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# Intramolecular Iron-Mediated Diene/Olefin Cyclocoupling: Formation of Carbon Spirocycles

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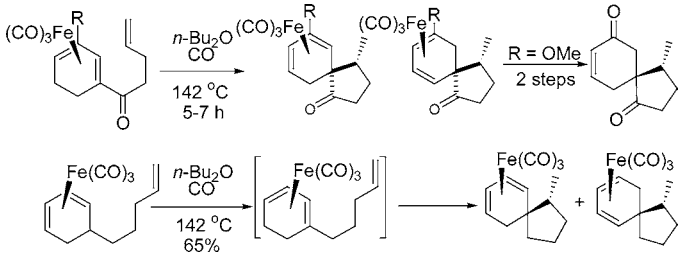
## ABSTRACT

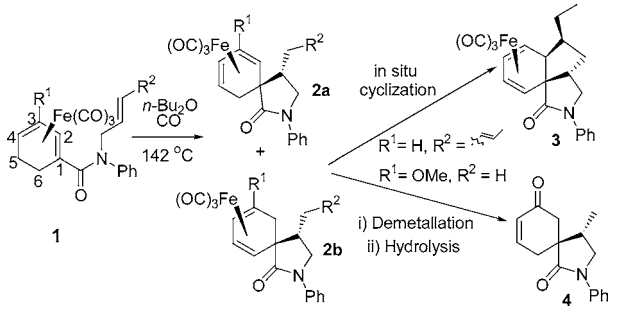



**A short and convenient diastereoselective synthesis of all-carbon spirocylic molecules was developed. A straightforward protocol that involves rearrangement of the diene–Fe(CO)$_3$ complex followed by cyclization delivers the desired product. The reaction substrates were easily prepared by reaction of an appropriate nucleophile and a cyclohexadienyl-Fe(CO)$_3$ cation.**

Spirocyclic systems constitute an important class of molecules owing to their frequent occurrence in many natural products.[1,2] Among them, spirocyclic sesquiterpenes continue to attract the attention of synthetic chemists because of the challenge of stereocontrolled construction of the spirocyclic carbon skeleton.[3,4] Whereas a wide range of methods directed to the synthesis of these classes of compounds are available, the stereocontrolled formation of the stereogenic spirocenter is extremely restricted,[5,6] and the cyclization yields are often poor.

A stereospecific cyclization reaction between cyclohexadiene−Fe(CO)$_3$ complexes and pendant alkenes has been developed in our laboratory to generate a pair of epimeric spiro-$\gamma$-lactams **2** in excellent yield (Scheme 1, R$^1$ = R$^2$ = H).[7] The net result is a [6 + 2] ene cyclization. Amide complexes **1** were prepared from the corresponding acid **5**[7,8] (Scheme 2). Introducing a methoxy group at the 3-position not only controls the overall stereochemistry of this reaction but also installs useful functionality, an enone, into the product (see structure **4**).[8] When an additional alkene (R$^2$ =

**Scheme 1.** Spirolactamization

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(1) Heathcock, C. L.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. Spirocyclic Systems. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, pp 264−313.
(2) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.
(3) Fraga, B. M. *Nat. Prod. Rep.* **1999**, *16*, 711.
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(7) Pearson, A. J.; Zettler, M. W. *J. Am. Chem. Soc.* **1989**, *111*, 3908.
(8) Pearson, A. J.; Dorange, I. B. *J. Org. Chem.* **2001**, *66*, 3140.

