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An Iron-Promoted Aldehyde−Diene Cyclocoupling Reaction

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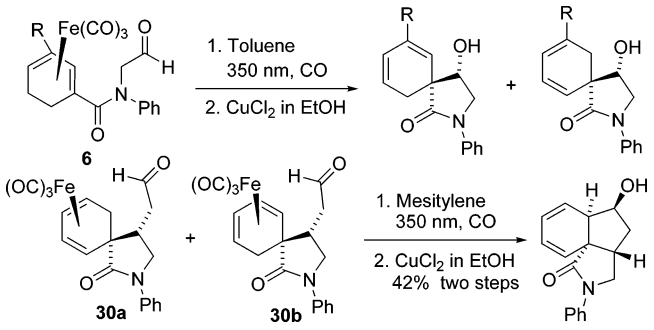

A stereospecific intramolecular iron tricarbonyl-promoted aldehyde−diene cyclocoupling reaction was investigated by using simple substrates **6** and more complicated substrates **30a**/**30b**. Demetalation of the initial products converts all complexed dienes to their pure organic counterparts. In addition, the nickel-catalyzed carbonyl−ene reaction and the Prins reaction were investigated with two different substrates.

Introduction

An intramolecular iron tricarbonyl promoted [6+2] ene type of spirocyclization reaction has been developed in our laboratory.[1] This reaction is based on substrates with a cyclohexadieneiron tricarbonyl moiety and a pendant olefin and affords two diastereomeric spirocyclic iron complexes, which can be readily converted to organic molecules by subsequent demetalation reactions (Scheme 1). The new carbon−carbon bonds (C4 and C5 in compounds **2a**/**2b**) are formed stereospecifically, but thermal rearrangement leads to isomerization of **2a** to **2b** by iron-mediated hydride shift. Further investigation showed this regioisomerization problem can be remedied through tandem double cyclization[2] or introduction of certain functional groups on the cyclohexadiene ring,[1,3] and excellent dynamic diastereoselectivity can also be obtained by introducing a chiral center on the side chain.[4] However, formation of a nonfunctionalized alkyl group at C4 limits the application of this spirocyclization reaction in organic synthesis.

Results and Discussion

To expand the scope of this iron tricarbonyl-promoted cyclization reaction, we examined the reactivity of substrates **6a**−**c** and **7**, each having a pendant carbonyl group, in anticipation that a carbonyl−ene-type of spirocyclization could also be promoted by iron to afford products with a functionalizable hydroxyl group at C4. Complexes **6a**−**c** were readily prepared in good yields starting with iron complexed dienylcarboxylic acids **4a**−**c**[5,6] through amidation followed by ester to aldehyde reduction with DIBAl-H at low temperature (Scheme 2). Treatment of **6a** with MeMgBr at −78 °C followed by in situ Mukaiyama oxidation of the alkoxide afforded substrate **7** with a pendant ketone in 62% yield over two steps.[7]

With these substrates in hand, we investigated their reactivity under various cyclization conditions previously found to effect diene/alkene cyclocoupling. Substrate **6a** was subjected to thermal cyclization conditions (*n*-Bu_2O, CO, 145 °C) and the anticipated spirolactam complex **8a** was isolated in only 4% yield with loss of most starting material (Table 1, entry 1).

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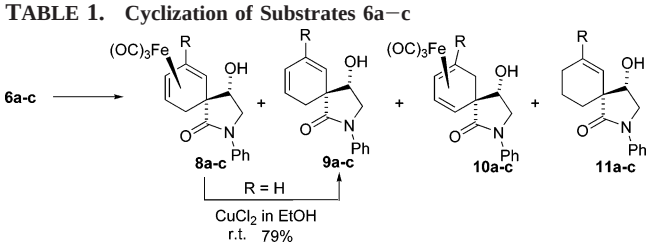
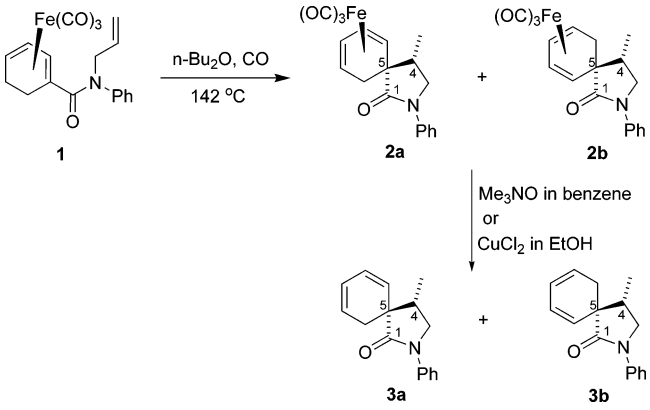
TABLE 1. Cyclization of Substrates 6a−c



				products (%)[b]			
entry	substrate	conditions[a]	time (h)	**8**	**9**	**10**	**11**
1	**6a**	A	8	4			
2	**6a**	B	12	17			5
3	**6a**	C	6	28	4	6	8
4	**6a**	D	6	18			12
5	**6a**	**E**	**12**	**47**	**6**	**7**	**8**
6	**6a**	**E**	**20**	**35**	**4**	**6**	**4**
7	**6b**	C	6	20		5	
8	**6c**	E	12	7			

[a] Conditions: (A) *n*-Bu_2O, 145 °C; (B) benzene, 350 nm, 80 °C; (C) toluene, 350 nm, 110 °C; (D) mesitylene, 350 nm, 160 °C; (E) toluene, 350 nm, 100 °C. [b] Isolated percent yields.

SCHEME 1



Photothermal cyclization (benzene, 350 nm, CO, 80 °C) afforded **8a** in better yield (17%) with 42% recovered starting material (Table 1, entry 2). Under these conditions, several minor side products were also observed, among which only one could be purified and fully characterized as the decomplexed monoolefinyl lactam **11a**, obtained in 5% yield. The hydrogen source for formation of this monoolefin compound has not been determined at this time. When the cyclization of **6a** was attempted under various conditions by changing solvent, reaction temperature, and reaction time (Table 1, entries 3−6), it was found that prolonged reaction time and higher temperature usually caused loss of material. Finally, the best results were obtained under photothermal conditions in toluene at 100 °C, which afforded both expected products **8a** (47%), **10a** (7%), demetalated product **9a** (6%) and side product **11a** (8%). The combined yield for both diene regioisomers was 60% in an 8:1 ratio ((**8a** + **9a**)/**10a**). Complexed **8a** was readily demetalated by $CuCl_2$ in EtOH to provide **9a** in 79% yield.[8]

Cyclization of methyl-substituted complex **6b** under photothermal conditions afforded a 4:1 mixture of regioisomeric spirolactam complexes **8b** and **10b** in 25% combined yield (Table 1, entry 7). Methoxy-substituted substrate **6c** underwent cyclization to give a single product **8c** but in only 7% yield (Table 1, entry 8). Substantial amounts of polar, uncharacterizable material were also formed during this reaction. Subjection of ketone substrate **7** to photothermal cyclization conditions gave uncyclized regioisomers from diene rearrangement and no cyclization products were observed.

