

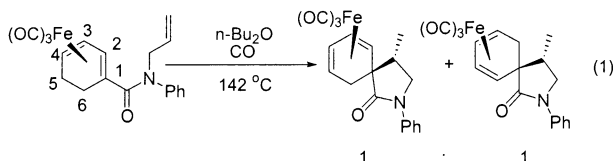
Double Cyclization via Intramolecular Coupling between Cyclohexadiene–Fe(CO)₃ Complexes and Pendant Conjugated Dienes

Anthony J. Pearson* and Xiaolong Wang

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

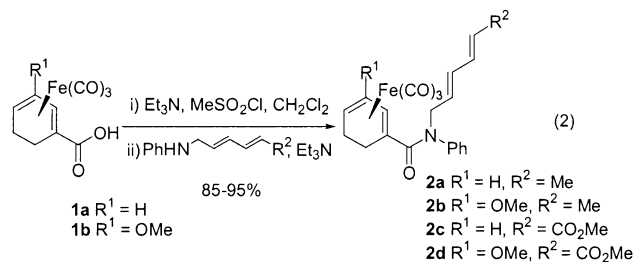
Received July 25, 2002; E-mail: ajp4@po.cwru.edu

The diene–Fe(CO)₃ moiety has been widely used for stereoselective construction of C–C bonds,¹ especially for the formation of quaternary carbon centers in synthesis.² Synthesis of spirocyclic and angularly fused tricyclic systems, which have such quaternary centers embedded in their molecular structures, is an area of much interest in terms of the presence of these frameworks in many naturally occurring compounds.³ An interesting intramolecular coupling between a cyclohexadiene–Fe(CO)₃ complex and a pendant olefin to generate spirocycles was introduced by our group.⁴ The best substrates for this reaction are amide complexes, which are converted to spiroactams (eq 1).



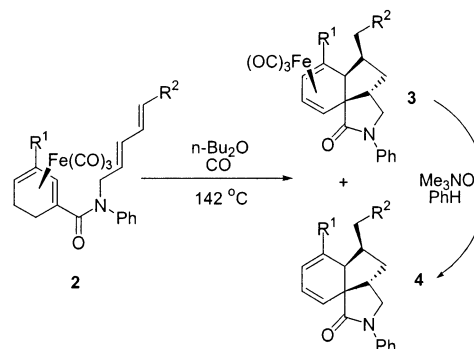
One of the problems with this reaction is that it produces a pair of epimers as a result of thermal rearrangement of the diene–Fe(CO)₃ system that involves a hydride migration.^{4,5} Although introducing a cyano or phenyl group at C(5) can control the diene regiochemistry, it brings in several restrictions^{4a} and makes the reaction difficult for practical use in synthesis.

With our continuing development of synthetic organoiron chemistry, we report here a double cyclization reaction which avoids epimerization of the product and gives a single diastereomerically pure tricyclic product. The whole process is similar to two successive ene-type reactions.



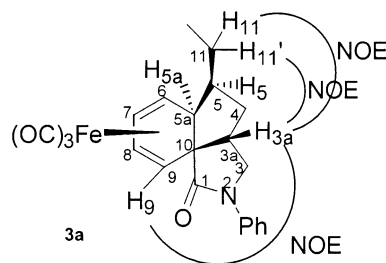
The substrates (2) for the cyclization were readily prepared in high yield from carboxylic acid complexes^{4b,6} (1) (eq 2). Refluxing **2a** in anhydrous di-*n*-butyl ether (0.02 mol/L) under carbon monoxide atmosphere for 10 h yielded a single diene–Fe(CO)₃ complex **3a** in 75% yield (Table 1). No other diastereomers were detected by ¹H NMR of the reaction mixture. The only detected side products appear to be isomers of the starting material (<2% yield). Demetalation of **3a** using trimethylamine *N*-oxide in benzene produced **4a** smoothly in almost quantitative yield.

Table 1. Cyclization of Amide Complexes **2**



reactant	R ¹ , R ²	time ^a (h)	product	concentration (mol/L) ^b	yield 4 ^c (%)
2a	H, Me	10	4a	0.02	75
2b	OMe, Me	24	4b	0.004	54
2c	H, CO ₂ Me	12	4c	0.004	51
2d	OCH ₃ , CO ₂ Me	24	4d	0.004	34

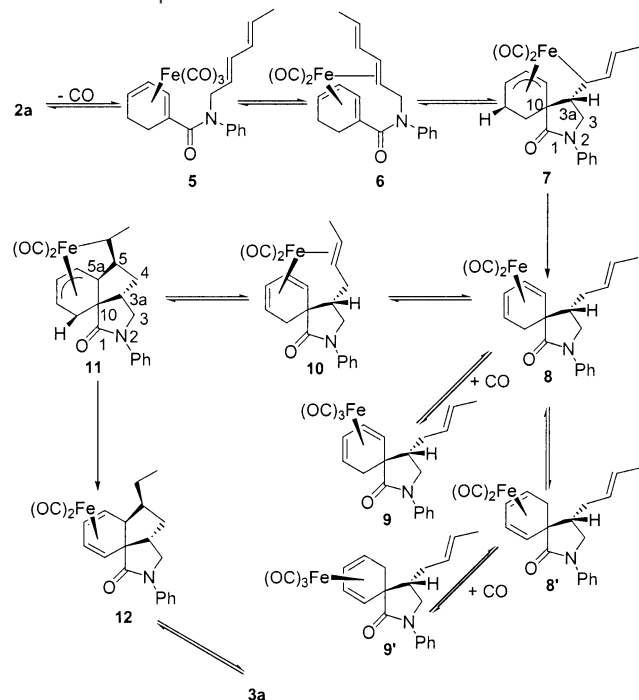
^a Reaction time for cyclization step. ^b Concentration of reactant **2**. ^c Overall yield from **2** after demetalation, two steps.



