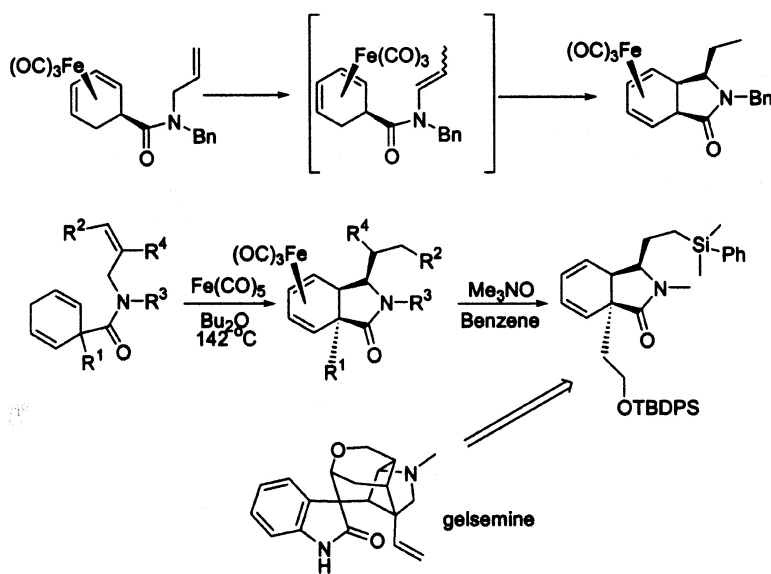Communication

A Convenient One-Pot Procedure to Afford Bicyclic Molecules by Stereospecific Iron Carbonyl Mediated [6 + 2] Ene-Type Cyclization: A Possible Approach to Gelsemine

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A Convenient One-Pot Procedure to Afford Bicyclic Molecules by Stereospecific Iron Carbonyl Mediated [6 + 2] Ene-Type Cyclization: A Possible Approach to Gelsemine

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Iron has been widely used in organic synthesis.[1] Fe(0) is known to promote isomerization of monoolefins[2] and cycloaddition of conjugated dienes.[3] For several years, we have been developing an intramolecular coupling reaction between cyclohexadiene−Fe-(CO)$_3$ complexes and pendant olefins, which cyclize to give spirocyclic molecules.[4] By tandem double cyclization, a complex tricyclic molecule can be prepared in a single step with complete diastereoselectivity (Scheme 1).[4d]
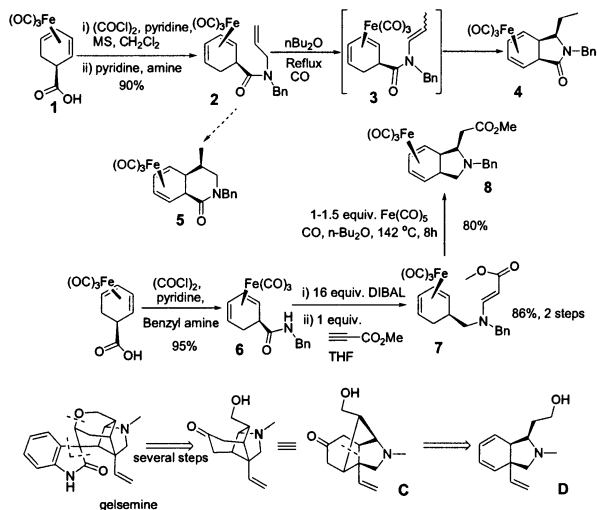
Scheme 1
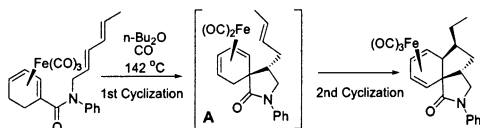
Looking only at the second cyclization suggests that a bicyclic structure might be formed in the absence of the lactam ring. If substrates (**B**) similar to the double cyclization intermediate (**A**) can be made (eq 1), this methodology may be extended to produce a variety of bicyclic molecules.
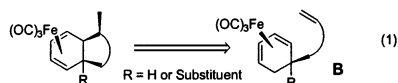