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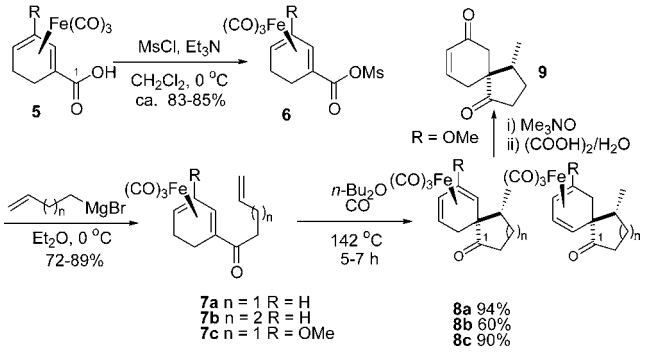
**Scheme 2.** All-Carbon Cyclization via Ketone Intermediate




1-propenyl) is present, a tricyclic molecule is formed by tandem double-cyclization (**3**, Scheme 1).[9]

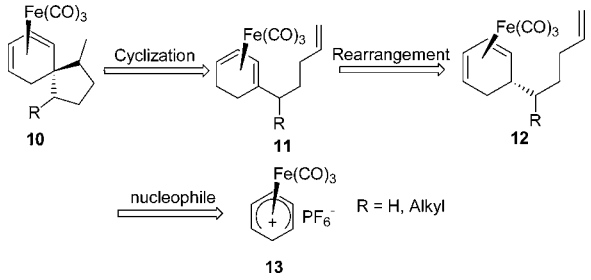
In this paper, we report the extension and application of this intramolecular coupling toward all-carbon spirocycles, which is envisioned to constitute a powerful route to the stereospecific formation of spiro[4,5]decane and spiro[5,5]-undecane systems. Surprisingly, the first challenge encountered was the formation of the required ketone **7** (Scheme 2). Nucleophilic addition to ester, acyl chloride, Weinreb amide, aldehyde, and acyl diphenylphosphinic anhydride, prepared from **5**, were uniformly unsuccessful. Fortunately, a two step sequence, acyl mesylate formation (**6**) followed by Grignard addition, gave ketone complexes **7a**−**c** in satisfactory yields.

With these ketone complexes in hand, their behavior toward cyclization was studied. Gratifyingly, when **7a** was subjected to thermal cyclization conditions[7] (*n*-$Bu_2O$, CO, reflux, 5 h) spiroketone **8a** was afforded in 94% yield as a pair of epimers resulting from diene−$Fe(CO)_3$ rearrangement.[7] Complex **7b** gave the spiro[5,5]undecane system by a six-membered ring formation, which requires longer reaction time (7 h). Methoxy-substituted ketone complex **7c** afforded, in excellent yield (90%, Scheme 2), a 1:1 mixture of regioisomeric spiroketone complexes **8c**, which were converted in two steps to a single enone diastereomer **9** in 75% yield (see also compound **4**, Scheme 1).

With the establishment of the all-carbon spirocyclization, one can envision applying this method to natural product synthesis. In many cases, this requires transformation of the 1-keto group (Scheme 2) to an alkyl group. Since it is not trivial to manipulate a ketone next to a spirocenter, we decided to introduce the alkyl group into the starting material, but this would require a protracted synthetic route from ketones such as **7**. Moreover, the acid complexes for preparing the ketones have to be synthesized in five steps from the corresponding benzoic acid derivatives. A simpler and more efficient approach was therefore investigated.

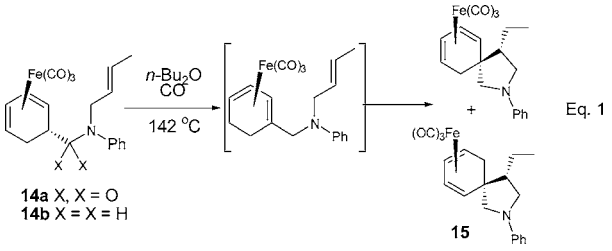
There is evidence that, in cyclohexadiene−iron tricarbonyl complexes, the iron moiety migrates around the ring by hydride transfer under our cyclization conditions.[7,10] The required cyclization substrates, 1-substituted cyclohexadiene−$Fe(CO)_3$ complexes **11**, might be formed from the 5-exo isomers **12** by in situ rearrangement prior to cyclization. Complexes **12** are very easily accessed from cyclohexadienyliron cation **13**[11] by nucleophile addition (Scheme 3).