This intramolecular iron tricarbonyl-promoted carbonyl−ene spirocyclization likely proceeds via a mechanism similar to the all-carbon [6+2] ene type of spirocyclization reported earlier.[1] Under either thermal or photothermal conditions, one carbonyl ligand is dissociated from the iron atom in substrate **6a** to lead to a 16e iron complex **12** with a vacant coordination site, which can be occupied by η^2 coordination of the iron atom with the aldehyde carbonyl double bond to form intermediate **13** (Scheme 3). Subsequent cyclization gives π allyl complex **14** followed by hydride migration to afford **15**. Then reductive elimination followed by recapture of one carbonyl group affords product **8a**, which can undergo diene migration through intermediates **16** and **17** under the reaction conditions to give regioisomer **10a** as a minor product. Generally, iron-promoted [6+2] ene spirocyclization affords these two regioisomers in equivalent amounts, but this carbonyl−ene reaction gives the directly formed lactam **8a** as the major product. This stereoselectivity is likely due to coordination of the iron atom with the newly formed hydroxyl group in a 16e complexed intermediate **16**, formed through dissociation of one carbonyl from **8a** under the reaction conditions, which stabilizes **16**. This coordination effect geometrically favors the position for the diene in the 16e intermediate **16** and disfavors postcyclization diene migration to form intermediate **17**, which can lead to minor product **10a**.

To investigate the capability of this iron-promoted carbonyl−ene reaction for formation of a 6-membered lactam, substrate **18** was prepared in good yield through homologation of aldehyde **6a** as shown in Scheme 4.[9] Subjection of **18** to photothermal conditions gave complexed secondary amide **19** as the sole product in 46% yield instead of formation of a 6-membered lactam. Thermal cyclization conditions gave similar results with formation of some unidentified demetalated products. Considering the side chain structure of **18**, a retro-Michael reaction to generate **19** is not unexpected under these reaction conditions.

18-Deoxycytochalasin H (Scheme 5) is a potent HIV-1 protease inhibitor and its derivatives can regulate plant growth.[10] Through retrosynthetic analysis, this natural product might be accessible from intermediate **20**, which comprises a tricyclic core structure with a 5-membered lactam, and this compound might be prepared from complexed aldehydes **22a**/**b** through this iron-promoted aldehyde−diene reaction with formation of a single complexed product **21**. The desired substrates **22a**/**b** might be available from known complexes **23a**/**b**, which have been obtained through an $Fe(CO)_3$-promoted [6+2] ene spirocyclization in excellent diastereoselectivity during our previous work.[4]

Before applying this iron-mediated aldehyde−diene coupling reaction to the synthesis of intermediate **21** for a projected total synthesis of 18-deoxycytochalasin H, a model reaction was designed and studied based on simple substrates. Accordingly, complexes **30a**/**b** and **31a**/**b** were prepared starting with commercially available aminoalcohol **24**, which was protected

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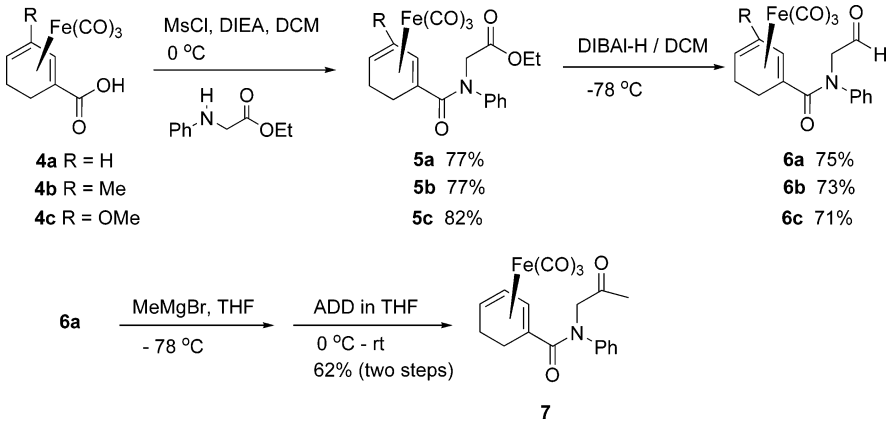
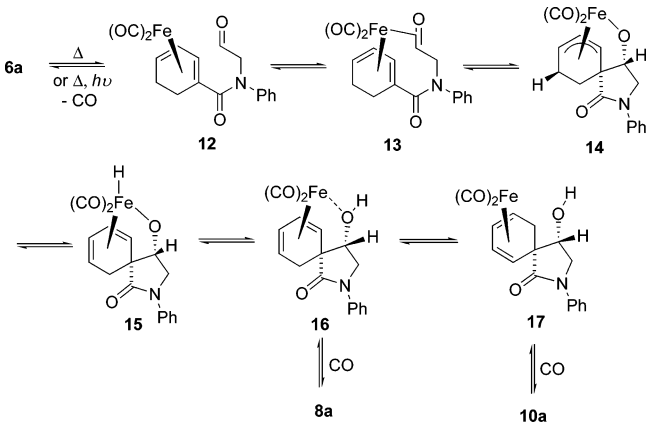
SCHEME 2



SCHEME 3



and then oxidized (Swern oxidation) to give aldehyde **25** in 88% yield over two steps (Scheme 6).[11] Treatment of **25** with triethyl phosphonoacetate under Masamune−Roush conditions,[12] followed by deprotection of the amino group afforded **26** in 73% yield over two steps. Coupling of acid **4a** via its acyl mesylate with secondary amine **26** afforded amide complex **27** (76% yield) with a pendant olefin, which underwent [6+2] ene type spirocyclization under photothermal conditions to give a 1.7:1 mixture of lactam complexes **28a** and **28b** in 78% yield.