The cyclization reaction proceeds via coordination of a pendant double bond to Fe,[4a] which should therefore be cis to Fe(CO)$_3$ in **B**. With this in mind, we began with amide complex **2**, which was prepared from known acid **1**[5] and N-benzyl allylamine (Scheme 2). Our initial plan was to make six-membered lactam **5**. To our surprise, refluxing **2** in di-n-butyl ether (0.02 mol/L) under CO

**Scheme 2**

Scheme 3
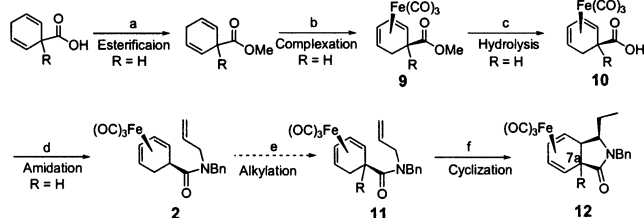
atmosphere for 6 h gave only traces of **5**. The major products were enamide **3** and five-membered lactam **4**. Extension of the reaction time led to decomposition. Varying the substrate concentration indicated an autocatalysis phenomenon. We concluded that six-membered lactam formation was not favored, and instead the reaction proceeded via isomerization (catalyzed by a diene−Fe-(CO)$_2$ residue), also observed in our previous work,[4c] followed by cyclization. Since it is known that Fe(CO)$_5$ catalyzes double bond migration,[2] we added 1−1.5 equiv of Fe(CO)$_5$, whereupon the isomerization−cyclization proceeded cleanly in 6 h to give **4** in 91% yield as the sole product! Direct cyclization of enamine iron complex **7** (preparation shown in Scheme 2) to afford **8**, without the ismerization step, was also realized.

Compounds **4** and **8** have a bicyclic framework and stereochemistry identical to that in gelsemine, a hexacyclic natural product which has attracted much attention from the synthetic community because of its unique cage structure.[6] If proper functionality could be introduced onto **4**, this reaction might provide a potential pathway to gelsemine via intermediate **D** or its equivalent.

To generate a possible approach to the gelsemine structure, a substituent is required at C(7a) (structure **12**, Scheme 3). Investigation of our protocol showed that this was problematic. If the R group (for example Me) is introduced before step c, the ester **9** cannot be hydrolyzed due to steric hindrance.[7] Similar difficulties are anticipated for direct conversion of **10** to **11** (R ≠ H). Attempts on alkylation (step e) of **2** were disappointing. Similar problems exist for alkylation of **4** to give **12** (R ≠ H).

This dilemma prompted us to devise an alternate strategy. Careful examination of Scheme 3 showed that preparation of the iron complex (step b) and cyclization (step f) share the same reaction conditions. We argued that these two steps might be combined, making the organic framework first, which is then treated with Fe-(CO)$_5$ in refluxing di-n-butyl ether as the last step (Scheme 4). This last step would require selective complexation of Fe(CO)$_3$ to the cyclohexadiene, and isomerization of the pendant double bond, followed by cyclization. Using our new one-pot protocol, only three operations are required to obtain the angularly substituted bicyclic lactam with stereochemistry matching the possible intermediate **D** toward gelsemine.

Scheme 4
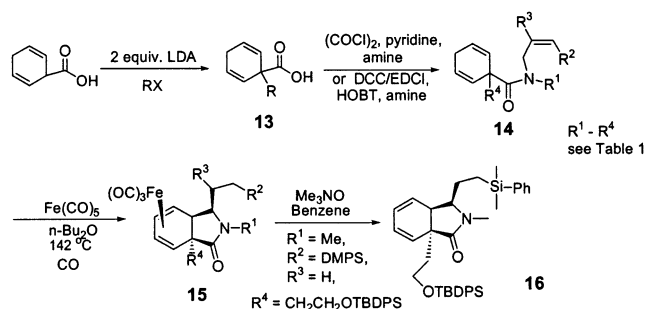
Table 1. One-Step Cyclization of **14** to Produce Bicycles **15**[a]