The stereochemistry of **3a** was determined by 2D COSY and 2D NOESY experiments. There was strong NOE between H_{3a} and H₉, but no effect between H_{3a} and H₅ or H_{3a} and H_{5a}, which indicated the stereochemical relationship between each of the latter pairs is *trans*. Strong NOE was also observed between H_{3a} and H₁₁, H_{11'}, which showed the *cis* relationship between H_{3a} and 5-ethyl and confirmed the *trans* relationship between H_{3a} and H₅. The structure was also supported by the coupling constant between H₅ and H_{5a} (*J* = 8.4 Hz).

The proposed mechanism, which is based on the above results and our previous work,⁴ is shown in Scheme 1. Under thermal conditions, dissociation of one CO ligand from complex **2a** creates a vacant coordination site, which is then occupied by one of the double bonds from the pendant diene (6). Cyclization (reductive elimination) leads to metallacycle **7**. The newly formed C(3a)–C(10) bond is *syn* to the metal, and the stability of the metallacycle fixes the configuration of C(3a).^{4a} Hydride migration and reductive

Scheme 1. Proposed Mechanism



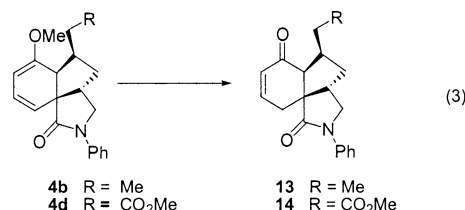
elimination delivers 16e intermediate **8**. Formation of **9** and **9'** (see later) could occur by addition of a CO ligand or rearrangement of the diene-Fe(CO)₃ system. Further coordination of **8** with the remaining double bond and subsequent second cyclization produces **11**. Again, the newly formed C(5)-C(5a) bond is endo to the metal, and C(5) stereochemistry is controlled by the metal just as for that at C(3a). Hydride migration, reductive elimination, and coordination of CO ligand yields the final product **3a**. Since H(5a) is exo to the Fe(CO)₃ group, hydride migration to C(9) is prevented.⁵

Encouraged by the excellent stereocontrol and good yield of this reaction, we examined the amide complex **2b**, which has a methoxy substituent on the cyclohexadiene ring. Surprisingly, heating **2b** in *n*-Bu₂O for 12 h only gave about 15% complex **3b** and 10% demetalated product **4b** along with some side products, none of which was starting material. Attempts to separate and unambiguously identify these side products were unsuccessful. The major mixture was found to contain alkene protons as evidenced by ¹H NMR. The IR spectrum indicated the presence of a five-membered lactam (1688 cm⁻¹). Most likely analogues of **9** and **9'** are formed, and the reaction needs more time to reach completion. The second cyclization is slow, which might be due to the steric effect of the methoxy group close to the reaction site. Optimization of the reaction conditions (0.004 mol/L, 24 h) led to the formation of a 1:1 ratio (¹H NMR) of **3b** and **4b** in 54% combined yield. Demetalation of a spiromethoxycyclohexadiene-Fe(CO)₃ during cyclization was also seen in our earlier work.⁶ Nevertheless, the reaction mixture was converted to **4b** in almost quantitative yield. The relatively lower yield is tentatively attributed to the demetalation of the monocyclized product on prolonged heating.

Iron carbonyl complexes prefer to be coupled with electron-deficient olefins⁷ and only highly electron-deficient alkenes were reported to undergo intermolecular coupling with diene-Fe(CO)₃

complexes.⁸ We therefore decided to add an ester group to the pendant diene system, hoping that it would facilitate the reaction and improve the yield. Unfortunately cyclization of **2c** and **2d** seemed to suffer from side reactions of the labile dienolate. High dilution of reactants is required; **4c** and **4d** were formed in 51% and 34% yields, respectively (Table 1).

Hydrolysis of methoxycyclohexadiene **4b** (oxalic acid, water and methanol)⁶ and **4d** (MeSiCl₃, CD₃CN, then water)⁹ gave enone **13** in 75% yield and **14** in 68% yield (eq 3), which are expected to be more useful than the aforementioned diene for further functionalization.



In conclusion, intramolecular double cyclization between a diene-Fe(CO)₃ complex and pendant diene provides a complex tricyclic molecule containing four contiguous chiral carbon centers, with excellent stereocontrol from relatively simple and easily available starting material. Similar structures are present in comimine, conamine and conessine.^{3d,10} The scope, application, and enantioselectivity of this reaction are currently under investigation.

Acknowledgment. We thank the National Science Foundation for financial support (CHE-0131043).

Supporting Information Available: Experimental procedures and Figures giving NMR spectra (¹H, ¹³C) of all new compounds, 2D COSY, NOESY of compound **3a**, 2D COSY of **3b** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0210188