Attempted direct reduction of ester **28** to aldehyde **30** with DIBAl-H was problematic. Aldehydes **30a**/**b** (as a 3.5:1 mixture) were therefore obtained by reducing esters **28a**/**b** with $LiBH_4$ to the corresponding alcohols **29a** and **29b**, obtained in a 1.4:1 ratio and 82% yield, followed by Mukaiyama oxidation. Presumably, the changes in ratio of **a**/**b** are a result of fractionation during these transformations, possibly reflecting different stabilities or reactivities of these isomers. Homologation of aldehydes **30a**/**b** by treatment with $MeOCH{=}PPh_3$ under Wittig olefination conditions and subsequent hydrolysis afforded aldehyde substrates **31a**/**b** in a 4:1 ratio and 88% yield over two steps.[9]

Subjection of **30a**/**b** to photothermal conditions (mesitylene, 350 nm, CO, 160 °C) gave a single complexed tricyclic compound **32** and its demetalation product **33** in 21% and 26% yields, respectively (Scheme 7). Complex **30a** can cyclize directly to give the desired products, but **30b** needs to be converted to **30a** first via thermal equilibrium under the cyclization conditions, and then undergoes cyclization.[1] Complex **32** was readily converted to pure organic compound **33** by demetalation with $CuCl_2$ in EtOH, and the combined yield for formation of **33** was 42% over two steps. The stereochemistry at C6 and C7 in compound **33** was assigned by NOE difference NMR spectra. A 1.6:1 mixture of known[1] compounds **34a**/**b** was also isolated in 17% yield, resulting from iron-promoted decarbonylation of **30a**/**b**.

To compare this iron-promoted carbonyl−diene reaction with the known nickel-catalyzed carbonyl−diene coupling reaction,[13] decomplexed aldehydes **35a**/**b** were prepared in good yields from complexed alcohols **29a**/**b** by demetalation and subsequent oxidation with Dess−Martin reagent (Scheme 8). Treatment of **35a** with $Ni(acac)_2$ and Et_2Zn in THF afforded two isomers in 9% and 52% yields, respectively. They were assigned as **36a** and **36b** based on the known characteristics of this nickel-catalyzed reaction and further confirmed by NMR spectra. Subsequent oxidation of **36a** and **36b** with Dess−Martin reagent gave two ketone isomers **37a** and **37b**, which further confirmed that **36a** and **36b** are a pair of regioisomers instead of two alcohol epimers. Similarly, **35b** was also treated with $Ni(acac)_2$ and Et_2Zn in THF to afford **38a** and **38b**, each in 11% yield. An increased amount of $Ni(acac)_2$ and Et_2Zn and an elongated reaction time caused loss of most material. Subsequent oxidation of **38a** and **38b** with Dess−Martin reagent also afforded two ketone isomers **39a** and **39b** in excellent yields. For this type of substrate, this comparison shows that our iron-promoted carbonyl−ene reaction has the advantage of affording a single major ene product with retention of the diene functional group.

Cyclization of **31a**/**b** was also investigated under both thermal and photothermal conditions and produced three regioisomers **40a**−**c** with formation of a five-membered ring instead of the expected six-membered ring. A plausible mechanism for this reaction is included in Scheme 9. One carbonyl ligand dissociates from iron under the reaction conditions and then subsequent oxidative addition of the aldehyde leads to intermediate **41**, on which decarbonylation occurs to give intermediate **42**. Then reductive elimination forms π allyl complex **43**, which can undergo a second reductive elimination and demetalation to afford **40b** or **40c**. Presumably **40a** results from double bond

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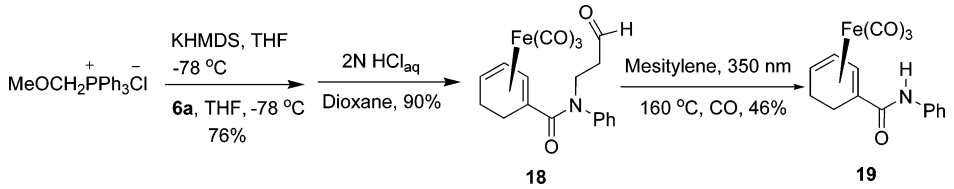
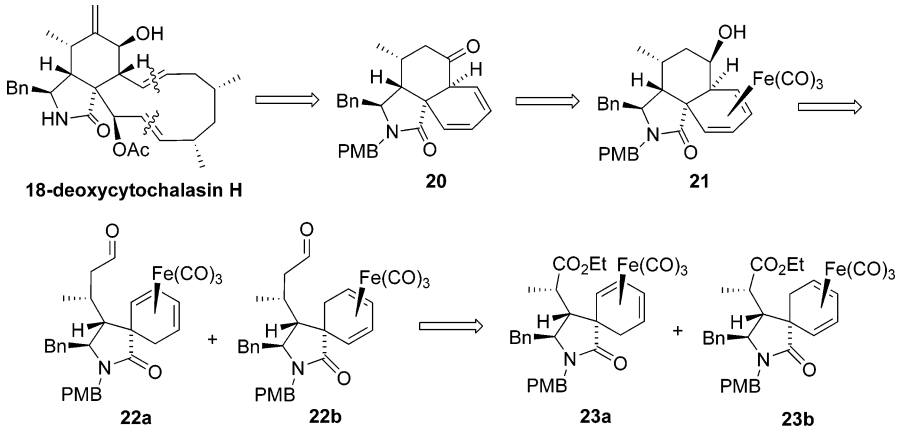
SCHEME 4



SCHEME 5



migration on the initial products. Note that substrate **30** also gives products of decarbonylation (**34**) but there is no decarbonylative cyclization because this would require 4-membered-ring formation.

To investigate alternate cyclization methods that can avoid decarbonylation, a 1:2.7 mixture of **44a**/**b** was prepared in 57% yield by treating complexes **31a**/**b** with Me_3NO in benzene (Scheme 10). Subsequent treatment of the **44a**/**b** mixture with 2 N HCl led to 100% recovery of **44b** and cyclization product **45** in 75% yield from its corresponding substrate **44a**, which was completely consumed after the reaction (path a in Scheme 10). A better combined yield for formation of **45**, 63% over two steps from **31a**/**b**, was obtained by demetalation with $CuCl_2$ in EtOH, followed by direct treatment of the product mixture with 2 N HCl (path b in Scheme 10). These results indicate **45** is formed through a Prins reaction from demetalated compound **44a** rather than a hetero-Diels−Alder reaction.[14] However, due to difficulty in forming a seven-membered ring with the diene in **44b**, this compound does not undergo the Prins reaction and remains unchanged under the conditions used here.

To conclude, an intramolecular iron-promoted aldehyde−diene coupling reaction was discovered and investigated to provide spirocyclic or bicyclic products. The ability to stereospecifically build new chiral centers, introduce a functionalizable hydroxyl group, and avoid isomerization of products significantly expands the scope of our previously reported [6+2] ene type of spirocyclization and tandem double cyclization.