**Scheme 3.** Proposed Rearrangement−Cyclization




It should be mentioned that the nucleophile additions to cation **13** and its derivatives have been extensively studied, a large number of substituted cations related to **13** are available and easily prepared, and a wide range of nucleophiles can be reacted with **13** in good to excellent yield and selectivity.[11]

Amide complex **14a**, an analogue of **12**, obtained as a side product in our earlier studies, was initially subjected to cyclization conditions to test the rearrangement−cyclization transformation sequence. Only traces of cyclization product were observed after 12 h, the remaining material being unreacted **14a**. The reluctance of **14a** to undergo rearrangement was tentatively attributed to a difficult hydride transfer from the α-position of the carbamide to the Fe group. On the basis of this proposition, amine **14b**, from the DIBALH reduction of **14a**, was subjected to spirocyclization. Spiroamine **15** was produced in good yield with 80% conversion upon heating for 12 h. Thus, the rearrangement−cyclization strategy is feasible.




Next, **16**, the simplest substrate, was prepared by Grignard addition[12] at −78 °C in dichloromethane to the known complex **13**, which is easily obtained in excellent yield[11,13] from cyclohexadiene in two steps, as shown in Scheme 4. Upon heating **16** for 12 h, **18a** and **18b** (ratio 1.5:1) were

(9) Pearson, A. J.; Wang, X. *J. Am. Chem. Soc.* **2003**, *125*, 638.
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(11) (a) Pearson, A. J. *Acc. Chem. Res.* **1980**, *13*, 463−469. (b) Pearson, A. J. *Iron Compounds in Organic Synthesis*; Academic Press: London, 1994.
(12) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553.
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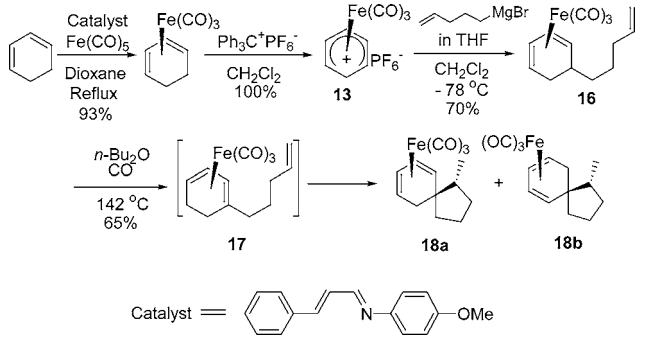
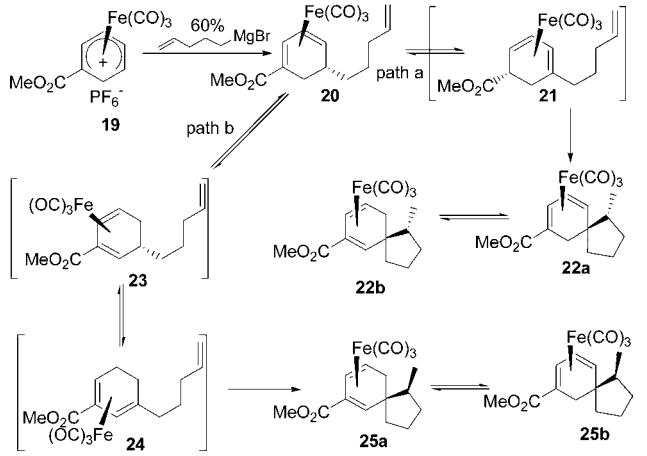
**Scheme 4.** Rearrangement−Cyclization




produced in 65% yield. Only four steps are required to produce spiro[4,5]decane derivatives from 1,3-cyclohexadiene (two steps from **13**, which is also commercially available) with good overall yield, which represents a significant improvement over our previous method.

