Federsel), Wiley-VCH, Weinheim, **2010**.
[3] For general reviews on iron catalysis, see: a) M. Darwish, M. Wills, *Catal. Sci. Technol.* **2012**, *2*, 243–255; b) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321; *Angew. Chem.* **2008**, *120*, 3363–3367.
[4] For selected reviews covering Fe-catalyzed AH, see: a) K. Gopalaiah, *Chem. Rev.* **2013**, *113*, 3248–3296; b) K. Junge, K. Schröder, M. Beller, *Chem. Commun.* **2011**, *47*, 4849–4859; c) R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282–2291.
[5] a) Y. Li, S. Yu, X. Wu, J. Xiao, W. Shen, Z. Dong, J. Gao, *J. Am. Chem. Soc.* **2014**, *136*, 4031–4039; b) P. O. Lagaditis, P. E. Sues, J. F. Sonnenberg, K. Y. Wan, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2014**, *136*, 1367–1380; c) A. Berkessel, S. Reichau, A. von der Höh, N. Leconte, J.-M. Neudörfl, *Organometallics* **2011**, *30*, 3880–3887; d) Y. Wang, M. Zheng, X. Li,

Table 3. Substrate screening for the ***act*-CK2**-catalyzed AH.[a]



Entry	Substrate	Conversion [%][b]	*ee* [%],[c] absolute configuration[d]
1	 **S2**	100	46, *S*
2	 **S3**	64	50, *S*
3	 **S4**	100	51, *S*
4	 **S5**	43	68, *S*
5	 **S6**	99	51, *S*
6	 **S7**	35	50, *S*
7	 **S8**	97	57, *S*
8[e]	 **S9**	25	77, *S*
9	 **S10**	100	13, *R*
10	 **S11**	78	59, *R*
11	 **S12**	89	61, *S*
12	 **S13**	76	0
13	 **S14**	22	77, *S*

[a] Reaction conditions: substrate/**CK2**/Me_3NO = 100:2:4, P_{H2} = 30 bar, solvent = *i*PrOH/H_2O (5:2), c_0(substrate) = 1.43 M, T = 70 °C, reaction time 18 h. [b] Determined by GC with a chiral capillary column (see the Supporting Information). [c] Determined by GC or HPLC with a chiral capillary column (see the Supporting Information). [d] Assigned by comparison of the sign of optical rotation with literature data (see the Supporting Information). [e] Substrate/**CK2**/Me_3NO = 100:5:10.

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charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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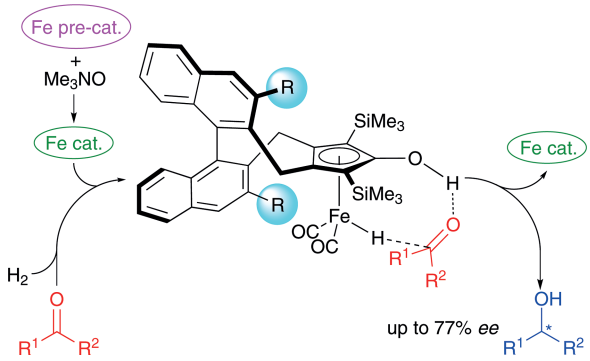

Reducto! Chiral (cyclopentadienone)iron complexes were synthesized and tested, after in situ activation, in the catalytic asymmetric hydrogenation of ketones leading to the highest enantiomeric excesses ever obtained with this type of catalysts.

Keywords: Asymmetric catalysis / Hydrogenation / Chiral auxiliaries / Iron / Homogeneous catalysis / Ketones / Reduction