Experimental Section

General Procedure for the Thermally Induced Cyclization. The appropriate amide was dissolved in freshly distilled *n*-Bu_2O ether (0.02 mmol/mL) under argon in a dried glass round-bottomed flask. The air in the solution was removed by the freeze−pump−thaw method three times, followed by bubbling with Ar for 10 min and then with CO for 10 min. The solution was refluxed under a balloon of CO for 6−20 h. The cooled reaction mixture was filtered through Celite and concentrated in vacuo. Flash chromatography or preparative TLC separation yielded the desired products. Deviations from this procedure are noted in the experimental description for specific compounds.

General Procedure for the Photothermally Induced Cyclization. The appropriate amide was dissolved in freshly distilled toluene or mesitylene (0.01−0.02 mmol/mL) under argon in a dried quartz tube or a glass round-bottomed flask. The air in the solution was removed by the freeze−pump−thaw method three times, followed by bubbling with Ar for 10 min and then with CO for 10 min. The reaction flask was put into an oil bath, heated to the boiling point of the solvent being used, and irradiated in a Rayonet reactor with a 350 nm light source, with magnetic stirring for 6−24 h under a balloon of CO. The cooled reaction mixture was filtered through Celite and concentrated in vacuo. Mesitylene was removed under oil pump vacuum at rt. Flash chromatography or preparative TLC separation yielded the desired products. Deviations from this procedure are noted in the experimental description for specific compounds.

General Procedure for Demetalation. Method A: To the solution of complexed intermediate in benzene was added trimethylamine oxide (30 equiv). The reaction mixture was stirred for 24 h at rt, then filtered through Celite and concentrated in vacuo. Purification by flash chromatography or preparative TLC afforded the pure products. **Method B:** To a small vial was added the iron carbonyl complex (0.1 mmol) and sat. $CuCl_2$ solution in EtOH (2.5 mL). The solution was stirred at rt for 3−24 h, then concentrated in vacuo. After water (4 mL) was added to the residue, the mixture was extracted with ether (3 × 3 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude products were purified by preparative TLC or flash chromatography.

Cyclization of 6a To Afford 8a, 9a, 10a, and 11a. According to the general procedure for the photothermally induced cyclization, a solution of aldehyde **6a** (43 mg, 0.11 mmol) in toluene (22 mL) was heated at 100 °C for 12 h. Flash chromatography (Hex:EA/3:1) afforded **8a** (20.2 mg, 47%) as a pale yellow solid. Mp 189−191 °C. R_f 0.60 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 9.2, 1.6 Hz, 2H), 7.37−7.33 (2H), 7.13 (t, J = 7.2 Hz,

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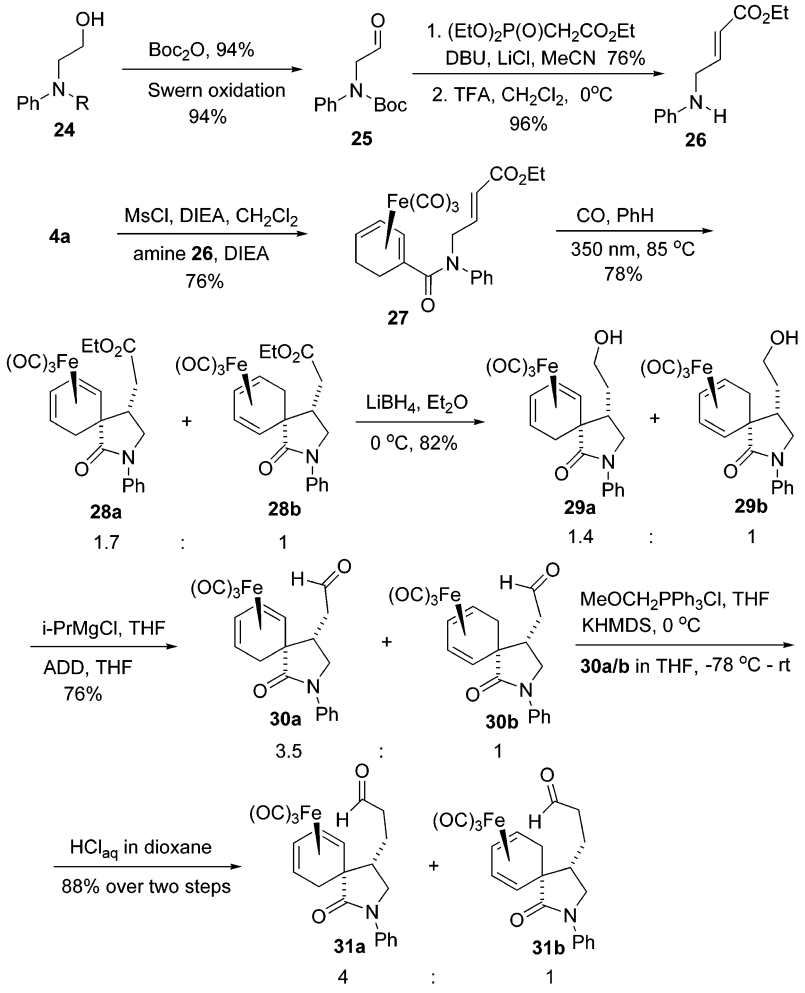
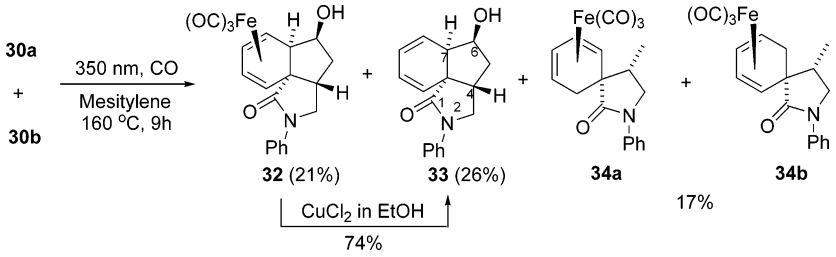
SCHEME 6