Migration of the $Fe(CO)_3$ in **16** can occur in two directions, "clockwise" and "anticlockwise". Clockwise, one-step rearrangement would give **17**, while two anticlockwise rearrangements will give *ent*-**17**. Both enantiomers of **17** cyclize to give enantiomeric products. Thus, even an enantioselective alkylation of **13** would not allow enantioselective synthesis of **18**. Introducing a substituent onto the cyclohexadiene ring of **16** (not at the para-position) serves to control this rearrangement. Regioselective addition of Grignard reagent to the 1-carbomethoxycyclohexadienyl tricarbonyliron cation **19**[11a] gave *exo*-5-(4-pentenyl)-1-carbomethoxycyclohexadieneiron tricarbonyl (**20**). Cyclization of **20** revealed the effect of the ester functionality, wherein a 1:1:1:7 (inseparable) mixture (by integration of the terminal methyl doublets, 600 MHz $^1$H NMR) of **22a**, **22b**, **25a**, and **25b** was formed in about 50% yield. $^1$H NMR and NOE difference studies of the major isomer established its structure as **25b**. A tentative explanation is presented in Scheme 5, in which the diene−$Fe(CO)_3$ rearranges in both directions, paths a and b. Although fewer steps are required to produce **22**

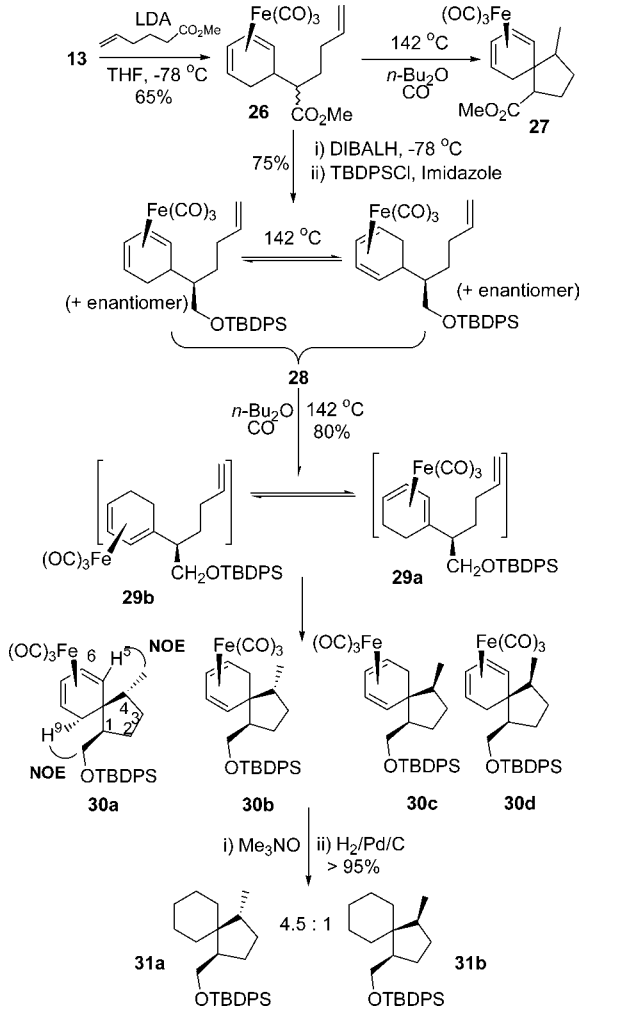
**Scheme 5.** Regiocontrolled Rearrangement−Cyclization




(path a), it appears that b is the major pathway where two successive diene rearrangements, followed by cyclization, gave **25**. The major product, **25b**, is thermodynamically more stable than **25a**.[14]

Treatment of methyl 5-hexenoate with 1 equiv of LDA in THF and subsequent addition[15] of **13** at −78 °C produced **26** as a 2:1 mixture of diastereomers (Scheme 6). Refluxing