| reactant	R¹, R², R³, R⁴	product	yield
14a	R¹ + R² = CH₂, R³ = H, R⁴ = Bn	**15a**	92
14b	R¹ + R² = CH₂CH₂, R³ = H, R⁴ = Bn	**15b**	85
14c	R¹ = Ph, R² = H, R³ = Me, R⁴ = Bn	**15c**	81[b]
14d	R¹ = Me, R² = R³ = H, R⁴ = Bn	**15d**	82[c]
14e	R¹ = R² = R³ = H, R⁴ = Bn	**15e**	20
14f	R¹ + R² = CH₂, R³ = H, R⁴ = CH₂CH₂OTBDPS	**15f**	68
14g	R¹ = Me, R² = DMPS, R³ = H, R⁴ = CH₂CH₂OTBDPS	**15g**	63

[a] Reaction times for cyclization step range from 24 to 36 h, see Supporting Information. [b] Including another isomer, where iron is on the other face of the cyclohexadiene ring.[11] [c] Including 21% demetalated product.

To our delight, the transformations worked as expected. Alkylation of 1,4-dihydrobenzoic acid[8] followed by amidation delivered *N*-allylamides **14a−g**, substrates that were subjected to the Fe-mediated one-pot cyclization reaction. When trienes **14** were refluxed in di-*n*-butyl ether (0.02 mol/L) under CO atmosphere in the presence of Fe(CO)₅, a single product **15** was obtained in good yield for all of the substrates except **14e** (Table 1). Tricyclic products were formed for **15a**, **b**, and **f**. In **15f** and **15g**, a vinyl equivalent (CH₂CH₂OTBDPS) was introduced at the angular position instead of a simple benzyl group (but note that phenyl group can be converted to carboxylic acid[9]). **15g** is especially noteworthy, where the organic part matches **D**, not only in terms of skeleton and stereochemistry, but also functionality, since dimethylphenylsilyl is a latent hydroxyl and TBDPS-protected hydroxyethyl is a potential vinyl group. It also showed that a vinylsilane is compatible with the reaction conditions. **15g** was chosen to demonstrate the demetalation of these diene−Fe(CO)₃ complexes,[4c] yielding the corresponding diene **16** quantitatively. With known chemistry to selectively functionalize conjugated cyclohexadienes,[10] we have good reason to envision compound **16** as a potential gelsemine intermediate.

Scheme 5 explains the diastereoselectivity of this reaction. The amide carbonyl directs Fe(CO)₃ to coordinate the diene on the same side,[12] followed by rearrangement of the allyl amide to enamide (steps a and b, Scheme 5) or vice versa (steps c and d) to give the intermediate **17**, which then readily cyclizes to give the final product **15**. Intermediate **17f** was isolated and fully identified. It should be mentioned that enamide **17** is difficult to make by conventional organic chemistry.

Interestingly, when *N*-propargylamide **18** was subjected to the above cyclization conditions in the presence of 3 equiv of triethylsilane, **19** and **20** were produced in 53% (unoptimized)

Scheme 5
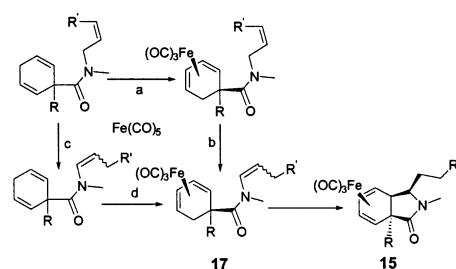
combined yield (eq 2). Here, four transformations are realized in a single operation, but there is little or no regiocontrol during the hydrosilation reaction (**19:20**/1.1:1).
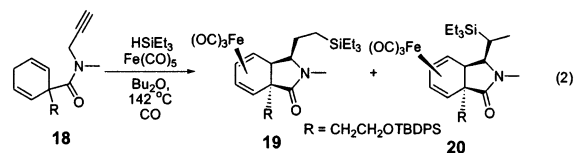
In conclusion, we have successfully developed a convenient one-pot (complexation, isomerization, and cyclization) procedure to construct angularly substituted bicyclic and tricyclic molecules with excellent diastereoselectivity. Further studies on this reaction including combination of the in situ hydrosilation of alkyne (eq 2) are underway. Synthetic approaches to gelsemine using this methodology are under consideration.

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

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