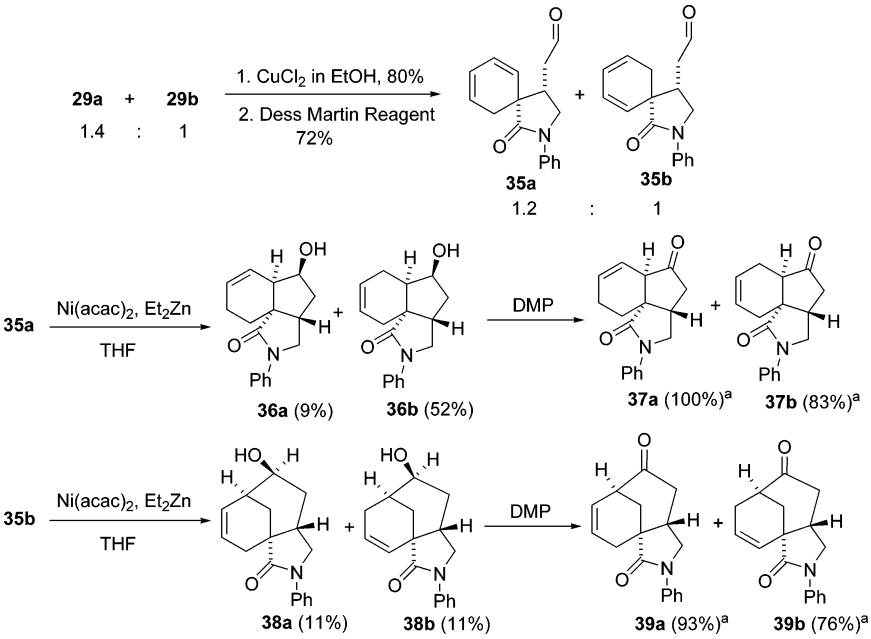


SCHEME 7



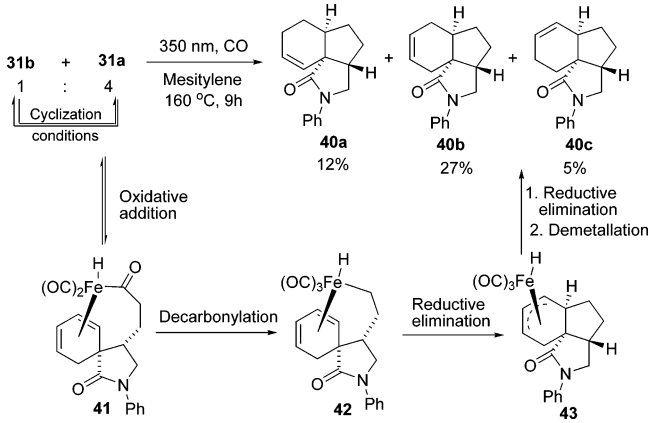
1H), 5.72−5.69 (m, 1H), 5.51 (dd, J = 5.6, 5.2 Hz, 1H), 4.40−4.30 (m, 1H), 3.94 (dd, J = 10.4, 4.8 Hz, 1H), 3.68 (dd, J = 10.8, 2.4 Hz, 1H), 3.21−3.18 (m, 1H), 3.09 (dd, J = 6.8, 1.2 Hz, 1H), 2.19 (br, 1H), 1.92−1.81 (2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 175.1, 139.5, 129.1, 124.8, 119.7, 86.8, 85.2, 74.4, 60.3, 57.8, 54.8, 53.1, 37.2. HRMS (FAB) calcd for MH^+ ($C_{18}H_{16}FeNO_5$) 382.0378, found 382.0378. Purification of the remaining material by preparative TLC (2% MeOH in CH_2Cl_2) gave recovered starting material (7.0 mg, 8%) and afforded **10a** (2.9 mg, 7%) as a pale yellow solid. Mp 50 °C dec. R_f 0.50 (2% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, CH_3OD:$CDCl_3$/1:1) δ 7.62−7.58 (2H), 7.39−7.34 (2H), 7.19−7.15 (m, 1H), 5.57 (dd, J = 5.6, 4.2 Hz, 1H), 5.39−5.36 (m, 1H), 4.29 (dd, J = 10.8, 4.4 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.48−3.40 (m, 1H), 2.84 (dd, J = 6.4, 1.2 Hz, 1H), 2.35 (dd, J = 16.0, 3.2 Hz, 1H), 1.93 (dd, J = 16.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, CH_3OD:$CDCl_3$/1:1) δ 211.5, 176.4, 139.6, 129.1, 124.9, 120.0, 88.8, 82.2, 71.8, 63.8, 60.8, 55.1, 54.7, 31.1. HRMS (FAB) calcd for [$MH^+ - Fe(CO)_3$] ($C_{15}H_{16}NO_2$) 242.1181, found 242.1173. **9a** (1.6 mg, 6%). Mp 155−157 °C. R_f 0.40 (2% MeOH in CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 9.2, 1.2 Hz, 2H), 7.41−7.30 (2H), 7.18−7.15 (m, 1H), 6.36 (dd, J = 9.6, 5.2 Hz, 1H), 6.06−6.02 (m, 1H), 5.92−5.87 (m, 1H), 5.74 (d, J = 9.6 Hz, 1H), 4.40−4.37 (m, 1H), 4.04 (dd, J = 10.8, 5.6 Hz, 1H), 3.73 (dd, J = 10.4, 3.2 Hz, 1H), 2.88 (d, J = 18.0 Hz, 1H), 2.21 (dd, J = 18.0, 5.6 Hz, 1H), 1.96 (d, J = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 139.4, 129.2, 125.4, 125.0, 124.0, 121.8, 120.1, 70.0, 53.0, 51.4, 30.0. HRMS (FAB) calcd for MH^+ ($C_{15}H_{16}NO_2$) 242.1181, found 242.1145. **11a** (2.2 mg, 8%). Mp 195−197 °C. R_f 0.30 (2% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 9.2, 1.2 Hz, 2H), 7.40−7.35 (2H), 7.17−7.13 (m, 1H), 6.28 (ddd, J = 10.0, 4.0, 3.6 Hz, 1H), 5.68 (d, J = 10.0 Hz, 1H), 4.26−4.22 (m, 1H), 4.09 (dd, J = 10.4, 5.6 Hz, 1H), 3.71 (dd, J = 10.4, 3.2 Hz, 1H), 2.23−2.05 (2H), 2.00−1.90 (2H), 1.89 (d, J = 4.8 Hz, 1H), 1.75−1.62 (2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 139.6, 135.8, 129.1, 124.8, 122.2,

SCHEME 8



[a] Yields are based on the corresponding single alcohol.

SCHEME 9



120.0, 73.3, 53.4, 52.0, 29.4, 24.9, 19.0. HRMS (FAB) calcd for MH^+ ($C_{15}H_{18}NO_2$) 244.1337, found 244.1331.

Demetalation of 8a To Afford 9a. According to the general procedure B of demetalation, complex **8a** (11 mg, 29 μmol) was treated with $CuCl_2$ in EtOH for 20 h. The crude products were purified by preparative TLC to give **9a** (5.5 mg, 79%).