**Scheme 6.** Diastereoselective Rearrangement−Cyclization




**26** in dibutyl ether for 14 h gave the spirocycle **27** (142 °C, about 60% yield) containing some inseparable side products along with about 10% of unreacted starting material. The relatively slower reaction is attributed to the effect of the electron-withdrawing ester group on the initial rearrangement that is needed for cyclization. Reduction of the ester **26** followed by TBDPS protection gave **28**, again as a 2:1 mixture. Since the two diastereomers of **28** can be interconverted during cyclization, and both can rearrange to give **29a** and **29b**, their stereochemistries were not fully assigned. The mixture cyclized in 80% yield to give a mixture of four

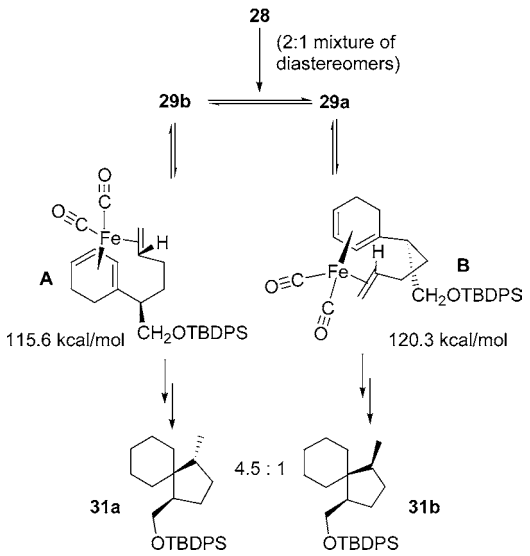
(14) This directing effect of an electron-withdrawing group was also observed in our previous work. For details see ref 7.

(15) Pearson, A. J.; Kole, S. L.; Yoon, J. *Organometallics* **1986**, *5*, 2077.

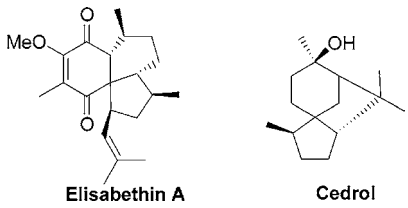
isomeric products **30a**−**d** with the ratio 4.5:4:1:1. Demetalation of **30** followed by hydrogenation gave a 4.5:1 mixture of **31a** and **31b** based on $^1$H NMR. The major products were shown to be a pair of trans spirocycles **30a** and **30b** by NOE difference study on the mixture of **30**. When the methyl doublet was irradiated, positive enhancement was observed with $H_5$ (**30a**, Scheme 6). Irradiation of the methylene hydrogens next to oxygen of $CH_2$OTBDPS showed positive NOE with a doublet ($\delta$ = 1.7 ppm, $J$ = 15.0 Hz), which was assigned as $H_9$. Since $H_5$ and $H_9$ are on different sides with respect to the five-membered ring, the methyl group and the TBDPS ether group must be trans.

The preference for a trans relationship is confirmed by molecular mechanics strain energy calculations using PC Spartan[16] on two intermediates (**A** and **B**, Scheme 7) that lead to the cyclization product. The trans intermediate **A** is lower in energy than cis intermediate **B** by 4.7 kcal/mol; therefore, the corresponding product from **A** would be the major one at 142 °C.

**Scheme 7**




Good diastereoselectivity during cyclization is observed here between C1 and C4 in product **30**. Therefore, in principle, the chirality at C1 can be utilized to control the configuration of the final product. It is noteworthy that the major product, **31a**, has much of the carbon skeleton corresponding to natural terpenoids such as cedrol and elisabethin A.




In summary, we have developed a convenient procedure to prepare all-carbon spirocycles. Future studies will address the scope of this reaction, tandem double cyclizations on the all-carbon system,[9] and application in the synthesis of natural products.

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**Supporting Information Available:** Experimental procedures and figures giving NMR spectra ($^1$H, $^{13}$C) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Spartan'02, Wavefunction, Inc., Invine, CA.