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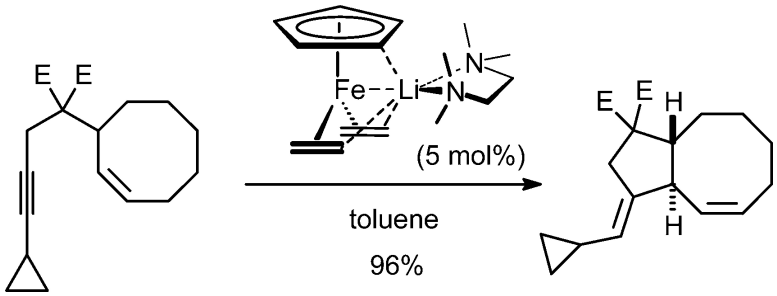

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Cycloisomerization of Enynes Catalyzed by Iron(0)−Ate Complexes

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Our recent investigations on iron-catalyzed cross-coupling reactions of organomagnesium reagents with various electrophiles were guided by the hypothesis that bare, low-valent iron clusters formed in situ from FeX_3 and excess RMgX might account for the catalytic turn-over.[1−4] Since the unambiguous characterization of such highly reactive species is problematic, our ongoing mechanistic studies rely on the use of the Fe(0)−ate complexes **1a**,**b** and the Fe(−II)−ate complex **2** as adequate surrogates. These structurally well-defined compounds[5] comprise very electron-rich metal centers within a coordination sphere of weakly bound alkene ligands. In fact, **1** and **2** turned out to be exceptionally potent catalysts able to induce even the cross-coupling of arylmagnesium halides with *alkyl* bromides and -iodides, which are particularly difficult to accomplish.[6−8]

Encouraged by these results, we launched a program to investigate the as of yet largely unexplored chemical behavior of such ferrate complexes in more detail. This seemed particularly attractive since **1** and **2** are readily available from inexpensive starting materials in multigram amounts (for the preparation of >23 g of **1** from ferrocene, see the Supporting Information).[5] We supposed that replacement of the weakly ligated alkenes in **1** by chelating substrates such as 1,6-enynes might engender oxidative cyclization due to the very electron-rich metal center of the ate complex and, hence, trigger, for example, skeletal reorganizations of the Alder-ene-type (Scheme 1).[9] Apart from a few remarkable exceptions,[10,11] Alder-ene reactions of enynes are commonly performed with *noble*

Scheme 1

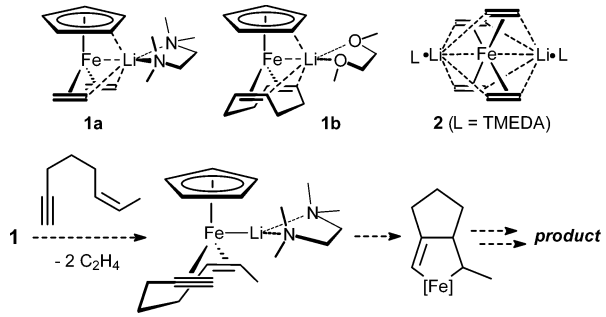
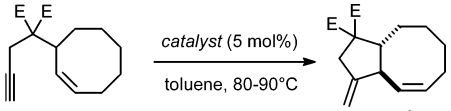
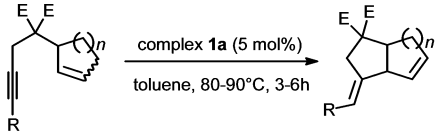


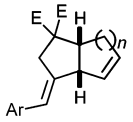
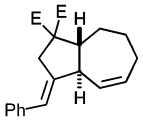
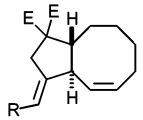
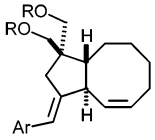
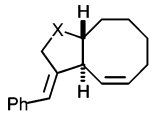
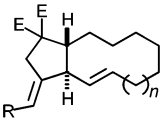
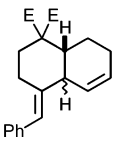
Table 1. Screening of Various Ferrate Complexes; E = COOEt



entry	catalyst	yield (%)
1	[CpFe(C_2H_4)$_2$] [Li(tmeda)] (**1a**)	83
2	[CpFe(cod)] [Li(dme)] (**1b**)	80
3	[CpFe(cod)] [Li(tmeda)] (**1c**)	82
4	[CpFe(CO)$_2$] Na (**3**)	0
5	[(C_2H_4)$_4$Fe] [Li(tmeda)]$_2$ (**2**)	0

Table 2. Iron-Catalyzed Cycloisomerizations of Enynes with Cyclic Alkene Moieties; E = COOEt, unless Stated Otherwise



Entry	Product		Isolated Yield
1		**5** (n = 1)	50%[a,b]
2		**6** (n = 2)	81%[c,d]
3		**7**	61%
4		**4a**	83% (R = H)
5		**4b**	93% (R = Me)
6		**4c**	95% (R = Ph)
7		**4d**	96% (R = cyclopropyl)
8		**4e**	70% (R = TMS)[a]
9		**4f**	68% (R = C(O)C_6H_{11})
10		**8a**	84% (R = Ac)[b]
11		**8b**	86% (R = TIPS)[b]
12		**8c**	96% (R, R = CMe_2)[b]
13		**9a**	70% (X = O)[e]
14		**9b**	93% (X = NBn)[e]
15		**9c**	94% (X = NTs)[e]
16		**10a** (n = 1)	76% (R = H)
17		**10b** (n = 1)	89% (R=C_6H_4-*p*-COOEt)
18		**11a** (n = 3)	81% (R = H)
19		**11b** (n = 3)	96% (R = *p*-MeO-C_6H_4)
20		**11c** (n = 3)	95% (R = *o*-Cl-C_6H_4)
21		**12**	68%[a,f]