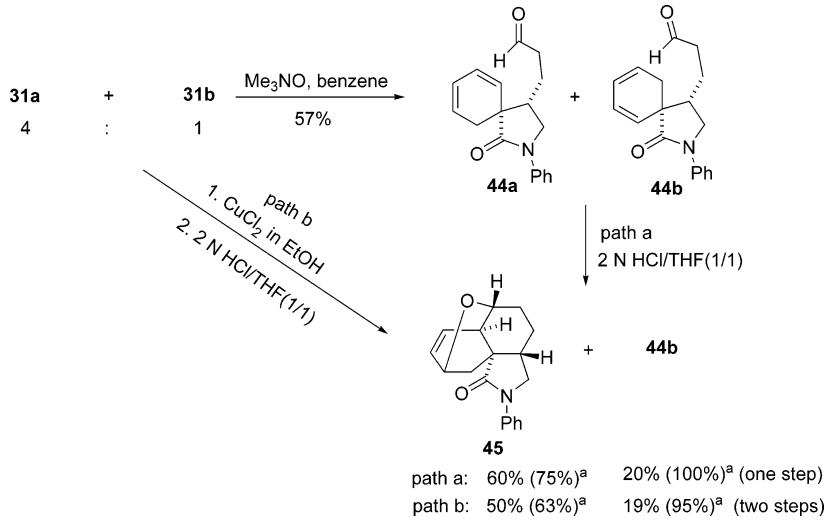
Cyclization of 6b To Afford 8b and 10b. According to the general procedure for the photothermally induced cyclization, a solution of aldehyde **6b** (23 mg, 0.06 mmol) in toluene (5.8 mL) was heated at 110 °C for 6 h. Flash chromatography (Hex:EA/3:1) afforded **8b** (4.5 mg, 20%) as a pale yellow solid. Mp 158−160 °C. R_f 0.70 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.56 (2H), 7.36−7.32 (2H), 7.15−7.11 (m, 1H), 5.41 (d, J = 6.4 Hz, 1H), 4.20−4.16 (m, 1H), 3.93 (dd, J = 11.2, 4.8 Hz, 1H), 3.70 (dd, J = 10.8, 2.0 Hz, 1H), 3.04 (d, J = 1.6 Hz, 1H), 3.02−2.99 (m, 1H), 2.31 (s, 3H), 2.16 (d, J = 4.0 Hz, 1H), 1.83−1.72 (2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 175.6, 139.5, 129.1, 124.8, 119.8, 104.2, 86.4, 74.3, 60.6, 56.4, 55.9, 53.4, 36.7, 22.6. HRMS (FAB) calcd for MH^+ ($C_{19}H_{18}FeNO_5$) 396.0534, found 396.0552. Further purification of the remaining material by preparative TLC (2% THF in CH_2Cl_2) gave recovered **6b** (4.5 mg, 19%) and afforded **10b** (1.2 mg, 5%). Mp 170 °C dec. R_f 0.20 (2% THF in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.60 (2H), 7.38−7.33 (2H), 7.16−7.12 (m, 1H), 5.47 (d, J = 4.0 Hz, 1H), 5.20 (dd, J = 6.0, 4.0 Hz, 1H), 4.31−4.28 (m, 1H), 4.22 (dd, J = 11.2, 4.4 Hz, 1H), 3.71 (d, J = 10.8 Hz, 1H), 2.62 (dd, J = 6.4, 1.2 Hz, 1H), 2.34 (d, J = 16.0 Hz, 1H), 1.96−1.91 (2H), 1.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 139.7, 129.1, 124.8, 119.6, 91.0, 80.3, 78.5, 72.6, 59.7, 55.5, 54.6, 36.9, 25.8. HRMS (FAB) calcd for MH^+ ($C_{19}H_{18}FeNO_5$) 396.0534, found 396.0542.

Cyclization of 6c To Afford 8c. According to the general procedure for the photothermally induced cyclization, aldehyde **6c** (29 mg, 0.07 mmol) in toluene (15 mL) was heated at 100 °C for 12 h. Preparative TLC (Hex:EA/2:1) afforded **8c** (1.9 mg, 7%). R_f 0.70 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.59 (2H), 7.36−7.32 (2H), 7.15−7.11 (m, 1H), 5.26−5.24 (m, 1H), 4.22−4.19 (m, 1H), 3.94 (dd, J = 10.8, 4.4 Hz, 1H), 3.77 (s, 3H), 3.70 (dd, J = 10.8, 1.6 Hz, 1H), 3.39 (d, J = 2.4 Hz, 1H), 2.74−2.70 (m, 1H), 2.25 (br, 1H), 1.75 (ddd, J = 14.8, 2.4, 0.8 Hz, 1H), 1.63 (dd, J = 14.8, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 141.3, 139.2, 128.8, 124.6, 119.4, 73.7, 67.6, 56.5, 55.2, 53.2, 51.6, 48.2, 36.7. HRMS (FAB) calcd for MH^+ ($C_{19}H_{18}FeNO_6$) 412.0484, found 412.0487.

[*N*-Phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (19). According to the general procedure for the photothermally induced cyclization, a solution of aldehyde **18** (31 mg, 0.09 mmol) in mesitylene (16 mL) was heated at 160 °C for 12 h. Flash chromatography (Hex:EA/3:1) recovered starting material (5.5 mg, 18%) and afforded **19** (12 mg, 46%). R_f 0.50 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (2H), 7.29−7.24 (3H), 7.06−7.02 (m, 1H), 6.16 (dd, J = 4.0, 0.8 Hz, 1H), 5.39−5.37 (m, 1H), 3.30−3.28 (m, 1H), 1.98−1.93 (2H), 1.75−1.64 (2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.6, 138.1, 129.3, 124.5, 120.4, 88.6, 85.0, 68.0, 61.8, 25.1, 24.7. HRMS (FAB) calcd for MH^+ ($C_{16}H_{14}FeNO_4$) 340.0272, found 340.0272.

[Ethyl 2-[6,9,η-2-phenyl-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]acetate]tricarbonyliron (28a and 28b). According to the general procedure for the photothermally induced cyclization, complex **27** (104 mg, 0.23 mmol) in benzene (15 mL) was heated at 80 °C under CO in a quartz tube (Rayonet reactor) for 6 h. Flash chromatography (Hex:EA/4:1) afforded two inseparable diastereomers **28a** and **28b** (81 mg, 78%) in a 1.7:1 ratio. R_f 0.50 (Hex:EA/4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.56 (4H, two isomers), 7.37−7.32 (4H, two isomers), 7.15−7.10 (2H, two

SCHEME 10



isomers), 5.55−5.53 (m, 1H, minor isomer), 5.51−5.49 (2H, major isomers), 5.34−5.31 (m, 1H, minor isomer), 4.18 (q, J = 7.6 Hz, 2H, major isomer), 4.14−4.05 (2H, minor isomer), 3.90 (dd, J = 14.4, 6.8 Hz, 1H, major isomer), 3.58−3.53 (2H, two isomers), 3.41−3.39 (m, 1H, minor isomer), 3.32−3.25 (m, 1H, major isomer), 3.02 (dd, J = 6.4, 1.2 Hz, 1H, minor isomer), 2.88 (dd, J = 15.2, 3.2 Hz, 1H, major isomer), 2.78−1.88 (10H, two isomers), 1.29 (t, J = 7.2 Hz, 3H, major isomer), 1.22 (t, J = 6.8 Hz, 3H, minor isomer). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 211.5, 176.2, 175.9, 172.2, 172.1, 139.8, 139.6, 129.1, 129.0, 124.8, 120.0, 119.6, 119.5, 89.0, 87.8, 83.6, 82.2, 63.2, 63.1, 62.2, 61.1, 59.0, 51.5, 50.0, 40.8, 39.7, 34.0, 33.5, 14.4, 14.3. HRMS (FAB) calcd for MH^+ ($C_{22}H_{22}FeNO_6$) 452.0797, found 452.0790.

[2-[6,9,η-2-Phenyl-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]ethanol]tricarbonyliron (29a and 29b). To a solution of esters **28a** and **28b** (451.0 mg, 1.0 mmol) in Et_2O (28 mL) under Ar was added $LiBH_4$ (110.0 mg, 5.0 mmol) in one portion. Stirring was continued for 12 h and the reaction was complete according to TLC. The reaction mixture was quenched with 1 N HCl (25 mL) at 0 °C, extracted with Et_2O (3 × 25 mL), washed with brine (2 × 15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (Hex:EA/4:1) afforded two inseparable diastereomers **29a** and **29b** (337.0 mg, 82%) in a 1.4:1 ratio. R_f 0.30 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.50 (4H, two isomers), 7.30−7.25 (4H, two isomers), 7.10−7.05 (2H, two isomers), 5.55−5.45 (m, 1H, minor isomer), 5.43−5.38 (2H, major isomer), 5.26−5.23 (m, 1H, minor isomer), 4.04 (dd, J = 14.4, 6.4 Hz, 1H, minor isomer), 3.77−3.51 (7H, two isomers), 3.35−3.32 (m, 1H, minor isomer), 3.26−3.23 (m, 1H, major isomer), 2.96 (dd, J = 6.4, 1.6 Hz, 1H, minor isomer), 2.74 (dd, J = 6.4, 1.6 Hz, 1H, major isomer), 2.38−2.32 (m, 1H, minor isomer), 2.18−2.14 (m, 1H, major isomer), 2.12−2.06 (m, 1H, major isomer), 2.03 (dd, J = 16.0, 2.8 Hz, 1H, major isomer), 1.97 (d, J = 3.2 Hz, 2H, minor isomer), 1.81 (dd, J = 15.6, 3.2 Hz, 1H, major isomer), 1.77−1.70 (m, 1H, minor isomer), 1.66−1.31 (5H, two isomers). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 211.7, 177.0, 176.6, 139.9, 139.8, 129.1, 129.0, 124.7, 124.6, 119.7, 119.6, 89.0, 87.9, 83.2, 82.3, 63.6, 63.5, 62.6, 61.2, 60.9, 59.7, 52.2, 51.6, 50.3, 49.9, 41.7, 39.8, 39.5, 33.2, 31.5, 30.7. HRMS (FAB) calcd for MH^+ ($C_{20}H_{20}FeNO_5$) 410.0691, found 410.0692.

[2-[6,9,η-2-Phenyl-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]acetaldehyde]tricarbonyliron (30a and 30b). To a solution of alcohol **29a**/**b** (155 mg, 0.37 mmol) in THF (2.0 mL) under Ar at 0 °C was added isopropylmagnesium bromide solution (2 M in THF, 0.24 mL, 0.47 mmol). After 30 min at 0 °C, a solution of 1,1′-(azodicarbonyl)dipiperidine (105.0 mg, 0.42 mmol) in THF (1.0 mL) was added. Stirring was continued for 30 min, then the mixture was allowed to warm to rt and stirred for 2.5 h. The reaction solution was quenched with brine (10 mL), extracted with Et_2O (2 × 10 mL), washed with a mixture of brine and water (1:1, 2 × 5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/3:1) afforded **30a** and **30b** (118 mg, 76% combined yield) in a 3.5:1 ratio. **30a** (91.7 mg, 59%): R_f 0.50 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.51−7.48 (2H), 7.29−7.25 (2H), 7.08−7.04 (m, 1H), 5.46−5.44 (2H), 3.91 (dd, J = 10.0, 6.4 Hz, 1H), 3.38 (dd, J = 10.0, 4.2 Hz, 1H), 3.27−3.24 (m, 1H), 3.02 (d, J = 14.4 Hz, 1H), 2.65−2.53 (3H), 2.05 (dd, J = 15.2, 2.8 Hz, 1H), 1.81 (dd, J = 15.6, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 200.4, 176.1, 139.5, 129.1, 124.9, 119.6, 87.9, 83.6, 62.4, 59.1, 51.3, 50.1, 43.0, 39.8, 38.4. HRMS (FAB) calcd for MH^+ ($C_{20}H_{28}FeNO_5$) 408.0534, found 408.0531. **30b** (26.2 mg, 17%): R_f 0.40 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.53−7.51 (2H), 7.30−7.26 (2H), 7.09−7.05 (m, 1H), 5.50−5.47 (m, 1H), 5.29−5.23 (m, 1H), 4.15 (ddd, J = 10.8, 6.0, 1.2 Hz, 1H), 3.34−3.32 (2H), 2.98 (dd, J = 6.4, 1.2 Hz, 1H), 2.79−2.74 (m, 1H), 2.65−2.60 (m, 1H), 2.37 (ddd, J = 18.4, 11.2, 1.2 Hz, 1H), 2.02 (dd, J = 15.6, 2.4 Hz, 1H), 1.83 (dd, J = 15.6, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 200.3, 175.9, 139.7, 129.1, 124.9, 119.5, 89.1, 82.3, 62.9, 62.9, 51.5, 50.9, 43.8, 36.6, 33.6. HRMS (FAB) calcd for MH^+ ($C_{20}H_{28}FeNO_5$) 408.0534, found 408.0527.