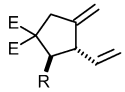
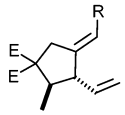
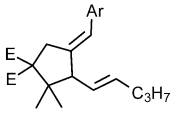
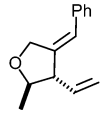
[a] With 15 mol % (**1a**), 72 h reaction time. [b] Ar = *p*-MeOC_6H_4. [c] Ar = Ph. [d] E = COOMe. [e] With 10 mol % (**1a**). [f] Ratio of *cis:trans* = 1:2.

metal catalysts.[12,13] Ferrate complexes might, therefore, constitute cheap, nontoxic, and benign alternatives that are readily available in quantity.

In line with this notion, enyne **3a** was converted to the Alder-ene product **4a** in excellent yield on exposure to 5 mol % of the Fe(0)−ate complex **1a** in toluene at 80−90 °C for 6 h (Table 1, entry 1). The analogous COD complexes **1b**,**c** were similarly

10.1021/ja0532739 CCC: $30.25

Table 3. Cycloisomerizations of Acyclic Enynes Catalyzed by Complex **1a**[a,b,c]

Entry	Product	Isolated Yield (*trans* : *cis*)
1	 **13a** (R = H)	0%
2	**13b** (R = Me)	93% (5.8:1)
3	 **14a** (R=*p*-MeO-C_6H_4)	97% (6.3:1)
4	**14b** (R=*p*-F_3C-C_6H_4)	96% (4.8:1)
5	**14c** (R=*p*-Me(O)C-C_6H_4)	91% (4.1:1)
6	**14d** (R=cyclopropyl)	97% (6.7:1)
7	 **15**	98%
8	 **16**	70% (9.8:1)[d]

[a] With 5 mol % of catalyst, toluene, 80−90 °C, 3−6 h, unless stated otherwise. [b] Only the major isomer is depicted. [c] E = COOEt. [d] **1a** (30 mol %), 1 h.

effective, although a somewhat longer reaction time (12 h) was necessary (entries 2 and 3). This rate difference might be explained by the more facile and irreversible substitution of the ethylene ligands in **1a** by the enyne, whereas the chelating COD in **1b** is arguably more difficult to replace, remains in solution, and might therefore compete with substrate binding. Formal replacement of the alkene groups in **1** by strongly bound CO (complex **3**,[14] entry 4) results in complete loss of catalytic activity, likely because an exchange of these ligands with the substrate cannot occur. The fact that the tetraethylene ferrate **2** is catalytically inert is ascribed to the lability of this complex at higher temperatures.

The scope of the iron-catalyzed Alder-ene reaction is evident from the results compiled in Tables 2 and 3. Although we were concerned about the potential basicity of complex **1a**, enynes containing terminal acetylene units posed no problems. Likewise, different substituents on the alkyne are well accommodated, including electron-withdrawing substituents, cyclopropyl- and silyl groups. The latter result is noteworthy as silylated enynes are unsuitable for Alder-ene reactions catalyzed by low-valent titanium reagents.[11] Particularly remarkable is the compatibility of the iron catalyst with various functional groups, including esters, ketones, acetals, silyl ethers, aryl halides, and cyclopropanes; even a tertiary amine in the tether does not interfere (cf. entry 14). Entry 21 shows that a 1,7-enyne could also be cyclized in decent yield. With regard to the cycloalkene part of the substrate, increase of the ring size renders the reaction more facile. This is evident from the fact that the [3.3.0]bicyclooctene derivative **5** was the most difficult to form among all products compiled in Table 2. While **5** and its homologue **6** are *cis*-annellated, all other products shown in Table 2 feature *trans*-annellated rings,[15,16] with the *exocyclic* double bond invariably showing the expected *E*-configuration. While the *endocyclic* alkene is forced to be *Z* in products **4**−**9** due to the small (≤8) size of the pre-existing ring, only the *E*-isomer is observed in the 10- and 12-membered series (entries 16−20),[17] even though the substrates used in these cases were isomeric mixtures.

Table 3 shows representative examples of iron-catalyzed reactions of acyclic enynes. The striking observation that a substituent R ≠ H next to reacting olefin moiety is required for productive cyclization (cf. entries 1 and 2) is general. Substrates of this type, however, perform exceptionally well, affording *trans*-disubstituted products as the major isomers in all cases investigated. Whether this effect indicates that a certain degree of conformational preorganization of the enyne is mandatory or if it has other mechanistic implications[9] is subject of ongoing studies in this laboratory.

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Supporting Information Available: Experimental part, including spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For the assignment of the stereochemistry, cf. Supporting Information.
(16) Precedence for the stereochemical switch from *cis* to *trans* on going to larger ring sizes is found in organopalladium chemistry, cf: Trost, B. M.; Grese, T. A. *J. Am. Chem. Soc*. **1991**, *113*, 7363.
(17) GC investigations show that the *E*-isomer does not result from equilibration but is the primary product of the reaction.

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