[2-[6,9,η-2-Phenyl-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]-propionaldehyde]tricarbonyliron (31a and 31b). To a mixture of methoxytrimethylphosponium chloride (146 mg, 0.43 mmol) in THF (3.3 mL) under Ar at 0 °C was added KHMDS (0.5 M in toluene, 0.94 mL, 0.47 mmol). Stirring was continued at this temperature for 30 min, then a solution of aldehyde **30a**/**b** (133 mg, 0.33 mmol) in THF (2.0 mL) was added at −78 °C and the reaction was maintained at this temperature for 1 h. The mixture was allowed to warm to rt and stirring was continued for 1 h. The reaction mixture was carefully quenched with brine (10 mL), extracted with Et_2O (3 × 7 mL), washed with brine (2 × 8 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in dioxane (3.0 mL) and treated with 2 N HCl (1.0 mL) for 3 h. Et_2O (50 mL) was added, then the solution was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (Hex:EA/3:1) afforded inseparable **31a** and **31b** (120 mg, 88%) in a 4:1 ratio. R_f 0.60 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, J = 1.6 Hz, 1H, major isomer), 9.74 (t, J = 1.6 Hz, 1H, minor isomer), 7.62−7.54 (4H, two isomers), 7.38−7.32 (4H, two isomers), 7.16−7.11 (2H, two isomers), 5.55−5.52 (m, 1H, minor isomer), 5.51−5.48 (2H, major isomer), 5.32−5.30 (m, 1H, minor isomer), 4.16−4.10 (m, 1H, minor isomer), 3.75 (dd, J = 10.0, 6.8 Hz, 1H, major

isomer), 3.48 (dd, J = 10.0, 6.0 Hz, 1H, major isomer), 3.44−3.40 (2H, minor isomer), 3.32−3.28 (m, 1H, major isomer), 2.98 (dd, J = 6.0, 0.8 Hz, 1H, minor isomer), 2.82−2.79 (m, 1H, major isomer), 2.60−2.2.0 (6H, two isomers), 2.11−2.03 (4H, two isomers), 1.91−1.71 (4H, two isomers). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 211.6, 201.2, 201.1, 176.6, 176.0, 139.6, 129.2, 129.1, 124.8, 119.6, 119.5, 89.0, 87.8, 83.6, 82.3, 63.4, 63.3, 62.2, 59.2, 52.2, 51.9, 50.1, 49.6, 43.9, 41.8, 41.4, 41.3, 39.9, 33.0, 21.4, 20.5. HRMS (FAB) calcd for MH^+ ($C_{21}H_{20}FeNO_5$) 422.0691, found 422.0711.

Cyclization of 30a/b To Afford Compounds 32 and 33. According to the general procedure for the photothermally induced cyclization, aldehydes **30a**/**b** (15.1 mg, 37 μmol) in mesitylene (3.0 mL) was heated under CO at 160 °C for 9 h. Preparative TLC (Hex:EA/3:1) recovered starting material (2.6 mg, 17%) and afforded decarbonylated products **34a**/**b** (2.4 mg, 17%), cyclization product **32** (3.2 mg, 21% from ^{1}H NMR, with some impurity), and demetalated product **33** (2.6 mg, 26%). According to the general demetalation procedure B, **33** was decomplexed by $CuCl_2$ in EtOH to afford **32** in 74% yield (42% combined yield over two steps). **33**: Mp 138−140 °C. R_f 0.40 (Hex:EA/2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.33−7.29 (2H), 7.11−7.07 (m, 1H), 6.17−6.13 (m, 1H), 5.94 (dd, J = 9.6, 4.2 Hz, 1H), 5.74 (dd, J = 9.6, 4.4 Hz, 1H), 5.56 (d, J = 9.6 Hz, 1H), 4.40−4.37 (m, 1H), 4.11 (dd, J = 10.0, 7.6 Hz, 1H), 3.56 (d, J = 14.4 Hz, 1H), 3.20−3.16 (m, 1H), 2.87 (dd, J = 18.0, 7.6 Hz, 1H), 2.06−2.01 (m, 1H), 1.81 (br, 1H), 1.38−1.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 139.7, 129.1, 125.6, 125.4, 125.0, 122.8, 122.3, 120.1, 77.5, 56.1, 50.6, 48.7, 44.1, 37.6. HRMS (FAB) calcd for MH^+ ($C_{17}H_{18}NO_2$) 268.1338, found 268.1332.

Cyclization of 31a/b To Afford Compounds 40a, 40b, and 40c. According to the general procedure for the photothermally induced cyclization, the mixture of aldehydes **31a**/**b** (20.1 mg, 48 μmol) in mesitylene (4.8 mL) was heated under CO at 160 °C for 9 h. Preparative TLC (Hex:EA/8:1) gave recovered starting material (2.6 mg, 10%) and afforded decarbonylated cyclization products **40a** (1.4 mg, 12%) and inseparable **40b** and **40c** (3.8 mg, 32% combined yield) in a 1:5 ratio. **40a**: R_f 0.35 (Hex:EA/8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (2H), 7.39−7.34 (2H), 7.15−7.13 (m, 1H), 6.02−5.97 (m, 1H), 5.63−5.60 (m, 1H), 4.10 (dd, J = 10.0, 8.4 Hz, 1H), 3.52 (dd, J = 10.0, 3.2 Hz, 1H), 2.60−2.54 (m, 1H), 2.51−2.45 (m, 1H), 2.25−2.12 (2H), 2.09−2.02 (m, 1H), 1.87−1.79 (2H), 1.61−1.56 (2H), 1.48−1.39 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4, 140.0, 130.1, 129.0, 127.2, 124.6, 120.0, 59.2, 53.5, 42.1, 42.0, 32.4, 31.2, 25.1, 23.0. HRMS (FAB) calcd for MH^+ ($C_{17}H_{20}NO$) 254.1545, found 254.1546. **40b** and **40c**: R_f 0.40 (Hex:EA/8:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.68 (4H, two isomers), 7.39−7.35 (4H, two isomers), 7.16−7.12 (2H, two isomers), 5.85−5.78 (2H, two isomers), 5.55−5.59 (2H, two isomers), 4.09 (dd, J = 10.0, 8.4 Hz, 1H, major isomer), 4.01 (dd, J = 10.0, 8.4 Hz, 1H, minor isomer), 3.58 (dd, J = 10.0, 2.0 Hz, 1H, minor isomer), 3.46 (dd, J = 10.0, 2.0 Hz, 1H, major isomer), 2.98−2.97 (m, 1H, major isomer), 2.60−1.40 (19H, two isomers). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.2, 178.6 140.0, 139.8, 130.7, 129.0, 127.0, 126.9, 124.6, 124.5, 120.1, 119.9, 57.3, 57.0, 54.1, 53.2, 43.1, 40.5, 39.5, 37.3, 33.8, 32.7, 31.6, 30.8, 29.9, 28.8, 27.5, 26.7, 21.2. HRMS (FAB) calcd for MH^+ ($C_{17}H_{20}NO$) 254.1545, found 254.1543.

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

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